Practical and Regioselective Amination of Arenes Using Alkyl Amines

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The formation of carbon-nitrogen bonds for the preparation of aromatic amines is among the top-five reactions carried out globally for the production of high-value materials, ranging from bulk chemicals to pharmaceuticals and polymers. As a result of this ubiquity and diversity, methods for their preparation impact the full spectrum of chemical synthesis in academia and industry. In general, these molecules are assembled through the stepwise introduction of a reactivity handle in place of an aromatic C–H bond (i.e. nitro group, halogen, or boronic acid) and a following functionalization or cross-coupling. Here we show that aromatic amines can be constructed by direct reaction of arenes and alkyl amines using photocatalysis without the need for pre-functionalization. The process enables the easy preparation of advanced building blocks, tolerates a broad range of functionalities and multi-gram scale can be achieved via a batch-to-flow protocol. The merit of this strategy as late-stage functionalization platform has been demonstrated by the modification of several drugs, agrochemicals, peptides, chiral catalysts, polymers and organometallic complexes.

Nitrogen-substituted aromatics are ubiquitous structural units in drugs, agrochemicals and organic materials[1]. Indeed, their preparation accounts for almost 30% of all nitrogen-manipulations carried out in the pharmaceutical industry[2,3]. Traditionally the introduction of nitrogen functionalities onto aromatics is conducted via nitration, followed by reduction and further multistep manipulation (Fig. 1A). The harsh conditions and low selectivity in the nitration step and the difficulties in the following functionalizations (e.g. selective alkylations), have propelled the development of alternative approaches. The Buchwald-Hartwig, Ullmann and Chan-Lam cross-couplings have revolutionized this area and are routinely used in academia and industry[4-7]. Despite their versatility, these methodologies are viable only on pre-functionalized aromatics, such as aryl-halides or aryl-organoborons, as they need to undergo oxidative addition or transmetalation with the metal catalyst. While this ensures site-selectivity, the aromatic pre-functionalization requires extra steps and can be problematic. Furthermore, the application of metal-catalysed couplings in the assembly of sp^2 C–N bonds on complex and multi-functionalised substrates is sometimes challenging especially in the context of late-stage drug leads modification[8].

Conversely, undirected arene C–H amination represents an attractive, cost-effective and atom-economical strategy for building these essential motifs. As such, considerable efforts have been made in the last few years towards the development of this type of reactions.[9] This has lead to protocol enabling the introduction of specific *N*-containing fragments like imides,[10,11] 1,4-diazabicyclo[2.2.2]octane (DABCO)[12] and azoles[13,14] onto unfunctionalized arenes, frequently through the generation of nitrogen-radicals.[15-17] The direct engagement of alkylamines (e.g. piperidine) in related reactivities is, however, much more challenging owing to the enhanced instability of their corresponding nitrogen-radicals. Indeed, these species are known to undergo very facile radical translocations resulting in highly stabilized α-*N* carbon-radicals.[18] In an effort to overcome these reactivity issues, we have reported a method relying

on the multistep preparation of pre-functionalized hydroxylamines as nitrogen-radical precursors,[19] and Nicewicz has identified conditions for the oxidation and nucleophilic trapping of highly electron rich aromatics in the presence of primary alkyl amines.[20] Despite partially addressing some of the issues associated to the fundamental quest for aromatic C–H amination, both methodologies have restricted scope on both the amine/hydroxylamine and the aromatic coupling partners which limits their application in target synthesis.

As such, a paramount synthetic challenge still stands as the direct use of alkyl amines in C–H aminations in a general and regioselective manner is beyond what currently possible (Figure 1B). This gap in synthetic methodology is remarkable considering the fact that secondary amines are by far the most used class of reagents in medicinal chemistry[21] and that 59% of small-molecule pharmaceuticals contain at least one *N*-heterocycle of which piperidine is the most prevalent[22]. As a result, a methodology able to selectively introduce amine functionalities onto drug leads in a single chemical step has the potential to by-pass lengthy synthetic routes and, more importantly, to provide increased capacity for chemical space exploration around high-value molecules. We present here a photoredox strategy that achieves this goal and enables the direct and high site-selective coupling of alkylamines and aromatics (Fig. 1C). This process represents a general C–H functionalization platform for the fast preparation of aromatic amines and for the efficient generation of chemical diversity.

Results and Discussion

Proposed Strategy. As part of an overarching goal to develop novel methods for C–N bond formation, we conjectured that simple amines (**A**) could be doubly activated via *in situ* generation of a traceless *N*-electrophore and subsequent protonation (Fig. 2A). We reasoned that *N*-chlorination (**B**) by reaction with *N*-chlorosuccinimide (NCS), followed by the addition of a Brönsted acid would provide the *N*-chloroammonium (**C**), which ought to represent such a suitably activated species to directly engage in a redox pathway. For this strategy to be effective the usual reactivity of **C** has to be bypassed. These species display an amplified electrophilic character at the chlorine-atom, making them excellent reagents in electrophilic aromatic chlorination (S_EAr) (**D**)[23,24]. Thus the success of our proposal hinged on the identification of conditions able to suppress this normal ionic reactivity, diverting the reaction towards a radical process. Previous methods that have sought this transformation require the reactions to be run in concentrated sulfuric acid as the solvent, sometimes under high-energy UV-irradiation with the arene partner in large excess[25,26]. Furthermore, as *N*-chloro-amines are often unstable and difficult-to-handle, a synthetically useful method would require their transient generation with no elaboration.

To address these challenges, our proposal for direct C–H amination was based on a strategy whereby a visible-light-excited photocatalyst (*PC)[27] would promote SET (single-electron-transfer) reduction of *in situ* generated **C** to access the aminium radical **E**[18,28]. This highly electrophilic species would then undergo regioselective radical addition with the arene to form a stabilized cyclohexadienyl-type radical **F**. The site-selectivity of this step is a mechanistic consequence of a highly polarized radical reaction whereby the natural nucleophilicity of the arene is harnessed to dictate the site of amination[29]. As such, the outcome of these reactions can be predicted in the same way as classical electrophilic aromatic substitutions. Finally, the low oxidation potential of **F** would enable SET with the oxidized photocatalyst closing the photoredox cycle and forming **G** which would aromatize by deprotonation to produce the protonated aniline **H**.

Optimisation of photocatalytic amination of arenes – overcoming aromatic electrophilic chlorination. To validate this mechanistic hypothesis, we studied the reactions of piperidine (**1**) with *tert*-butylbenzene (**2**) and anisole (**3**), to model weakly and strongly electron-rich aromatics, in the presence of NCS and the photocatalyst $Ru(bpy)_3Cl_2$ in acetonitrile (CH_3CN) (Fig. 2B and Supplementary Table 1–4). Using acetic acid (AcOH) neither amination nor chlorination was observed with both arenes (entry 1). Trifluoroacetic acid (TFA) did not lead to any reactivity with **2** but provided the unwanted chloroanisole **5'** in moderate yield (entry 2). Analogously, while **3** underwent almost quantitative chlorination in the presence of stronger *para*-toluene sulfonic acid (*p*TsOH), **2** did not react (entry 3). Conversely, perchloric acid ($HClO_4$) completely suppressed the unwanted chlorination and produced the desired aminated products **4** and **5** with good-to-moderate *para*-selectivity (entry 4). Amine **4** was obtained in quantitative yield by switching the solvent to 1,1,1,3,3,3-hexafluoro-*i*-propanol (HFIP)[30], however this led to chlorination of **3**.[31] In this solvent, the weaker acid TFA could also be used albeit in slightly lower yields (entry 6). Overall, these experiments identified $HClO_4$ as the optimum acid and CH_3CN or HFIP as the solvent of choice depending on the electron density of the arene partner, CH_3CN for highly electron-rich aromatics and HFIP for weakly electron-rich ones. These reactions proved very robust and reproducible and they could be conducted under open air without any erosion in yield. The aromatic partner does not need to be used in excess and equimolar reactions worked well with only minimum decrease in the reaction yield (see Supplementary Table 2).

Mechanistic Investigations. To investigate the reaction mechanism, we performed cyclic voltammetry (CV) studies, in order to quantify the variation of redox properties of *N*-chloropiperidine **1-Cl** upon protonation (Fig. 2C and Supplementary Fig. 11 and Table 7). As the *N*-chloroammonium salt is expected to be a much stronger σ*-electrophore, this should translate into a more facile photoinduced SET. CV analysis of **1-Cl** revealed a profile with E^{ox} = +1.50 V and E^{red} = –1.80 V (vs saturated calomel electrode, SCE) in CH_3CN which precludes direct reduction from *Ru(II) ($*E^{ox}$ = –0.81 V)[27]. Upon addition of $HClO_4$, a change in the CV spectra was observed resulting in the progressive suppression of the oxidation peak and the appearance of a reduction peak with E^{red} = +0.43 V. A positive value of E^{red} means that upon protonation **1-Cl** becomes a strong σ*-electrophore and should be easily reduced by *Ru(II). Emission quenching experiments are in line with this observation, showing that the excited state of the photocatalyst is quenched by protonated **1-Cl** at nearly the rate of diffusion (Stern-Volmer quenching constant: k_q = 1.5 10^9 M s^{-1}), while no effect was observed in the absence of acid (see Supplementary Table 8–9 and Fig. 10). In order to rule out a Dexter energy transfer (i.e. triplet sensitization) between *Ru(II) and protonated **1-Cl** we performed UV/Vis absorption studies. As shown in Fig. 2D, $Ru(bpy)_3Cl_2$ shows a maximum of absorption in the blue region (λ ≈ 450 nm). Addition of **1-Cl** and $HClO_4$ did not change this absorption profile when the sample was kept in the dark. However, upon 10 s irradiation with blue LEDs the typical Ru(II) absorbance disappeared and two bands matching the absorption of $Ru(III)(bpy)_3$ were observed together with an immediate color change from orange [Ru(II)] to green [Ru(III)] (see Supplementary Fig. 11). Overall, these investigations provide evidence for photoinduced SET as the mechanism for the aminium radical generation (Fig. 2A). Quantum yields (Φ) were determined for the reaction of **1** and **2** in CH_3CN and HFIP. The experimental values of Φ(CH_3CN) = 0.28 and Φ(HFIP) = 0.93 suggest that short-lived chain propagations might be present but should not be responsible for the overall reaction efficiency (see Supplementary Table 10).

Evaluation of Aromatic Coupling Partners and Gram-Scale Reaction in Flow. With the optimized protocol for arene amination we evaluated the aromatic scope using piperidine **1** (Table 1). Mono-substituted benzenes provided the *para*-products in high yields and selectivity (**4**–**22**). The strong preference for *para*-amination, especially in the case of halobenzenes (**18**–**21**), is noteworthy as other C–H functionalizations normally provide isomeric mixtures. These results are a clear manifestation of how the polarized addition of highly electrophilic aminium radicals to arenes can efficiently channel the regioselectivity of the reaction and this can be readily rationalized and predicted by considering the Fukui indexes for the aromatic coupling partner (see Supplementary Fig. 12). Other aromatics with different functionalities were also compatible as demonstrated by the formation of **23**–**39**. The ability to tolerate halides and boron-/silicon-functionalities shows that this process is fully orthogonal to classical cross-couplings and can proceed further C–C, C–N and C–O bond formations.

Research conducted at AstraZeneca has showcased the feasibility of the method on large scale. The preparative multi-gram synthesis of **21** via a batch-to-flow[32,33] protocol operates in comparable yield and high productivity rate (5.7 g, 67%, in 1.5 h, see Supplementary Fig. 2–8). Experiments monitoring the variation of internal pressure and temperature were conducted and they alleviate some of the concerns around the use of reactive *N*-chloroamines and $HClO_4$ on scale. Overall, these studies provide promising results for further application in industrial settings.

The reaction was then demonstrated on a range of substituted naphthalenes (**31**–**37**) that, owing to their lower ionization potentials, enabled the presence of electron-withdrawing groups. The reaction was also successful on other heteroarenes including methoxylated (iso)quinolines (**40**–**44**). In this case, the increased aromatic deactivation given by the N-atom in the aromatic ring means that quinoline is not suitable with this protocol and represents a limitation of the method (see Supplementary Table 6). Nevertheless, electron poor *N*-heterocycles (e.g. pyridine) are compatible with the process and therefore molecules containing these motifs can be selectively aminated at the more electron rich ring (**38**). As the amine is installed with *para*-selectivity, our reaction is orthogonal to established C–H activation strategies that, by harnessing the ability of the directing group, deliver products of *ortho*-functionalization.[34-36]

Evaluation of Amine Coupling Partners. Next, we explored the amines scope in conjunction with benzene as a model of non-activated aromatics (Table 2). Because piperidine is the most prevalent *N*-heterocycle in pharmaceuticals [2,22], and substituents on this heterocycles are often found at the C4 and C3-positions, we evaluated a broad range of functionalized derivatives. It was quickly discovered that substrates containing unprotected and polar functional groups were compatible (**45**–**59**). These include free alcohols, esters, azide, alkyl halides, sulfonamides and ketones, which are sometimes troublesome in classical cross-coupling methodologies[2,8].

Other *N*-heterocycles routinely used in medicinal chemistry programs are also well tolerated (**60**–**71**). These include perhydro-(iso)quinolines, pyrrolidines, including 3-azabicyclo[3.1.0]hexane, which is found in many antibiotics (e.g. trovafloxacin), (benz)azepines and northropine. As many amines are commercially available as hydrochloride salts, we have adapted our methodology to their direct use in the process.

The introduction of small heterocycles is a popular strategy in medicinal chemistry programs aimed at the exploration of chemical space around lead compounds[2,37,38]. As an example, the *N*-aryl-azetidine motif is found in more than 3,000 biologically active compounds including several commercially available drugs (e.g. delafloxacin, antibiotic used in the treatment of acute skin infections) according to the PubChem database. Despite this prominence, there are no reported examples of aromatic C–H functionalization

with 4-membered amines. We were pleased to see that our protocol enabled the installation of several azetidines (**69**–**71**), including a spirocyclic bioisoster of morpholine (**71**). Acyclic dialkyl and primary amines were also suitable as demonstrated by the successful formation of **72**–**80**, which contain labile functionalities. The formation of **77** and **80** is noteworthy as efficient access to hindered anilines is important in medicinal chemistry, where it is frequently used to block oxidative metabolic pathways,[39] but remains challenging using other protocols. Finally, this method also enabled the use of commercial water solutions of gaseous dimethylamine and methylamine (**81**, **82**). The direct use of these two amines in C–H functionalization is unprecedented despite the fact that dimethyl amino-containing aromatics are one of the largest classes of bioactive anilines. Furthermore, this method gives direct access to products that are typically manufactured by aromatic nitration followed by reduction and selective alkylation at 250 ºC over aluminium oxide[40].

Application in Late-Stage Functionalization and Parallel Screening. The identification of novel medicines as well as other high-value products greatly benefits from the ability to directly modify the core structure of natural products or existing lead molecules. Therefore, to demonstrate the potential of this reaction in medicinal chemistry, complex and bioactive molecules were subjected to our protocol (Fig. 3A). Strychnine (*Strychnos* alkaloid), fenoprofen (Nalfon, a NSAID), dichlorprop (herbicide used on ton-scale worldwide) and ramipril (Altace, a top selling ACE inhibitor), display many redox-active and Lewis basic functionalities and underwent functionalization in good yields and selectivity (**83**–**88**). We also prepared a structural analogue of AC-262536 (selective androgen receptor modulator) (**89**) and a truncated analogue of donepezil (Aricept, Alzheimer's disease palliative) (**90**) from commercially available materials. Furthermore, using commercial building blocks we accessed **91**, which can be converted into delamanid (Deltyba, treatment of multi-drug resistant tuberculosis) in just one step.

Microscale parallel experimentation is a growing field of research that is currently attracting significant interest across academia and the wider pharmaceutical industry owing to its ability to accelerate drug discovery.[41,42] To evaluate the feasibility of this process in small parallel screening settings, 24 different secondary and primary amines were reacted with equimolar amounts of the cough suppressant dextromethorphane (Robitussin) using a commercially available 24 well-plate photoredox reactor (Fig. 3B and Supplementary Fig. 9–10). All reactions tested provided the desired amination products with yields higher than 50% in most cases. With this information in hand, we successfully translated three experiments on higher scale and similar efficiency (**92–94**). Overall, these examples indicate the presented method is a fast and powerful tool for drug discovery, with current development at AstraZeneca directed towards the automation of this reaction in large high-throughput setting.

Peptides are an important class of biomolecules for which late-stage functionalization is highly desirable (Fig. 4A)[43-45] and current methods target mostly cysteine, tryptophan, tyrosine and C-terminal residues.[46,47] Pleasingly, this reaction enables the underdeveloped functionalization of L-phenylalanine (**95**), which could also be performed on a tetrapeptide (**97**). As the azide functionality is tolerated, this approach allows the introduction of handles for bio-conjugation and/or stapling strategies (**96** and **98**).

The ability to add nitrogen functionality where needed may also prove useful in asymmetric catalysis when tuning the structure of a chiral ligand because it by-passes the need for *de novo* ligand synthesis. As shown in Fig. 4B, we successfully performed diamination of 2,2'-dibromo-1,1'-binaphtyl (**99** and **100**), which is the precursor of Noyori's BINAP, and modified Evans oxazolidinone (**101**). The level of functional group compatibility also enabled the modification of MacMillan imidazolidinone (**102**) and a

PyBOX (**103**) ligand, two of the most used catalysts in asymmetric synthesis, as well as (+)-dihydroquinine (**104**), which is part of the AD-mix for the Sharpless asymmetric dihydroxylation.
Strategies for the post-polymerization-functionalization of C–H bonds are highly sought after[48], as they can provide access to high-value materials from inexpensive precursors. Using our methodology we obtained good degrees of functionalization on commercially available polystyrene beads with dimethylamine (Fig. 4C, **105**).
Finally, we evaluated the late-stage amination on organometallic complexes and selected $[Ru(ppy)(bpy)_2](PF_6)$, which has applications in solar energy storage[49] (Fig. 4D). Pleasingly, our reaction enabled selective amination of the 2-phenylpyridine ligand in 37% yield (**106**). This modification improved the complex absorptivity in the visible-near-IR regions, which is highly desirable for dye-sensitized solar cells (see Supplementary Fig. 13). Cyclometallated rhodium complexes have applications as anti-cancer agents[50] and we succeeded in the di-azetidination of $[Rh(ppy)_2(tbbpy)](PF_6)$ (**107**). In both cases the amines are selectively installed at the most nucleophilic position *para* to the C–transition metal σ-bond[51]. These examples pave the way for the development of unprecedented *meta*-aminations of arenes by tandem C–H activation, nitrogen-radical addition.

Conclusions. We have reported the direct and selective coupling of amine and aromatics under photoredox conditions. This transformation has been applied to a range of poly-functionalized and structurally complex building blocks as well as scaled effectively to multi-gram via batch-to-flow. The ability to tolerate halogens, boron and silicon functionality makes it orthogonal to cross-couplings. The potential in late-stage functionalization has been demonstrated by chemical space exploration around bioactive molecules. The versatility of the method has also been showcased by the direct amination of many high-value materials spanning small peptides, chiral catalysts, polymers and organometallic complexes. The operational ease, broad functional group tolerance and scalability of this reaction make it suitable for adoption in both academic and industrial settings.

Data Availability: The authors declare that all data supporting the findings of this study are available within the supplementary information file. These include: reaction procedures, products characterization, batch-to-flow experiment procedure, microscale parallel screening procedure, cyclic voltammograms, UV/Vis, DFT and NMR spectra.

Acknowledgments: We gratefully acknowledge Dr Marco Simonetti and Dr Francisco Juliá-Hernandez for useful discussions. D.L. thanks EPSRC for a Fellowship (EP/P004997/1) and the European Research Council for a research grant (758427). A.R. thanks the Marie Curie Actions for a Fellowship (703238).

Author contributions: A. R., F. J. and D. L. designed the project. A. R., F. J., T. D. S. and A. J. M. performed all the synthetic experiments. J. J. D performed the batch to flow optimization and scale-up. All the authors analysed the results and wrote the manuscript.

Competing interests: Authors declare no competing interests.

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Figures:

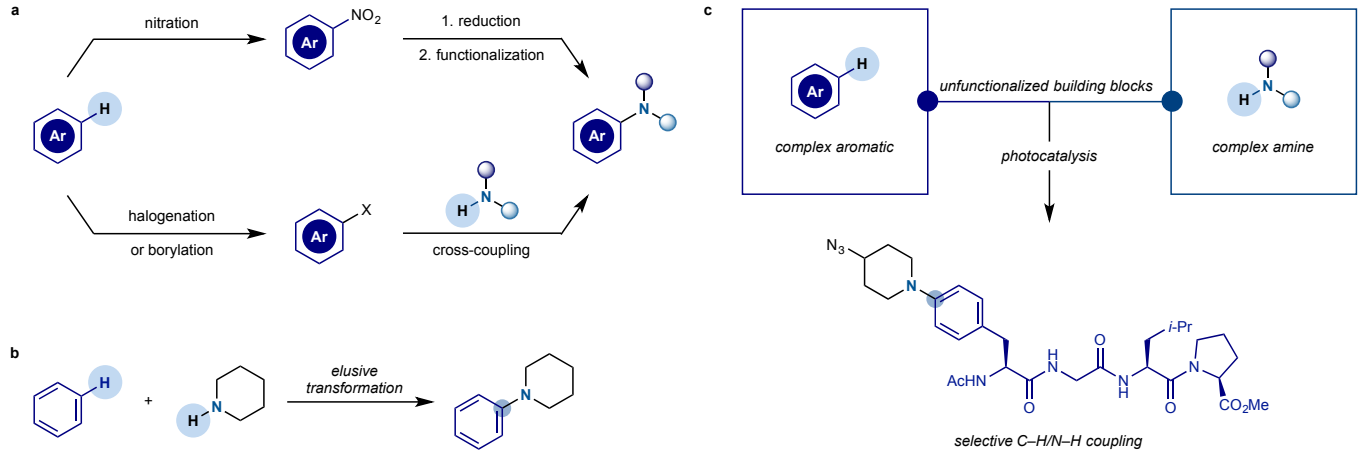
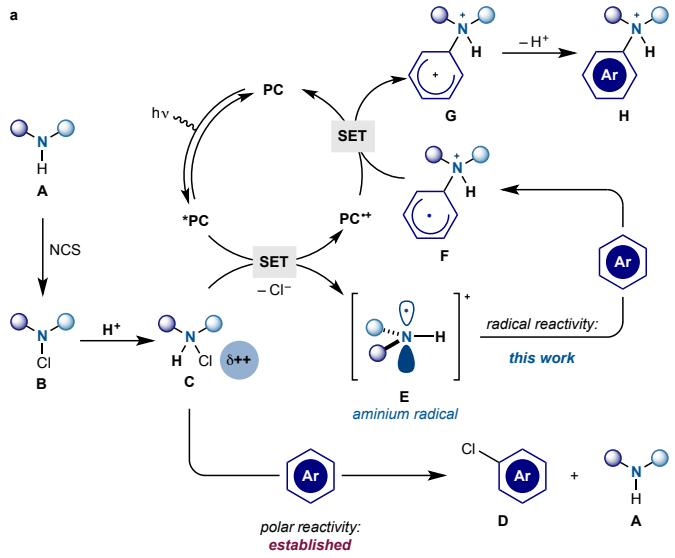
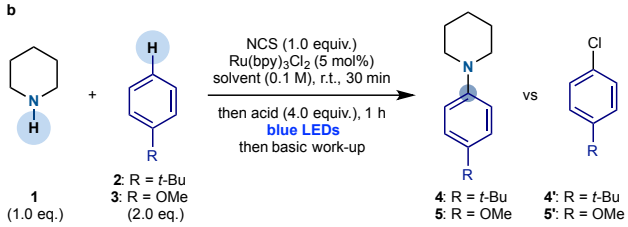
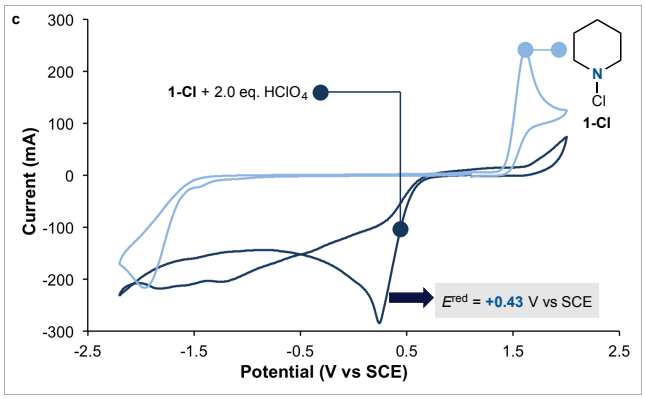


Figure 1. Amination of aromatics. **a)** In general, classical approaches for the preparation of anilines requires functionalized aromatics like nitro-arenes, aryl halides and aryl organoborons. **b)** The direct coupling of amines and aromatics is an elusive transformation. Such a method would complement current strategies especially for the late-stage modification of complex and densely functionalized substrates. **c)** Outline of a general photoredox strategy for the direct coupling of unfunctionalized amines and aromatics.





Entry	Acid	Solvent	amination 4 (%) (*p*:*m*)	chlorination 4' (%)	amination 5 (%) (*p*:*o*)	chlorination 5' (%)
1	AcOH	CH_3CN	–	–	–	–
2	TFA	CH_3CN	–	–	–	17
3	*p*TsOH	CH_3CN	–	–	–	90
4	$HClO_4$	CH_3CN	71 (3:1)	–	94 (3:2)	–
5	$HClO_4$	HFIP	98 (7:1)	–	–	79
6	TFA	HFIP	88 (10:1)	–	–	55



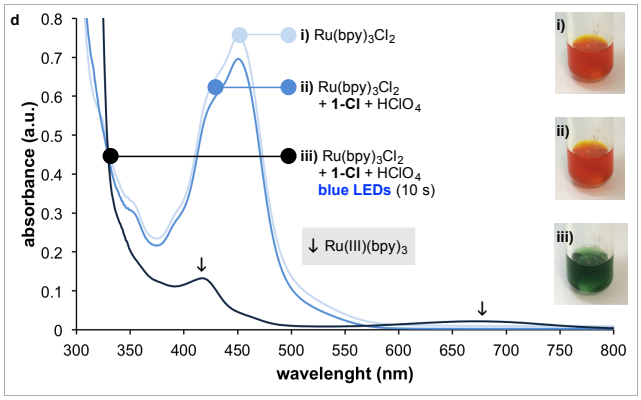


Figure 2. Development of a photocatalytic strategy for direct aromatic C–H amination. **a)** Design plan and mechanistic proposal: the process starts with the *in situ* conversion of a primary and secondary amine

into an *N*-chloramine and its following activation by protonation (**A→B→C**). As protonated *N*-chloroamines are strong electrophiles in Friedel-Craft reactions with aromatics, central to the success of this strategy is to divert their reactivity from ionic to radical. A photoredox cycle enables the redox formation of an aminium radical that undergoes highly polarised addition to an aromatic. The turnover of the photoredox cycle is coupled with the oxidation of the aminated cyclohexadienyl radical. The Brönsted acid has a dual role activating the *N*-chloroamine and insulating the aniline from over-amination and photoredox oxidation. **b)** Development of photocatalytic C–H amination of aromatics using piperidine. The Brönsted acid–solvent combination modulates the reactivity of *N*-chloropiperidine enabling the desired redox process. **c)** Cyclic voltammetry studies show that upon protonation the reduction potential of *N*-chloropiperidine is shifted towards positive values, which confirms its facile SET reduction. **d)** Stoichiometric UV/Vis absorption studies using $Ru(bpy)_3Cl_2$ and protonated *N*-chloropiperidine demonstrate that SET takes place upon blue light irradiation.

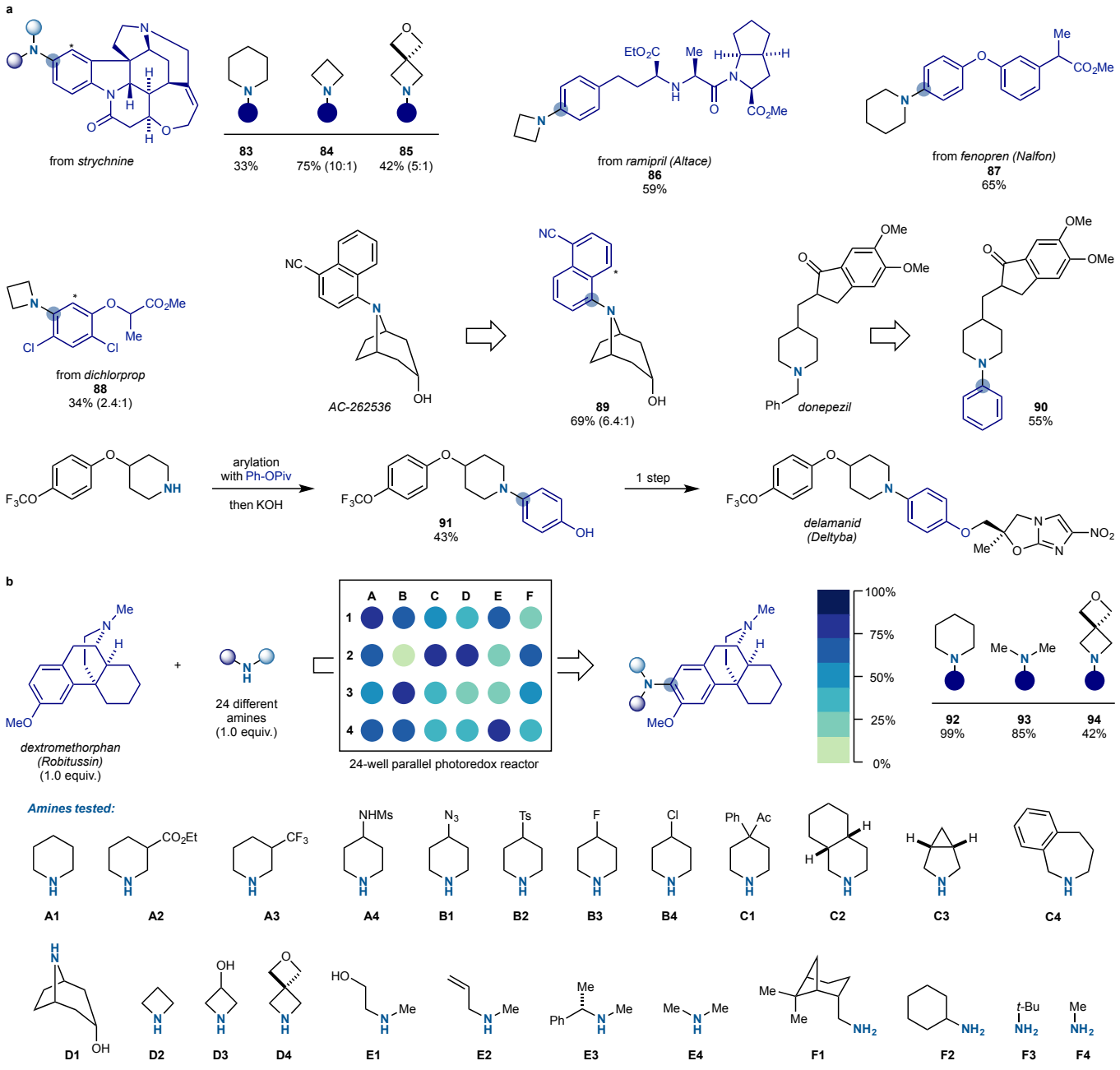


Figure 3. Late-stage diversification of bioactive molecules via photoredox C–H amination. **a)** The late-stage aminations of this series of complex molecules show predictable selectivity and compatibility with several reactive functionality. **b)** Application of the amination strategy in microscale parallel screening shows the fast late-stage diversification of a blockbuster drug.

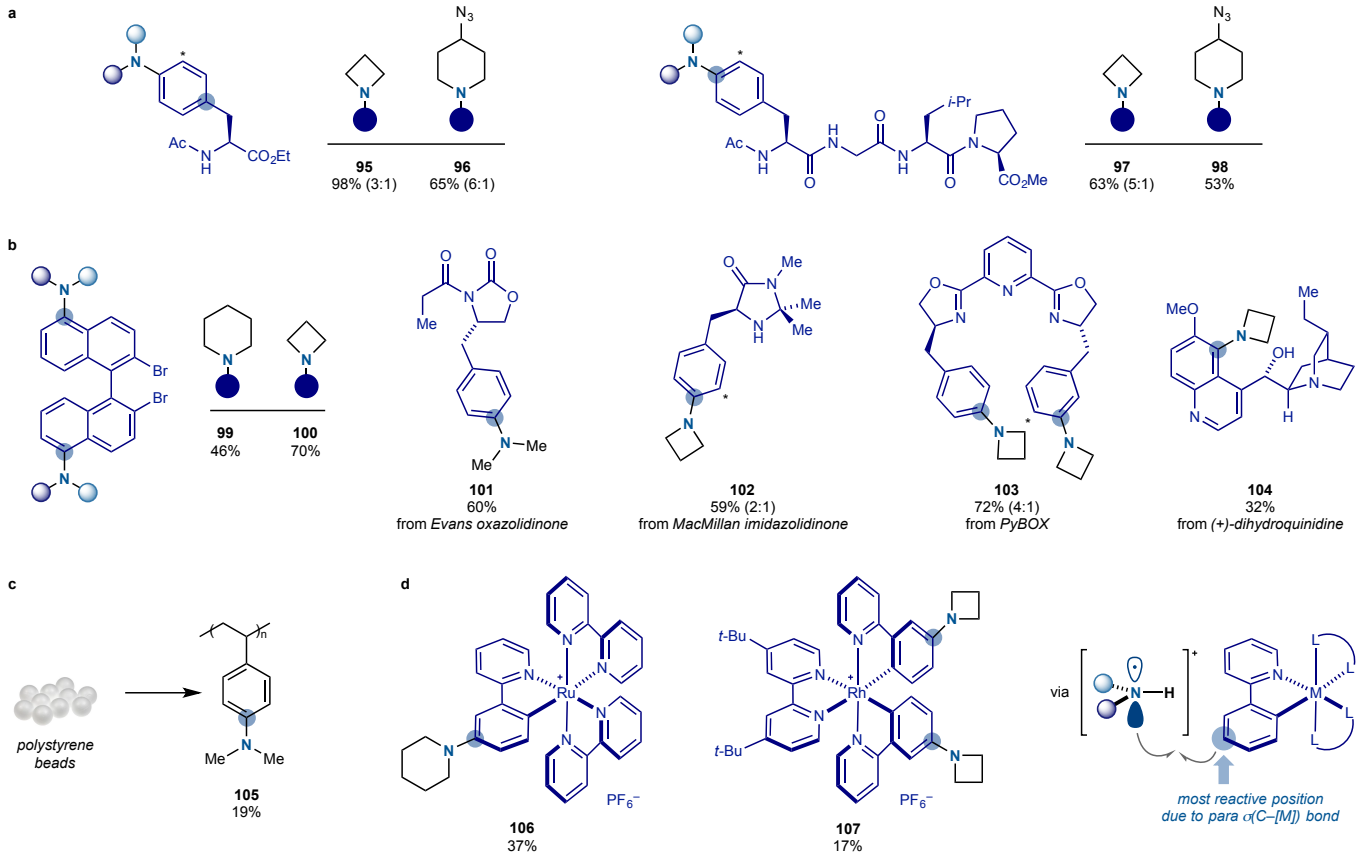
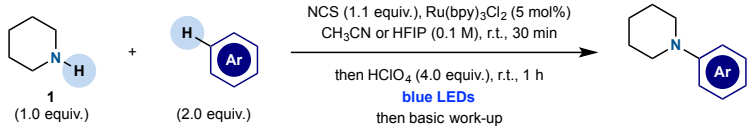
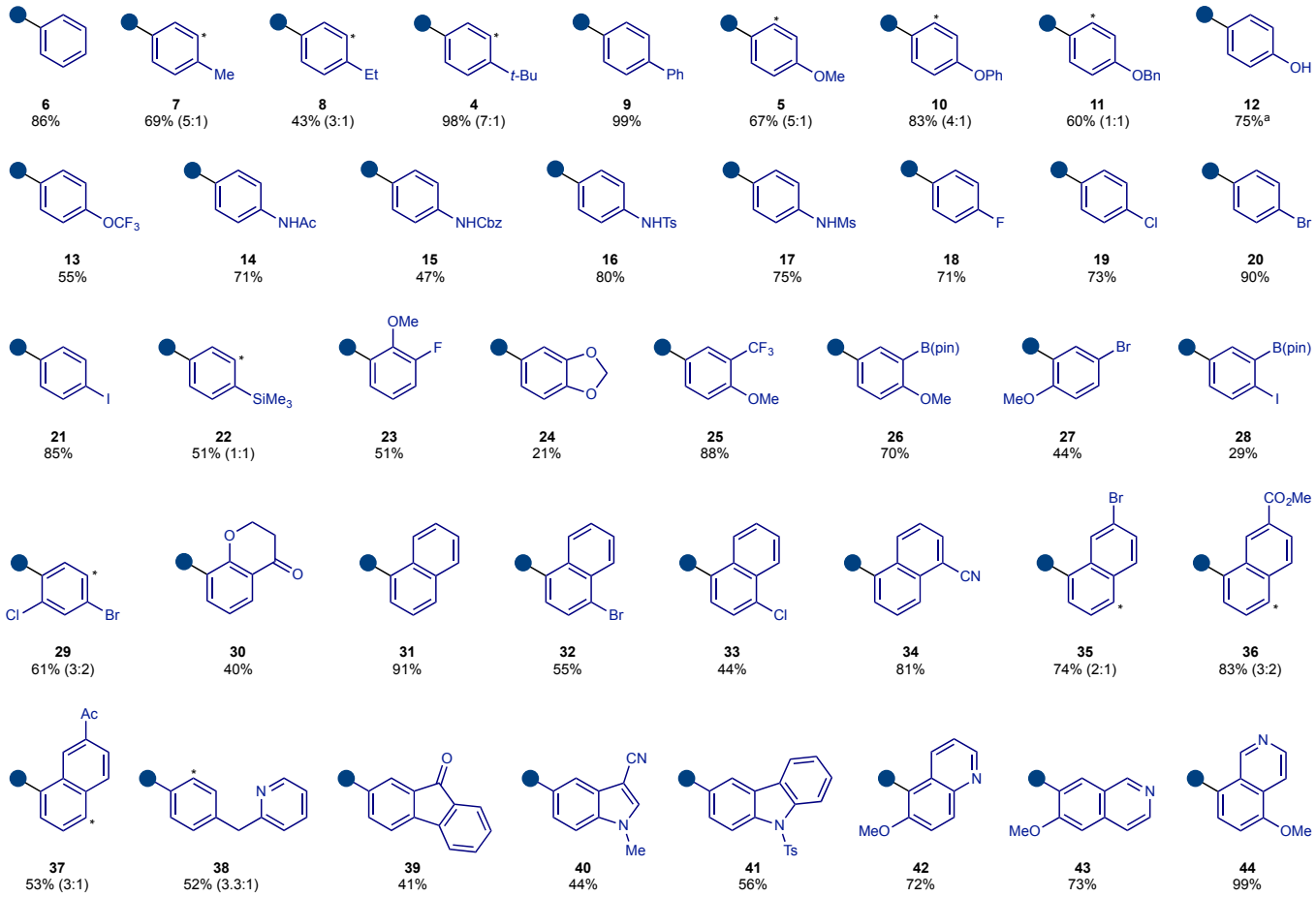


Figure 4. Applications of the aromatic C–H amination reaction. **a)** Aromatic amination of phenyl alanine residues in the protected aminoacid as well as a tetrapetide enables the preparation of unnatural aminoacids and also the introduction of functionality handles for chemical ligation. **b)** Aromatic residues embedded into chiral auxiliary and catalyst scaffolds undergo selective amination. **c)** Reaction with commercial polystyrene beads leads to high degrees of polymer functionalization. **d)** The process is used to introduce amine groups onto the cyclometallated ligands of Ru- and Rh-organometallic complexes. The selectivity of the reaction is explained by the enhanced aromatic nucleophilicity at the carbon *para* to the site of cyclometallation.

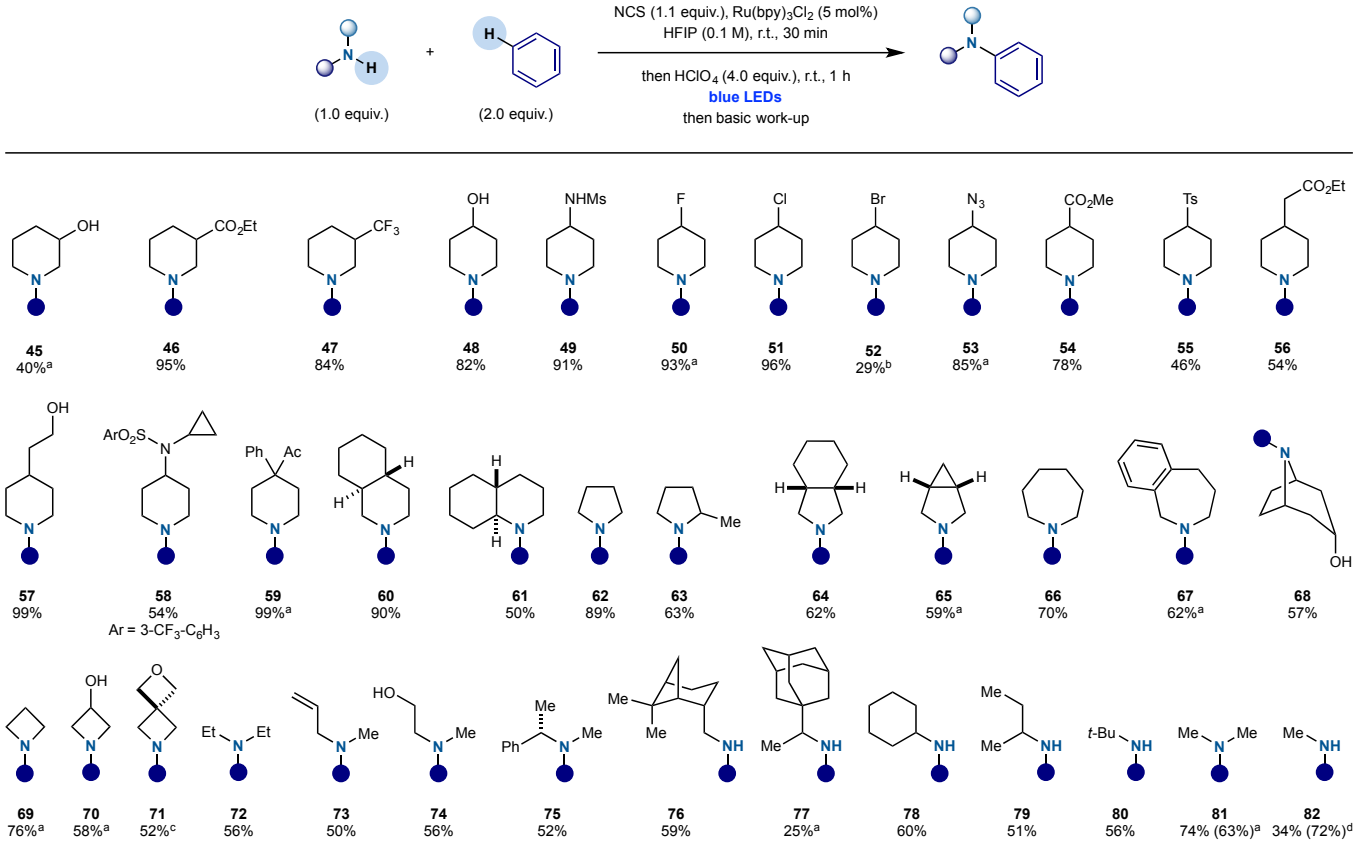
Table 1. Aromatic scope for the photocatalytic aromatic C–H amination.





a) Ph–OPiv was used as the aromatic

Table 2. Secondary and primary amine scope for the photocatalytic aromatic C–H amination.



a) In this case the amine was used as the hydrochloride salt and (*i*-Pr)$_2$NEt (1.1 equiv.) was added to aid the chlorination step. For details concerning the procedure, see General Procedure 2 in Supplementary Section 3.2 for more details. b) The amine was used the hydrobromide salt and (*i*-Pr)$_2$NEt (1.1 equiv.) was added to aid the chlorination step. For details concerning the procedure, see General Procedure 2 in Supplementary Section 3.2 for more details. c) The amine was used as the oxalate salt and (*i*-Pr)$_2$NEt (1.1 equiv.) was added to aid the chlorination step. For details concerning the procedure, see General Procedure 2 in Supplementary Section 3.2 for more details. d) Yield for the reaction with *t*-Bu-benzene.