How to cite: *Angew. Chem. Int. Ed.* **2023,** *62,* e202301656
doi.org/10.1002/anie.202301656

VIP **Photocatalysis** *Very Important Paper*

Dual Photochemical H-Atom Transfer and Cobalt Catalysis for the Desaturative Synthesis of Phenols from Cyclohexanones

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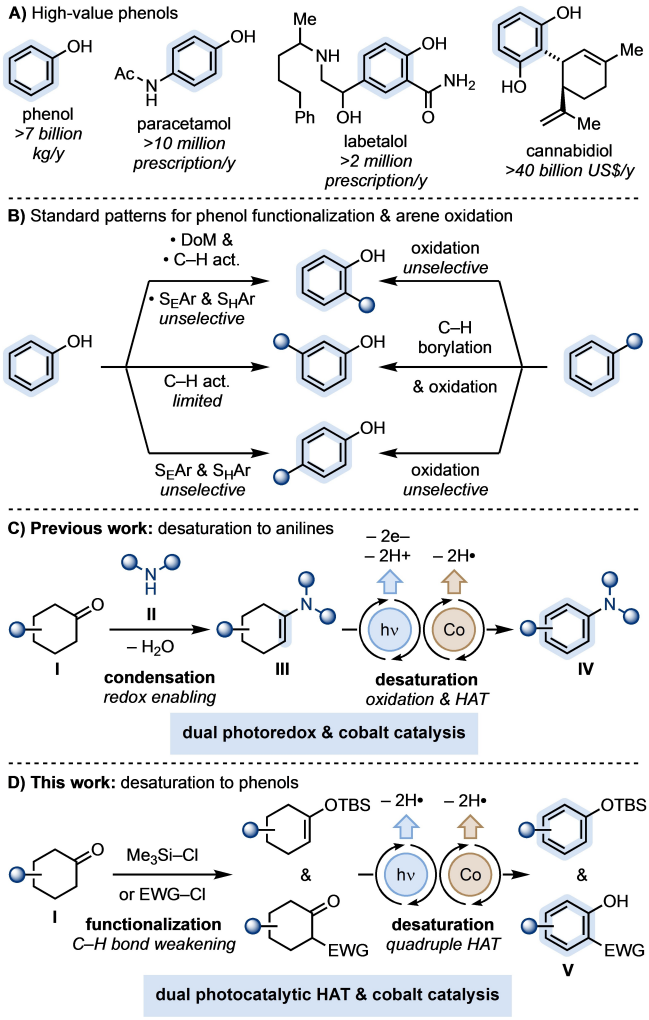
Abstract: Phenols are integral aromatic molecules widely encountered in the structure of natural products and routinely utilised for the synthesis of high-value materials. Accessing highly substituted derivatives can often be difficult, especially when their functionalization pattern does not match the intrinsic reactivity leveraged by electrophilic aromatic substitution (S_EAr) chemistry. Here, we provide an alternative and mechanistically distinct approach for phenol synthesis using saturated cyclohexanone precursors. This process operates at ambient temperature, under simple purple light irradiation, and features a dual catalytic manifold carrying four sequential H-atom transfer processes.

Phenols are a ubiquitous class of aromatic molecules widely distributed among the structure of natural products, bioactive materials (pharmaceuticals and agrochemicals), as well as food additives and organic dyes.[1] The value and impact that these molecules have on our society can be aptly realised considering that the bulk chemical industry produces >7 billion kg of phenol annually,[2] and over 60% of the small-molecule drugs approved by the FDA in 2020 contained a phenol functionality (Scheme 1A).[1a,3]

In the teaching of organic chemistry, phenol is the archetypal substrate used to explain the *ortho,para* selectivity that electron-rich substrates display in electrophilic aromatic substitution (S_EAr) chemistry.[4] Synthetic strategies based on this reactivity are heavily used but they often require harsh conditions, and generally delivers mixtures of *ortho* vs *para* vs *ortho,para* products which can be difficult to separate (Scheme 1B).[5] This over-reliance on S_EAr is reflected in the composition of aromatic cores in small-molecule drugs with *ortho*-, *para*- and *ortho,para*-substituted aromatics making up 53% of all benzenoid-containing drugs approved by the FDA in 2019.[6]

In a similar vein, the addition of electrophilic radicals (i.e. homolytic aromatic substitution, S_HAr) is very effective,



Scheme 1. (**A**) Examples of high-value phenols. (**B**) Standard reactivities for the functionalization of phenols (left) and the oxidation of aromatics (right). (**C**) Dual photoredox-cobalt catalysis for the desaturative synthesis of anilines from cyclohexanones and amines. (**D**) This work merges photocatalytic H-atom transfer catalysis with desaturative cobalt catalysis for the synthesis of phenols. Y = year.

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but also often results in mixtures of products.[7] Strong *ortho* selectivity can be achieved by manipulating the OH functionality, in order to render it a suitable directing group, for *ortho*-metalation with organolithium bases (D*o*M)[8] or C–H activation with transition metal catalysts.[9] Targeting *meta* is generally more difficult, albeit specific types of functionalization manifolds have been developed.[10]

Phenol synthesis by arene oxidation can be equally difficult, as it is still achieved via nitration (often unselective), followed by multi-step functionalization required for Sandmeyer chemistry.[11] Good selectivity for *ortho* or *meta* oxidation can be achieved by Ir-catalysed C–H borylation, followed by Brown oxidation, in the case of substrates equipped with directing groups (*ortho*) or featuring strong steric bias (*meta*).[12]

In recent years, significant interest has been devoted to the development of chemical strategies for phenol synthesis starting from non-aromatic precursors.[13] In particular, approaches based on the desaturation of cyclohexanone (and/or cyclohexenone) derivatives are of retrosynthetic interest because, before conversion into the benzenoid system, the saturated carbocycle can be pre-functionalised using regioselective carbonyl reactivity (e.g. enolate functionalization, 1,4-addition…) rather than aromatic chemistry. These strategies are generally performed under oxidative conditions in the presence of (mostly) [Pd^{II}][14] or [Cu^{II}][15] catalysts, at high temperatures and, as a result, can suffer from poor functional group compatibility.[16]

We have recently reported a mechanistically distinct desaturative process whereby anilines (**IV**) are assembled using cyclohexanone (**I**) and amine (**II**) building blocks (Scheme 1C).[17] This chemistry occurs under blue light irradiation and harnesses the synergistic interplay of a dual photoredox–cobalt catalytic manifold. Specifically, the condensation between **I** and **II** is used to access a redox-active enamine (**III**), from which the photoredox manifold removes two electrons and two protons, whilst the cobalt manifold completes the desaturation via formal removal of two H-atoms ($H^{\bullet}$) to give the aniline (**IV**).[18]

We recently questioned if the merger of photocatalysis and cobalt catalysis could also be exploited to access high-value phenols (**V**), from cyclohexanones (**I**), under mild reaction conditions (Scheme 1D). Herein, we discuss the successful implementation of this goal, that however required the use of photocatalytic H-atom transfer (HAT), rather than the previous photoredox manifold for substrate activation.[19] This distinct mechanistic blueprint means that aromatization is achieved via an unprecedented quadruple HAT sequence.

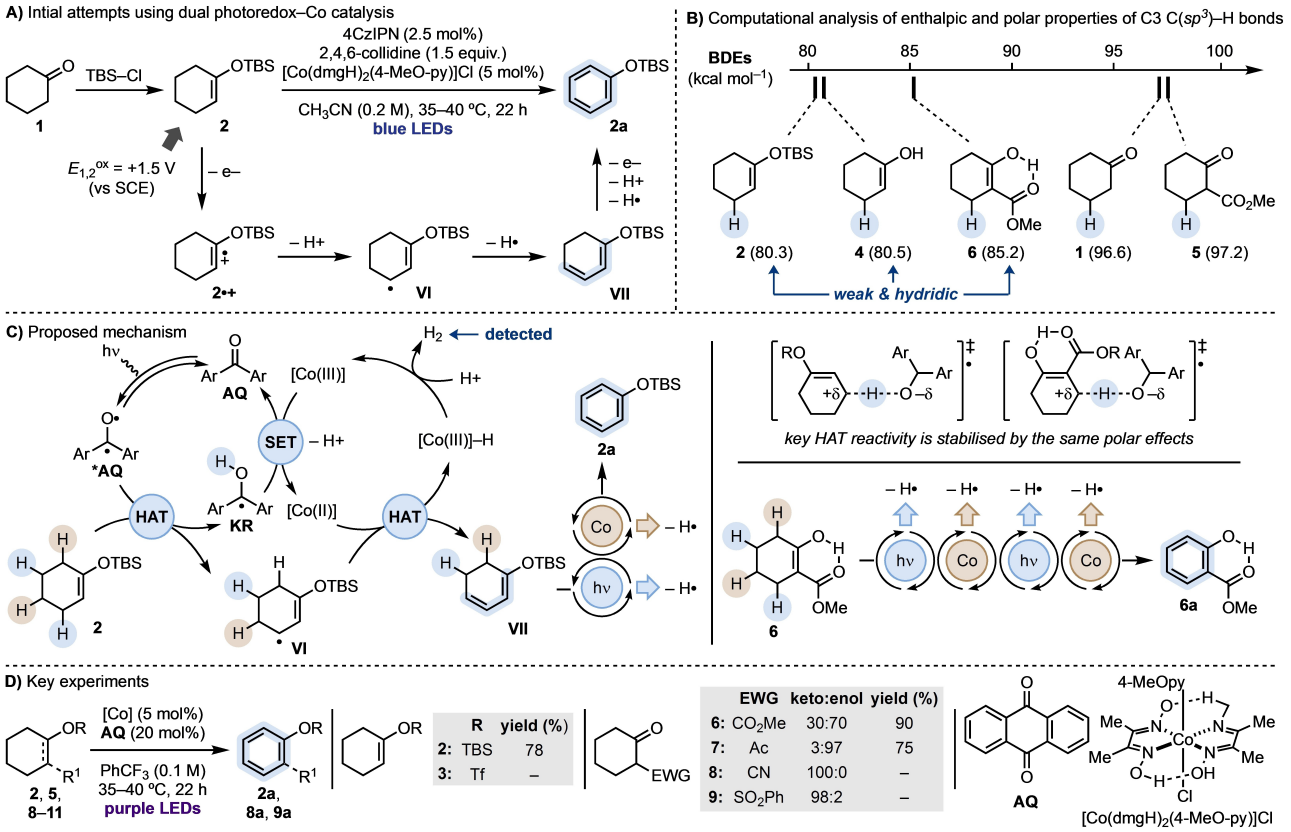
Our initial approach towards the development of a desaturative strategy for phenol synthesis was centred on the conversion of electron-poor cyclohexanone **1** into electron-rich silyl enol ether **2**.[20] However, whilst **2** is a competent nucleophile in ionic chemistry, its oxidation potential ($E_{1/2}^{ox} = +1.52$ V vs SCE)[21] makes it a challenging substrate for application in redox settings. Indeed, despite extensive optimization efforts, the conversion of **2** to **2a** was only realized in low yield (25 %) using a dual photoredox-cobalt catalytic approach. (Scheme 2A). We believe the high oxidation potential of **2** renders the integration of the dual catalysis required for two rounds of sequential oxidation (**2**→$\mathbf{2}^{\bullet+}$), deprotonation ($\mathbf{2}^{\bullet+}$→**VI**) and desaturation (**VI**→**VII**) difficult.

It is interesting to note that silyl enol ether formation does not only alter the electronic properties of the cyclohexanone (i.e. **1** is electron poor while **2** is electron-rich) but it also impacts the properties of its neighbouring C(sp^3)–H bonds. The most dramatic effect can be seen in terms of both BDE (bond dissociation enthalpy) and polarity at C3. In **1**, this position is characterised by rather strong C(sp^3)–H bonds, that become comparatively weaker in **2** given their allylic nature (Scheme 2B). Furthermore, the hyperconjugation effect from the neighbouring electron-rich π-system controls their polarity, making them of hydridic character. These two features make **2** a prime candidate for HAT chemistry with electrophilic abstractors, to directly access radical **VI**, without silyl enol ether oxidation and deprotonation.

Based on this analysis we envisaged a different type of dual catalysis to achieve aromatization. As depicted in Scheme 2C, we proposed that a diaryl ketone photocatalyst (e.g. anthraquinone, **AQ**) might, upon population of its triplet excited state (***AQ**), convert **2** into **VI** by enthalpy- and polarity-controlled HAT.[22] The resulting radical **VI** could then be desaturated, by a [Co^{II}] co-catalyst, to give the diene **VII**.[23] A second round of photoinduced HAT and Co-mediated desaturation would provide the desired protected phenol **2a**. At the end of every desaturation cycle, the putative [Co^{III}]–H ought to react with a proton source, thus evolving H_2 and providing an electron poor [Co^{III}] species.[24] At this point, since ketyl radicals (**KR**) are very electron rich species, the HAT and cobalt cycle should merge via SET, to readjust the catalysts oxidation states.[25] Overall, this strategy would provide a desaturation mode different to our previous aniline synthesis, whereby aromatization is achieved by sequential removal of four formal H-atoms, one from each sp^3 carbon of the saturated precursor.

While the Supporting Information details all optimization work performed, we identified **AQ** and [Co(dmgH)$_2$(4-MeO-py)]Cl as the optimum HAT photocatalyst and Co-catalyst, respectively (Scheme 2D).[26] With the aid of these systems, **2** underwent efficient desaturation to **2a**, upon simple purple LEDs irradiation (390 nm) in trifluorotoluene, at ambient temperature. Control experiments demonstrated the requirement for both catalysts, as well as continuous light irradiation. In addition to this, we also detected the formation of H_2, which is evidence in support of the proposed desaturation pathway.[26] We also considered other types of enols, like enol triflate **5**, but this could not be engaged in the reactivity.[27]

So far, desaturation is achieved by conversion of the cyclohexanone into its corresponding silyl enol ether. This enolization event is the key step that intrinsically provides the required enthalpic and polar properties for substrate activation. Whilst the ketone-enol tautomerization of **1**→**4** is not favourable enough to be exploited, we wondered if modification of the cyclohexanone scaffold could be used to facilitate this, and thus enable phenol synthesis without silyl



Scheme 2. (**A**) Initial attempts towards cyclohexanone desaturation using dual photoredox-cobalt catalysis were low yielding. (**B**) Computation analysis of key C(sp^3)–H bonds BDEs for HAT activation [method: SMD(DCE)-B3LYP-BJD3/cc-pVTZ(–f),cc-pVTZ on Si//SMD(DCE)-B3LYP-BJD3/6-31G(d,p)]. (**C**) Proposed dual photocatalytic HAT-cobalt catalysis for cyclohexanone desaturation and key polar effects in the HAT transition states. (**D**) Key experiments leading to reaction development (keto:enol ratios were determined by ^{1}H NMR spectroscopy analysis using $CDCl_3$ as the solvent).

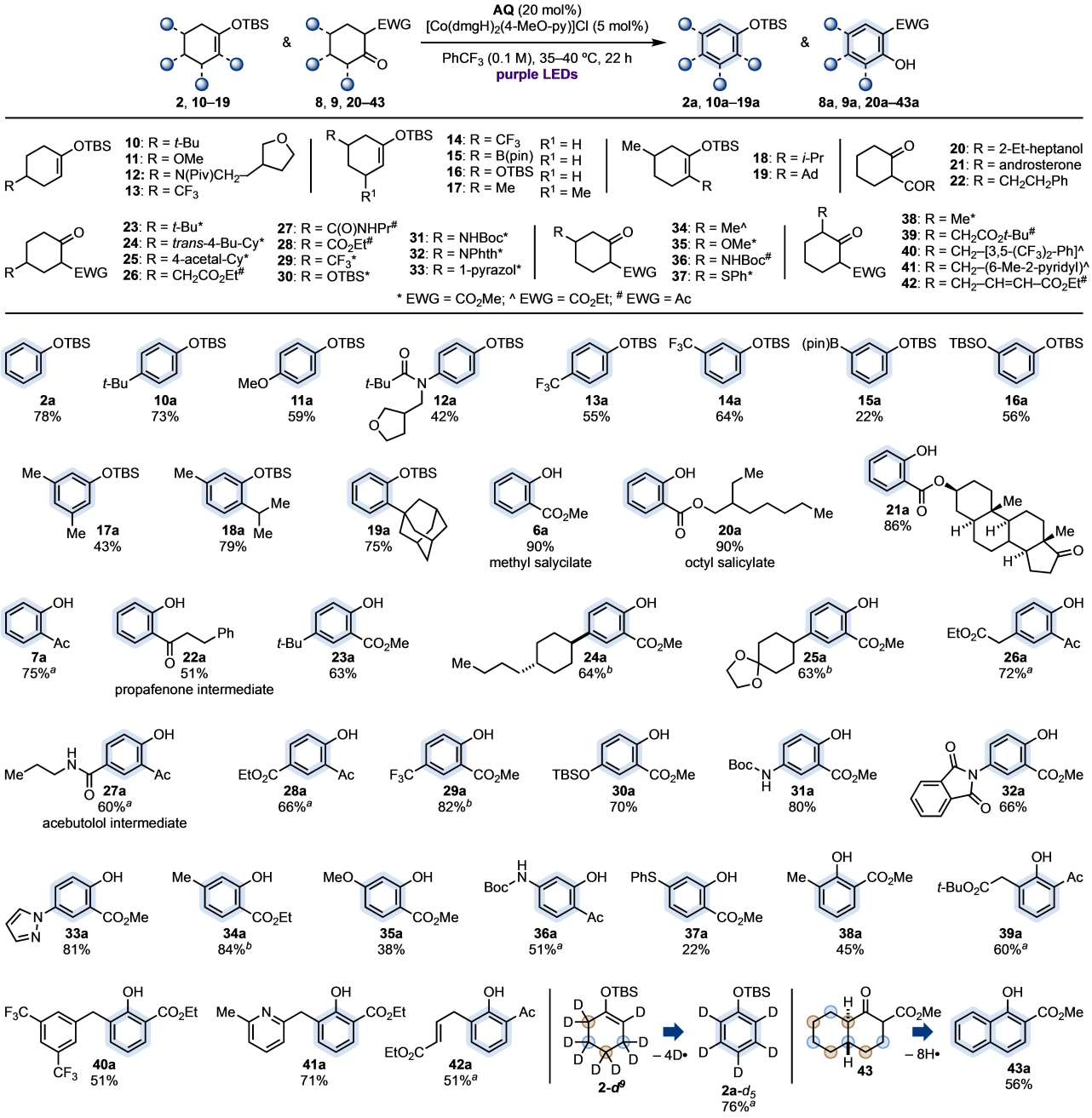
enol ether formation.[28] In particular, we speculated that the introduction of an ester group at C2 (**5**) might facilitate HAT at C3 via the formation of the 6-membered ring H-bonded complex **6**, which indeed features similar enthalpic and polar activation (Scheme 2B and 2C). Pleasingly, exposure of **6** to the optimised reaction conditions provided methyl salicylate **6a** in high yield. This approach effectively by-passes the *ortho* vs *para* selectivity issues often observed in Kolbe-Schmitt approaches that are generally employed to access related phenol derivatives.[29] The key importance of the ester group, in populating the reactive enol tautomer **8**, was demonstrated by evaluating other electron withdrawing groups in the C2 position (see **7**–**9** Scheme 2D). CN- and SO_2Ph-containing derivatives (**8** and **9**) fail to lead to enol formation (^{1}H NMR spectroscopy analysis) and thus did not furnish the desired product. Conversely, β-diketone **7** displayed keto-enol tautomerization and successfully gave **7a** in good yield.

With the optimised conditions in hand, we evaluated the scope of the desaturative methodology for the synthesis of poly-substituted phenols (Scheme 3). We started by looking at the reactivity of C4 substituted silyl enol ethers, that provided the corresponding *para*-functionalised phenols, **10a**–**13a**. It is interesting to note that despite their structural simplicity, these species are still challenging substrates as current methods for their preparation either lead to mixture of isomers or require multi-step sequences.[30] C3- and C3,C5-substituted cyclohexanones led to *meta* and *meta*,*meta*-functionalised phenols **14a**–**17a**. Cyclohexanone substitution at C2 and C5 provided access to *ortho*,*meta*-substituted phenols **18a** and **19a** in good yields. These are also challenging targets for aromatic reactivity because

(i) typically the functionalization of *para*-substituted toluenes takes place *ortho* to the Me group, which hampers oxidation next to sterically encumbered groups (e.g. *i*-Pr and adamantly) and

(ii) the previous synthesis of **18a** was based on Friedel–Crafts (S_EAr) alkylation of *meta*-Me-phenol S_EAr that results in *ortho*,*para*-polyfunctionalized mixtures.[31]

We then evaluated the reactivity of several β-ketoesters, which led to the preparation of the sunscreen octyl salicylate **20a** and **21a** featuring an androsterone unit. These are mechanistically interesting entries, as **20** and **21** contain multiple positions that are enthalpically and polarity activated for HAT chemistry (e.g. tertiary and α-O-secondary), none of which interfere with the desaturative platform.[32] Other electron withdrawing groups at the C2 position, which can enable effective keto-enol tautomerism, were evaluated. We succeeded in using ketone function-



Scheme 3. Scope of the desaturative synthesis of phenols. [a] Deviations from the standard reaction conditions = **AQ** (40 mol%), [Co(dmg)$_2$(4MeO-py)]Cl (10 mol%), DCE (0.025 M); b These reactions were run with AcOH (1.0 equiv) as the additive.

alities that enabled the preparation of **22a** which is the phenol core of the anti-arrhythmic medication propafenone.[33] We then used the methodology to access *ortho*,*para* disubstituted phenols featuring alkyl (**23a**–**26a**) (**23a** is a key fragment in the Vertex synthesis of Deutivacaftor),[34] amide (**27a**, found in the structure of the β-blocker acebutolol),[35] ester (**28a**) and CF_3 (**29a**) functionalities. Aromatic scaffolds containing multiple heteroatoms are still difficult to prepare due to the lack of reagents for direct S_EAr chemistry. Pleasingly, our strategy enabled access to phenols containing O- (**30a**) and N-based (**31a**–**33a**) functionalities at the *para* position in high to moderate yields. The high yielding formation of **31a**–**33a** provides an alternative route to aromatic scaffolds, often encountered in the patented preparation of bioactive molecules,[36] which require either phenol nitration followed by reduction and N-functionalization or halogenation for Buchwald-Hartwig cross-coupling.[37]

Disubstituted phenols with the C2,C5 substitution pattern were targeted next and, once again, we were able to extend this reactivity to alkyl (**34a**) as well as O- (**35a**), and N- (**36a**) and S-based (**37a**) substituents in good to moderate yields.[38]

To further explore the types of functionalisation patterns amenable to this strategy, we looked at using C6 functionalized β-ketoesters in order to target *bis-ortho*-substituted phenols **38a**–**42a**. These derivatives are often problematic in terms of selectivity as the *ortho*-alkyl or the ester substituents are generally introduced by S_HAr, which provides mixtures of *ortho* vs *para* functionalization.[39] In the case of our desaturative approach, we were able to selectively introduce *bis*-ortho functionality via double enolisation and electrophilic trapping followed by aromatization.

Interestingly, the fully deuterated silyl enol ether **2**-d_8 was also amenable to this desaturation reactivity, thus leading to penta-deuterated phenol **2a**-d_5 which demonstrates the sequential removal of 4D$^\bullet$. So far, the strategy presented here has focused on the preparation of polysubstituted phenols. Pleasingly, we succeeded in engaging *trans*-decalinone **43** to obtain 1-napthol **43a** in moderate yield. We believe this example demonstrates a rare example of octuple HAT activation from sequential HAT and cobalt catalysis.

In conclusion, we have demonstrated a novel approach for the preparation of substituted phenols from easily accessible saturated cyclohexanone derivatives. The scope of the reaction has been exemplified by incorporation of a diverse range of functionality and substitution patterns. This strategy exploits the synergistic interplay of photocatalytic HAT and cobalt catalysis, that alternate each other, in sequentially removing four H-atoms from the saturated precursors. Since cyclohexanones can be conveniently prepared and functionalised by mainstream carbonyl chemistry, we hope that this strategy might become a complementary tool for the more efficient preparation of high-value materials.

Acknowledgements

D.L. thanks The Leverhulme Trust for funding (Philip Leverhulme Prize). H.P.C. thanks AstraZeneca for a PhD CASE Award. Z. Z. thanks the Marie Curie Actions for a Fellowship (840318). The authors thank the assistance given by the Research IT and the use of the Computational Shared facility at the University of Manchester. Open Access funding enabled and organized by Projekt DEAL.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Cobalt Catalysis · Desaturation · H-Atom Transfer · Phenols

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Manuscript received: February 2, 2023
Accepted manuscript online: April 4, 2023
Version of record online: May 9, 2023