

A photochemical dehydrogenative strategy for aniline synthesis

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Chemical reactions that reliably join two molecular fragments together (cross-couplings) are essential to the discovery and manufacture of pharmaceuticals and agrochemicals^{1,2}. The introduction of amines onto functionalized aromatics at specific and pre-determined positions (*ortho* versus *meta* versus *para*) is currently achievable only in transition-metal-catalysed processes and requires halogen- or boron-containing substrates^{3–6}. The introduction of these groups around the aromatic unit is dictated by the intrinsic reactivity profile of the method (electrophilic halogenation or C–H borylation) so selective targeting of all positions is often not possible. Here we report a non-canonical cross-coupling approach for the construction of anilines, exploiting saturated cyclohexanones as aryl electrophile surrogates. Condensation between amines and carbonyls, a process that frequently occurs in nature and is often used by (bio-)organic chemists⁷, enables a predetermined and site-selective carbon–nitrogen (C–N) bond formation, while a photoredox- and cobalt-based catalytic system progressively desaturates the cyclohexene ring en route to the aniline. Given that functionalized cyclohexanones are readily accessible with complete regiocontrol using the well established carbonyl reactivity, this approach bypasses some of the frequent selectivity issues of aromatic chemistry. We demonstrate the utility of this C–N coupling protocol by preparing commercial medicines and by the late-stage amination–aromatization of natural products, steroids and terpene feedstocks.

At present, the most reliable way to selectively introduce amines into specific positions on functionalized aromatics (*ortho* versus *meta* versus *para*), is to use palladium- or copper-catalysed strategies⁸. For these processes to work, the aromatic coupling partner needs to be pre-equipped with a (pseudo)halide (Buchwald–Hartwig^{4,9} and Ullmann⁶ cross-couplings) or a boronic acid (Chan–Lam cross-coupling⁵) in order to generate aryl–palladium or aryl–copper species that, after amine coordination and reductive elimination, deliver the aniline to the required position.

However, site-selective preparation of functionalized aryl halides and boronic esters can be synthetically challenging owing to the ‘double-edged sword’ nature of aromatic chemistry. Although one can accurately predict where functionalities are to be introduced, it implies that all other aromatic positions are frequently not accessible using the same method (Fig. 1a). A classic example is electrophilic aromatic substitution chemistry¹⁰: although it is easy to halogenate the *para*-position of an electron-rich aromatic, targeting the *meta*-site is difficult and multi-step sequences remain the only viable option. Conversely, *meta*-halogenation of electron-poor aromatics is feasible but direct *ortho*- or *para*-functionalization is not. Likewise, aromatic C–H borylation is controlled mainly by steric factors, which makes *ortho* functionalization attainable only in the presence of directing groups¹¹. Furthermore, when either electronic or steric bias is not present, both aromatic halogenation and borylation methods often lead

to a mixture of constitutional isomers. More recently, direct radical C–H amination strategies have emerged^{12–14}, but they require the use of electron-rich aromatics and generally display strong *para*-selectivity. Taken together, these aspects highlight some of the synthetic challenges that are encountered while attempting ‘user-defined’ aromatic functionalizations in which the targeted position is contrary to the one controlled by electronic or steric factors.

Hence, the development of a robust catalytic strategy that relies on coupling partners that have different functionalization chemistries could enable access to synthetically challenging targets. In this work, we report a protocol for aniline preparation based on the coupling between amines and cyclohexanones as saturated aryl electrophile surrogates. This approach centres on two main aspects, as follows. (1) The general and benchmarked reactivity of the carbonyl group is harnessed to install, with complete control, various functionalities around the pre-aromatic building block. (2) Condensation between ketones and amines, a process fundamental in nature¹⁵ as well as organic synthesis¹⁶ and catalysis¹⁷, is used as the blueprint for site-selective *sp*² C–N bond formation in place of reductive elimination.

The prospect of using saturated aryl surrogates for the synthesis of aromatic building blocks was pioneered by Stahl’s oxidative dehydrogenation of cyclohexanones into phenols using Pd(II)-catalysis under O₂ atmosphere at high temperature¹⁸. Although attempts have been made to extend this reactivity mode to cyclohexanone imines for aniline

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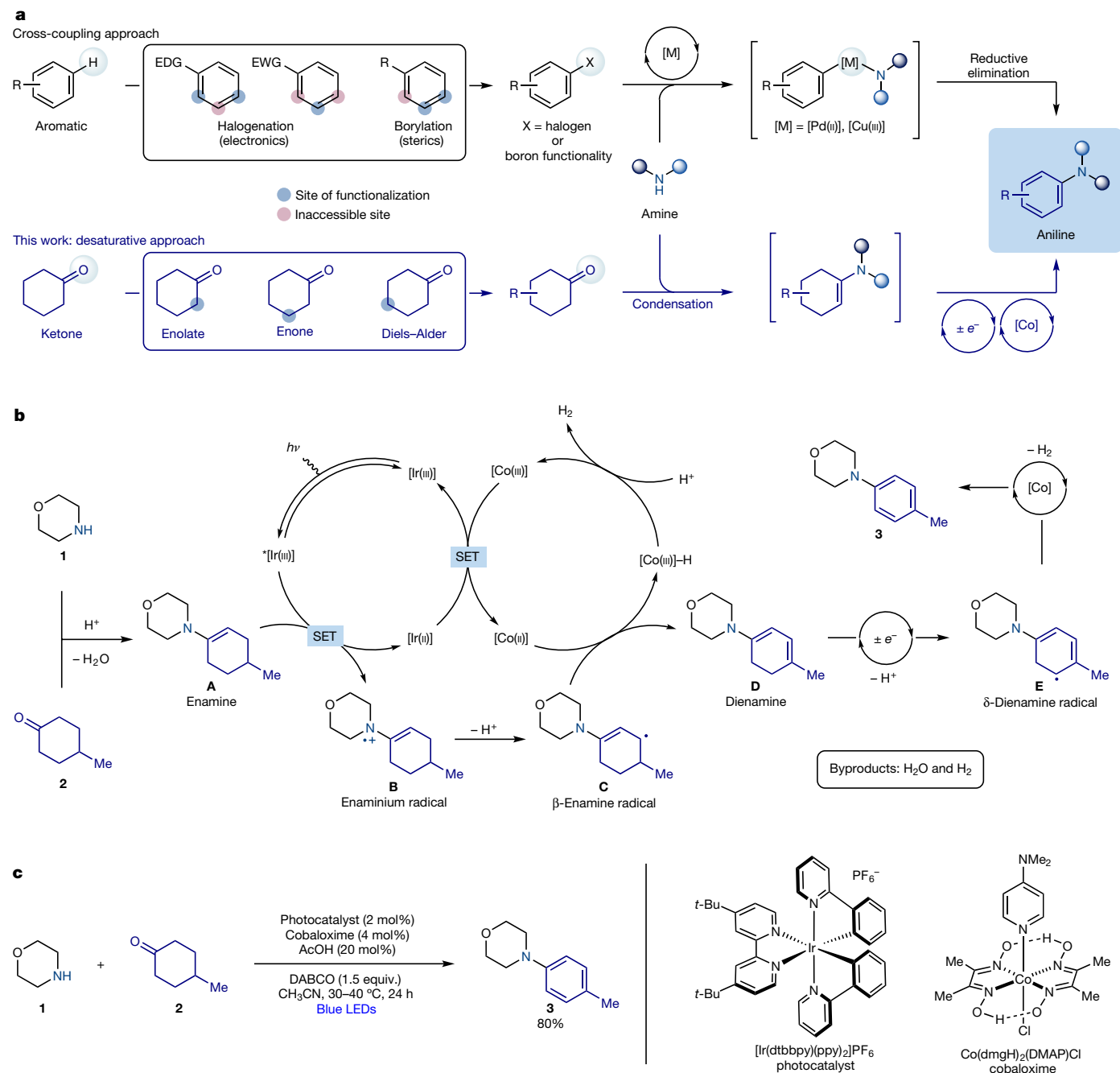


Fig. 1 | Cross-coupling strategies for aniline synthesis. **a**, Anilines are generally prepared via the initial halogenation or borylation of aromatics followed by a metal-catalysed cross-coupling. The strategy developed here uses cyclohexanones as aryl halides or boronic acid surrogates. LED, light-emitting diode. *p*-Tol, *para*-toluyl; EDG, electron-donating group; EWG, electron-withdrawing group. **b**, Proposed mechanism for the dual photoredox-cobalt dehydrogenative coupling between amine **1** and cyclohexanone **2**. **c**, The optimized dehydrogenative coupling between amine **1** and cyclohexanone **2** gives the desired aniline **3** in high yield.

synthesis, the harsh reaction conditions have limited functional-group compatibility and synthetic applications^{19,20}. We conjectured that an alternative strategy based on photo-induced single-electron transfer could provide a general and reliable framework for the preparation of complex anilines with drug-like structural features. To achieve this goal, we became interested in the possibility of merging enamine oxidation chemistry^{21,22} with the known ability of cobaloxime systems to intercept carbon radicals and trigger dehydrogenation reactions^{23–25}.

A mechanistic outline for the coupling between morpholine **1** and 4-methylcyclohexanone **2** is depicted in Fig. 1b. Upon condensation, the in situ-generated enamine **A** can be efficiently oxidized (oxidation potential $E_{\text{ox}} = +0.56$ V versus saturated calomel electrode, SCE;

electron-withdrawing group. **b**, Proposed mechanism for the dual photoredox-cobalt dehydrogenative coupling between amine **1** and cyclohexanone **2**. **c**, The optimized dehydrogenative coupling between amine **1** and cyclohexanone **2** gives the desired aniline **3** in high yield.

Stern–Volmer quenching constant $k_{\text{SV}} = 2,882 \text{ M}^{-1}$) by the visible light-excited photocatalyst $[\text{Ir}(\text{dtbbpy})(\text{ppy})_2]\text{PF}_6$ ($E_{\text{red}} = +0.66$ V versus SCE)²⁶ (here dtbbpy is 4,4'-di-*tert*-butyl-2,2'-dipyridyl and ppy is 2-phenylpyridyl). Owing to the enhanced acidity of the β -methylene unit in the enaminium radical **B** (ref. ²⁷), a deprotonation can take place, leading to the nucleophilic $5\pi e^-$ β -enamine radical **C** (ref. ²²). The reaction between alkyl radicals and Co(II) complexes is reported to occur at nearly diffusion-control rates and give organocobalt(III) intermediates that undergo facile β -hydride eliminations²⁸. We therefore proposed that intermediate **C** might be intercepted by the cobaloxime co-catalyst to deliver di-enamine **D** along with a cobalt(III) hydride species. By reaction with protic sources (for example, DABCO- H^+), Co(III)-H

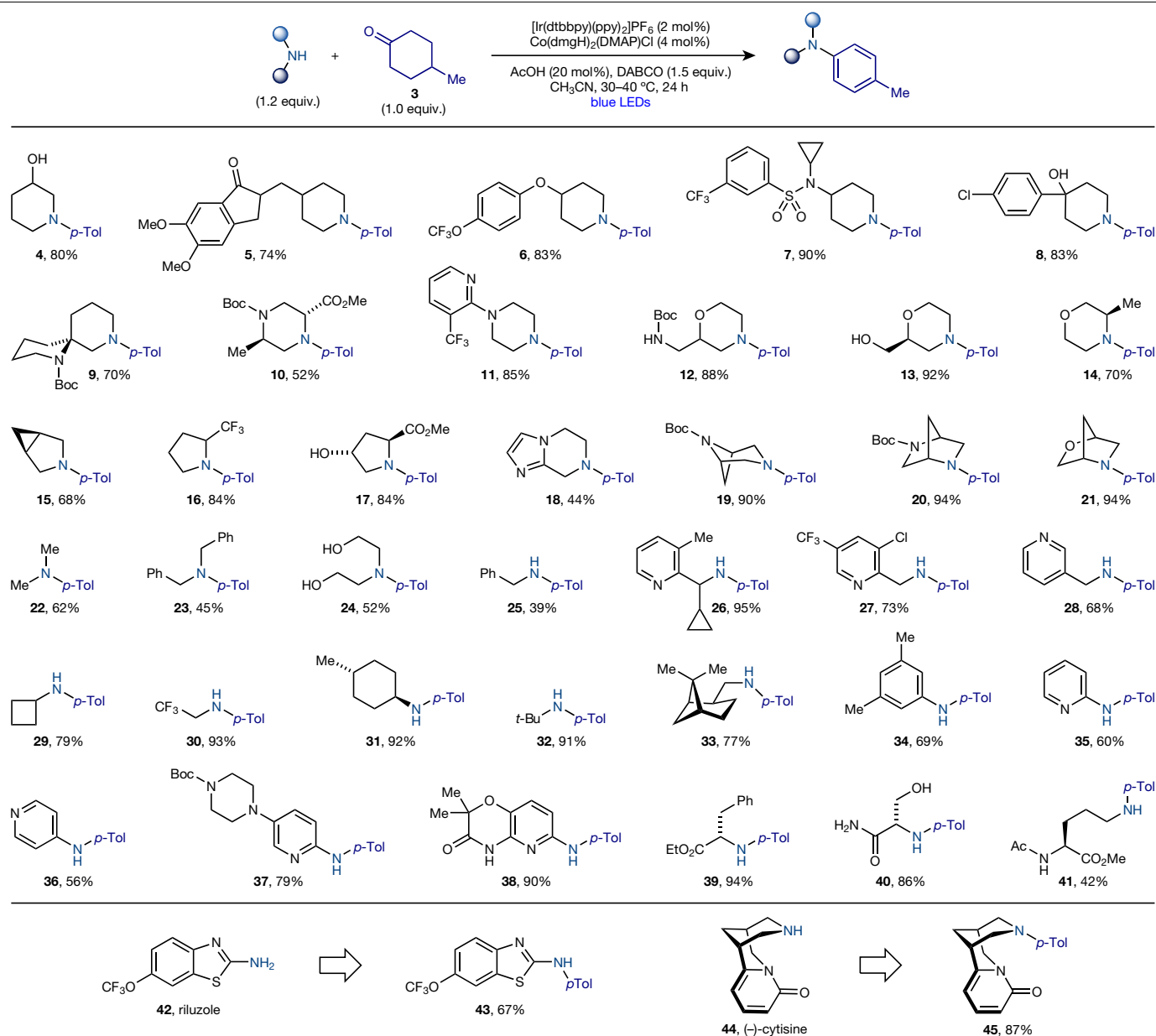


Fig. 2 | Scope of the amine partner in the dehydrogenative amination.

derivatives have been reported to evolve H₂ (ref. ²⁹), resulting in Co(III) complexes (for Co(dmgH)₂(DMAP)Cl: $E_{\text{red}} = -0.47$ V versus SCE); here DABCO is (1,4-diazabicyclo[2.2.2]octane), dmg is dimethylglyoximate and DMAP is 4-dimethylaminopyridine. This species could therefore undergo a single-electron transfer with the reduced Ir(II) photocatalyst ($E_{\text{red}} = -1.51$ V versus SCE)²⁶, thus simultaneously turning over the photoredox and the cobalt cycles. At this point, we posited that the highly electron-rich dianamine **D** might participate as the starting material in a second and identical oxidation–dehydrogenation process to produce the fully aromatized aniline **3**. Critical for the success of this strategy is the use of photocatalysts with moderate oxidative power in order to achieve the selective and sequential oxidation of **A** and **D** over **3** ($E_{\text{ox}} = +0.88$ V versus SCE), which would lead to decomposition pathways (a more detailed discussion on the experiments carried out to support this mechanistic proposal can be found in the Supplementary Information). Overall, with the realization of this strategy, we would use classic imine condensation chemistry to forge a *sp*² C–N bond while the Ir–Co system would effectively ‘chain-walk’ around the cyclohexyl ring, triggering two sequential dehydrogenations en route

to a thermodynamically stable aromatic system. Finally, it is worth considering that, in contrast to classical cross-couplings based on aryl halides or boronic acids, this reaction would generate H₂O and H₂ as the sole stoichiometric byproducts, thus exhibiting excellent atom economy.

Pleasingly, the realization of this amination platform was enabled by using AcOH as the Brønsted acid additive (to aid enamine formation) and DABCO as the base in CH₃CN solvent under blue light irradiation (Fig. 1c; the details of the reaction optimization are discussed in the Supplementary Information). Under these mild reaction conditions, amine **1** and cyclohexanone **2** gave aniline **3** in 80% yield.

With an optimized set of reaction conditions in hand, the scope of both the amine and the cyclohexanone partners was investigated (Figs. 2, 3). As part of an ongoing collaboration, we consulted with AstraZeneca to benchmark this novel process for aniline synthesis using a diverse set of substrates relevant to the pharmaceutical sector.

Piperidine is the most prevalent *N*-heterocycle in commercial drugs and the most common sites for functionalization are C-3 and C-4 (ref. ³⁰). Pleasingly, many sensitive polar functionalities³¹ such as free alcohol

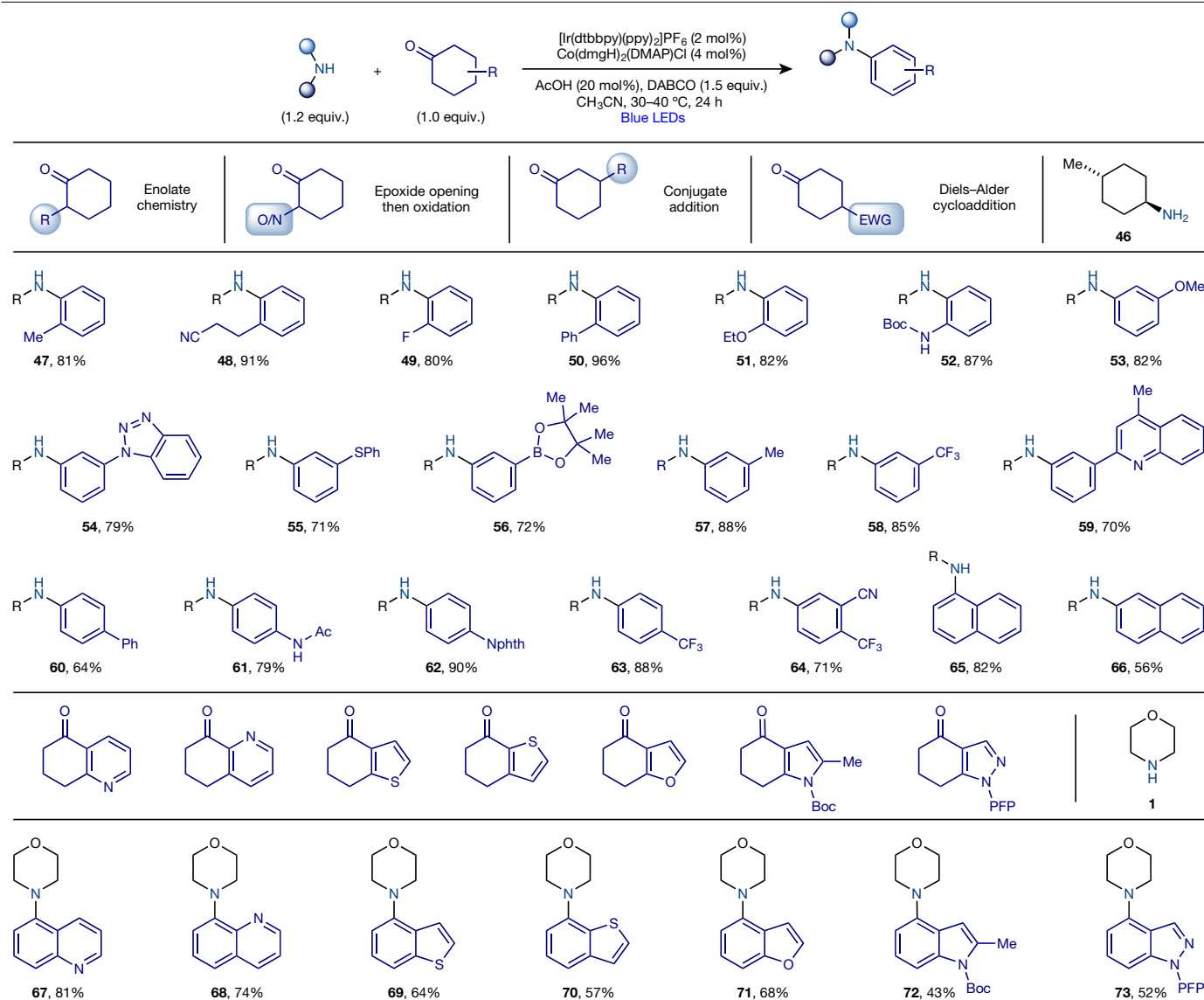


Fig. 3 | Scope of the cyclohexanone partner in the dehydrogenative amination. Nphth, N-phthalimide; PFP, *p*-F-phenyl.

(4), ketone (5), which could interfere with the enamine formation, aryl ether (6) and sulphonamide (7) at either C-3 or C-4 were tolerated. Other important motifs like a C-4 tertiary benzylic alcohol, frequently found in the core of many antipsychotic drugs (for example, haloperidol) (8) and a C-3 spirocyclic *N*-Boc protected piperidine ring (9), could be present (here Boc is *tert*-butoxycarbonyl). Piperazines, the second-most frequent *N*-heterocycle in medicines³⁰, were competent in the process despite the decreased nucleophilicity of their free amine group. In this case we succeeded in using a 2,5-disubstituted enantiopure cyclic α -aminoester (10) and an *N*-arylated substrate resulting in an unsymmetrical *N,N*-diaryl piperazine (11). The chemistry was also extended to functionalized morpholines (12–14) and pyrrolidines (15–17) and this included an enantiopure C-2 alkylated building block (14) that is known to be troublesome under transition-metal catalytic approaches owing to unwanted epimerization³², which we engaged in our protocol without loss of enantiopurity. We also successfully engaged bicyclic heterocycles (18–21) of high *sp*³ content, which are privileged motifs in current drug discovery programmes. Both acyclic secondary and primary amines worked well (22–25), which allowed us to benchmark the process with substrates containing C-2 and C-3 substitute pyridines (26–28). The high-yielding formation of 29 and 30 is noteworthy because cyclobutyl amine cannot be used in nitrogen-radical-based approaches (competitive ring-opening)³³, while fluoroalkylamines

require forcing conditions in palladium cross-couplings³⁴. Having evaluated electronic effects, we also confirmed that steric encumbrance does not hamper reactivity, as demonstrated by the high-yielding preparation of 31–33, which includes the arylation of the terpenoid (–)-*cis*-myrtanlylamine (33). Anilines are viable starting materials, as demonstrated by the formation of 34–38, which includes C-2, C-3 and C-4 functionalized pyridine derivatives. Amino acids were tested next and we successfully engaged L-phenylalanine (39), L-serinamide (40) and L-lysine (41), thus demonstrating that both side-chain and central NH functionality can be targeted. As the final element to the amine substrate scope, we used this reaction for the arylation of riluzole (42 → 43), a medicine used for the treatment of amyotrophic lateral sclerosis, and (–)-cytisine (44 → 45), an alkaloid with an interesting biological profile. The *N*-arylation of this natural product has only been attempted using nucleophilic aromatic substitution chemistry under harsh conditions³⁵, which demonstrates the complementarity that this approach might bring to mainstream ionic and cross-coupling technologies.

To further explore the capability and generality of this strategy, the reaction was evaluated with respect to the cyclohexanone scope using *trans*-4-methylcyclohexylamine 46 (Fig. 3). In this case, we were interested in leveraging classic carbonyl chemistry to access α -, β - and γ -functionalized cyclohexanones that would correspond to the synthetically challenging *ortho*-, *meta*- and *para*-functionalized aryl

carbon-based substituents for the following efficient *meta*-amination (**53**–**59**). Conversely, the preparation of *para*-substituted anilines is trivial in electron-rich aromatics by either ionic halogenation and coupling, or radical amination and can also be achieved in our method using γ -substituted cyclohexanones (**60**–**62**). However, *para*-functionalization is considerably more challenging in systems containing electron-withdrawing groups (for example, to give **63**). In our case, the textbook Diels–Alder reaction with Danishefsky's diene was used to access the desired cyclohexanones that were converted into **63** and **64** in high yields. Furthermore, 1- and 2-tetralones were used to access 1- and 2-naphthylamine derivatives **65** and **66**, respectively, in high yields.

A final class of aryl surrogates that we considered were heterocycle-annulated cyclohexanones (Fig. 3). As these materials are easily accessed by classic condensation chemistry, their implementation would provide a valuable alternative for the preparation of aminated heterocycles, which are a known synthetic challenge both in terms of preparation of the aryl halide or boronic acid starting materials and the subsequent cross-coupling³⁶. Pleasingly, using **1** as the amine, we efficiently prepared 5- and 8-morpholino-quinolines (**67** and **68**) and -benzothiophenes (**69** and **70**), as well as 5-morpholino-benzofuran (**71**), -indole (**72**) and -indazole (**73**).

An interesting application of this reactivity would be the use of ammonia to access free anilines, an important class of building blocks. We evaluated this possibility by performing late-stage aromatization–amination of commercial and high-value materials. As shown in Fig. 4a, using stoichiometric quantities of ammonia (7 M in MeOH), we converted the A ring of the birth-control medicine levonorgestrel (**74**) and *estra-5,9-diene-3,17-dione* (**75**) into anilines **79** and **80** in high yields. This protocol can also be used for the valorization of feedstocks. For instance, cheap and readily available terpenes such as dihydrocarvone (**76**, US\$1.7 per gram) and (–)-menthone (**77**, US\$1.3 per gram) were elaborated into the corresponding *ortho*, *meta*-disubstituted anilines **81** and **82**, which are high-value chemicals currently manufactured via aromatic nitration followed by reduction (**81**: US\$685 per gram and **82**: US\$851 per gram). Finally, we applied this reactivity to cycloheximide (**78**), a naturally occurring fungicide. In this case, aromatization–amination was achieved but concomitant removal of the lateral β -hydroxy functionality took place, leading to **83** in high yield. We believe this unexpected outcome introduces a powerful retrosynthetic disconnection where aldehydes and ketones can be used as alkyl surrogates for the assembly of challenging *ortho*-alkyl anilines (Fig. 4b). Accordingly, simple aldol chemistry can be used to create the '*ortho*' C–C bond which, upon photoredox dehydrogenative amination, would be converted into the alkyl chain **84**–**86**. As the β -hydroxyl group is removed as part of a cascade process involving an initial elimination unimolecular conjugate base step, the presence of stabilizing aryl or vinyl groups alter this reactivity and can be used to install olefin functionalities (**87** and **88**; the proposed mechanism for these cascade reactions is discussed in the Supplementary Information).

Finally, Fig. 4c–i depicts seven representative examples of how this orthogonal retrosynthetic approach might be used to access and potentially simplify the preparation of medicines. (1) The local anaesthetic lidocaine (**91**) is currently manufactured by unselective and low-yielding nitration of *meta*-xylene. Given that 2,6-dimethylcyclohexanone **89** is readily available by enolate chemistry, dehydrogenative amination with ammonia (**90**) and amide formation enabled its quantitative synthesis in two steps. (2) The need for nitration chemistry was also bypassed in the preparation of the antidepressant vortioxetine (**94**). Straightforward enolate chemistry gave **92** in one step, which, following amination with commercial **93** and acid work-up, gave **94** in two steps. (3) Phentolamine (**97**) is a vasodilator with a challenging *meta*-aminophenol unit. We used enone β -boration (**95**) to ensure correct *O* versus *N* disposition upon dehydrogenative amination with *para*-toluidine (**96**) and oxidative work-up. *N*-alkylation completed the synthesis of **97** in two steps. (4) Another

challenging *meta*-amination is required to synthesize naluzotan (**100**), a serotonergic drug prepared by nitration chemistry. For use in dehydrogenative amination chemistry, we relied on a β -selective oxidation³⁷ of *N*-Ac-cyclohexylamine that gave **98**. A subsequent aromatization–amination, followed by acid work-up, with commercial **99** gave the corresponding monoarylated piperazine, alkylated as described in the literature to give **100** in two steps. (5) The copper-catalysed conjugate addition of an aryl Grignard was exploited to establish the bis-*meta*-substituted biphenyl unit present in solabegron (**103**), a drug used for the treatment of irritable bowel syndrome. Simple coupling of **101** with the *N*-Boc-protected ethylene diamine **102** gave, following known epoxide opening and ester hydrolysis³⁸, the desired drug **103**. (6) We used classical aldol annulation chemistry to make **104**, which was converted into the intravenous local anaesthetic tetracaine (**106**) by aromatization–amination with *n*-BuNH₂ (**105**) and amidation. (7) Finally, a powerful application of this dehydrogenative reactivity was envisaged by analysis of the cardiotonic agent vesnarinone (**109**). The C-6 amino-dihydroquinone motif is currently assembled from the corresponding C-6 bromide, requiring a multi-step synthesis³⁹. A retrosynthetic analysis involving hexahydroquinoline-2,6-dione **107** suggested the possibility of a shorter synthesis by exploiting classical aldol and Robinson annulation chemistry. Indeed, we prepared **107** in two steps, which we directly telescoped into the cross-coupling reaction (1.5 g) with commercial piperazine **108** to give **109** in 81% yield (2.9 g).

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41586-020-2539-7>.

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Data availability

Materials and methods, experimental procedures, useful information, mechanistic studies, optimization studies, ^1H NMR spectra, ^{13}C NMR spectra and mass spectrometry data are available in the Supplementary Information. Raw data are available from the corresponding author on reasonable request.

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Competing interests The authors declare no competing interests.

Additional information

Supplementary information is available for this paper at <https://doi.org/10.1038/s41586-020-2539-7>.

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