A General Strategy for the Amination of Electron-Rich and Electron-Poor Heteroaromatics by Desaturative Catalysis[††]

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The introduction of alkylamines onto heteroaromatics is integral to the preparation of high-value molecules. Typical methods rely on heteroaromatic pre-functionalization by halogenation or nitration, followed by metal-catalysed cross-coupling or multi-step manipulation of the nitrogen functionality. This results in often unselective or low-yielding synthetic routes. Here we show an alternative approach where saturated heterocyclic ketones are used as aryl surrogates for desaturative coupling with amines. The process operates under mild photochemical conditions, is compatible with complex amines and delivers both electron-poor and electron-rich heteroaromatics difficult to access by other methods. Since ketones are readily decorated by carbonyl chemistry, this retrosynthetic tactic escapes the rules and limitations of aromatic reactivity and metal-catalysed cross-couplings. Our process uses enamine formation to create the key carbon-nitrogen bond, followed by two rounds of photoredox oxidation and cobalt-catalysed desaturation. The two desaturation steps are distinct, as the cobaloxime firstly acts as H-atom abstractor and then oxidant.

Introduction

The construction of carbon–nitrogen bonds is one of the most frequent tasks in organic chemistry, especially when applied to the preparation of bioactive molecules.[1-3] In particular, the installation of amine functionalities onto aromatic rings to access anilines covers >40% of all transformations carried out by the pharmaceutical industry.[4-6] This number however is significantly lower if one restricts the analysis to the amination of heteroaromatics, either electron-poor or electron-rich, like pyridine or pyrrole, despite their relevance in high-value materials (Fig. 1a). This lack of synthetic applications is a clear reflection of the many challenges that hamper the development of such processes. In these cases, the intrinsic electronic properties of the heteroarene controls the site-selectivity of the functionalization process with respect to the heteroatom, thus rendering many substitution patterns very challenging to achieve (Fig. 1b).[7] As an example, C2 amination of pyridines is feasible using Chichibabin[8,9] reactivity or stepwise halogenation followed by nucleophilic aromatic substitution (S_NAr).[10-12] Conversely, targeting C3 and/or C4 is more challenging because the reduced π-nucleophilicity of the pyridine ring (10^6 times less reactive than benzene) thwarts nitration/halogenation at these sites. This means that starting material preparation rather than traditional S_NAr or C–N cross-couplings (i.e. Buchwald-Hartwig[13] or Ullman[14,15]), becomes the limiting factor.[16-19] In a similar vein, the electron-rich 5-membered ring heterocycles pyrrole, furan and thiophene intrinsically favour C2 halogenation for following functionalization, while C3 is strongly deactivated.[7] This limits availability of coupling partners, which cannot undergo S_NAr reactivity and are notoriously difficult to engage in Pd-catalyzed processes[20,21] mostly due to energetically demanding C–N reductive eliminations.[22-24] Overall, the amination of heteroaromatics is still a relevant challenge in organic synthesis, with issues spanning from starting materials preparation, catalysis development and scope generalization.

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Our group has recently developed a mechanistically and retrosynthetically distinct approach for aniline synthesis using desaturative catalysis (Fig. 1c).[25-38] This strategy uses cyclohexanones (**A**) as saturated aryl electrophile surrogates, that upon simple condensation with primary and secondary amines (**B**), generate a redox active enamine (**C**). At this point, two rounds of photoredox oxidation, deprotonation and cobalt-mediated HAT (H-atom transfer) desaturation provide aniline (**E**) via a dienamine intermediate (**D**).
In this manuscript, we present the development of a synthetic platform based on desaturative catalysis for the coupling of primary and secondary amines with ketone-containing saturated heterocycles (Fig. 1d). This provides convenient access to synthetically challenging 3- and 4-amino-pyridines as well as 3-amino-pyrroles, -furans, -thiophenes and pyrazoles. A relevant aspect of this chemistry is that heterocyclic ketones can be selectively decorated using standard carbonyl chemistry, which features different selectivity rules than standard aromatic reactivity. This has enabled us to by-pass many of the intrinsic electronic effect related to either S_EAr or S_NAr reactivity as well as inherent limitations of cross-coupling methodologies. Furthermore, while amination via standard aromatic reactivity (i.e. S_EAr or S_NAr) or cross-coupling chemistry generally requires tailored conditions depending on the heteroaromatic of interest, this desaturative strategy enables one set of reaction conditions to target both electron-poor and electron-rich systems. Interestingly, as it will be discussed below, detailed mechanistic and computational studies have revealed a rather different interplay of dual catalysis to the one operating under our previous aniline synthesis.[25-33,39]

Results

Reactions Design and Development

In pursuit of a general strategy for heteroaromatic amination, we initially focused on the preparation of C_4-functionalised pyridines (**M**). We recognized that the application of our desaturative catalysis mode on a 4-piperidone (**F**) could provide a versatile entry point into these derivatives, without the need for site-selective aromatic functionalization prior to S_NAr or cross-coupling. As depicted in Fig. 2a, we envisaged that condensation of **F** with an amine nucleophile could be used as C–N bond forming event, via the generation of electron-rich enamine **G**. At this point, photoredox oxidation would generate the enaminium radical **H** that, upon deprotonation, could be converted in the electron-rich $7\pi e^-$ system **I**. According to our previous work,[32,40] [Co(II)]-mediated HAT would desaturate the system to the α,β-unsaturated imine **J**. Another round of photoredox oxidation (**K**) and deprotonation (**L**), followed by [Co(II)]-mediated desaturation would then provide the desired 4-aminated pyridine product **M**.[41,42] However, the simple concept introduced above belies a highly complex reaction cascade, with many potential pitfalls since the C_4 methylene unit in **A** is now replaced by an NH group. Most importantly, **F** is required to react preferentially with the amine rather than self-condense (issue 1); upon α-enamine radical generation (**I**) the [Co] catalyst needs to perform a desaturation across the N–H bond, something that has little precedence in the field (issue 2); and the push-pull imine-enamine intermediate **J** is expected to be more difficult to oxidize than a standard dienamine (**D**) thus hampering a second photoredox activation (issue 3).
Perhaps unsurprisingly, the desired desaturative amination proved highly challenging to realize in practice: treatment of **1a** and **2a** using a range of photoredox and cobaloxime catalysts, as well as other additives under blue LEDs irradiation, did not deliver any of the desired C_4-aminated pyridine product **3**. Surprisingly, the somewhat counterintuitive use of *N*-Boc-protected **1b**, resulted in high yield formation of **3**. This result was achieved using $[Ir(dtbppy)(ppy)]PF_6$ as the photocatalyst, commercial [Co(dmgH)Cl(DMAP)] as the desaturative catalyst in the presence of DABCO and AcOH in CH_3CN solvent at 60 °C (the optimization studies, control experiments and reproducibility studies are detailed in Supplementary Tables 1-16). Interestingly, while *N*-Cbz-, *N*-Fmoc- and *N*-Ac-protected **1c**–**1e** also resulted in useful conversions, other derivatives featuring *N*-Ts, *N*-Bn, *N*-*t*-Bu and *N*–Me derivatives (**1f**–**1i**, see Supplementary Table 1 for more details) were significantly less effective. It is interesting to note that high yields could only be achieved by employing a slight excess of **2a**. Overall, the successful coupling between **1b** and **2a** provides a desaturative retrosynthetic disconnection similar to the one we have reported for aniline synthesis (Fig. 2a) that however, as it will be discussed below, points to a rather different mechanistic picture.

With a set of optimized reaction conditions in hand, we explored the amine scope in conjunction with piperidone **1b** (Fig. 3). Pleasingly, the process was compatible with many cyclic systems of different sizes like azetidine (**4**), pyrrolidine (**5**), piperidine (**6**) and azepane (**7**). Since piperidine is the most common *N*-heterocycle in drugs,[43] we further tested several derivatives containing various functionalities at either C_4 or C_3. This demonstrated tolerance of acetal (**8**), sulfonamide (**9**) and *gem*-difluoro (**10**) groups, as well as a C_3 spirocyclic unit (**11**). The successful formation of **10** and **11** is noteworthy considering the reduced nucleophilicity and high steric hindrance of the corresponding amine nucleophiles. Other *N*-heterocycles, routinely used in medicinal chemistry programs, such as *N*-aryl (**12**), NH piperazines (**13**), as well as conformationally restricted piperazine (**14**) and morpholine (**15** and **16**) analogues were pleasingly tolerated. The selective and high-yield formation of **13** indicates a strong steric control for these reactions, as this example features two potential amine functionalities for condensation with **1b**, in which the less sterically hindered amine group is favored.

Acyclic and primary amines were evaluated next and while we successfully included Bn_2NH (**17**), albeit in moderate yield, the use of primary amines and anilines required a minor re-evaluation of the reaction conditions (see Supplementary Table 16for more details). Pleasingly, upon slight modifications we successfully engaged α-branched amines (**18**–**19**), which are generally problematic using standard cross-coupling conditions,[44,45] bicyclo[1.1.1]pentylamine (**20**) and several anilines (**21**–**23**) including 3-aminopyridine (**24**).

Having established the broad types of amines compatible with this desaturative strategy, we were keen to evaluate the scope around the piperidone core. Substitution by carbonyl chemistry, rather than aromatic, would allow for introducing substituents around resulting pyridine ring in a complementary fashion. Using morpholine **2a** as the amine, we extended the strategy to several C_3-substitued piperidones that are easily prepared by enolate reactivity. These derivatives resulted in C_2-alkylated (**25**–**30**) as well as ester- and amide-containing (**31-32**) products. In terms of functional group compatibility, these examples demonstrate tolerance of HAT activated benzylic positions[46,47] as well as lactone functionalities that might be prone to nucleophilic addition from the amine.[48] The successful formation of **31** and **32** highlights the complementarity that this strategy might provide in pyridine functionalization chemistry. Indeed, selective C_4-halogenation of ester-containing derivatives is challenging and requires either metalation with cadmium bases or previous C_4 phosphorylation.[49,50] The preparation of $C_{2,4}$-disubstituted derivatives was targeted next, and was found to be readily accessible by starting from C_2-functionalized piperidones made from conjugate addition of the corresponding *N*-Boc-dihydropiperidone (see the Synthesis of Starting Materials in the Supplementary Methods for more details). These examples featured an ester (**33**), amide (**34**), several alkyl chains (**35**–**41**) and aromatic groups (**42** and **43**). In the C_2-alkylated series, while Me (**35**), primary (**36**-**37**), cyclohexyl (**38**), benzyl (**41**) and *i*-Pr (**39**) groups gave high yields, the larger *t*-Bu (**40**) resulted in lower reactivity. We believe the successful formation of **42** and **43** highlights the complementarity that our chemistry can offer to the selective functionalization of molecules containing multiple aromatic rings. Indeed, these substrates feature two electron-rich aromatic groups (**42**: *p*-MeO-phenyl; **43**: thiophenyl) which would make targeting of the deactivated pyridine ring at C_4 by any S_EAr-based functionalization chemistry (e.g. bromination,[51,52] nitration[53]) rather challenging. Furthermore, the strategy was found compatible for the assembly of sterically hindered 4-aminopyridines (**44** and **45**), which are often a demanding class of derivatives for cross-coupling reactivity.

The desaturative strategy is also compatible with the late-stage functionalization of high-value molecules. This was showcased by the C_4-pyridination of the alkaloid nortropine (**46**), the smoke cessation medicine (–)-cytisine (**47**), the blockbuster drugs atomoxetine (ADHD treatment) (**48**), the antiarrhytmic drug mexiletine (**49**) and paroxetine (antidepressant) (**50**). Furthermore, the orthogonal opportunities provided by carbonyl chemistry for pyridine functionalization were showcased in the C_3-alkylation of **1b** with the anti-inflammatory natural product alantolactone (**1u**), that provided, **51** in good yield after desaturation.

An interesting aspect of this methodology is that it shares the same types of building blocks used in reductive amination, a process widely applied in the patented MedChem literature for the preparation of tertiary alkylamines. We therefore envisaged that our desaturative methodology might offer a branching

diversification opportunity for targeting different areas of chemical space using the same starting materials. This was illustrated by taking *N*-Boc-piperidone **1b** and complex amine **2am**, that Genetech reductively aminate to give **52**, the precursor of a potential phosphoinositide 3-kinase inhibitor.[54] Pleasingly, the same building blocks can be used under our conditions, though in our case the C–N bond formation is diverted towards desaturation (**53**). This offers an alternative for the modification of functional materials by condensation chemistry.

The amination of pyridine at the C_3 position is still a relevant synthetic challenge for which there is no general[55-57] solution.[18,19,58,59] Hence, we were keen to evaluate the ability of our method to provide access to these highly sought-after materials. Pleasingly, by adopting the previously described conditions with minimum variation ($PhCF_3$ as solvent, TFA as the acid additive, and $Co(dmgH)(dmgH_2)Cl_2$ as the cobaloxime, see Supplementary Tables 5-9), we successfully coupled *N*-Boc-piperidone **1j** with primary and secondary amines. These included several cyclic derivatives such as morpholine (**54**), thiomorpholine (**55**), *N*-heteroaryl and *N*-Boc piperazines (**56** and **57**), C-4-substituted piperidines (**58** and **59**), and a sp^3-rich bicyclic piperazine derivative (**60**), which provided the corresponding C_3-aminated pyridines in moderate to high yields. The chemistry was then extended to *t*-Bu–NH_2 giving **61** in good yield. The ability of our method to engage α-tertiary amines is noteworthy considering they are notoriously challenging partners for Pd-catalysed cross-couplings.[60-62]
Evaluation of di-substitution in the C_3 series was executed employing morpholine **2a** as the amine. In these cases, reaction yields were generally lower than what obtained in the C_4 aminopyridine synthesis (see Fig. 2), likely because the C_3-piperidones undergo rather slow enamine formation due to the preferential population of the stabilized, but less reactive, enol tautomer. Nevertheless, the method enabled access to challenging aminated substitution patterns such as C_2,C_3- (**62** and **63**), and C_3,C_5-disubstituted (**64** and **65**), for which other methods require difficult multi-step synthetic sequences. As an example, halogenation of 2-substituted pyridines for following amination is often unselective leading to mixtures of C_3 and C_5 products,[63,64] while 3-aminopyridines direct halogenation selectively at C6 due to the intrinsic selectivity of S_EAr chemistry.[65] Indeed, the common synthetic routes for the preparation of substrates featuring a substitution pattern similar to the one of **65** generally require a Diels-Alder reaction using 1,2,4-tetrazines.[66,67]
Application of the desaturative coupling in complex settings was demonstrated by the C_3-pyridination of the alkaloid nortropine (**66**), the blockbuster drug amantadine (treatment of Parkinson's disease) (**67**) and a nor-dextromethorphan derivative (**68**) (cough suppressant).

The introduction of amine functionalities across electron-rich heteroaromatics is still a relevant challenge in the field, due to difficulties in the preparation of precursors, as well as the execution of cross-coupling reactions.[20-24] In particular, 3-aminated derivatives are generally assembled using either cycloaddition processes or via multi-component reactions, however both have their inherent synthetic limitations.[68-74] We were eager to evaluate if this desaturative strategy could be used to partially solve these issues.
This was demonstrated by the use of *N*-Boc-pyrrolidine-3-one **1k** in conjunction with morpholine **2a**, which afforded **69** in high yield. Pleasingly, the strategy could be extended to access both 3-morpholino-furane (**70**), thiophene (**71**) and *N*-Boc-pyrazole (**72**) by using the corresponding saturated precursors **1l**, **1au** and **1aw**. Also in this case, our chemistry could be applied to the installation of structurally complex and functionalized amines, as demonstrated by the formation of **73**–**77**, which feature conformationally restricted piperazine (**73**) and morpholine (**74**) building blocks as well as C_4-substituted piperidines (**75**) and differentially protected piperazines (**76**–**77**). As mentioned above, accessing these derivatives by standard Pd-catalysis is challenging both in terms of starting material preparation and following cross-coupling chemistry. Furthermore, it is important to note that these products were obtained using essentially the same reaction conditions developed for the previous synthesis of the pyridine derivatives (Figs. 3 and 4a). Therefore, this desaturative coupling effectively enables targeting of both electron-poor and electron-rich heteroaromatics, something often difficult to achieve under standard metal catalysis where *ad hoc* utilization of catalyst-ligand-based combinations is generally required.

The scope around the heteroaromatic core was evaluated using morpholine **2a** as the amine. Using epoxide opening and oxidation, we successfully prepared C_4-alkylated heterocycles that led to various C_3,C_4-disubstituted derivatives containing alkyl (**78**–**79, 82-83**), allyl (**80**), Ph (**81**) and pyridyl (**84**) substituents. This effectively enables targeting of the two most deactivated positions in the heteroaromatic core, without prior protection of the intrinsically more reactive C2 and C6. Furthermore, we showcased the use of this approach for the preparation of other pyrroles featuring C2,C_4 and C2,C_3-disubstitution patterns (**87-90**). Interestingly, the use of a derivative featuring a C2-ester functionality resulted in *in situ N*-Boc deprotection thus leading to **88**.

As a final element of substrate scope, we evaluated the chemistry in the late-stage pyrazolination and pyrrolidination using (–)-cytisine **2ag**, atomoxetine **2ae**, dextromethorphan **2aj** as well as the nor-derivative of the antihistaminic chlorcyclizine **2ah** and the antibiotic ciprofloxacin **2ai**. Pleasingly, these complex derivatives provided **91**–**95** in good yield, thus further confirming the high functional group tolerance of the methodolog

Mechanistic Studies.

The proposed mechanism for the desaturative coupling leading to C_4-aminated pyridines is depicted in Fig. 5A. The condensation between **1b** and **2a** is facilitated by the presence of a weak Brønsted acid and leads to the formation of electron rich enamine **96** (E_{ox} = +0.65 V vs SCE). This species can be efficiently oxidised by the photoexcited *[Ir(III)] catalyst ($*E_{red}$ = +0.66 V vs SCE)[75] to the corresponding enaminium radical **97**, which is activated towards deprotonation at C2 (calculated pK_a = 1.7, see Supplementary Figure 14). However, the electron-rich 7πe^- system **98** cannot undergo Co-mediated desaturation across C2–N due to the presence of the *N*-Boc functionality. Instead, since this species features significant spin density at C_4 (see Supplementary Figure 19), we propose desaturation by HAT at C_5 to give the di-enamine **99**.[76-78]

In order to close the dual photoredox-cobalt manifold, we believe the resulting [Co(III)]–H undergoes SET with the reduced [Ir(II)] photocatalyst to generate a [Co(II)]–H species (calculated ΔG^{o}_{SET} = –16 kcal mol^{-1}, see Supplementary Figure 17) from which H_2 evolution can take place upon protonation. Crucially, H_2 generation was confirmed by running the desaturative coupling in a Young tube followed by immediate analysis by ^{1}H NMR spectroscopy (see Supplementary Figure 7). We exclude H_2 evolution taking place upon direct protonation of [Co(III)]–H as this would require the presence of a significantly stronger Brønsted acid,[79-83] which is not compatible with our reaction conditions and the large excess of amines present.

Now that the first desaturation has occurred, a second photoredox oxidation would generate the enaminium radical **100** followed by C6 deprotonation (calculated pK_a = 2.1, see Supplementary Figure 14) to give radical **101**. It is interesting to note that at this point, Co-mediated HAT desaturation cannot occur due to a lack of abstractable H-atoms. While this makes conceiving a final step towards aromatization problematic, computational studies using density functional theory (DFT) highlighted two plausible pathways. (i) Radical fragmentation across the *N*-Boc group was calculated to be exothermic and kinetically accessible. This step would generate **3** extruding CO_2 and *t*-Bu•, that could close the dual catalytic manifold by desaturation to *iso*-butene (see Supplementary Figure 22). However, careful monitoring of the crude reaction mixture did not reveal the formation of this by-product but rather showed the stoichiometric generation of *N*-Boc-morpholine **103** (see Supplementary Table 20for more information). The unexpected formation of this species took place also when performing the desaturative coupling for C_3-amination. This experimental evidence led us to question the possibility of whether the cobaloxime co-catalyst acts as a redox mediator instead of a H-abstractor. (ii) Hence, [Co(II)]-mediated oxidation of dienamine radical **101** could lead to *N*-Boc-pyridinium **102**[84] from which Boc transfer to **2a** would give **3** and **103** .[85,86] Cyclic voltammetry analysis and computational studies revealed that SET between **101** (E_{ox} = +1.17 V vs SCE)[87] and [Co(II)] (E_{red} = –1.13 V vs SCE) is feasible (ΔG^{o}_{SET} = –13.3 kcal mol^{-1}). Furthermore, this mechanistic path would also release a proton, crucial for the conversion of [Co(I)] into [Co(III)]–H for reduction and H_2 evolution.[75,79-83] Overall, it is noteworthy to point out that this desaturative amination is made possible owing to the ability of the cobaloxime co-catalyst to manifest a bifunctional role, acting sequentially as a HAT and SET mediator in conjunction with the same reductive quenching photoredox cycle.

We believe this mechanistic blueprint is translatable to the amination of C3-piperidone **1j** (Fig. 5B). In this case, enamine formation (**104**, E_{ox} = +0.23 V vs SCE) followed by oxidation would lead to radical cation **105**. Interestingly, according to our calculations, this species should be preferentially deprotonated at C4 rather than C6 (calculated pK_as = 10.7 vs 15.7, respectively) to give the radical **106**. Co-mediated desaturation via HAT would then generate the cross-conjugated dienamine **107**. Mirroring the pathway delineated for 4-amino-pyridine synthesis, **107** would undergo photoredox oxidation (**108**), deprotonation (**109**) and Co-mediated oxidation to give pyridinium **110** ready for Boc transfer to **2a** (see Supplementary Figure 8 and Supplementary Table 20 for experimental evidence for H_2 evolution and Boc transfer, respectively, as well as Supplementary Figure 20 for computational studies).
As a final element of mechanistic discussion, the desaturative coupling towards 3-aminated electron-rich heterocycles is depicted in Fig 5c. In this case, the aromatization requires enamine formation (**112**), followed by oxidation (**113**), C3 deprotonation (**114**) and Co-mediated HAT desaturation (**115**).

Conclusions.

In conclusion, the integration of photoredox catalysis and cobalt catalysis has led to the development of a general platform for the preparation of amine-substituted heteroaromatics. The use of non-aromatic starting materials bypasses some of the challenges that currently impact the synthesis of these derivatives via either aromatic reactivity or cross-coupling chemistry. The desaturative reactions described in this manuscript occur under mild conditions and can be used for the introduction of complex, densely functionalized amine nucleophiles. The proposed reaction mechanism suggests a dual role for the cobaloxime co-catalyst, that first acts as a H-atom abstractor and then as an oxidant to give the desired heteroaromatic products. Notably, through this desaturation logic, we have developed a general set of reaction conditions that can be used to prepare amine containing heteroaromatics of different nature like electron-poor pyridines and electron-rich pyrroles, furans, thiophenes and pyrazoles.

Methods

General procedure for the synthesis of 4-aminopyridines.

A dry tube equipped with a stirring bar was charged with the 4-piperidone (1.0 equiv.), $Co(dmgH)_2Cl(DMAP)$ (4 mol%), $[Ir(dtbbpy)(ppy)_2]PF_6$ (2 mol%), DABCO (1.5 equiv.), and the amine if solid (3.0 equiv.). The tube was capped with a Supelco aluminium crimp seal with septum PTFE/butyl), evacuated and refilled with N_2 ($\times$3). Dry and degassed CH_3CN (0.1 M), amine if liquid (3.0 equiv), and AcOH (20 mol%) were added. The mixture was stirred for 15 minutes at 80 ˚C using a metal block heater. The vial was cooled to rt over 10 min and the vial was placed under the lamp and the distance from the lamp to the bottom of the vial was set to 3.5 cm. The entire reaction set up was wrapped in aluminium foil and the mixture was stirred under irradiation at the specified time and temperature. The tube was opened, and the mixture was diluted with water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (x 2) and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and evaporated. The resulting residue was purified by column chromatography on silica gel to give the product.

General procedure for the synthesis of 3-aminopyridines

A dry tube equipped with a stirring bar was charged with the 3-piperidone (1.0 equiv.), $Co(dmgH)_2Cl(DMAP)$ (4 mol%), $[Ir(dtbbpy)(ppy)_2]PF_6$ (2 mol%), KOPiv (1.5 equiv.) and the amine if solid (3.0 equiv.). The tube was capped with a Supelco aluminium crimp seal with septum PTFE/butyl), evacuated and refilled with N_2 ($\times$3). Dry and degassed $PhCF_3$ (0.1 M), amine if liquid (3.0 equiv), and TFA (20 mol%) were added. The mixture was stirred for 15 minutes at 80 ˚C using a metal block heater. The vial was cooled to rt over 10 min and the vial was placed under the lamp and the distance from the lamp to the bottom of the vial was set to 3.5 cm. The entire reaction set up was wrapped in aluminium foil and the mixture was stirred under irradiation at the specified time and temperature. The tube was opened, and the mixture was diluted with water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (x 2) and the combined organic layers were washed with brine,

dried ($MgSO_4$), filtered and evaporated. The resulting residue was purified by column chromatography on silica gel to give the product.

General procedure for the synthesis of 3-amino-pyrroles
A dry tube equipped with a stirring bar was charged with the 3-oxo-heterocycle derivative (1.0 equiv.), Co(dmgH)(dmgH$_2$)Cl (4 mol%), [Ir(dtbbpy)(ppy)$_2$]PF$_6$ (2 mol%), DABCO (1.5 equiv.) and the amine if solid (1.1 equiv.). The tube was capped with a Supelco aluminium crimp seal with septum PTFE/butyl), evacuated and refilled with N_2 ($\times$3). Dry and degassed CH_3CN (0.1 M), amine if liquid (1.1 equiv), and AcOH (20 mol%) were added. The mixture was stirred for 15 minutes at 80 ˚C using a metal block heater. The vial was cooled to rt over 10 min and the vial was placed under the lamp and the distance from the lamp to the bottom of the vial was set to 3.5 cm. The entire reaction set up was wrapped in aluminium foil and the mixture was stirred under irradiation at the specified time and temperature. The tube was opened, and the mixture was diluted with water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (x 2) and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and evaporated. The resulting residue was purified by column chromatography on silica gel to give the product.

Data Availability: The authors declare that the data supporting the findings of this study are available within the paper and its Supplementary Information or from the authors upon reasonable request.

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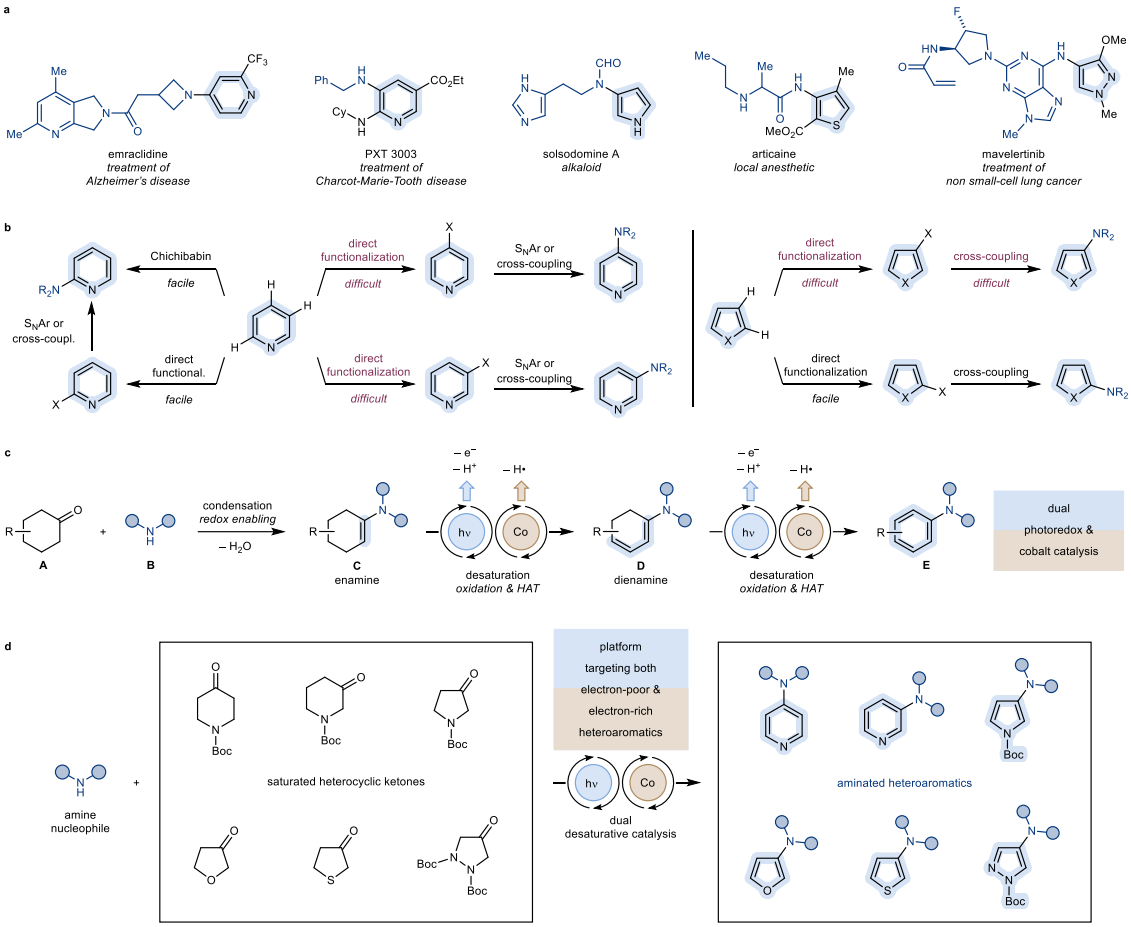
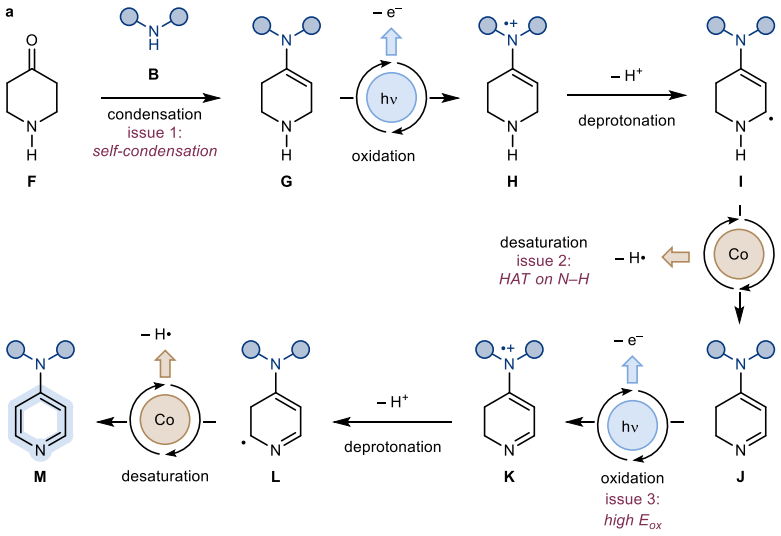
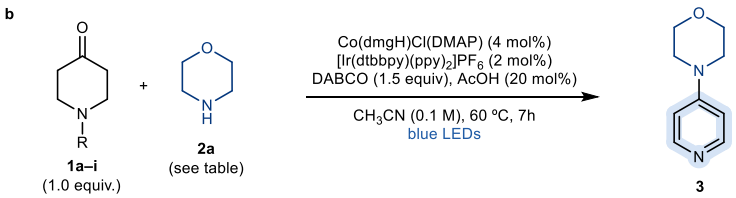


Figure 1. Relevance and preparation of aminated heteroaromatics. a) Relevant examples of aminated heterocycles. **b)** Challenges and patterns in amination of electron-poor and electron-rich heterocycles. **c)** Previous synthesis of anilines by desaturative catalysis described by our group.[32] **d)** This work: desaturative platform for the amination of electron-poor and electron-rich heteroaromatics.





entry	substrate	R	**2a** (equiv.)	yield (%)
1	**1a**	H	1.2	–
2	**1b**	Boc	1.2	59
3	**1b**	Boc	3.0	89
4	**1c**	Cbz	3.0	80
5	**1d**	Fmoc	3.0	43
6	**1e**	Ac	3.0	63
7	**1f**	Ts	3.0	15
8	**1g**	Bn	3.0	25
9	**1h**	*t*-Bu	3.0	8
10	**1i**	Me	3.0	traces

Figure 2. Design and development of a desaturative approach to 4-aminopyridines. a) Proposed mechanism and challenges for the desaturative coupling between 4-piperidone and amines. **b)** Reaction development.

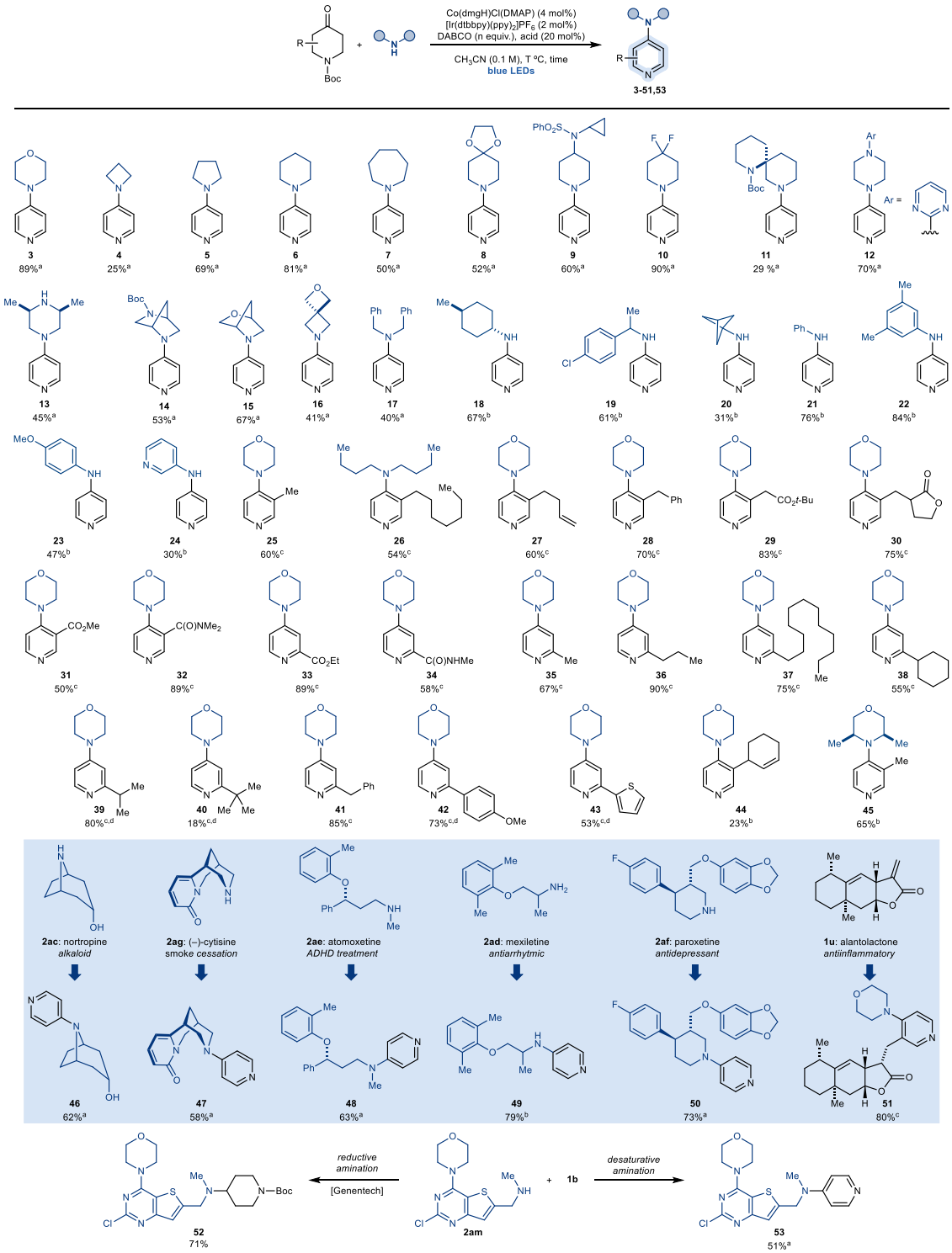


Figure 3. Substrate scope for the synthesis of 4-aminopyridines. [a]AcOH (20 mol%), DABCO (1.5 equiv.), 60 ºC, 7 h. [b]$Sc(OTf)_3$ (20 mol%), DABCO (3.0 equiv), 75 ºC, 24 h. [c]AcOH (20 mol%), DABCO (1.5 equiv), 45-50 ºC, 16 h. [d]From *N*-Cbz instead of *N*-Boc piperidone. Boc, *tert*-butoxycarbonyl; Cbz, benzyloxicarbonyl.

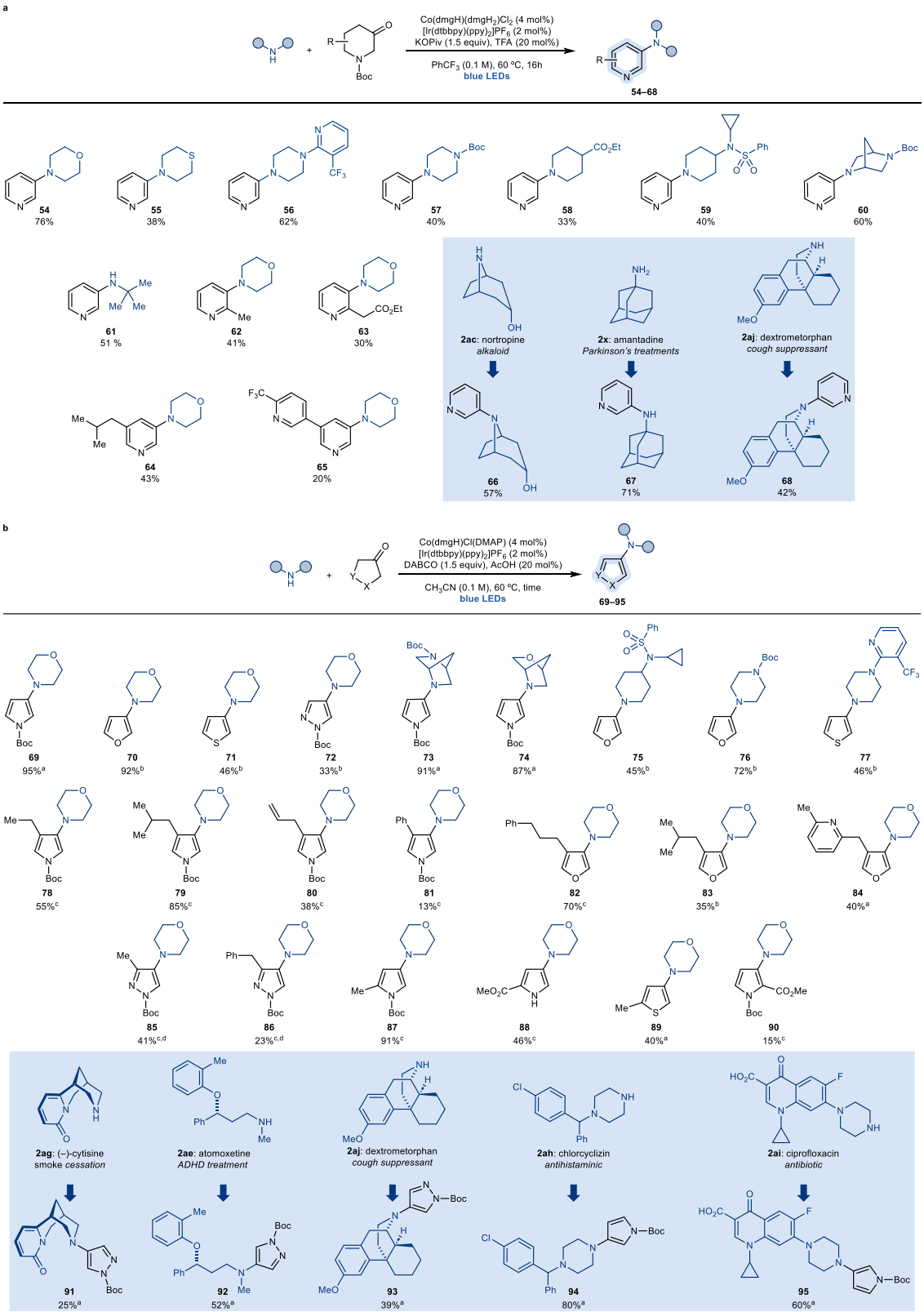


Figure 4. Substrate scope for the synthesis of 3-amino-pyridines, pyrroles, furans, thiophenes and pyrazoles. a) Scope for the synthesis of 3-aminopyridine products. Boc, *tert*-butoxycarbonyl. **b)** Scope for the synthesis of electron-rich aminated products. [a]Reaction run for 7h. [b]Reaction run for 6h. [c]Reaction run for 16h. [d] Mixture of regioisomers (rr = 1.1:1). Boc, *tert*-butoxycarbonyl.

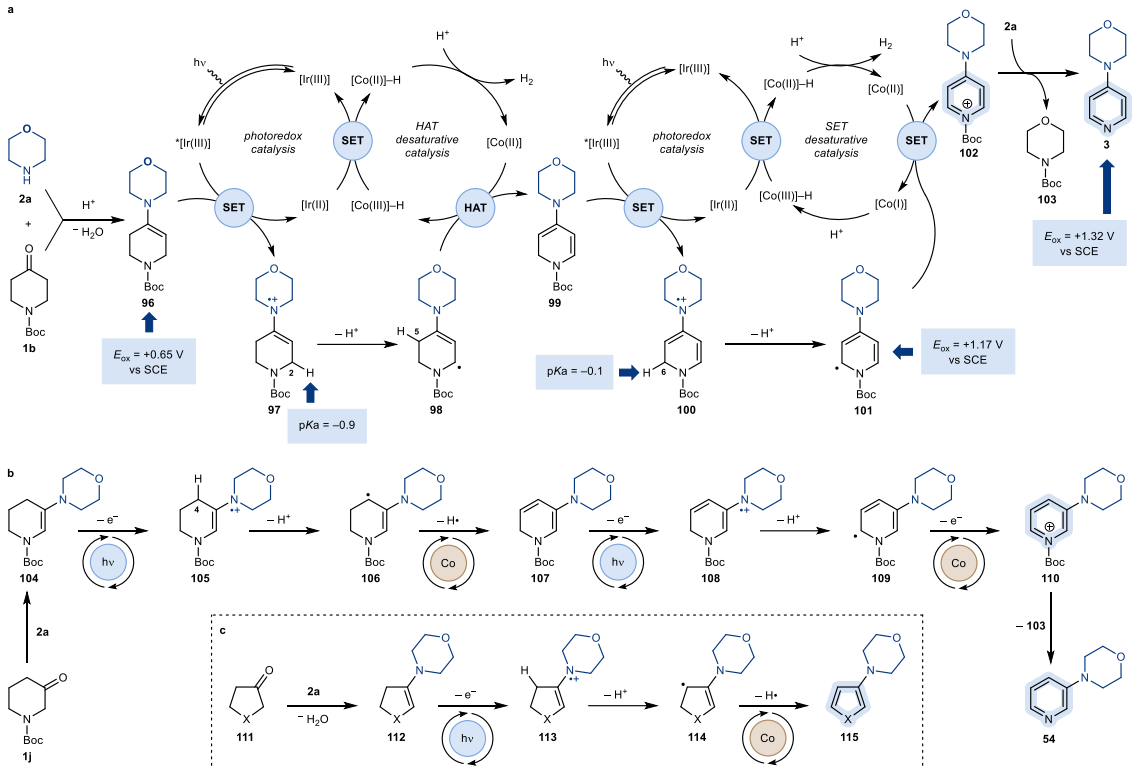


Figure 5. Proposed mechanism for the desaturative aminations. a) Proposed catalytic cycle for the formation of 4-aminopyridines by sequential Co-mediated HAT and SET processes. **b)** Mechanistic proposal for C3-aminopyridines. **c)** Mechanistic proposal for aminated electron-rich heterocycles.

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