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Removal of the Pyridine Directing Group from α-Substituted *N*-(Pyridin-2-yl)piperidines Obtained via Directed Ru-Catalyzed sp^3 C−H Functionalization

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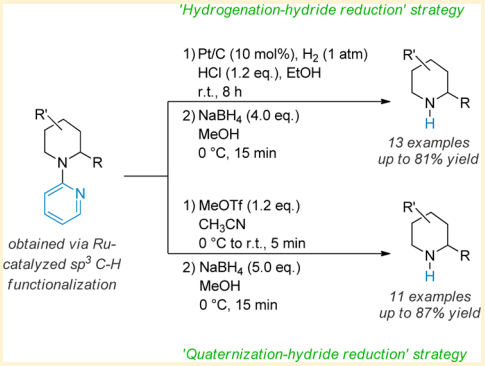
Supporting Information

ABSTRACT: Two strategies, "hydrogenation−hydride reduction" and "quaternization−hydride reduction", are reported that make use of mild reaction conditions (room temperature) to efficiently remove the *N*-pyridin-2-yl directing group from a diverse set of C-2-substituted piperidines that were synthesized through directed Ru-catalyzed sp^3 C−H functionalization. The deprotected products are obtained in moderate to good overall yields irrespective of the strategy followed, indicating that both methods are generally equally effective. Only in the case of 2,6-disubstituted piperidines, could the "quaternization−hydride reduction" strategy not be used. The "hydrogenation−hydride reduction" protocol was successfully applied to *trans*- and *cis*-2-methyl-*N*-(pyridin-2-yl)-6-undecylpiperidine in a short synthetic route toward (±)-solenopsin A (trans diastereoisomer) and (±)-isosolenopsin A (cis diastereoisomer). The absolute configuration of the enantiomers of these fire ant alkaloids could be determined via VCD spectroscopy.



INTRODUCTION

The concept of direct functionalization via transition metal-catalyzed C−H activation has attracted much attention in the past decade.[1] Methods that allow for the direct functionalization of inert C−H bonds are undoubtedly of high synthetic value and have recently become a useful tool in the synthesis of complex substrates such as pharmaceuticals, natural products, and organic materials.[2] Because C−H bonds are ubiquitous in organic molecules, one of the major challenges in this area is to develop reactions that work with predictable regioselectivity. Both in sp^2 and sp^3 C−H activation, regioselectivity can be achieved with the aid of pre-existing or deliberately built-in functional groups that coordinate to the metal and position it for a regioselective C−H bond cleavage.[3] The majority of directed C−H activation methods reported so far rely on nitrogen-, sulfur-, or phosphorus-containing directing groups (e.g., pyridine, oxazoline, thioether, and phosphine), which are strongly coordinating and form a thermodynamically stable five- or six-membered metallacycle with the transition metal in the C−H activation step.[3b,4] Weakly coordinating directing groups such as ketones, carboxylic acids, esters, alcohols, and ethers on the other hand have been less actively studied.[3b,5] A stable directing group is often required to make direct functionalization via C−H activation possible but also has an associated major drawback in that stable directing groups, when not required in the final target structures, are difficult to remove after the functionalization step.

Recently, our group has disclosed directed ruthenium-catalyzed (hetero)arylation and alkylation reactions that, applied to piperidines and related cyclic amines, deliver the corresponding α-substituted heterocycles.[6] Essential for the success of these C-2 functionalization reactions is the presence of a stable pyridine directing group on the nitrogen atom of the cyclic amine. An ideal directing group should be easily introduced onto the cyclic amine prior to C-2 functionalization, be perfectly stable under the reaction conditions required for the C−H functionalization process, and finally, be removed in a straightforward manner from the C-2-substituted reaction product (Scheme 1). When inefficiency at the stage of the

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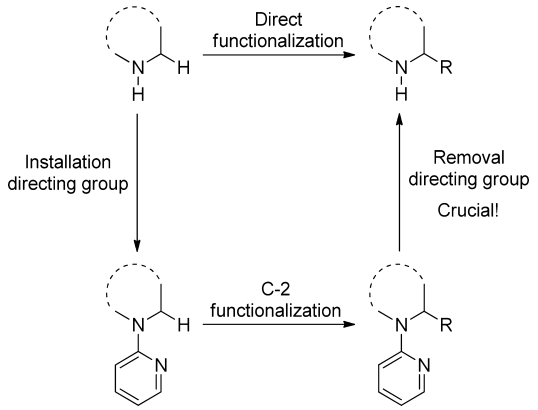
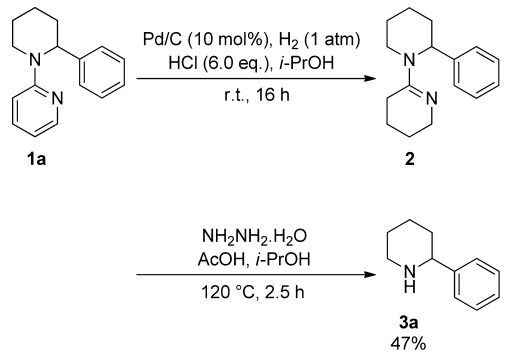
Scheme 1. General Concept of Using a Pyridine Directing Group in the Direct C-2 Functionalization of Saturated Cyclic Amines via Transition Metal-Catalyzed sp^3 C−H Activation



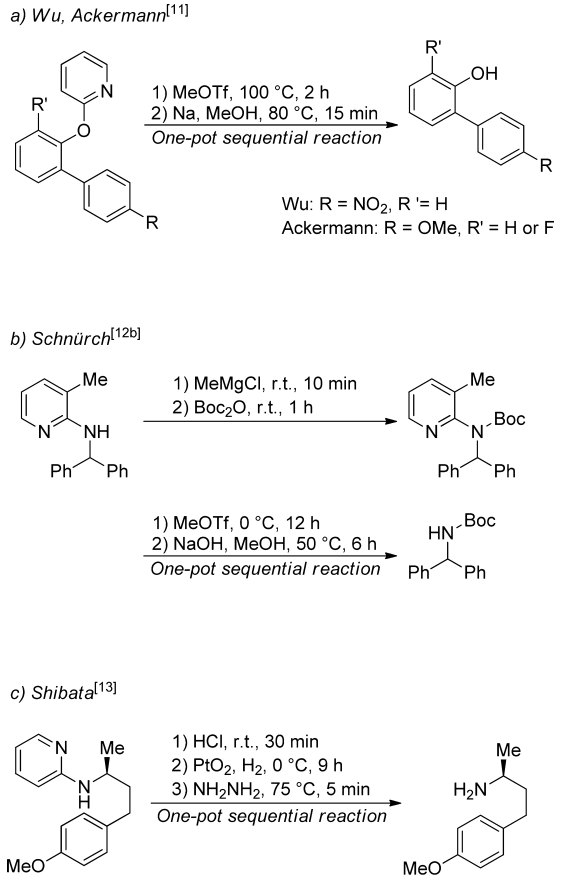
removal of the directing group is encountered, the functionalization process itself loses part of its synthetic appeal. *N*-(Pyridin-2-yl) derivatives of cyclic amines can be easily obtained by applying a Buchwald−Hartwig reaction[7] or via nucleophilic aromatic substitution, starting from readily available cyclic amines and 2-halopyridines. On the other hand, pyridine removal from the corresponding α-substituted reaction products appeared, at the outset of our study, not straightforward. Nevertheless, we were able to show in a concept reaction the first example of such an *N*-(pyridin-2-yl) group removal by "deprotecting" model substrate 2-phenyl-*N*-(pyridin-2-yl)piperidine (**1a**) in a one-pot sequential protocol (Scheme 2).[6a,8] The pyridinyl moiety was first partially reduced via a Pd/C-catalyzed hydrogenation and subsequent cleavage of the resulting amidine functionality was achieved by treatment with NH_2NH_2.[9]

Scheme 2. One-Pot Sequential Protocol for the Removal of the Pyridine Group from 2-Phenyl-*N*-(pyridin-2-yl)piperidine (1a) via a Method That Has Been Described Previously by Our Group



The use of pyridine to efficiently direct both sp^2 and sp^3 C−H activation is well documented in the literature.[10] Nevertheless, only in a limited number of reports is its removal from the functionalized products discussed. Wu and Ackermann (Scheme 3a) reported that ortho-arylated *O*-(pyridin-2-yl)-phenols can be converted into the corresponding free phenols by a two-step protocol involving methylation of the pyridine nitrogen with methyl triflate at 100 °C, followed by treatment of the *N*-methylpyridinium salt with Na in MeOH at 80 °C.[11]

Scheme 3. Removal of the Pyridine Directing Group from Reaction Products Obtained via Transition Metal-Catalyzed Directed sp^2 or sp^3 C−H Functionalization



The group of Schnürch (Scheme 3b) applied a three-step method for the removal of the pyridine group from α-arylated *N*-benzyl-*N*-(3-methylpyridin-2-yl)amines.[12] Carbamoylation of the secondary amine nitrogen is followed by subsequent methylation of the pyridine nitrogen using methyl triflate at 0 °C and hydrolysis of the resulting pyridinium salt at 50 °C, to eventually give Boc-protected α-arylated benzylic amines. Reaction conditions similar to those originally developed by our group for **1a** were reported by Shibata (Scheme 3c) for α-alkylated *N*-alkyl-*N*-(pyridin-2-yl)amines.[13] In a three-step protocol, the corresponding HCl-salt of (*S*)-*N*-(4-(4-methoxyphenyl)butan-2-yl)pyridin-2-amine was first formed and then subjected to a PtO_2-catalyzed hydrogenation reaction at 0 °C, followed by treatment with hydrazine at 75 °C. Although these initial results on pyridine group removal reported by our group and others are promising, the "deprotection" is always shown for one "model substrate" which is usually acyclic. In addition, there is only very limited information on the compatibility of the developed method with functional groups. Moreover, harsh reaction conditions are sometimes required (e.g., MeOTf and NH_2NH_2 at higher temperatures). Herein, we report two strategies that make use of mild reaction conditions (room temperature) to efficiently remove the pyridine directing group from a diverse set of C-2-substituted piperidines that were obtained through directed Ru-catalyzed sp^3 C−H functionalization.

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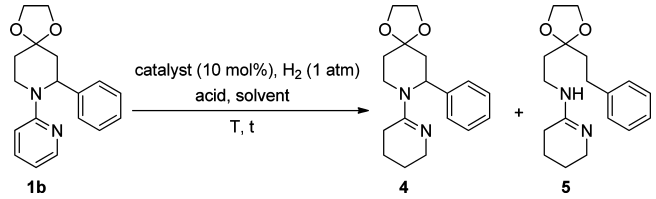
Table 1. Optimization of the Transition Metal-Catalyzed Hydrogenation of 2-Aryl-*N*-(pyridin-2-yl)piperidines with 4-Ketal-2-phenyl-*N*-(pyridin-2-yl)piperidine (1b) as Model Substrate[a]



entry	catalyst	acid	solvent	*T*, °C	*t*, h	LC-MS yield[h] (%) **1b**/**4**/**5**
1	Pd/C[b]	HCl[f] (6.0 equiv)	*i*-PrOH (3.6 mL)	rt	16	22/19/2[i]
2	Pd/C[c]	AcOH (6.0 equiv)	*i*-PrOH (10 mL)	50	16	1/1/98
3	Pd/C[c]	AcOH (6.0 equiv)	*i*-PrOH (10 mL)	rt	16	86/8/6
4	PtO_2[d]	AcOH (6.0 equiv)	EtOH (5 mL)	rt	18	95/5/0
5	Pt/C[e]	AcOH (6.0 equiv)	EtOH (5 mL)	rt	18	52/48/0
6	Pt/C[e]	HCl[g] (6.0 equiv)	EtOH (2.6 mL)	rt	18	0/4/0[j]
7	Pt/C[e]	HCl[g] (1.2 equiv)	EtOH (4.5 mL)	rt	18	0/92/0[k]
8	Pt/C[e]	HCl[g] (1.2 equiv)	EtOH (4.5 mL)	rt	8	0/100/0

[a]All reactions were performed on a 0.5 mmol scale under 1 atm H_2 pressure in the presence of the mentioned catalyst (10 mol % or 0.05 mmol of metal [Pd or Pt]), acid, and solvent, using the indicated temperature (*T*) and time (*t*). [b]Pd/C with 10% Pd-basis. [c]Pd/C with 5% Pd-basis. [d]PtO_2 with 83% Pt-content. [e]Pt/C with 5% Pt-basis. [f]6.0 M HCl in *i*-PrOH. [g]1.25 M HCl in EtOH. [h]Uncorrected LC-MS yields. [i]52% side products with a hydrolyzed ketal functionality were detected. [j]A complex mixture of side products was formed. MS indicates that the ketal functionality is hydrolyzed or completely removed. Additional cleavage of the C_2–N benzylic bond and/or reduction of the C_2-phenyl ring was also detected. [k]8% side product with additional reduction of the C_2-phenyl ring was detected.

RESULTS AND DISCUSSION

The need for a new, efficient and general method became apparent when we applied the hydrogenation conditions originally developed for **1a** (Scheme 2) to more challenging substrates. Full conversion of the C-2 phenylated piperidine **1a** to the corresponding *N*-(tetrahydropyridin-2-yl)amine **2** was previously accomplished by making use of a Pd/C-catalyzed hydrogenation in the presence of HCl. However, when the same hydrogenation conditions were applied to 4-ketal-2-phenyl-*N*-(pyridin-2-yl)piperidine (**1b**), incomplete conversion to the desired *N*-(tetrahydropyridin-2-yl)amine **4** was observed (Table 1, entry 1). Moreover, hydrolysis of the ketal functionality occurred as a major side reaction, and a small amount of acyclic *N*-(tetrahydropyridin-2-yl)amine **5** was formed as a result of undesired cleavage of the benzylic C_2–N bond. Clearly, novel hydrogenation conditions were required to develop a pyridine removal method that is applicable to a broad range of C-2 arylated *N*-(pyridin-2-yl)piperidine derivatives.

Previous work in our laboratory showed that 1-(pyridin-2-yl)-4-piperidinone ethylene ketal, the nonphenylated derivative of **1b**, could be fully converted to the corresponding *N*-(tetrahydropyridin-2-yl)amine without side product formation by performing a Pd/C-catalyzed hydrogenation at 50 °C in the presence of an excess of weak acid (AcOH) instead of HCl.[6a] Unfortunately, when these hydrogenation conditions were applied to 4-ketal-2-phenyl-*N*-(pyridin-2-yl)piperidine (**1b**), nearly complete conversion to the undesired acyclic *N*-(tetrahydropyridin-2-yl)amine **5** was observed (entry 2). At room temperature, the majority of the starting material **1b** remained and a mixture of the desired compound **4** and the C_2–N benzylic-cleaved compound **5** was obtained (entry 3). As it is documented that Pd has the tendency to induce hydrogenolysis at benzylic positions,[14] we reasoned that the formation of side product **5** might be prevented by using another transition metal to catalyze the hydrogenation. Because Pt is used for the reduction of pyridines without affecting benzylic positions,[15] we attempted the hydrogenation step in the presence of catalytic amounts of PtO_2, unfortunately without a positive outcome (entry 4). Gratifyingly, in the presence of Pt/C as the catalyst, a reasonable conversion to the desired *N*-(tetrahydropyridin-2-yl)amine **4** could be obtained at room temperature (entry 5). Because our goal was to develop a mild pyridine removal method, we preferred to keep the reaction at room temperature and tried to fully convert **1b** to **4** by switching again to the stronger acid HCl to mediate the Pt/C-catalyzed hydrogenation. To our delight, we found that the ketal functionality stayed intact when only a small excess of HCl was used (1.2 equiv instead of 6.0 equiv), and we could obtain the desired compound **4** in 92% LC-MS yield (entries 6 and 7). Because additional reduction of the phenyl ring starts taking place after 18 h, we shortened the reaction time to 8 h and found the *N*-(tetrahydropyridin-2-yl)amine **4** to be formed chemoselectively in 100% LC-MS yield (entry 8).

The remaining amidine functionality in compound **4** can be reduced by subjecting it to the previously established conditions that make use of NH_2NH_2, and in this way the deprotected product **3b** was obtained in 80% overall isolated yield (Scheme 4a). Because of the hazardous nature of hydrazine as a reagent (especially at higher temperatures), we continued our search for a milder and more generally applicable alternative for the second step of our "deprotection" protocol. Unfortunately, attempts to cleave the amidine group with nucleophilic reagents such as NaO*t*-Bu or NH_3, even at temperatures up to 120 °C, failed. As mentioned above, the imine moiety of the remaining amidine in compound **4** is not reduced if the Pt/C-catalyzed hydrogenation is performed for a longer time, but instead undesired reduction of the phenyl ring takes place. Also, when the hydrogenation was carried out at a higher H_2 pressure (10 atm instead of 1 atm), **1b** could not be directly converted to the corresponding deprotected product **3b**. Again, the amidine bond is not reduced and the reaction stops at the stage of the *N*-(tetrahydropyridin-2-yl)amine **4**.

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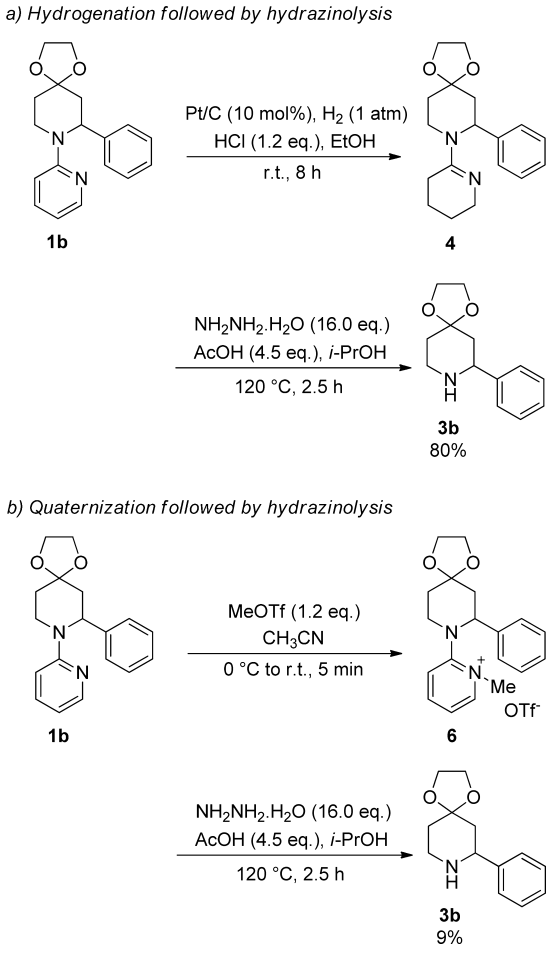
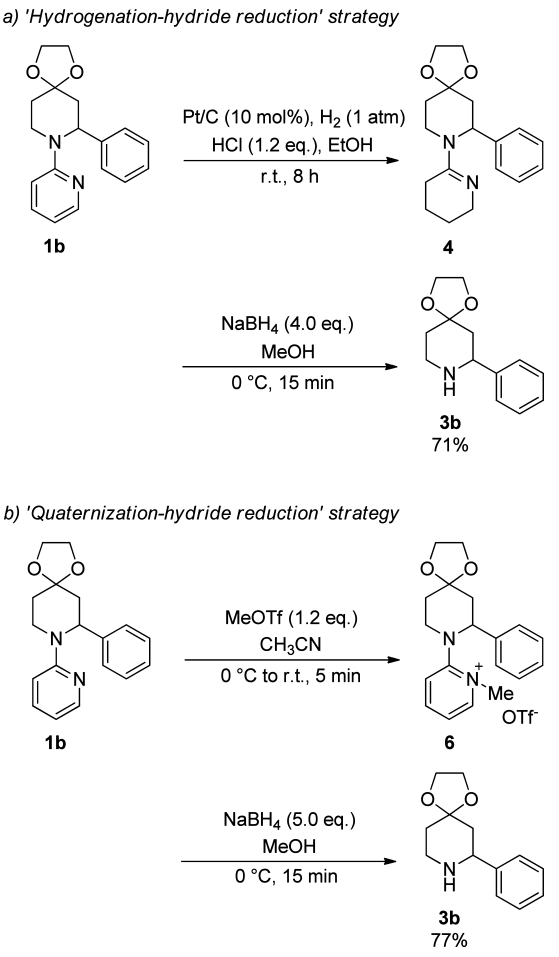
Scheme 4. Pyridine Group Removal via One-Pot Sequential Reactions Involving (a) Pt/C-Catalyzed Hydrogenation Followed by Hydrazinolysis and (b) *N*-Methylpyridinium Formation Followed by Hydrazinolysis



Scheme 5. Optimized Reaction Conditions for Removing the Pyridine Group from 4-Ketal-2-phenyl-*N*-(pyridin-2-yl)piperidine (1b) via (a) the One-Pot Sequential "Hydrogenation−Hydride Reduction" Strategy and (b) the One-Pot Sequential "Quaternization−Hydride Reduction" Strategy



Because compound **4** is formed as its hydrochloride salt, it occurred to us that a simple reduction of the protonated amidine with $NaBH_4$ could deliver the desired free piperidine (Scheme 5a).[16] Indeed, protonation reduces the electron density of the amidine and makes it more prone to nucleophilic attack by a reducing agent. In this way, an unstable aminal is formed which decomposes in situ, delivering the deprotected product **3b** in 71% overall isolated yield.

Along with the "hydrogenation−hydride reduction" strategy shown in Scheme 5a, an alternative route was developed based on the formation of an *N*-methylpyridinium salt. As depicted in Scheme 5b, this "quaternization−hydride reduction" strategy relies on the use of a methylating agent to form *N*-methylpyridinium salt **6**, which is then reduced by $NaBH_4$. This concept of quaternization−hydride reduction is well documented in the literature[17] but has never been applied previously to 2-aminopyridine systems such as **1b**. Treatment of **1b** with a slight excess of methyl triflate in acetonitrile at room temperature produced the desired pyridinium salt **6** quantitatively. Compound **6** was then easily reduced at room temperature by adding $NaBH_4$ to yield an unstable aminal, which in situ decomposes to the deprotected piperidine derivative. The free amine **3b** was isolated in 77% overall yield. Whereas the amidine bond in *N*-(tetrahydropyridin-2-yl)amine **4** (obtained after hydrogenation of **1b**) can be cleaved with NH_2NH_2 instead of $NaBH_4$ (Scheme 4a), only 9% of the desired deprotected product **3b** could be isolated when *N*-methylpyridinium salt **6** (obtained after methylation of **1b**) was treated with NH_2NH_2 in *i*-PrOH at 120 °C for 2.5 h (Scheme 4b). Importantly, both the "hydrogenation−hydride reduction" and the "quaternization−hydride reduction" strategy are one-pot sequential procedures consisting of two steps, meaning that only limited (filtration) or even no workup is performed after the first step of the protocols.

Having established two different strategies, we explored their scope (Scheme 6). Both the "hydrogenation−hydride reduction" and the "quaternization−hydride reduction" approach were found effective in removing the pyridine directing group from a variety of substituted piperidines (**1**) that were obtained via directed Ru-catalyzed sp^3 C−H functionalization.[6] Because both methods consist of two sequential reaction steps, the results displayed in Scheme 6 have to be considered as overall isolated yields, indicating that moderate to good conversions/yields are achieved in each step of the protocols. Only in a few cases did one method prove superior over the other (**3c**, **3f**, **3k**). Functional groups on a C-2 aryl substituent are tolerated by both methodologies, and no real electronic effects can be noticed when comparing the results obtained for compounds

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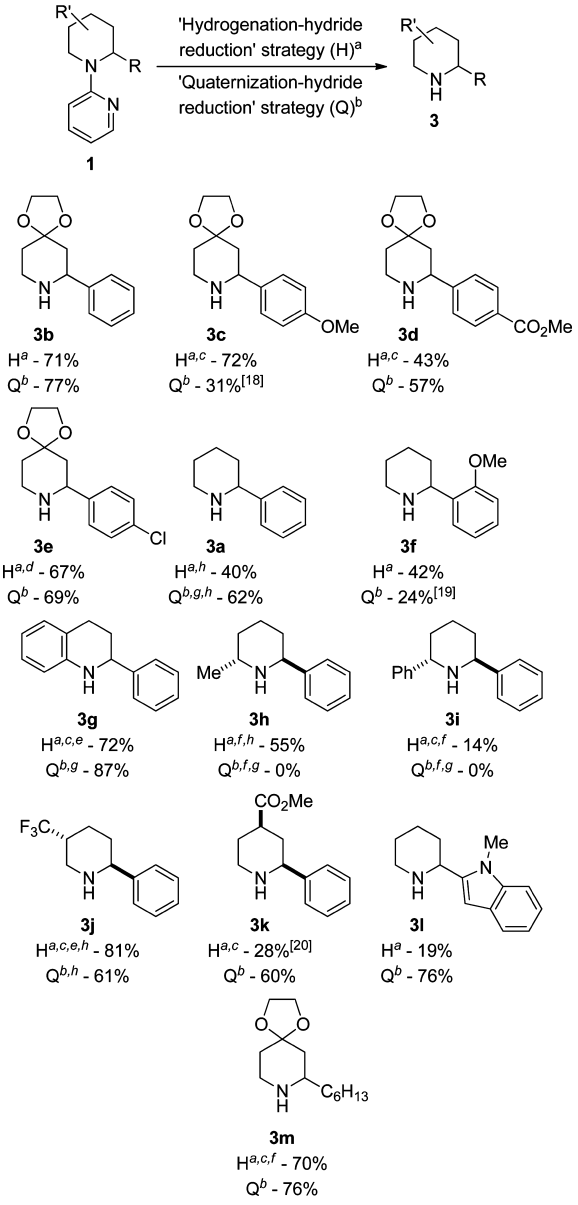
Scheme 6. Removal of the Pyridine Directing Group from α-Substituted *N*-(Pyridin-2-yl)piperidines 1



[a]The reactions were performed on a 0.5 mmol scale under 1 atm H_2 pressure in the presence of Pt/C (10 mol %; Pt/C with 5% Pt-basis used; 10 mol % refers to the amount of Pt-metal), HCl (1.2 equiv; 1.25 M HCl in EtOH used), and EtOH (4.5 mL) at room temperature for 8 h. After filtration of the catalyst and evaporation of the volatiles, MeOH (5 mL) and $NaBH_4$ (4.0 equiv) were added and the reaction mixture was stirred at 0 °C for 15 min. [b]The reactions were performed on a 0.5 mmol scale in the presence of methyl triflate (1.2 equiv) and acetonitrile (1 mL) at 0 °C going to room temperature over 5 min. After this time, MeOH (5 mL) and $NaBH_4$ (5.0 equiv) were added and stirring was continued at 0 °C for 15 min. [c]A longer reaction time was needed in the hydrogenation step. [d]The reaction was stopped after 7 h hydrogenation. [e]Complete conversion to the deprotected product upon hydrogenation. A subsequent reduction step with $NaBH_4$ was not necessary. [f]6.0−10.0 equiv of $NaBH_4$ was used in the reduction step. [g]2.4−3.6 equiv of methyl triflate was used in the quaternization step. [h]Isolated as the respective HCl-salt due to the volatile nature of the free amine.

3b-e. It is noteworthy that the 4-Cl substituent in **3e** is also compatible with the hydrogenation strategy, as no significant hydrodechlorination was observed. 2,4- and 2,5-Disubstituted piperidine derivatives could be smoothly deprotected using either of both strategies (**3b−e**, **3k**, and **3j**). However, with 2,6-disubstituted piperidines, the corresponding deprotected products could not be obtained by implementing the "quaternization−hydride reduction" strategy (**3h,i**). The methylation step proceeds smoothly, but the subsequent hydride reduction step does not occur. Hydride addition by $NaBH_4$ presumably suffers from steric hindrance caused by the C-6 substituent. Interestingly, the stereochemical information of the diastereomerically pure compounds **3h−k** is preserved throughout the "deprotection" process, irrespective of whether the "hydrogenation−hydride reduction" or "quaternization−hydride reduction" strategy is followed. Remarkably, **3g** and **3j** are immediately obtained after hydrogenation and no subsequent reduction with $NaBH_4$ is needed. This indicates that hydrogenation of the pyridine moiety to a hexahydropyridin-2-yl occurred, followed by spontaneous cleavage of the unstable aminal formed. To our delight, heteroaryls of the azole type are also compatible with the developed methodology as exemplified for an α-(*N*-methyl)indol-2-yl substituent which gave a high yield when applying the "quaternization−hydride reduction" strategy (**3l**). On the contrary, the desired deprotected product **3l** could only be isolated in 19% yield via the "hydrogenation−hydride reduction" protocol. Indeed, protonation can occur on the pyridinyl and pyrrolyl moiety, thus allowing hydrogenation of both rings (observed in LC-MS) and leading to a low yield for target compound **3l**. Gratifyingly, next to C-2 aryl and heteroaryl groups, also an α-alkyl substituent is tolerated by either of the two strategies. Comparably to the α-phenylated model substrate **3b**, both protocols gave excellent isolated yields of α-hexylated piperidine **3m**. All reactions displayed in Scheme 6 were performed with 0.5 mmol of a *N*-(pyridin-2-yl)piperidine substrate **1**. The feasibility to scale-up the newly developed pyridine removal protocols to 2.5 mmol was tested on model substrate **1b**. The resulting isolated yields for the corresponding free amine **3b** ("hydrogenation−hydride reduction" strategy: 73%, "quaternization−hydride reduction" strategy: 81%) were comparable to those obtained on a 0.5 mmol scale.

To further showcase the potential of the newly developed mild pyridine removal methods, we wondered if we could apply them in a synthetic route toward enantiomerically pure solenopsin A and isosolenopsin A (**9**) (Scheme 7).[21] These alkaloids were originally isolated from fire ants and consist of a 2,6-dialkylated piperidine ring. The α-undecylated product **8** was synthesized from racemic 2-methyl-*N*-(pyridin-2-yl)-piperidine **7** via a directed Ru-catalyzed sp^3 C−H alkylation procedure recently established by our group.[6b] 2-Methyl-*N*-(pyridin-2-yl)-6-undecylpiperidine (**8**) was then separated into its four stereoisomers (*trans*-**8a**, *trans*-**8b**, *cis*-**8a**, and *cis*-**8b**) by preparative SFC (super critical fluid chromatography). Subsequent removal of the *N*-(pyridin-2-yl) group using the "quaternization−hydride reduction" strategy did not give any **9**, which is in agreement with our findings on 2,6-disubstituted piperidines **3h** and **3i** (Scheme 6). When the "hydrogenation−hydride reduction" protocol was applied to enantiomerically pure 2-methyl-*N*-(pyridin-2-yl)-6-undecylpiperidines **8**, the corresponding "deprotected" products (solenopsins *trans*-**9a**, *trans*-**9b**, and isosolenopsins *cis*-**9a**, *cis*-**9b**) were isolated in moderate to good yields.

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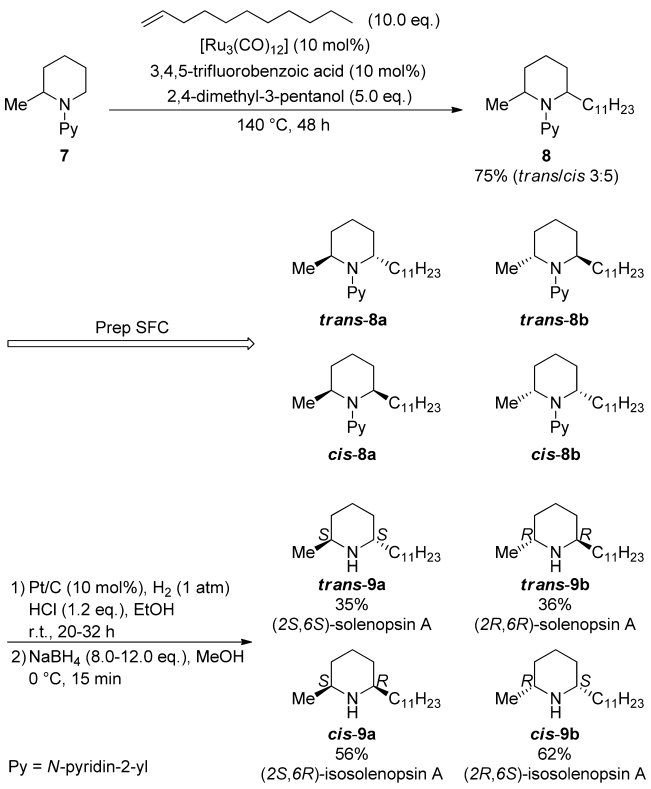
Scheme 7. Synthesis of Solenopsin A and Isosolenopsin A (9)



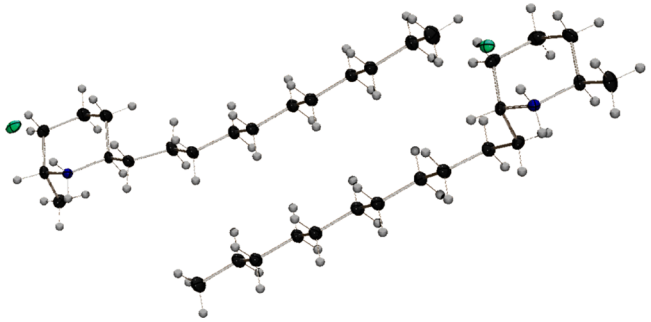


Figure 1. X-ray structure of (2*R*,6*R*)-solenopsin A·HCl (*trans*-**9b**·HCl).

The stereochemical information of enantiomerically pure piperidines **8** is preserved throughout the pyridine removal process, as was observed earlier for diastereomers **3h**–**k** (Scheme 6). The absolute configuration of 2-methyl-6-undecylpiperidines **9** was determined by VCD (vibrational circular dichroism) spectroscopy. In this way, *trans*-**9a** and *trans*-**9b** could be identified as (2*S*,6*S*)- and (2*R*,6*R*)-solenopsin A, while the isosolenopsins *cis*-**9a** and *cis*-**9b** were found to have a (2*S*,6*R*)- and (2*R*,6*S*)-configuration, respectively. The structure of *trans*-**9b** was additionally confirmed by X-ray crystallographic analysis of the corresponding HCl-salt (Figure 1).[22] To the best of our knowledge, this is the first reported X-ray structure for solenopsin A.

CONCLUSION

We have developed two novel synthetic strategies requiring mild reaction conditions (room temperature) to remove the *N*-pyridin-2-yl directing group from a diverse set of α-substituted piperidines that were synthesized through directed Ru-catalyzed sp^3 C–H functionalization. The reaction products are obtained in moderate to good overall yields irrespective of whether the "hydrogenation–hydride reduction" or "quaternization–hydride reduction" strategy is followed, indicating that both methods are equally effective. Only in the case of 2,6-disubstituted piperidines could the "quaternization–hydride reduction" protocol not be used. There are no significant electronic effects and the stereochemical information in diastereomerically and enantiomerically pure compounds is preserved throughout the "deprotection" processes. The "hydrogenation–hydride reduction" method was successfully applied in a short synthetic route toward fire ant alkaloids involving a directed sp^3 C–H alkylation reaction.

EXPERIMENTAL SECTION

General Considerations. Reagents and solvents were used as purchased without further purification. $NaBH_4$ was available as granules. Methyl trifluoromethanesulfonate was delivered in 10 g ampules. α-Substituted *N*-(pyridin-2-yl)piperidines **1a**, **1b**, and **1f**–**m** have already been described in previous publications from our group, and their synthesis and characterization will not be reported here.[6] Preparative HPLC and preparative SFC were performed as described below. Flash chromatography was carried out using an automated chromatography system. Proton nuclear magnetic resonance spectra were recorded on a 400 MHz spectrometer in $CDCl_3$ or DMSO-d_6; resonances are reported as chemical shifts (δ) in parts per million (ppm) with tetramethylsilane (TMS) as reference. Splitting is reported as s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, td = triplet of doublets, tt = triplet of triplets, qd = quartet of doublets, and m = multiplet; coupling constants (*J*) are given in hertz (Hz). The number of protons per signal is represented as *n*H. Carbon NMR spectra were recorded on the same instrument (100 MHz) with total proton decoupling. High resolution mass spectrometry samples were prepared by dissolving 0.1–5.0 mg of the compound in 80/20 MeOH/H_2O containing 0.1% formic acid, in such a way that a concentration of 10^{-6}–10^{-5} mol/L was obtained. Ten microliters of the samples was injected and electrosprayed through the nano-electrospray source. The latter was operated in positive ion mode at an electrospray potential of 1.5 kV. Samples were injected with an interval of 3 min, and positive ion mode accurate mass spectra were acquired. The MS was calibrated prior to use with a 0.2% H_3PO_4 solution. The spectra were lock mass corrected using the known mass of the nearest H_3PO_4 cluster or the phthalate background ions. All analytes are detected as protonated molecules.

General Procedure 1. A 100 mL round-bottom flask was charged with the appropriate *N*-(pyridin-2-yl)piperidine (10.0 mmol) and arylboronate ester (40.0 mmol, 4.0 equiv), [$Ru_3(CO)_{12}$] (511 mg, 0.8 mmol, 8 mol %), and 3-ethyl-3-pentanol (1.38 mL, 10.0 mmol, 1.0 equiv). The round-bottom flask was fitted with a reflux condenser, and the reaction mixture was then heated to reflux, the temperature of the oil bath being set at 153 °C, under magnetic stirring for 24 h. After this time, the reaction mixture was cooled and volatiles were removed under reduced pressure. To the residue was added 20 g of a commercially available ruthenium scavenger (Siliabond DMT, Silicycle), along with 300 mL of CH_2Cl_2. The resulting suspension was stirred at rt for 60 h (over the weekend). Subsequently, the solids were removed by filtration through dicalite, the pad was washed with CH_2Cl_2 (4 × 50 mL), and the combined filtrate was evaporated to dryness. The residue, being a mixture of monoarylated and diarylated products, was purified by prep HPLC to obtain the desired monoarylated product.

7-(4-Methoxyphenyl)-8-(pyridin-2-yl)-1,4-dioxa-8-azaspiro-[4.5]decane (1c). Prepared as per general procedure 1, starting from 8-(pyridin-2-yl)-1,4-dioxa-8-azaspiro[4.5]decane (2.20 g, 10.0 mmol), [$Ru_3(CO)_{12}$] (511 mg, 0.8 mmol, 8 mol %), 2-(4-methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaborinane (8.80 g, 40.0 mmol, 4.0 equiv), and 3-

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ethyl-3-pentanol (1.38 mL, 10.0 mmol, 1.0 equiv). The crude product was purified by prep HPLC on C18 silica, eluting with (0.25% NH_4HCO_3 solution in H_2O)/CH_3CN, to give **1c** as a yellow semisolid in 27% (868 mg) yield. ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (ddd, J = 5.0, 1.9, 0.8 Hz, 1H), 7.33 (ddd, J = 8.7, 7.1, 1.9 Hz, 1H), 7.18 (d, J = 8.9 Hz, 2H), 6.81 (d, J = 8.9 Hz, 2H), 6.54 (ddd, J = 7.1, 5.0, 0.8 Hz, 1H), 6.46 (d, J = 8.7 Hz, 1H), 5.31 (t, J = 5.8 Hz, 1H), 4.40 (dt, J = 13.8, 4.3 Hz, 1H), 3.97−3.81 (m, 4H), 3.74 (s, 3H), 3.52 (ddd, J = 13.8, 9.9, 4.3 Hz, 1H), 2.35 (dd, J = 14.0, 5.8 Hz, 1H), 2.16 (dd, J = 14.0, 5.8 Hz, 1H), 1.96−1.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 158.2, 147.9, 137.4, 132.2, 127.3, 113.8, 112.9, 107.8, 107.5, 64.3, 64.0, 55.2, 54.9, 40.2, 38.9, 34.7; HRMS (ESI): calculated for $C_{19}H_{23}N_2O_3^+$ $[M + H]^+$: 327.1703, observed: 327.1700.

Methyl 4-(8-(Pyridin-2-yl)-1,4-dioxa-8-azaspiro[4.5]decan-7-yl)benzoate (1d). Prepared as per general procedure 1, starting from 8-(pyridin-2-yl)-1,4-dioxa-8-azaspiro[4.5]decane (2.20 g, 10.0 mmol), $[Ru_3(CO)_{12}]$ (511 mg, 0.8 mmol, 8 mol %), methyl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate (9.92 g, 40.0 mmol, 4.0 equiv), and 3-ethyl-3-pentanol (1.38 mL, 10.0 mmol, 1.0 equiv). The crude product was purified by prep HPLC on C18 silica, eluting with (0.25% NH_4HCO_3 solution in H_2O)/CH_3CN, to give **1d** as a yellow semisolid in 15% (528 mg) yield. ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (ddd, J = 4.9, 1.9, 0.8 Hz, 1H), 7.95 (d, J = 8.3 Hz, 2H), 7.38 (ddd, J = 8.8, 7.1, 1.9 Hz, 1H), 7.34 (d, J = 8.3 Hz, 2H), 6.57 (ddd, J = 7.1, 4.9, 0.8 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 5.57 (t, J = 5.5 Hz, 1H), 4.32 (dt, J = 13.6, 4.2 Hz, 1H), 3.98−3.88 (m, 2H), 3.87 (s, 3H), 3.85−3.76 (m, 2H), 3.52 (ddd, J = 13.6, 10.5, 4.2 Hz, 1H), 2.39 (dd, J = 13.9, 5.5 Hz, 1H), 2.20 (dd, J = 13.9, 5.5 Hz, 1H), 1.96−1.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 158.8, 148.0, 147.9, 137.5, 129.7, 128.3, 126.3, 113.2, 107.6, 107.3, 64.3, 64.1, 55.1, 51.9, 40.6, 38.4, 34.5; HRMS (ESI): calculated for $C_{20}H_{23}N_2O_4^+$ $[M + H]^+$: 355.1652, observed: 355.1648.

7-(4-Chlorophenyl)-8-(pyridin-2-yl)-1,4-dioxa-8-azaspiro-[4.5]decane (1e). Prepared as per general procedure 1, starting from 8-(pyridin-2-yl)-1,4-dioxa-8-azaspiro[4.5]decane (2.20 g, 10.0 mmol), $[Ru_3(CO)_{12}]$ (511 mg, 0.8 mmol, 8 mol %), 2-(4-chlorophenyl)-5,5-dimethyl-1,3,2-dioxaborinane (8.98 g, 40.0 mmol, 4.0 equiv), and 3-ethyl-3-pentanol (1.38 mL, 10.0 mmol, 1.0 equiv). The crude product was purified by prep HPLC on C18 silica, eluting with (0.25% NH_4HCO_3 solution in H_2O)/CH_3CN, to give **1e** as a yellow oil in 16% (521 mg) yield. ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (ddd, J = 5.0, 1.8, 0.7 Hz, 1H), 7.39 (ddd, J = 8.6, 7.2, 1.8 Hz, 1H), 7.31−7.19 (m, 4H), 6.58 (ddd, J = 7.2, 5.0, 0.7 Hz, 1H), 6.49 (d, J = 8.6 Hz, 1H), 5.44 (t, J = 5.6 Hz, 1H), 4.30 (dt, J = 13.5, 4.6 Hz, 1H), 3.99−3.79 (m, 4H), 3.49 (ddd, J = 13.5, 10.6, 4.6 Hz, 1H), 2.34 (dd, J = 13.9, 5.6 Hz, 1H), 2.17 (dd, J = 13.9, 5.6 Hz, 1H), 1.95−1.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 147.9, 140.6, 137.6, 132.0, 128.4, 127.8, 113.3, 107.8, 107.3, 64.3, 64.1, 54.7, 40.5, 38.5, 34.5; HRMS (ESI): calculated for $C_{18}H_{20}ClN_2O_2^+$ $[M + H]^+$: 331.1208, observed: 331.1211.

"Hydrogenation−Hydride Reduction" Strategy, General Procedure 2. Step 1: A 50 mL hydrogenation tube was charged with the appropriate C-2-functionalized *N*-(pyridin-2-yl)piperidine (0.5 mmol) and Pt/C (5% Pt, 195 mg, 0.05 mmol, 10 mol %). Under N_2, EtOH (4.5 mL) was added. To the resulting black suspension, was added 1.25 M HCl in EtOH (0.5 mL, 0.6 mmol, 1.2 equiv), and the reaction mixture was subsequently flushed twice with H_2. The reaction mixture was then stirred under H_2 at rt for 7−24 h. After this time, the solids were removed by filtration through dicalite, the pad was washed with CH_2Cl_2 (5 × 20 mL), and the combined filtrate was evaporated to dryness. Step 2: The residue of step 1 was dissolved in MeOH (5 mL), and the resulting solution was cooled to 0 °C using an ice/water-bath. $NaBH_4$ (2.0−4.0 mmol, 4.0−8.0 equiv) was added portionwise (ca. 10 mg each portion) to the cooled solution under magnetic stirring, avoiding intense evolution of H_2 and keeping the temperature constant at 0 °C. After complete addition of $NaBH_4$, the reaction mixture was stirred further at 0 °C for 15 min. After this time, the volatiles were removed in vacuo. The residue was purified by straight phase or reversed phase flash chromatography to obtain the desired C-2-functionalized piperidine as either the free base or the corresponding HCl-salt.

"Quaternization−Hydride Reduction" Strategy, General Procedure 3. Step 1: A 50 mL round-bottom flask was charged with the appropriate C-2-functionalized *N*-(pyridin-2-yl)piperidine (0.5 mmol) and CH_3CN (1 mL). The resulting solution was cooled to 0 °C using an ice/water-bath. Under N_2, ice-cold methyl trifluoromethanesulfonate (0.6−1.8 mmol, 1.2−3.6 equiv) was added dropwise over 1 min under magnetic stirring. After complete addition of the methyl triflate, the ice/water-bath was removed and stirring of the reaction mixture was continued at rt for 5 min. Step 2: After this time, MeOH (5 mL) was added and the reaction mixture was again cooled to 0 °C using an ice/water-bath. $NaBH_4$ (2.5−5.0 mmol, 5.0−10.0 equiv) was added portionwise (ca. 10 mg each portion) to the cooled solution under magnetic stirring, avoiding intense evolution of H_2 and keeping the temperature constant at 0 °C. After complete addition of $NaBH_4$, the reaction mixture was stirred further at 0 °C for 15 min. After this time, volatiles were removed in vacuo. The residue was purified by straight phase or reversed phase flash chromatography to obtain the desired C-2-functionalized piperidine as either the free base or the corresponding HCl-salt.

7-Phenyl-1,4-dioxa-8-azaspiro[4.5]decane (3b). Prepared as per general procedure 2, using in step 1 (8 h reaction time): 7-phenyl-8-(pyridin-2-yl)-1,4-dioxa-8-azaspiro[4.5]decane (**1b**, 148 mg, 0.5 mmol), Pt/C (5% Pt, 195 mg, 0.05 mmol, 10 mol %), EtOH (4.5 mL), and 1.25 M HCl in EtOH (0.5 mL, 0.6 mmol, 1.2 equiv), and in step 2: MeOH (5 mL) and $NaBH_4$ (76 mg, 2.0 mmol, 4.0 equiv). The crude product was purified by straight phase flash chromatography on NH silica, eluting with a heptane/EtOAc gradient (from 100% heptane up to heptane/EtOAc, 85/15), to obtain **3b** as a colorless oil in 71% (77 mg) yield. Alternatively prepared as per general procedure 3, using in step 1: 7-phenyl-8-(pyridin-2-yl)-1,4-dioxa-8-azaspiro[4.5]decane (**1b**, 148 mg, 0.5 mmol), CH_3CN (1 mL), and methyl trifluoromethanesulfonate (68 μL, 0.6 mmol, 1.2 equiv), and in step 2: MeOH (5 mL) and $NaBH_4$ (95 mg, 2.5 mmol, 5.0 equiv). The crude product was purified by straight phase flash chromatography on NH silica, eluting with a heptane/EtOAc gradient (from 100% heptane up to heptane/EtOAc, 9/1), to obtain **3b** as a colorless oil in 77% (84 mg) yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.35 (m, 2H), 7.31 (t, J = 7.4 Hz, 2H), 7.24 (tt, J = 7.4, 1.8 Hz, 1H), 4.03−3.91 (m, 4H), 3.85 (dd, J = 11.9, 2.6 Hz, 1H), 37 (ddd, J = 11.8, 4.8, 2.4 Hz, 1H), 2.99 (td, J = 12.1, 3.3 Hz, 1H), 1.87 (dt, J = 12.9, 2.6 Hz, 1H), 1.79−1.71 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 128.5, 127.3, 126.7, 107.9, 64.4, 64.2, 59.4, 44.5, 43.6, 35.3; HRMS (ESI): calculated for $C_{13}H_{18}NO_2^+$ $[M + H]^+$: 220.1332, observed: 220.1331.

7-(4-Methoxyphenyl)-1,4-dioxa-8-azaspiro[4.5]decane (3c). Prepared as per general procedure 2, using in step 1 (10.5 h reaction time): 7-(4-methoxyphenyl)-8-(pyridin-2-yl)-1,4-dioxa-8-azaspiro[4.5]decane (**1c**, 163 mg, 0.5 mmol), Pt/C (5% Pt, 195 mg, 0.05 mmol, 10 mol %), EtOH (4.5 mL), and 1.25 M HCl in EtOH (0.5 mL, 0.6 mmol, 1.2 equiv), and in step 2: MeOH (5 mL) and $NaBH_4$ (76 mg, 2.0 mmol, 4.0 equiv). The crude product was purified by straight phase flash chromatography on NH silica, eluting with a heptane/EtOAc gradient (from 100% heptane up to heptane/EtOAc, 9/1), to obtain **3c** as a pale yellow oil in 72% (90 mg) yield. Alternatively prepared as per general procedure 3, using in step 1: 7-(4-methoxyphenyl)-8-(pyridin-2-yl)-1,4-dioxa-8-azaspiro[4.5]decane (**1c**, 163 mg, 0.5 mmol), CH_3CN (1 mL), and methyl trifluoromethanesulfonate (68 μL, 0.6 mmol, 1.2 equiv), and in step 2: MeOH (5 mL) and $NaBH_4$ (95 mg, 2.5 mmol, 5.0 equiv). The crude product was purified by straight phase flash chromatography on HP silica, eluting with a CH_2Cl_2/(NH_3, 7 N in MeOH) gradient (from 100% CH_2Cl_2 up to CH_2Cl_2/(NH_3, 7 N in MeOH), 92/8), to obtain **3c** as a pale yellow oil in 31% (38 mg) yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 4.03−3.92 (m, 4H), 3.81 (dd, J = 11.3, 2.8 Hz, 1H), 3.79 (s, 3H), 3.16 (ddd, J = 11.8, 4.8, 2.7 Hz, 1H), 2.98 (td, J = 11.8, 4.2 Hz, 1H), 1.95 (br s, 1H), 1.85 (dt, J = 12.8, 2.8 Hz, 1H), 1.80−1.72 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 136.0, 127.8, 113.9, 107.9, 64.4, 64.2, 58.8,

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55.3, 44.4, 43.6, 35.2; HRMS (ESI): calculated for $C_{14}H_{20}NO_3^+$ [M + H]$^+$: 250.1438, observed: 250.1432.

Methyl 4-(1,4-Dioxa-8-azaspiro[4.5]decan-7-yl)benzoate (3d). Prepared as per general procedure 2, using in step 1 (12 h reaction time): methyl 4-(8-(pyridin-2-yl)-1,4-dioxa-8-azaspiro[4.5]-decan-7-yl)benzoate (**1d**, 177 mg, 0.5 mmol), Pt/C (5% Pt, 195 mg, 0.05 mmol, 10 mol %), EtOH (4.5 mL), and 1.25 M HCl in EtOH (0.5 mL, 0.6 mmol, 1.2 equiv), and in step 2: MeOH (5 mL) and $NaBH_4$ (76 mg, 2.0 mmol, 4.0 equiv). The crude product was purified by straight phase flash chromatography on HP silica, eluting with a CH_2Cl_2/(NH_3, 7 N in MeOH) gradient (from 100% CH_2Cl_2 up to CH_2Cl_2/(NH_3, 7 N in MeOH), 96/4), to obtain **3d** as a pale yellow oil in 43% (60 mg) yield. Alternatively prepared as per general procedure 3, using in step 1: methyl 4-(8-(pyridin-2-yl)-1,4-dioxa-8-azaspiro[4.5]decan-7-yl)benzoate (**1d**, 114 mg, 0.32 mmol), CH_3CN (1 mL), and methyl trifluoromethanesulfonate (44 μL, 0.39 mmol, 1.2 equiv), and in step 2: MeOH (5 mL) and $NaBH_4$ (61 mg, 1.6 mmol, 5.0 equiv). The crude product was purified by reversed phase flash chromatography on C18 silica, eluting with a H_2O/CH_3CN gradient (from 100% H_2O up to H_2O/CH_3CN, 8/2), to obtain **3d** as a colorless oil in 57% (51 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 4.05−3.94 (m, 4H), 3.92 (dd, J = 12.4, 2.9 Hz, 1H), 3.90 (s, 3H), 3.19 (ddd, J = 11.7, 4.8, 2.6 Hz, 1H), 3.00 (td, J = 11.7, 4.8 Hz, 1H), 1.87 (dt, J = 12.8, 2.6 Hz, 1H), 1.84−1.73 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 149.1, 129.9, 129.2, 126.7, 107.7, 64.5, 64.3, 59.2, 52.1, 44.4, 43.7, 35.3; HRMS (ESI): calculated for $C_{15}H_{20}NO_4^+$ [M + H]$^+$: 278.1387, observed: 278.1385.

7-(4-Chlorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane (3e). Prepared as per general procedure 2, using in step 1 (7 h reaction time): 7-(4-chlorophenyl)-8-(pyridin-2-yl)-1,4-dioxa-8-azaspiro[4.5]-decane (**1e**, 165 mg, 0.5 mmol), Pt/C (5% Pt, 195 mg, 0.05 mmol, 10 mol %), EtOH (4.5 mL), and 1.25 M HCl in EtOH (0.5 mL, 0.6 mmol, 1.2 equiv), and in step 2: MeOH (5 mL) and $NaBH_4$ (76 mg, 2.0 mmol, 4.0 equiv). The crude product was purified by straight phase flash chromatography on HP silica, eluting with a CH_2Cl_2/(NH_3, 7 N in MeOH) gradient (from 100% CH_2Cl_2 up to CH_2Cl_2/(NH_3, 7 N in MeOH), 99/1), to obtain **3e** as a yellow oil in 67% (86 mg) yield. Alternatively prepared as per general procedure 3, using in step 1: 7-(4-chlorophenyl)-8-(pyridin-2-yl)-1,4-dioxa-8-azaspiro[4.5]decane (**1e**, 165 mg, 0.5 mmol), CH_3CN (1 mL) and methyl trifluoromethanesulfonate (68 μL, 0.6 mmol, 1.2 equiv), and in step 2: MeOH (5 mL) and $NaBH_4$ (95 mg, 2.5 mmol, 5.0 equiv). The crude product was purified by straight phase flash chromatography on HP silica, eluting with 100% CH_2Cl_2, to obtain **3e** as a yellow oil in 69% (87 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.26 (m, 4H), 4.03−3.93 (m, 4H), 3.83 (dd, J = 11.9, 2.5 Hz, 1H), 3.16 (ddd, J = 11.7, 4.4, 2.6 Hz, 1H), 2.97 (td, J = 11.7, 5.5 Hz, 1H), 1.94 (br s, 1H), 1.83 (dt, J = 12.8, 2.5 Hz, 1H), 1.79−1.69 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 132.9, 128.6, 128.1, 107.7, 64.4, 64.3, 58.7, 44.3, 43.7, 35.2; HRMS (ESI): calculated for $C_{13}H_{17}ClNO_2^+$ [M + H]$^+$: 254.0942, observed: 254.0943.

2-Phenylpiperidine·HCl (3a·HCl). Prepared as per general procedure 2, using in step 1 (8 h reaction time): 2-phenyl-1-(pyridin-2-yl)piperidine (**1a**, 119 mg, 0.5 mmol), Pt/C (5% Pt, 195 mg, 0.05 mmol, 10 mol %), EtOH (4.5 mL), and 1.25 M HCl in EtOH (0.5 mL, 0.6 mmol, 1.2 equiv), and in step 2: MeOH (5 mL) and $NaBH_4$ (76 mg, 2.0 mmol, 4.0 equiv). The crude product was purified by reversed phase flash chromatography on C18 silica, eluting with a H_2O/CH_3CN gradient (from 100% H_2O up to H_2O/CH_3CN, 3/7). The fractions containing the desired product **3a** were combined, and 0.5 mL of 1.25 M HCl in EtOH was added. After 1 min stirring, volatiles were removed in vacuo. To the remaining colorless oil was added Et_2O (10 mL), and crystallization of the resulting emulsion was induced upon stirring. Subsequently, volatiles were removed under reduced pressure to obtain **3a**·HCl as a white solid (mp = 192 °C) in 40% (40 mg) yield. Alternatively prepared as per general procedure 3, using in step 1: 2-phenyl-1-(pyridin-2-yl)piperidine (**1a**, 119 mg, 0.5 mmol), CH_3CN (1 mL), and methyl trifluoromethanesulfonate (136 μL, 1.2 mmol, 2.4 equiv), and in step 2: MeOH (5 mL) and $NaBH_4$ (95 mg, 2.5 mmol, 5.0 equiv). The crude product was purified by reversed phase flash chromatography on C18 silica, eluting with a H_2O/CH_3CN gradient (from 100% H_2O up to H_2O/CH_3CN, 2/8). The fractions containing the desired product **3a** were combined, and 0.5 mL of 1.25 M HCl in EtOH was added. After 1 min stirring, volatiles were removed in vacuo. To the remaining colorless oil was added Et_2O (10 mL), and crystallization of the resulting emulsion was induced upon stirring. Subsequently, volatiles were removed under reduced pressure to obtain **3a**·HCl as a white solid (mp = 193 °C) in 62% (62 mg) yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.47 (br s, 1H), 9.21 (br s, 1H), 7.59 (dd, J = 8.1, 1.5 Hz, 2H), 7.46−7.37 (m, 3H), 4.23−4.16 (m, 1H), 3.31 (br d, J = 12.8 Hz, 1H), 3.06−2.98 (m, 1H), 1.91−1.76 (m, 5H), 1.69−1.53 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 136.6, 127.4 (two overlapping signals), 126.1, 58.3, 43.5, 29.1, 21.2, 20.0; HRMS (ESI): calculated for $C_{11}H_{16}N^+$ [M + H]$^+$: 162.1277, observed: 162.1285.

2-(2-Methoxyphenyl)piperidine (3f). Prepared as per general procedure 2, using in step 1 (8 h reaction time): 2-(2-(2-methoxyphenyl)piperidin-1-yl)pyridine (**1f**, 134 mg, 0.5 mmol), Pt/C (5% Pt, 195 mg, 0.05 mmol, 10 mol %), EtOH (4.5 mL), and 1.25 M HCl in EtOH (0.5 mL, 0.6 mmol, 1.2 equiv), and in step 2: MeOH (5 mL) and $NaBH_4$ (76 mg, 2.0 mmol, 4.0 equiv). The crude product was purified by reversed phase flash chromatography on C18 silica, eluting with a H_2O/CH_3CN gradient (from 100% H_2O up to H_2O/CH_3CN, 2/8), to obtain **3f** as a pale yellow oil in 42% (41 mg) yield. Alternatively prepared as per general procedure 3, using in step 1: 2-(2-(2-methoxyphenyl)piperidin-1-yl)pyridine (**1f**, 134 mg, 0.5 mmol), CH_3CN (1 mL), and methyl trifluoromethanesulfonate (68 μL, 0.6 mmol, 1.2 equiv), and in step 2: MeOH (5 mL) and $NaBH_4$ (95 mg, 2.5 mmol, 5.0 equiv). The crude product was purified by reversed phase flash chromatography on C18 silica, eluting with a H_2O/CH_3CN gradient (from 100% H_2O up to H_2O/CH_3CN, 4/6), to obtain **3f** as a pale yellow oil in 24% (23 mg) yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42 (dd, J = 7.7, 1.5 Hz, 1H), 7.17 (td, J = 7.7, 1.5 Hz, 1H), 6.93 (d, J = 7.7 Hz, 1H), 6.90 (td, J = 7.7, 1.5 Hz, 1H), 3.84 (br d, J = 10.6 Hz, 1H), 3.77 (s, 3H), 3.04 (br d, J = 11.0 Hz, 1H), 2.67−2.58 (m, 1H), 2.10 (br s, 1H), 1.78−1.68 (m, 2H), 1.56−1.49 (m, 1H), 1.47−1.31 (m, 2H), 1.23−1.11 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.9, 133.8, 127.3, 126.4, 120.3, 110.5, 55.3, 54.3, 47.3, 33.5, 25.8, 25.3; HRMS (ESI): calculated for $C_{12}H_{18}NO^+$ [M + H]$^+$: 192.1383, observed: 192.1393.

2-Phenyl-1,2,3,4-tetrahydroquinoline (3g). Prepared as per general procedure 2, using in step 1 (14 h reaction time): 2-phenyl-1-(pyridin-2-yl)-1,2,3,4-tetrahydroquinoline (**1g**, 143 mg, 0.5 mmol), Pt/C (5% Pt, 195 mg, 0.05 mmol, 10 mol %), EtOH (4.5 mL), and 1.25 M HCl in EtOH (0.5 mL, 0.6 mmol, 1.2 equiv). There was no need to perform a subsequent reduction step, because complete conversion to the desired product **3g** occurred in step 1. After purification of the crude product by straight phase flash chromatography on HP silica, eluting with 100% CH_2Cl_2, **3g** was obtained as a pale yellow oil in 72% (75 mg) yield. Alternatively prepared as per general procedure 3, using in step 1: 2-phenyl-1-(pyridin-2-yl)-1,2,3,4-tetrahydroquinoline (**1g**, 143 mg, 0.5 mmol), CH_3CN (1 mL), and methyl trifluoromethanesulfonate (136 μL, 1.2 mmol, 2.4 equiv), and in step 2: MeOH (5 mL) and $NaBH_4$ (95 mg, 2.5 mmol, 5.0 equiv). The crude product was purified by straight phase flash chromatography on HP silica, eluting with 100% CH_2Cl_2, to obtain **3g** as a pale yellow oil in 87% (91 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.29 (m, 4H), 7.28−7.22 (m, 1H), 7.01−6.95 (m, 2H), 6.63 (td, J = 7.4, 1.1 Hz, 1H), 6.48 (d, J = 7.4 Hz, 1H), 4.38 (dd, J = 9.1, 3.3 Hz, 1H), 3.96 (br s, 1H), 2.88 (ddd, J = 16.5, 10.6, 5.5 Hz, 1H), 2.69 (td, J = 16.5, 4.8 Hz, 1H), 2.12−2.04 (m, 1H), 2.00−1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 143.7, 128.2, 127.5, 126.4, 125.8, 125.5, 119.8, 116.1, 112.9, 55.2, 29.9, 25.3; HRMS (ESI): calculated for $C_{15}H_{16}N^+$ [M + H]$^+$: 210.1277, observed: 210.1280.

***trans*-2-Methyl-6-phenylpiperidine·HCl (3h·HCl).** Prepared as per general procedure 2, using in step 1 (8 h reaction time): 2-(*trans*-2-methyl-6-phenylpiperidin-1-yl)pyridine (*trans*-**1h**, 126 mg, 0.5 mmol), Pt/C (5% Pt, 195 mg, 0.05 mmol, 10 mol %), EtOH (4.5 mL), and 1.25 M HCl in EtOH (0.5 mL, 0.6 mmol, 1.2 equiv), and in

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step 2: MeOH (5 mL) and $NaBH_4$ (132 mg, 3.5 mmol, 7.0 equiv). The crude product was purified by reversed phase flash chromatography on C18 silica, eluting with a H_2O/CH_3CN gradient (from 100% H_2O up to H_2O/CH_3CN, 3/7). The fractions containing the desired product **3h** were combined, and 0.5 mL of 1.25 M HCl in EtOH was added. After 1 min stirring, volatiles were removed in vacuo. To the remaining colorless oil, Et_2O (10 mL) was added and crystallization of the resulting emulsion was induced upon stirring. Subsequently, volatiles were removed under reduced pressure to obtain **3h**·HCl as a white solid (mp = 256 °C) in 55% (58 mg) yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 (br s, 1H), 9.10 (br s, 1H), 7.65 (dd, J = 8.4, 1.8 Hz, 2H), 7.46−7.36 (m, 3H), 4.45−4.38 (m, 1H), 3.66 (br s, 1H), 2.13−2.04 (m, 1H), 1.90−1.75 (m, 3H), 1.70−1.54 (m, 2H), 1.41 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 136.5, 127.3, 127.2, 126.3, 51.8, 47.4, 29.3, 25.0, 16.1, 13.0; HRMS (ESI): calculated for $C_{12}H_{18}N^+$ $[M + H]^+$: 176.1434, observed: 176.1432.

***trans*-2,6-Diphenylpiperidine (3i).** Prepared as per general procedure 2, using in step 1 (10 h reaction time): 2-(*trans*-2,6-diphenylpiperidin-1-yl)pyridine (*trans*-**1i**, 157 mg, 0.5 mmol), Pt/C (5% Pt, 195 mg, 0.05 mmol, 10 mol %), EtOH (4.5 mL), and 1.25 M HCl in EtOH (0.5 mL, 0.6 mmol, 1.2 equiv), and in step 2: MeOH (5 mL) and $NaBH_4$ (151 mg, 4.0 mmol, 8.0 equiv). The crude product was purified by straight phase flash chromatography on HP silica, eluting with a $CH_2Cl_2/(NH_3$, 7 N in MeOH) gradient (from 100% CH_2Cl_2 up to $CH_2Cl_2/(NH_3$, 7 N in MeOH), 95/5), to obtain **3i** as a pale yellow oil in 14% (17 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (br d, J = 7.3 Hz, 4H), 7.36 (t, J = 7.3 Hz, 4H), 7.25 (tt, J = 7.3, 1.5 Hz, 2H), 4.12 (dd, J = 6.6, 4.4 Hz, 2H), 2.05−1.89 (m, 4H), 1.87 (br s, 1H), 1.74−1.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 128.5, 126.8, 126.6, 54.8, 31.5, 20.8; HRMS (ESI): calculated for $C_{17}H_{20}N^+$ $[M + H]^+$: 238.1590, observed: 238.1593.

***trans*-2-Phenyl-5-(trifluoromethyl)piperidine·HCl (3j·HCl).** Prepared as per general procedure 2, using in step 1 (24 h reaction time): 2-(*trans*-2-phenyl-5-(trifluoromethyl)piperidin-1-yl)pyridine (*trans*-**1j**, 153 mg, 0.5 mmol), Pt/C (5% Pt, 195 mg, 0.05 mmol, 10 mol %), EtOH (4.5 mL), and 1.25 M HCl in EtOH (0.5 mL, 0.6 mmol, 1.2 equiv). There was no need to perform a subsequent reduction step, because complete conversion to the desired product **3j** occurred in step 1. After purification of the crude product by reversed phase flash chromatography on C18 silica, eluting with a H_2O/CH_3CN gradient (from 100% H_2O up to H_2O/CH_3CN, 4/6), the fractions containing the desired product were combined and 0.5 mL of 1.25 M HCl in EtOH was added. After 1 min stirring, volatiles were removed in vacuo to obtain **3j**·HCl as a white solid (mp = 229 °C) in 81% (108 mg) yield. Alternatively prepared as per general procedure 3, using in step 1: 2-(*trans*-2-phenyl-5-(trifluoromethyl)piperidin-1-yl)pyridine (*trans*-**1j**, 153 mg, 0.5 mmol), CH_3CN (1 mL), and methyl trifluoromethanesulfonate (68 μL, 0.6 mmol, 1.2 equiv), and in step 2: MeOH (5 mL) and $NaBH_4$ (95 mg, 2.5 mmol, 5.0 equiv). The crude product was purified by reversed phase flash chromatography on C18 silica, eluting with a H_2O/CH_3CN gradient (from 100% H_2O up to H_2O/CH_3CN, 4/6). The fractions containing the desired product **3j** were combined, and 0.5 mL of 1.25 M HCl in EtOH was added. After 1 min stirring, volatiles were removed in vacuo to obtain **3j**·HCl as a white solid (mp = 229 °C) in 61% (81 mg) yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (br s, 1H), 9.75 (br s, 1H), 7.61 (dd, J = 8.1, 1.5 Hz, 2H), 7.49−7.39 (m, 3H), 4.36 (br s, 1H), 3.47 (app d, J = 8.4 Hz, 1H), 3.26−35 (m, 2H), 2.13−2.03 (m, 3H), 1.82−1.71 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 137.1, 128.9, 128.8, 127.5, 126.3 (q, J = 279.6 Hz), 58.8, 42.3 (q, J = 3.6 Hz), 36.4 (q, J = 29.7 Hz), 28.4, 21.8 (q, J = 1.8 Hz); HRMS (ESI): calculated for $C_{12}H_{15}F_3N^+$ $[M + H]^+$: 230.1151, observed: 230.1147.

***cis*-Methyl 2-phenylpiperidine-4-carboxylate (3k).** Prepared as per general procedure 2, using in step 1 (10 h reaction time): *cis*-methyl 2-phenyl-1-(pyridin-2-yl)piperidin-4-carboxylate (*cis*-**1k**, 148 mg, 0.5 mmol), Pt/C (5% Pt, 195 mg, 0.05 mmol, 10 mol %), EtOH (4.5 mL), and 1.25 M HCl in EtOH (0.5 mL, 0.6 mmol, 1.2 equiv), and in step 2: MeOH (5 mL) and $NaBH_4$ (76 mg, 2.0 mmol, 4.0 equiv). The crude product was purified by straight phase flash chromatography on HP silica, eluting with a $CH_2Cl_2/(NH_3$, 7 N in MeOH) gradient (from 100% CH_2Cl_2 up to $CH_2Cl_2/(NH_3$, 7 N in MeOH), 9/1), to obtain **3k** as a pale yellow oil in 28% (30 mg) yield. Alternatively prepared as per general procedure 3, using in step 1: *cis*-methyl 2-phenyl-1-(pyridin-2-yl)piperidin-4-carboxylate (*cis*-**1k**, 148 mg, 0.5 mmol), CH_3CN (1 mL), and methyl trifluoromethanesulfonate (68 μL, 0.6 mmol, 1.2 equiv), and in step 2: MeOH (5 mL) and $NaBH_4$ (95 mg, 2.5 mmol, 5.0 equiv). The crude product was purified by reversed phase flash chromatography on C18 silica, eluting with a H_2O/CH_3CN gradient (from 100% H_2O up to 100% CH_3CN), to obtain **3k** as a colorless oil in 60% (66 mg) yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.36 (dd, J = 7.0, 1.5 Hz, 2H), 7.30 (t, J = 7.0 Hz, 2H), 7.23 (tt, J = 7.0, 1.5 Hz, 1H), 3.58 (s, 3H), 3.56 (dd, J = 11.3, 2.2 Hz, 1H), 3.09 (ddd, J = 11.7, 4.1, 2.6 Hz, 1H), 2.66 (td, J = 12.1, 2.6 Hz, 1H), 2.56 (tt, J = 12.1, 3.7 Hz, 1H), 1.93−1.87 (m, 1H), 1.84−1.77 (m, 1H), 1.46 (qd, J = 12.6, 4.1 Hz, 1H), 1.35 (q, J = 12.1 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.8, 145.2, 128.1, 126.8, 126.5, 59.9, 51.4, 45.7, 41.6, 37.3, 28.2; HRMS (ESI): calculated for $C_{13}H_{18}NO_2^+$ $[M + H]^+$: 220.1332, observed: 220.1329.

1-Methyl-2-(piperidin-2-yl)-1*H*-indole (3l). Prepared as per general procedure 2, using in step 1 (8 h reaction time): 1-methyl-2-(1-(pyridin-2-yl)piperidin-2-yl)-1*H*-indole (**1l**, 146 mg, 0.5 mmol), Pt/C (5% Pt, 195 mg, 0.05 mmol, 10 mol %), EtOH (4.5 mL), and 1.25 M HCl in EtOH (0.5 mL, 0.6 mmol, 1.2 equiv), and in step 2: MeOH (5 mL) and $NaBH_4$ (76 mg, 2.0 mmol, 4.0 equiv). The crude product was purified by reversed phase flash chromatography on C18 silica, eluting with a H_2O/CH_3CN gradient (from 100% H_2O up to H_2O/CH_3CN, 2/8), to obtain **3l** as an off-white solid (mp = 69 °C) in 19% (20 mg) yield. Alternatively prepared as per general procedure 3, using in step 1: 1-methyl-2-(1-(pyridin-2-yl)piperidin-2-yl)-1*H*-indole (**1l**, 146 mg, 0.5 mmol), CH_3CN (1 mL), and methyl trifluoromethanesulfonate (68 μL, 0.6 mmol, 1.2 equiv), and in step 2: MeOH (5 mL) and $NaBH_4$ (95 mg, 2.5 mmol, 5.0 equiv). The crude product was purified by reversed phase flash chromatography on C18 silica, eluting with a H_2O/CH_3CN gradient (from 100% H_2O up to H_2O/CH_3CN, 2/8), to obtain **3l** as a white solid (mp = 69 °C) in 70% (75 mg) yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 (d, J = 7.7 Hz, 1H), 7.40 (d, J = 7.7 Hz, 1H), 7.10 (t, J = 7.7 Hz, 1H), 6.99 (t, J = 7.7 Hz, 1H), 6.33 (s, 1H), 3.84−3.74 (m, 4H), 3.05 (br d, J = 12.1 Hz, 1H), 2.70 (br t, J = 11.5 Hz, 1H), 2.07 (br s, 1H), 1.94−1.86 (m, 2H), 1.65−1.39 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 142.8, 135.8, 125.7, 119.2, 118.4, 117.5, 107.9, 96.2, 52.0, 45.5, 30.7, 28.4, 24.8, 23.5; HRMS (ESI): calculated for $C_{14}H_{19}N_2^+$ $[M + H]^+$: 215.1543, observed: 215.1544.

7-Hexyl-1,4-dioxa-8-azaspiro[4.5]decane (3m). Prepared as per general procedure 2, using in step 1 (16 h reaction time): 7-hexyl-8-(pyridin-2-yl)-1,4-dioxa-8-azaspiro[4.5]decane (**3m**, 152 mg, 0.5 mmol), Pt/C (5% Pt, 195 mg, 0.05 mmol, 10 mol %), EtOH (4.5 mL), and 1.25 M HCl in EtOH (0.5 mL, 0.6 mmol, 1.2 equiv), and in step 2: MeOH (5 mL) and $NaBH_4$ (113 mg, 3.0 mmol, 6.0 equiv). The crude product was purified by straight phase flash chromatography on HP silica, eluting with a $CH_2Cl_2/(NH_3$, 7 N in MeOH) gradient (from 100% CH_2Cl_2 up to $CH_2Cl_2/(NH_3$, 7 N in MeOH), 9/1), to obtain **3m** as a pale yellow oil in 70% (80 mg) yield. Alternatively prepared as per general procedure 3, using in step 1: 7-hexyl-8-(pyridin-2-yl)-1,4-dioxa-8-azaspiro[4.5]decane (**3m**, 152 mg, 0.5 mmol), CH_3CN (1 mL), and methyl trifluoromethanesulfonate (68 μL, 0.6 mmol, 1.2 equiv), and in step 2: MeOH (5 mL) and $NaBH_4$ (95 mg, 2.5 mmol, 5.0 equiv). The crude product was purified by straight phase flash chromatography on HP silica, eluting with a $CH_2Cl_2/(NH_3$, 7 N in MeOH) gradient (from 100% CH_2Cl_2 up to $CH_2Cl_2/(NH_3$, 7 N in MeOH), 9/1), to obtain **3m** as a pale yellow oil in 76% (86 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98−3.93 (m, 4H), 3.07 (ddd, J = 12.3, 4.8, 2.2 Hz, 1H), 2.83 (td, J = 12.4, 3.3 Hz, 1H), 2.74−2.68 (m, 1H), 1.76−1.59 (m, 3H), 1.38−1.24 (m, 12H), 0.87 (t, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.0, 64.3, 64.1, 54.6, 44.0, 42.3, 37.0, 35.8, 31.8, 29.4, 25.8, 22.6, 14.1; HRMS (ESI): calculated for $C_{13}H_{26}NO_2^+$ $[M + H]^+$: 228.1958, observed: 228.1957.

2-(2-Methyl-6-undecylpiperidin-1-yl)pyridine (8). An 80 mL stainless steel autoclave was charged with 2-(2-methylpiperidin-1-

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yl)pyridine **7** (881 mg, 5 mmol), $[Ru_3(CO)_{12}]$ (320 mg, 0.5 mmol, 10 mol %), 3,4,5-trifluorobenzoic acid (88 mg, 0.5 mmol, 10 mol %), 2,4-dimethyl-3-pentanol (3.5 mL, 25 mmol, 5 equiv), and 1-undecene (10.3 mL, 50 mmol, 10 equiv). The reactor was purged with N_2, sealed tight, and heated at 140 °C for 48 h. After this time, the content was transferred to a round-bottom flask and evaporated to dryness. The crude product was purified by straight phase flash chromatography on silica gel, eluting with a heptane/EtOAc gradient (from heptane/EtOAc, 99/1 to heptane/EtOAc, 9/1), to obtain the diastereomeric mixture **8** (*trans*/*cis* 3:5) as a pale yellow oil in 75% (1.24 g) yield. Pure *trans*- and *cis*-enantiomers (*trans*-**8a**, *trans*-**8b** and *cis*-**8a**, *cis*-**8b**) were obtained by separating the diastereomeric mixture **8** via prep SFC (1. eluting with CO_2, *i*-PrOH with 0.2% *i*-PrNH_2, giving *trans*-**8b**, *cis*-**8a** and a mixture of *trans*-**8a** and ***cis*-8b**; 2. eluting with *i*-PrOH with 0.4% *i*-PrNH_2, giving *trans*-**8a** and impure *cis*-**8b**; 3. eluting with CO_2, EtOH with 0.4% *i*-PrNH_2, giving ***cis*-8b**). *trans*-**8a** and *trans*-**8b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (ddd, J = 5.1, 2.0, 0.7 Hz, 1H), 7.42 (ddd, J = 8.7, 7.0, 2.0 Hz, 1H), 6.54 (ddd, J = 7.0, 5.1, 0.8 Hz, 1H), 6.49 (d, J = 8.7 Hz, 1H), 4.16−4.08 (m, 1H), 3.85−3.79 (m, 1H), 2.04−1.89 (m, 2H), 1.85−1.78 (m, 1H), 1.75−1.60 (m, 3H), 1.58−1.43 (m, 2H), 1.26 (br s, 18H), 1.21 (d, J = 6.4 Hz, 3H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 148.0, 136.6, 112.0, 109.3, 53.1, 47.0, 31.9, 31.8, 29.7, 29.7, 29.6, 29.6, 29.6, 29.3, 28.6, 27.0, 24.2, 22.7, 19.6, 14.5, 14.1; HRMS (ESI): calculated for $C_{22}H_{39}N_2^+$ $[M + H]^+$: 331.3108, observed: 331.3119. ***cis*-8a** and ***cis*-8b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (ddd, J = 4.8, 2.2, 0.9 Hz, 1H), 7.40 (ddd, J = 8.7, 7.0, 2.2 Hz, 1H), 6.51−6.46 (m, 2H), 4.63−4.55 (m, 1H), 4.21 (br s, 1H), 1.84−1.68 (m, 3H), 1.67−1.55 (m, 3H), 1.53−1.39 (m, 2H), 1.26 (br s, 18H), 1.17 (d, J = 6.8 Hz, 3H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 148.1, 137.1, 111.2, 106.4, 50.5, 45.3, 33.2, 32.0, 31.0, 29.9, 29.7 (four overlapping signals), 29.4, 28.0, 27.3, 22.7, 18.9, 14.8, 14.1; HRMS (ESI): calculated for $C_{22}H_{39}N_2^+$ $[M + H]^+$: 331.3108, observed: 331.3119.

2(*S*)-Methyl-6(*S*)-undecylpiperidine, (2*S*,6*S*)-Solenopsin A (*trans*-9a). Step 1: A 50 mL hydrogenation tube was charged with *trans*-**8a** (63 mg, 0.19 mmol) and Pt/C (5% Pt-basis, 74.5 mg, 0.019 mmol, 10 mol %). Under N_2, EtOH (4.8 mL) was added. To the resulting black suspension was added 1.25 M HCl in EtOH (0.2 mL, 0.23 mmol, 1.2 equiv), and the reaction mixture was subsequently flushed twice with H_2. The reaction mixture was then stirred under H_2 at rt for 24 h. After this time, the solids were removed by filtration through a syringe filter unit (PTFE membrane) using CH_2Cl_2 (30 mL) as solvent, and the filtrate was evaporated to dryness. *Step 2*: The residue of step 1 was dissolved in MeOH (5 mL) and the resulting solution was cooled to 0 °C using an ice/water-bath. $NaBH_4$ (58 mg, 1.5 mmol, 8.0 equiv) was added portionwise (ca. 10 mg each portion) to the cooled solution under magnetic stirring, avoiding intense evolution of H_2 and keeping the temperature constant at 0 °C. After complete addition of $NaBH_4$, the reaction mixture was stirred further at 0 °C for 15 min. After this time, the volatiles were removed in vacuo. The residue was purified by straight phase flash chromatography on HP silica, eluting with a CH_2Cl_2/(NH_3, 7 N in MeOH) gradient (from 100% CH_2Cl_2 up to CH_2Cl_2/(NH_3, 7 N in MeOH), 9/1). The resulting pale yellow solid was treated with 1% aq. NaOH (3 mL) to remove any residual salts formed during purification. Subsequent extractive workup (3 × 3 mL CH_2Cl_2) yielded the free base as a pale yellow oil in 35% (17 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.11−3.03 (m, 1H), 2.91−2.85 (m, 1H), 1.68−1.37 (m, 6H), 1.26 (br s, 20H), 1.07 (d, J = 6.6 Hz, 3H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.9, 45.9, 34.0, 32.9, 31.9, 30.7, 29.8, 29.7, 29.7, 29.6 (two overlapping signals), 29.4, 26.5, 22.7, 21.2, 19.6, 14.1; HRMS (ESI): calculated for $C_{17}H_{36}N^+$ $[M + H]^+$: 254.2842, observed: 254.2846.

2(*R*)-Methyl-6(*R*)-undecylpiperidine, (2*R*,6*R*)-Solenopsin A (*trans*-9b). Step 1: A 50 mL hydrogenation tube was charged with *trans*-**8b** (70 mg, 0.21 mmol) and Pt/C (5% Pt-basis -83 mg, 0.021 mmol, 10 mol %). Under N_2, EtOH (4.8 mL) was added. To the resulting black suspension was added 1.25 M HCl in EtOH (0.2 mL, 0.25 mmol, 1.2 equiv), and the reaction mixture was subsequently flushed twice with H_2. The reaction mixture was then stirred under H_2 at rt for 20 h. After this time, the solids were removed by filtration through a syringe filter unit (PTFE membrane) using CH_2Cl_2 (30 mL) as solvent, and the filtrate was evaporated to dryness. Step 2: The residue of step 1 was dissolved in MeOH (5 mL), and the resulting solution was cooled to 0 °C using an ice/water-bath. $NaBH_4$ (64 mg, 1.7 mmol, 8.0 equiv) was added portionwise (ca. 10 mg each portion) to the cooled solution under magnetic stirring, avoiding intense evolution of H_2 and keeping the temperature constant at 0 °C. After complete addition of $NaBH_4$, the reaction mixture was stirred further at 0 °C for 15 min. After this time, the volatiles were removed in vacuo. The residue was purified by straight phase flash chromatography on HP silica, eluting with a CH_2Cl_2/(NH_3, 7 N in MeOH) gradient (from 100% CH_2Cl_2 up to CH_2Cl_2/(NH_3, 7 N in MeOH), 9/1). The resulting pale yellow solid was treated with 1% aq. NaOH (3 mL) to remove any residual salts formed during purification. Subsequent extractive workup (3 × 3 mL CH_2Cl2) yielded the free base as a pale yellow oil in 36% (19 mg) yield. The spectral data of *trans*-**9b** were in accordance with those reported above for *trans*-**9a**.

2(*S*)-Methyl-6(*R*)-undecylpiperidine, (2*S*,6*R*)-Isosolenopsin A (*cis*-9a). Step 1: A 50 mL hydrogenation tube was charged with *cis*-**8a** (165 mg, 0.5 mmol) and Pt/C (5% Pt-basis, 195 mg, 0.05 mmol, 10 mol %). Under N_2, EtOH (4.5 mL) was added. To the resulting black suspension was added 1.25 M HCl in EtOH (0.5 mL, 0.6 mmol, 1.2 equiv), and the reaction mixture was subsequently flushed twice with H_2. The reaction mixture was then stirred under H_2 at rt for 32 h. After this time, the solids were removed by filtration through dicalite, the pad was washed with CH_2Cl_2 (5 × 20 mL), and the combined filtrate was evaporated to dryness. Step 2: The residue from step 1 was dissolved in MeOH (5 mL), and the resulting solution was cooled to 0 °C using an ice/water-bath. $NaBH_4$ (227 mg, 6 mmol, 12.0 equiv) was added portionwise (ca. 10 mg each portion) to the cooled solution under magnetic stirring, avoiding intense evolution of H_2 and keeping the temperature constant at 0 °C. After complete addition of $NaBH_4$, the reaction mixture was stirred further at 0 °C for 15 min. After this time, the volatiles were removed in vacuo. The residue was purified by straight phase flash chromatography on HP silica, eluting with a CH_2Cl_2/(NH_3, 7 N in MeOH) gradient (from 100% CH_2Cl_2 up to CH_2Cl_2/(NH_3, 7 N in MeOH), 9/1). The resulting pale yellow solid was treated with 1% aq. NaOH (10 mL) to remove any residual salts formed during purification. Subsequent extractive workup (3 × 10 mL CH_2Cl_2) yielded the free base as a pale yellow oil in 56% (72 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66−2.58 (m, 1H), 2.51−2.44 (m, 1H), 1.80−1.72 (m, 1H), 1.66−1.55 (m, 2H), 1.38−1.22 (m, 21H), 1.06 (d, J = 6.3 Hz, 3H), 1.08−0.92 (m, 2H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 57.2, 52.5, 37.5, 34.5, 32.3, 31.9, 29.9, 29.7, 29.6, 29.6 (two overlapping signals), 29.4, 26.0, 24.9, 23.1, 22.7, 14.1; HRMS (ESI): calculated for $C_{17}H_{36}N^+$ $[M + H]^+$: 254.2842, observed: 254.2846.

2(*R*)-Methyl-6(*S*)-undecylpiperidine, (2*R*,6*S*)-Isosolenopsin A (*cis*-9b). Step 1: A 50 mL hydrogenation tube was charged with *cis*-**8b** (165 mg, 0.5 mmol) and Pt/C (5% Pt-basis, 195 mg, 0.05 mmol, 10 mol %). Under N_2, EtOH (4.5 mL) was added. To the resulting black suspension was added 1.25 M HCl in EtOH (0.5 mL, 0.6 mmol, 1.2 equiv), and the reaction mixture was subsequently flushed twice with H_2. The reaction mixture was then stirred under H_2 at rt for 24 h. After this time, the solids were removed by filtration through dicalite, the pad was washed with CH_2Cl_2 (5 × 20 mL), and the combined filtrate was evaporated to dryness. Step 2: The residue from step 1 was dissolved in MeOH (5 mL), and the resulting solution was cooled to 0 °C using an ice/water-bath. $NaBH_4$ (227 mg, 6 mmol, 12.0 equiv) was added portionwise (ca. 10 mg each portion) to the cooled solution under magnetic stirring, avoiding intense evolution of H_2 and keeping the temperature constant at 0 °C. After complete addition of $NaBH_4$, the reaction mixture was stirred further at 0 °C for 15 min. After this time, the volatiles were removed in vacuo. The residue was purified by straight phase flash chromatography on HP silica, eluting with a CH_2Cl_2/(NH_3, 7 N in MeOH) gradient (from 100% CH_2Cl_2 up to CH_2Cl_2/(NH_3, 7 N in MeOH), 9/1). The resulting pale yellow solid was treated with 1% aq. NaOH (10 mL) to remove any residual salts formed during purification. Subsequent extractive workup (3 × 10 mL

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CH_2Cl_2) yielded the free base as a pale yellow oil in 62% (78 mg) yield. The spectral data of *cis*- **9b** were in accordance with those reported above for *cis*-**9a**.

■ ASSOCIATED CONTENT

Supporting Information

Analytical SFC data for 2-methyl-*N*-(pyridin-2-yl)-6-undecylpiperidines **8**, VCD spectra for (iso)solenopsins **9**, and more information on the X-ray structure of *trans*-**9b**·HCl. Description of the scale-up experiments performed on model substrate **1b**. ^{1}H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(18) LC-MS analysis after methylation shows 95% conversion of the pyridine protected starting material **1c** to the corresponding *N*-methylpyridinium salt; LC-MS analysis after subsequent hydride reduction indicates 52% of the desired free piperidine **3c**, 8% of the pyridine protected starting material **1c**, and 40% side product with MW = 298.

(19) LC-MS analysis after methylation shows 93% conversion of the pyridine protected starting material **1f** to the corresponding *N*-methylpyridinium salt; LC-MS analysis after subsequent hydride reduction indicates 65% of the desired free piperidine **3f**, 19% of the pyridine protected starting material **1f**, and 15% side products.

(20) LC-MS analysis after hydrogenation shows 82% conversion of the pyridine protected starting material *cis*-**1k** to the corresponding *N*-(tetrahydropyridin-2-yl)amine; LC-MS analysis after subsequent hydride reduction indicates 61% of the desired free piperidine **3k** and 39% of the pyridine-protected starting material *cis*-**1k**.

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(22) The origin of HCl in the crystal is the solvent (CH_2Cl_2) which was used for the crystallization.