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 following manufacture of high-value materials like pharmaceuticals and agrochemicals.[1,2] In this area, the introduction of amines onto functionalised aromatics at specific and pre-determined positions (*ortho* vs *meta* vs *para*) is currently a prerogative of transition metal-catalysed processes and requires halogen/boron-containing substrates.[3-6] The introduction of these groups around the aromatic unit is dictated by the intrinsic reactivity profile of the method (*e.g.* electrophilic halogenation, C–H borylation) so selective targeting of all possible positions is often not possible. Here we report a non-canonical cross-coupling approach for the programmable construction of anilines on demand, exploiting saturated cyclohexanones as aryl electrophile surrogates. The condensation between amines and carbonyls, a process extensively used by Nature and (bio)organic chemists,[7] is the enabling feature that ensures a pre-determined and site-selective carbon–nitrogen bond formation, while a synergistic photoredox and cobalt catalytic system is simultaneously employed to progressively desaturate the cyclohexene ring *en route* to the aniline. As functionalised cyclohexanones are readily accessible with complete regiocontrol by well-established carbonyl chemistry, this approach offers a solution to bypass some of the frequent selectivity issues of aromatic chemistry. The utility of this novel C–N coupling protocol was demonstrated by the preparation of commercial medicines and the late-stage amination–aromatization of natural products, steroids and terpene feedstocks.

Innovations in synthetic chemistry are integral to the discovery and production of high-value materials and medicines, and as a result, the well-being of society. In particular, chemical transformations able to couple together complex and functionalized building blocks in a site-selective and programmable manner are fundamental to downstream

access to increasingly complex molecules. Within the realm of cross-coupling reactions, processes leading to the construction of C–N bonds across aromatic systems have played a fundamental role in assembling anilines, key structural elements of drugs, agrochemicals and materials.[8-10]

Currently, the most reliable way to selectively introduce amines into specific positions on functionalised aromatics (*ortho* vs *meta* vs *para*), is to use palladium- or copper-catalysed strategies.[11] For these processes to work, the aromatic coupling partner needs to be pre-equipped with a (pseudo)halide (Buchwald-Hartwig[4,12] and Ullmann[6] cross-couplings) or a boronic acid (Chan-Lam cross-coupling[5]) in order to generate aryl-palladium/copper species that, after amine coordination and reductive elimination, deliver the aniline in the required position.

However, site-selective preparation of functionalised aryl halides and boronic esters can be synthetically challenging due to the "double-edged-sword" nature of aromatic chemistry. While text-book knowledge can accurately predict where functionalities are to be introduced, it implies all other aromatic positions are frequently not accessible using the same method (Figure 1A). A classic example is electrophilic aromatic substitution chemistry (S_EAr)[13]: while 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 mainly controlled by steric factors, which makes *ortho* functionalization attenable only in the presence of directing groups.[14] Furthermore, when either electronic or steric bias are not present, both aromatic halogenation and borylation methods lead to mixture of constitutional isomers. More recently, direct radical C–H amination strategies have emerged,[15-17] 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 when the targeted position is contrary to that controlled by electronic and/or steric factors.

Hence, the development of a robust catalytic strategy that relies on coupling partners with different functionalization chemistry can 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 electrophiles surrogates. This approach centres on two main aspects: (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 and (2) the condensation between ketones and amines, a process fundamental in Nature[18] as well as organic synthesis[19] and catalysis,[20] is used as 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 has been pioneered by Stahl's oxidative dehydrogenation of cyclohexanones into phenols using Pd(II)-catalysis under O_2 atmosphere at high temperature.[21] While attempts have been made to extend this reactivity mode to cyclohexanone imines for anilines synthesis, the harsh reaction conditions have somewhat limited functional group compatibility and synthetic applications.[22,23] We conjectured if an alternative strategy based on photoinduced SET (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[24,25] with the known ability of cobaloxime systems to intercept carbon-radicals and trigger dehydrogenation reactions.[26-28]

A mechanistic outline for the coupling between morpholine **1** and 4-methylcyclohexanone **2** is depicted in Figure 1B. Upon condensation, the *in situ* generated enamine **A** can be efficiently oxidized (E_{ox} = + 0.56 V vs SCE; k_{SV} = 2882 M^{-1}) by the visible light-excited photocatalyst $[Ir(dtbbpy)(ppy)_2]PF_6$ ($^*E_{red}$ = +0.66 V vs SCE).[29] Due to the enhanced acidity of the α-methylene unit in the enaminium radical **B**,[30] a deprotonation can take place leading to the nucleophilic 5πe^- α-enamine radical **C**.[25] 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 eliminations.[31] 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 (e.g. DABCO–H^+), Co(III)–H derivatives have been reported to evolve H_2[32] resulting in Co(III) complexes (for $Co(dmgH)_2(DMAP)Cl$: E_{red} = –0.47 V vs SCE). This species could therefore undergo a SET with the reduced Ir(II) photocatalyst (E_{red} = –1.51 V vs SCE)[29] thus simultaneously turning over the photoredox and the cobalt cycles. At this point, we posited that the highly electron rich dienamine **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_{ox} = +0.88 V vs 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 ESI). 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/boronic acids, this redox-neutral reaction would generate H_2O and H_2 as the sole stoichiometric by-products thus exhibiting excellent atom-economy.

Pleasingly, the realization of this amination platform was possible by using AcOH as the Brønsted acid additive (to aid enamine formation) and DABCO (1,4-diazabicyclo[2.2.2]octane) as the base in CH_3CN solvent under blue light irradiation (Figure 1C; the details of the reaction optimization are discussed in the ESI). Under these mild reaction conditions, amine **1** and cyclohexanone **2** gave aniline **3** in 80% yield.

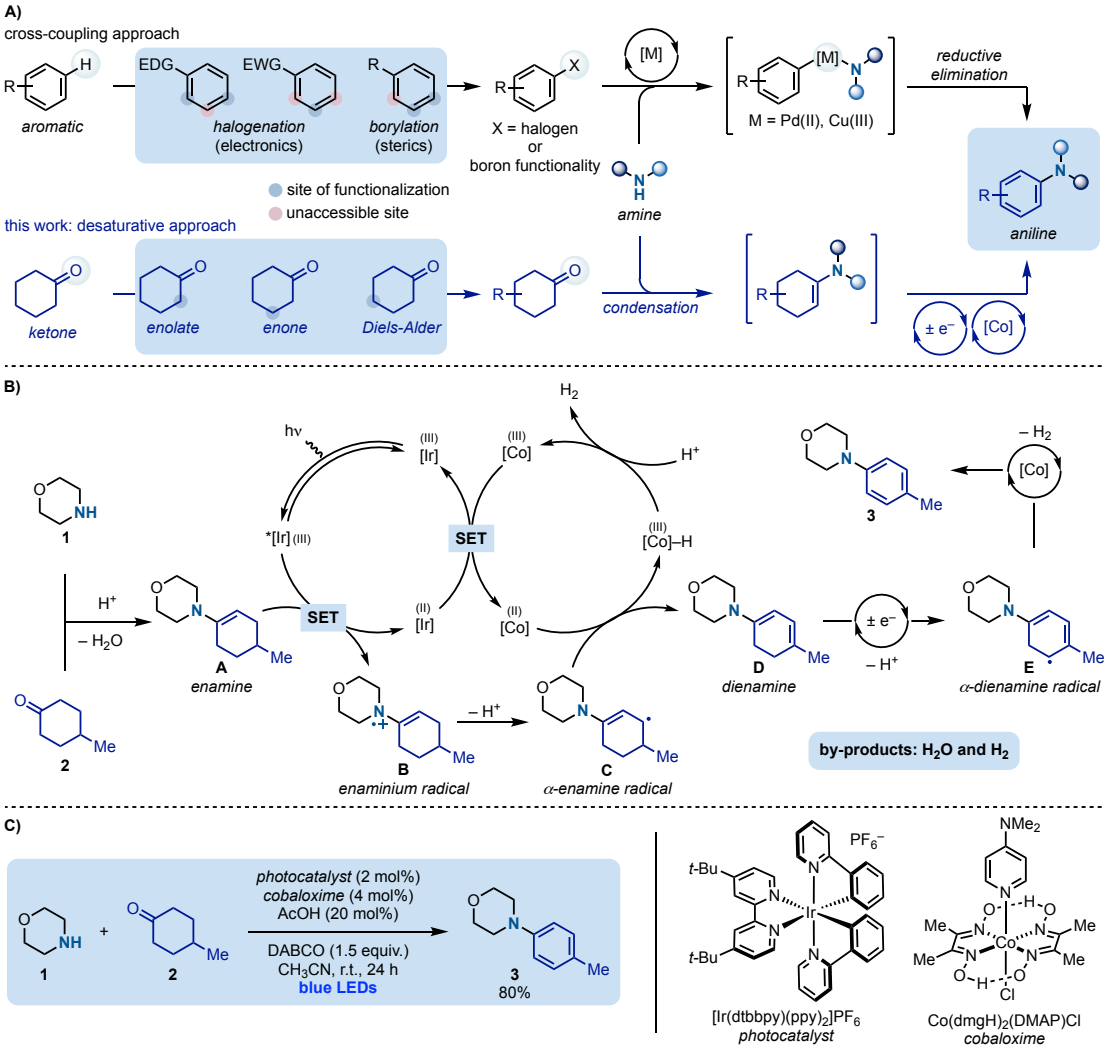

Figure 1. (A) Anilines are prepared via the initial halogenation or borylation of aromatics followed by a metal-catalysed cross coupling. This strategy uses cyclohexanones as aryl halides/boronic acid surrogates. **(B)** Proposed mechanism for the dual photoredox-cobalt dehydrogenative coupling between amine **1** and cyclohexanone **2**. **(C)** The optimised dehydrogenative coupling between amine **1** and cyclohexanone **2** gives the desired aniline **3** in high yield.

With an optimised set of reaction conditions in hand, the scope of both the amine and the cyclohexanone partners was investigated (Figures 2 and 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.[33] Pleasingly, many sensitive polar functionalities[34] like free alcohol (**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 (e.g. haloperidol) (**8**) and a C-3 spirocyclic *N*-Boc protected piperidine ring (**9**), could be present. Piperazines, the second most frequent *N*-heterocycle in medicines,[33] 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 due to unwanted epimerization[35], 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 programs. 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 as cyclobutyl amine cannot be used in nitrogen-radical based approaches (competitive ring-opening),[36] while fluoroalkylamines require forcing conditions in palladium cross-couplings.[37] 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 include the arylation of the terpenoid (–)-*cis*-myrtanylamine (**33**). Anilines are powerful starting materials as demonstrated by the formation of **34**–**38** which include C-2, C-3 and C-4 functionalized pyridines derivatives. Aminoacids 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 interesting biological profile. The *N*-arylation of this natural product has only been attempted using S_NAr chemistry under harsh conditions,[38] which demonstrates the complementarity that this approach might bring to mainstream cross-coupling technologies.

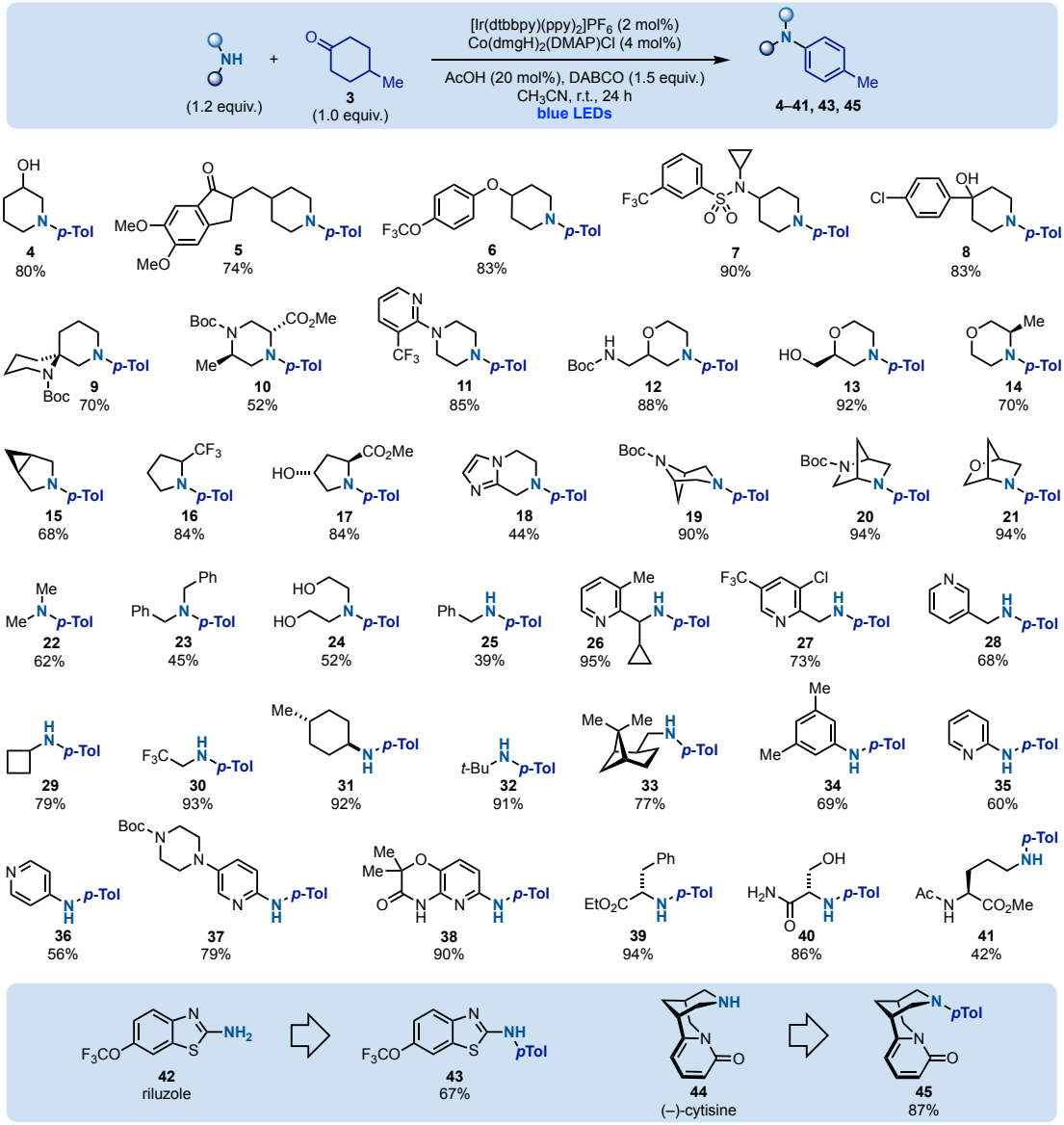

Figure 2. Scope of the amine partner. Boc = *tert*-butoxycarbonyl; *p*-Tol = *para*-toluyl.

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** (Figure 3A). In this case, we were interested in leveraging classic carbonyl chemistry to access α-, β- and γ-functionalized cyclohexanones, that would correspond to synthetically challenging *ortho*-, *meta*- and *para*-functionalised aryl halides/boronics required for cross-coupling. Simple enolate chemistry enabled α-substitution, which was used to access *ortho*-alkyl (**47** and **48**), fluoro (**49**) and aryl (**50**) anilines, while ring-opening of cyclohexene oxide delivered functionalised *ortho*-aminophenol and phenylenediamine (**51** and **52**). The preparation of *meta*-aminophenols (e.g. **53**) is synthetically challenging, but overcome in our approach by

harnessing enone conjugate addition (both ionic and radical) to install of β-oxygen, nitrogen, sulfur, boron and carbon-based substituents for the following efficient *meta*-amination (**53**–**59**). Conversely, the preparation of *para*-substituted anilines is trivial on 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 on system containing electron withdrawing groups (e.g. to give **63**). In our case, the text-book 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-napthylamine derivatives **65** and **66** respectively in high yields.

A final class of aryl surrogates that we considered were heterocycle-annulated cyclohexanones (Figure 3B). 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 aryl halide/boronic acid starting material synthesis and following cross-coupling.[39] 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**).

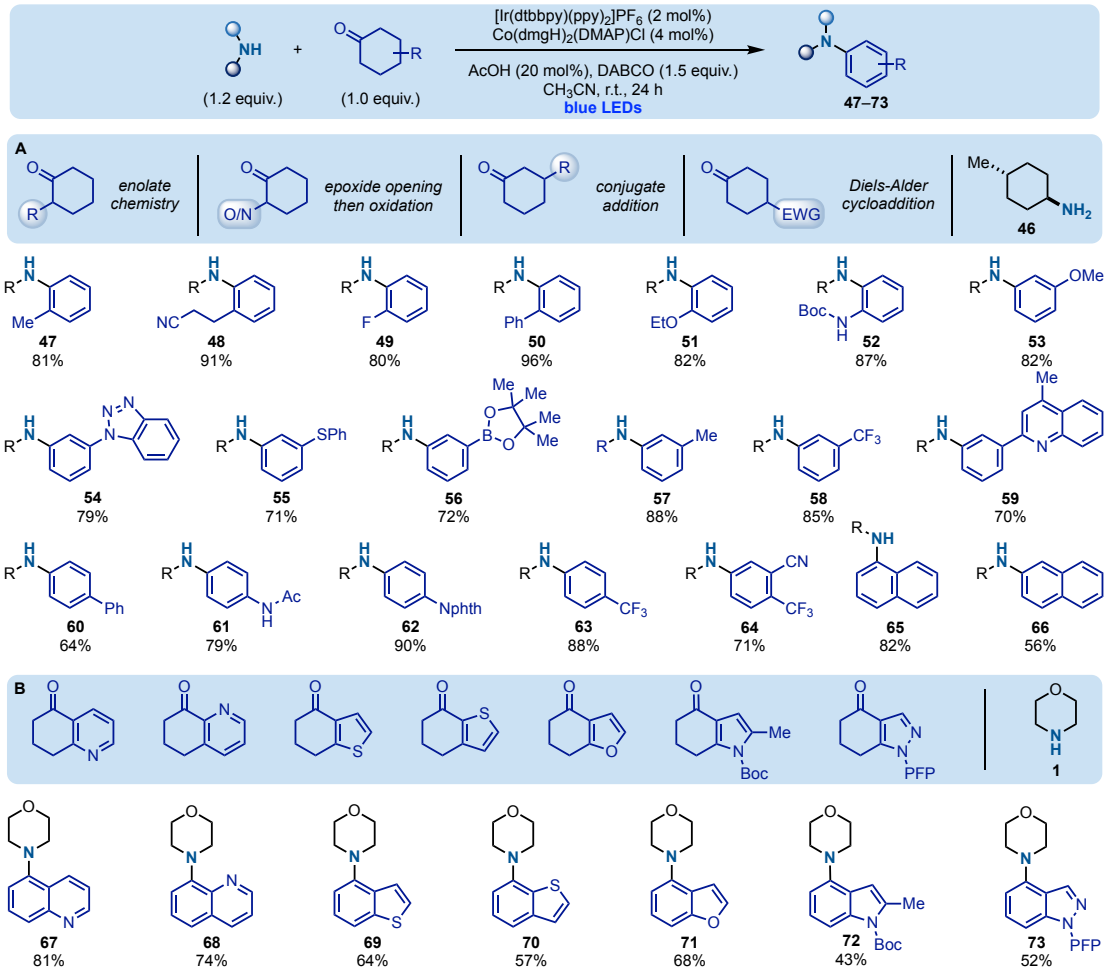

Figure 3. Scope of the cyclohexanone partner. Boc = *tert*-butoxycarbonyl; B(pin) = pinacolatoboron; phth = phthalimidyl; PFP = *p*-F-phenyl

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 Figure 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 (**76**) into anilines **75** and **77** in high yields. This protocol can also be used for the valorisation of feedstocks. For instance, cheap and readily available terpenes like dihydrocarvone (**78**, 1.7 USD/gram) and (–)-menthone (**80**, 1.3 USD/gram) were elaborated into the corresponding *ortho*,*meta*-disubstituted anilines **79** and **81**, which are high-value chemicals currently manufactured via aromatic nitration followed by reduction (**79**: 685 USD/gram and **81**: 851 USD/gram). Finally, we applied this reactivity to cycloheximide (**82**), 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 (Figure 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 E1cB 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 are discussed in the ESI).

Finally, Figures 4C–I depict seven representative examples of how this orthogonal retrosynthetic approach might be used to access and potentially simplify the preparation of medicines. (1) The local anesthetic lidocaine (**91**) is currently manufactured by unselective and low-yielding nitration of *meta*-xylene. As 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 by-passed 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* vs *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 case of challenging *meta*-amination is represented by naluzotan (**100**), a serotonergic drug prepared by nitration chemistry. For use in dehydrogenative amination chemistry, we relied on a β-selective oxidation[40] of *N*-Ac-cyclohexylamine that gave **98**. A following aromatization–amination, followed by acid work-up, with commercial **99** gave the corresponding monoarylated piperazine, that was 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 established 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 hydrolysis,[41] the desired drug **103**. (6) We used classical aldol annulation chemistry to

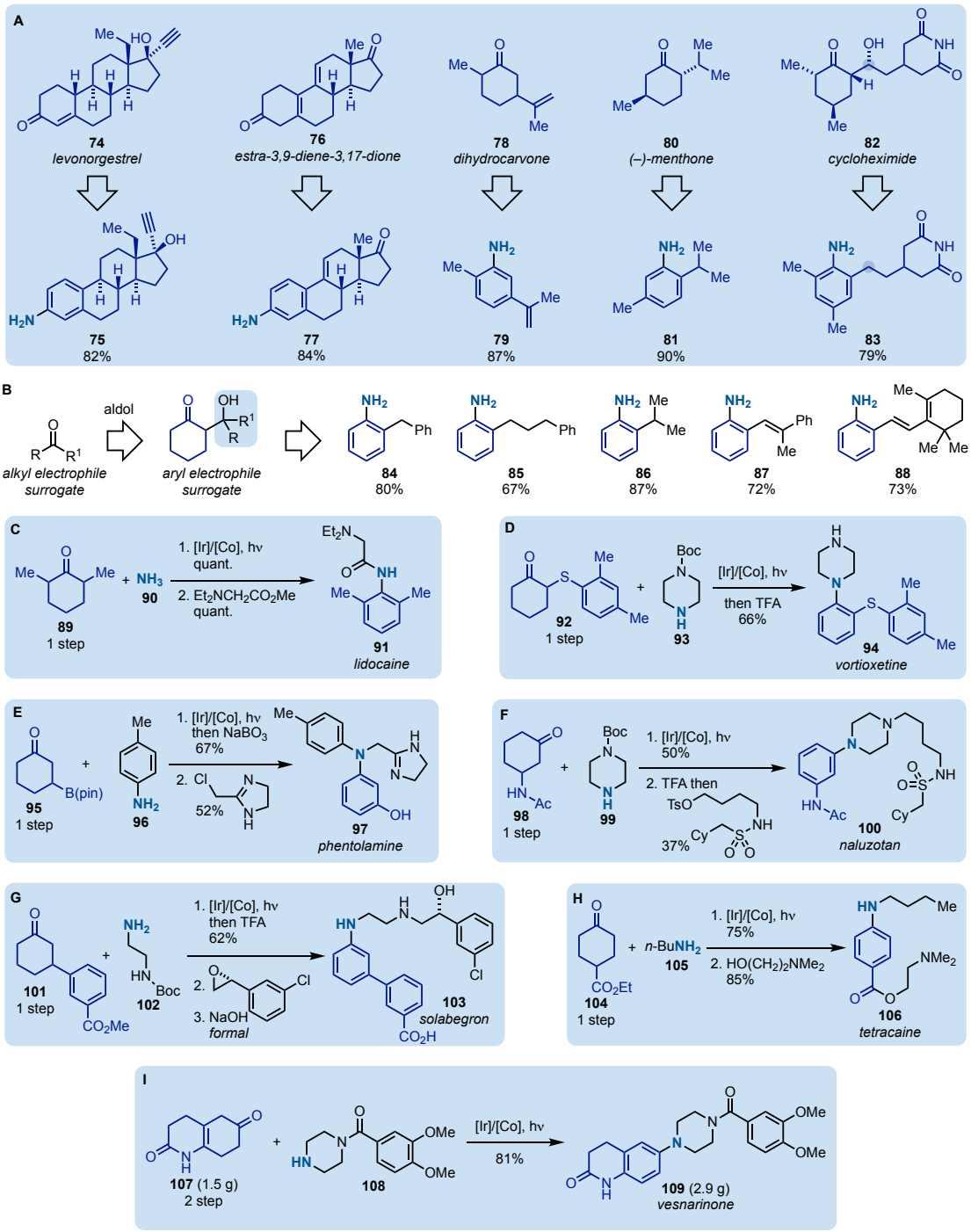

Figure 3. (A) Late-stage dehydrogenative amination using ammonia to give free anilines. **(B)** Aldol condensation on cyclohexanones can be used to target *ortho*-alkyl and alkenyl anilines. **(C–I)** Application of the process to the synthesis of seven blockbuster drugs. TFA = trifluoroacetic acid.

make **104** that was converted into the intravenous local anesthetic tetracaine (**106**) by aromatization–amination with *n*-BuNH$_2$ (**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 that requires multi-steps synthesis.[42] 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 was directly telescoped into the cross-coupling reaction (1.5 g) with commercial piperazine **108** to give **109** in 81% yield (2.9 g).

The mild conditions and broad functional group compatibility of this coupling protocol between amines and cyclohexanones opens up access to anilines that are difficult to prepare using either nitration chemistry or classical cross-coupling reactions. We believe this strategy introduces a novel retrosynthetic disconnection for the assembly of complex and densely functionalised nitrogenated aromatics of academic and industrial interest.

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References:

1 Blakemore, D. C. *et al.* Organic synthesis provides opportunities to transform drug discovery. *Nat. Chem.* **10**, 383-394 (2018).

2 Campos, K. R. *et al.* The importance of synthetic chemistry in the pharmaceutical industry. *Science* **363**, 244 (2019).

3 Hartwig, J. F. Carbon−Heteroatom Bond-Forming Reductive Eliminations of Amines, Ethers, and Sulfides. *Acc. Chem. Res.* **31**, 852-860 (1998).

4 Ruiz-Castillo, P. & Buchwald, S. L. Applications of Palladium-Catalyzed C−N Cross-Coupling Reactions. *Chem. Rev.* **116**, 12564-12649 (2016).

5 West, M. J., Fyfe, J. W. B., Vantourout, J. C. & Watson, A. J. B. Mechanistic Development and Recent Applications of the Chan–Lam Amination. *Chem. Rev.* **119**, 12491-12523 (2019).

6 Beletskaya, I. P. & V.Cheprakov, A. Copper in cross-coupling reactions: The post-Ullmann chemistry. *Coord. Chem. Rev.* **248**, 2337-2364 (2004).

7 MacMillan, D. W. C. The advent and development of organocatalysis. *Nature* **455**, 304-308 (2008).

8 Ricci, A. Amino Group Chemistry: From Synthesis to the Life Sciences. Wiley-VCH, Weinheim, Germany (2008).

9 Wittcoff, H. A., Rueben, B. G. & Plotkin, J. S. Industrial Organic Chemicals (Wiley- Interscience, New York, ed. 2, 2004).

10 Lawrence, S. A. Amines: Synthesis, Properties and Applications. Cambridge University Press (2004).

11 Crawley, M. L. & Trost, B. M. Applications of Transition Metal Catalysis in Drug Discovery and Development: An Industrial Perspective (John Wiley & Sons, 2012).

12 Hartwig, J. F. Carbon–heteroatom bond formation catalyzed by organometallic complexes. *Nature* **455**, 314-322 (2008).

13 Olah, G. A. Friedel-Crafts and Related Reactions (Wiley, New York). (1963).

14 Mkhalid, I. A. I., Barnard, J. H., Marder, T. B., Murphy, J. M. & Hartwig, J. F. C-H Activation for the Construction of C-B Bonds. *Chem. Rev.* **110**, 890-931 (2010).

15 Romero, N. A., Margrey, K. A., Tay, N. E. & Nicewicz, D. A. Site-selective arene C-H amination via photoredox catalysis. *Science* **349**, 1326-1330 (2015).

16 Ruffoni, A. *et al.* Practical and Regioselective Amination of Arenes Using Alkylamines. *Nat. Chem.* **11**, 426 (2019).

17 Boursalian, G. B., Ham, W. S., Mazzotti, A. R. & Ritter, T. Charge-transfer-directed radical substitution

enables para-selective C–H functionalization. *Nat. Chem.* **8**, 810-815 (2016).

18 K. Johnsson, Allemann, R. K., Widmer, H. & Benner, S. A. Synthesis, structure and activity of artificial, rationally designed catalytic polypeptides. *Nature* **365**, 530-532 (1993).

19 Grondal, C., Jeanty, M. & Enders, D. Organocatalytic cascade reactions as a new tool in total synthesis. *Nat. Chem.* **2**, 167-178 (2010).

20 Silvi, M. & Melchiorre, P. Enhancing the potential of enantioselective organocatalysis with light. *Nature* **554**, 41-49 (2018).

21 Izawa, Y., Pun, D. & Stahl, S. S. Palladium-Catalyzed Aerobic Dehydrogenation of Substituted Cyclohexanones to Phenols. *Science* **333**, 209-2013 (2011).

22 Koizumi, Y. *et al.* Selective Synthesis of Primary Anilines from NH3 and Cyclohexanones

by Utilizing Preferential Adsorption of Styrene on the Pd Nanoparticle

Surface. *Angew. Chem. Int. Ed.* **58**, 10893-10897 (2019).

23 Hong, W. P., Iosub, A. V. & Stahl, S. S. Pd-Catalyzed Semmler−Wolff Reactions for the Conversion of Substituted Cyclohexenone Oximes to Primary Anilines. *J. Am. Chem. Soc.* **135**, 13664-13667 (2013).

24 Li, Y., Wang, D., Zhang, L. & Luo, S. Redox Property of Enamines. *J. Org. Chem.* **84**, 12071-12090 (2019).

25 Pirnot, M. T., Rankic, D. A., Martin, D. B. C. & MacMillan, D. W. C. Photoredox Activation for the Direct

b-Arylation of Ketones and Aldehydes. *Science* **339**, 1593-1596 (2013).

26 West, J. G., Huang, D. & Sorensen, E. J. Acceptorless dehydrogenation of small molecules through cooperative base metal catalysis. *Nature Communications* **6**, 10093, doi:10.1038/ncomms10093 (2015).

27 Sun, X., Chen, J. & Ritter, T. Catalytic dehydrogenative decarboxylefination of carboxylic acids. *Nature Chemistry* **10**, 1229-1233, doi:10.1038/s41557-018-0142-4 (2018).

28 Weiss, M. E., Kreis, L. M., Lauber, A. & Carreira, E. M. Cobalt-Catalyzed Coupling of Alkyl Iodides with Alkenes: Deprotonation of Hydridocobalt Enables Turnover. *Angew. Chem. Int. Ed.* **50**, 11125-11128 (2011).

29 Prier, C. K., Rankic, D. A. & MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **113**, 5322-5363 (2013).

30 Nicholas, A. M. d. P. & Arnold, D. R. Thermochemical parameters for organic radicals and radical ions. Part 1. The estimation of the pKa of radical cations based on thermochemical calculations. *Can. J. Chem.* **60**, 2165-2179 (1982).

31 Gridnev, A. A. & Ittel, S. D. Catalytic Chain Transfer in Free-Radical Polymerizations. *Chemical Reviews* **101**, 3611-3660, doi:10.1021/cr9901236 (2001).

32 Dempsey, J. L., Brunschwig, B. S., Winkler, J. R. & Gray, H. B. Hydrogen Evolution Catalyzed by Cobaloximes. *Accounts of Chemical Research* **42**, 1995-2004, doi:10.1021/ar900253e (2009).

33 Vitaku, E., Smith, D. T. & Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **57**, 10257-10274 (2014).

34 Santanilla, A. B. *et al.* Nanomole-scale high-throughput chemistry for the synthesis of complex molecules. *Science* **347**, 44-49 (2015).

35 Park, N. H., Vinogradova, E. V., Surry, D. S. & Buchwald, S. L. Design of New Ligands for the Palladium-Catalyzed Arylation of a-Branched Secondary Amines. *Angew. Chem. Int. Ed.* **54**, 8259-8262 (2015).

36 Morris, S. A., Wang, J. & Zheng, N. The Prowess of Photogenerated Amine Radical Cations in Cascade Reactions: From Carbocycles to Heterocycles. *Acc. Chem. Res.* **49**, 1957-1968 (2016).

37 Bruscoe, A. T. & Hartwig, J. F. Palladium-Catalyzed Arylation of Fluoroalkylamines. *J. Am. Chem. Soc.* **137**, 8460-8468 (2015).

38 Dobrikov, G. M. *et al.* Synthesis and anti-enterovirus activity of new analogues of MDL-860. *Bioorg. & Med. Chem. Lett.* **27**, 4540-4543 (2017).

39 Sulur, M. *et al.* Development of Scalable Manufacturing Routes to AZD1981. Application of the Semmler–Wolff Aromatisation for Synthesis of the Indole-4-amide Core. *Org. Process. Res. Dev.* **16**, 1746-1753 (2012).

40 Zhao, Y., Yim, W.-L., Tan, C. K. & Yeung, Y.-Y. An Unexpected Oxidation of Unactivated Methylene C–H Using DIB/TBHP Protocol. *Org. Lett.* **13**, 4308-4311 (2011).

41 Cooke, J., Glover, B. N., Lawrence, R. M., Sharp, M. J. & Tymoschenko, M. F. WO 02/066418 (Glaxo-SmithKline), US. (2002).

42 See, Y. Y., Dang, T. T., Chen, A. & Seayad, A. M. Concise Synthesis of Vesnarinone and Its Analogues by Using Pd-Catalyzed C–N Bond-Forming Reactions. *Eur. J. Org. Chem.*, 7405-7412 (2014).