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Introduction

Alkenes, a fundamental cornerstone of the organic synthetic toolbox, are present in a broad range of important biologically active compounds and extensively used as the most versatile intermediates and feedstocks in industries and fine chemicals.¹ Compared with traditional synthetic methods, which relied on pre-functionalized starting materials, the development of highly selective dehydrogenation as in the desaturase enzyme system² has been attracting considerable attention. In general, highly reactive radical species are the key intermediates for intra- or intermolecular selective HAT efficiently.^{3,4} In 2012, Baran *et al.* developed a TEMPO-mediated remote dehydrogenation with aryltriazenes as aryl radical precursors.^{3b} Recently, Gevorgyan *et al.* have developed elegant strategies which employed reactive C-radical species produced from aryl or alkyl iodides to mediate the remote dehydrogenation by palladium photocatalysis.^{3c-e} The same strategy has also been demonstrated efficiently with N-radical species by the Studer^{3f} and

Cobalt-catalyzed chemoselective dehydrogenation through radical translocation under visible light†

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The transformations that allow the direct removal of hydrogen from their corresponding saturated counterparts by the dehydrogenative strategy are a dream reaction that has remained largely underexplored. In this report, a straightforward and robust cobaloxime-catalyzed photochemical dehydrogenation strategy *via* intramolecular HAT is described for the first time. The reaction proceeds through an intramolecular radical translocation followed by the cobalt assisted dehydrogenation without needing any other external photosensitizers, noble-metals or oxidants. With this approach, a series of valuable unsaturated compounds such as α,β -unsaturated amides, enamides and allylic and homoallylic sulfonamides were obtained in moderate to excellent yields with good chemo- and regioselectivities, and the synthetic versatility was demonstrated by a range of transformations. And mechanistic studies of the method are discussed.

Nagib^{3g} groups (Scheme 1a). In addition, Huang,^{4a} Sorensen^{4b} and Morandi^{4c} *et al.* reported dehydrogenation of aliphatics by intermolecular HAT strategies. However, polar effects usually control the regioselectivity of the HAT process from hydridic or neutral sites rather than acidic sites, and thus more challenging and difficult amide α,β -dehydrogenation is still underdeveloped. Amide α,β -dehydrogenation is more challenging and difficult. In addition, a series of unexpected byproducts tended to form due to low regioselectivity in the dehydrogenation

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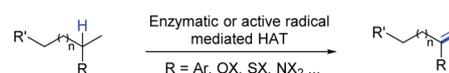
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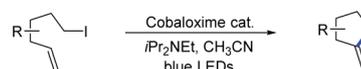
† Electronic supplementary information (ESI) available: CCDC 2117638, 2142047. For ESI and crystallographic data in CIF or other electronic format see <https://doi.org/10.1039/d2sc02291e>

a) Neutral or hydridic H atom abstraction (Baran, Gevorgyan and Nagib *et al.*)

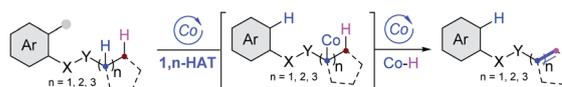


Undeveloped: activation of acidic C-H sites
avoiding competitive radical cyclization and double bond isomerization
really general dehydrogenation with a broad of substrate scope

b) Coupling of alkyl iodides with alkenes (Carreira *et al.*)



c) Regurable, remote dehydrogenation with aryl iodides (this work)



- First site-selective HAT and secondary cobalt-mediated β -H elimination
- Photocatalyst free • Mild conditions • Broad substrate scope
- Noble-metal free • High E-selective • Excellent functional group compatibility

Scheme 1 Dehydrogenation strategies for alkene synthesis.



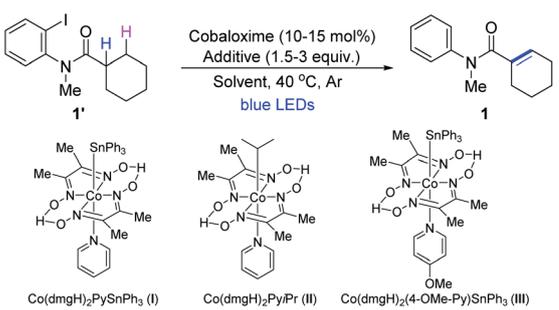
process, which limited further explorations and applications along this line. As a consequence, developing a cost-effective methodology for more broadly applicable and general dehydrogenation with high regioselectivity remains an unsolved challenge in modern synthetic chemistry.

The application of earth-abundant transition metal cobalt complexes for both efficient and eco-friendly organic synthesis has been actively explored in the past several years.⁵ Cobaloxime as a mimic of vitamin B₁₂, was developed as one of the powerful catalysts to carry out water splitting and chemical dehydrogenation that occur efficiently under mild conditions.⁶ In 2011, Carreira *et al.* reported cobaloxime-catalyzed intramolecular Heck reactions, and amine base conditions were demonstrated to convert the hydridocobaloxime to cobalt(i) species (Scheme 1b).⁷ Recently, Wu *et al.* reported the oxidation of *H*-phosphine oxide by excited cobaloxime to generate the phosphinoyl radical for subsequent addition to terminal alkenes or alkynes without using a photocatalyst.⁸ Subsequently, West *et al.* reported a vitamin B₁₂-catalyzed alkyl halide alkenylation where the Co(i) intermediate was used to access the alkyl-Co(III) species by S_N2 displacement.⁹ And Leonori *et al.* reported E2-type eliminations on alkyl halides merging halogen-atom transfer (XAT) and cobalt catalysis to obtain high olefin positional selectivity.¹⁰ In this context, taking advantage of the ability of cobaloxime catalysts to mediate transformations that allow the direct generation of unsaturated alkenes from their corresponding saturated counterparts by the dehydrogenation strategy is very attractive. Despite many reports involving alkylcobalt intermediates generated from the alkylation of cobalt catalysts with alkyl electrophiles, the application of aryl halides is still limited.¹¹ On the basis of our previous exploration of alkene dehydrogenative silylation,¹² we sought to adapt the photochemistry of cobaloxime¹³ into a synthetic method to achieve remote site-selective dehydrogenation (Scheme 1c). In these transformations, a variety of target compounds including α,β -unsaturated amides, enamides, allylic- or homoallylic amine derivatives, *etc.* could be smoothly afforded *via* intramolecular 1,*n*-HAT (*n* = 5–7) processes with excellent olefin positional selectivities, wide substrate scope, and without any external photosensitizers under extremely mild reaction conditions.

Results and discussion

To explore the feasibility of cobaloxime catalyzed dehydrogenation reactions, we started to apply the 1,5-HAT process¹⁴ to synthesize α,β -unsaturated amides using *N*-(2-iodophenyl)-*N*-methylcyclohexanecarboxamide as a model substrate. To our delight, when the substrate was treated with a catalytic amount of the cobaloxime catalyst (I) (10 mol%), 2.0 equivalent of NEt₃, at 40 °C for 24 h under irradiation with blue LEDs, the expected dehydrogenation product **1** was smoothly obtained in a yield of 68% (Table 1, entry 1). Further variations on the ligands of cobaloxime complexes showed that different cobaloximes with triphenyltins were all suitable for catalyzing the chemical transformations. However, only a trace of the target product **1** was obtained when Co(dmgh)₂PyiPr(II) was used as the catalyst (Table 1, entry 2).¹⁵ Among the cobaloximes investigated,

Table 1 Optimization of the reaction conditions^a



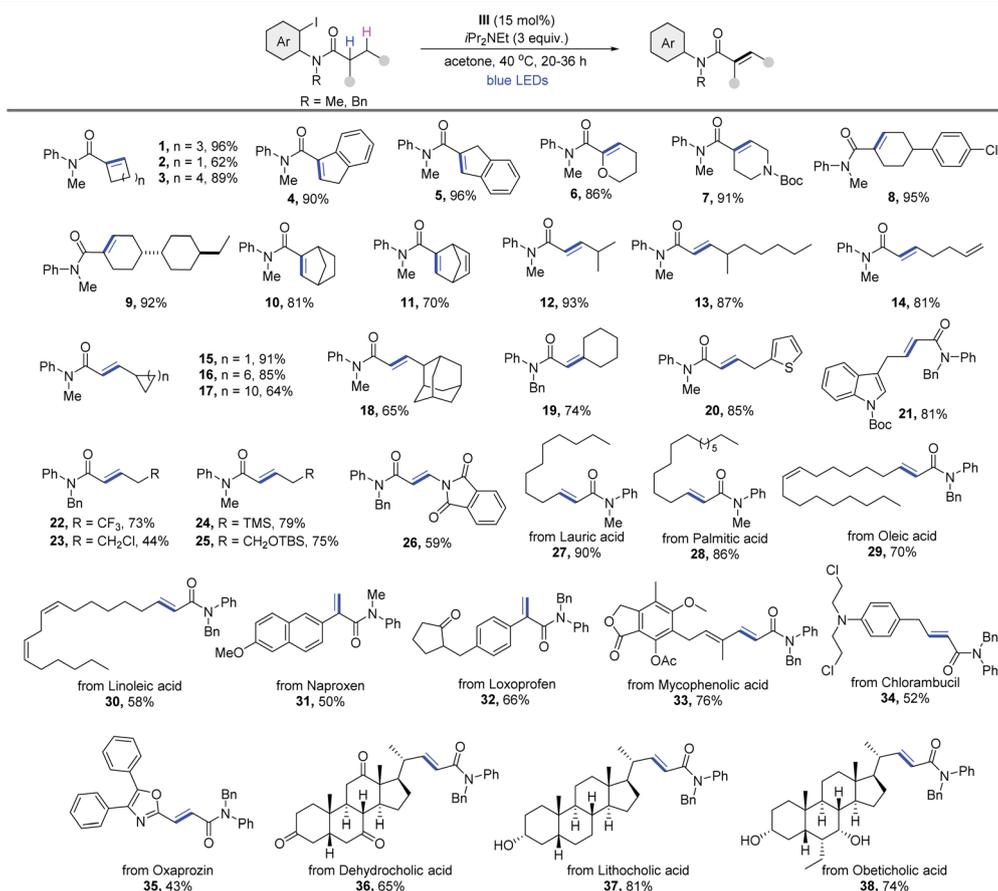
Entry	Cobaloxime (mol%)	Additive (equiv.)	Solvent	Time (h)	Yield (%) ^b
1	I (10)	NEt ₃ (2.0)	CH ₃ CN	24	68
2	II (10)	NEt ₃ (2.0)	CH ₃ CN	36	Trace
3	III (10)	NEt ₃ (2.0)	CH ₃ CN	24	72
4	III (15)	NEt ₃ (2.0)	CH ₃ CN	24	79
5	III (15)	<i>i</i> Pr ₂ NEt (2.0)	CH ₃ CN	24	83
6	III (15)	DABCO (2.0)	CH ₃ CN	24	31
7	III (15)	<i>i</i> Pr ₂ NEt (3.0)	CH ₃ CN	24	90
8 ^c	III (15)	Na ₂ CO ₃ (2.0)	CH ₃ CN	36	19
9	III (15)	Na ₂ CO ₃ (2.0) Zn (1.5)	CH ₃ CN	24	58
10	III (15)	<i>i</i> Pr ₂ NEt (3.0)	Acetone	20	96
11 ^d	III (15)	<i>i</i> Pr ₂ NEt (3.0)	Acetone	20	65

^a Unless otherwise noted, reaction conditions are as follows: on 0.1 mmol scale, cobalt catalyst (0.01–0.015 mmol), additive (0.15–0.3 mmol), solvent (2 mL), blue LEDs (λ = 450–460 nm), 40 °C and under an Ar atmosphere. ^b Isolated yield. ^c 50 °C. ^d 25 °C. dmgh = dimethylglyoximate.

Co(dmgh)₂(4-OMe-Py)SnPh₃ displayed the best photocatalytic activity with the product in 79% yield (entries 3,4 and Table S1[†]). Next screening a series of bases showed that the amines were either able or unable to form α -aminoalkyl radicals such as *i*Pr₂NEt and DABCO could smoothly afford the product (entries 5–7 and Table S2[†]). Na₂CO₃ worked with a longer reaction time at 50 °C (entry 8 and Table S2[†]). And the product **1** was also afforded with the combination of Na₂CO₃ and the reductant Zn at 40 °C (entry 9).^{11,16} A survey of solvents revealed that acetone was the optimal reaction medium (entry 10). Obviously, the dehydrogenation reaction proceeded slowly at 25 °C (entry 11). Lastly, no product was detected in the absence of cobaloxime (III), or *i*Pr₂NEt, or light by the control experiments, demonstrating the need for all these components (Table S4[†]).

With the reaction conditions optimized, the generality of this cobaloxime catalyzed dehydrogenation method was then evaluated. As outlined in Table 2, a wide range of 2-iodoaniline derived amides were compatible with this protocol. Notably, substrates derived from cycloalkyl carboxylic acids could be dehydrogenated smoothly *via* the 1,5-HAT pathway in excellent yield (1–5). Heterocycles (6 and 7), cyclohexyl derivatives (8 and 9) and bridged systems such as bicyclo[2.2.1]heptane (10) and norbornene (11) formed the desired products efficiently. Moreover, the reaction was also suitable for substrates with 2° α -C–H. A variety of α,β -unsaturated amides with excellent E-



Table 2 Amide α,β -dehydrogenation^a

^a Reaction conditions: on 0.1 mmol scale, [Co] (0.015 mmol), *i*Pr₂NEt (0.3 mmol), acetone (2 mL), blue LEDs ($\lambda = 450\text{--}460$ nm), 40 °C and under an Ar atmosphere. Isolated yield.

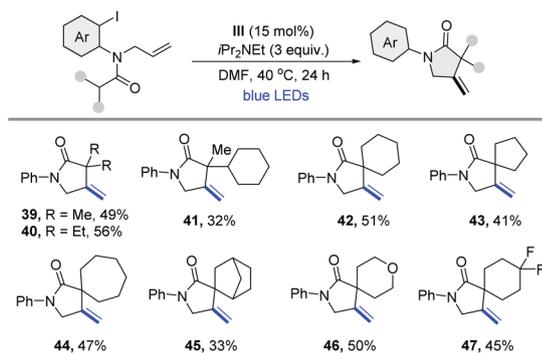
selectivity were produced from readily available primary carboxylic acid precursors, such as 4-methylvaleric acid (**12**) and 4-methylnonanoic acid (**13**). Product **14** derived from the acid that contains the terminal alkenyl group was obtained in 81% yield. Substituents with varying ring sizes at the β -position (**15–17**), large steric hindrance (**18**), cyclohexyl at the α -position (**19**) and aromatic heterocycles (**20** and **21**) were all compatible with the reaction. And the medically important trifluoromethyl group was also suitable (**22**). Other heteroatom substituents bearing Cl (**23**), TMS (**24**), acid-sensitive OTBS (**25**) and phthalimide groups (**26**) were obtained in moderate yields. The scope of the reaction was further evaluated with substrates that are derived from natural products and active pharmaceutical ingredients. The dehydrogenation of fatty amides was then investigated, and products derived from lauric (**27**), palmitic (**28**), oleic (**29**) and linoleic (**30**) acids were produced in good to excellent yields. The method could also be extended to late-stage modification of naproxen (**31**), loxoprofen (**32**), mycophenolic acid (**33**), chlorambucil (**34**) and oxaprozin (**35**). Finally, three bile amides were subjected to the process and the desaturated products were all obtained in good yields (**36–38**).

All cases were obtained without a regioisomer, making this reaction fully regioselective. Because of the reduced acidity of α -C–H in contrast to aldehyde and ketone, amide α,β -dehydrogenation¹⁷ is still less explored. Thus, this process is quite useful for the synthesis of α,β -unsaturated amides in terms of the atom economy and applicability.

The γ -lactam ring is part of the core structure of lots of natural and non-natural compounds covering a broad spectrum of biological activities.¹⁸ The efficient synthesis of γ -lactams is still highly desirable in contemporary organic chemistry. Under similar reaction conditions, a series of β -methylene- γ -(spiro) lactams were synthesized through a tandem intramolecular 1,5-HAT and 5-*exo-trig* cyclization process. As shown in Table 3, the starting materials possessing various alkyl or cycloalkyl groups at the α -position of the amide could deliver the corresponding products in modest yields (**39–47**).

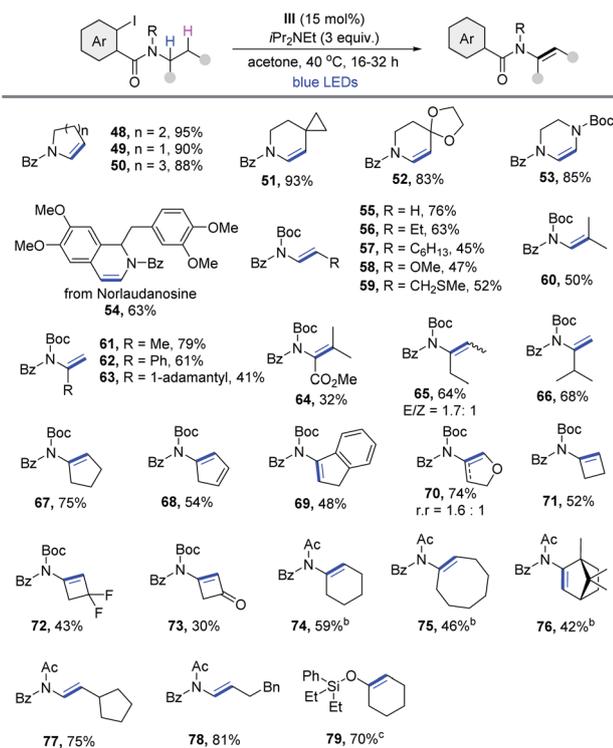
Enamides have proven to be extremely valuable products and chemical intermediates due to their higher stability and reaction tunability compared with enamine and are widely used in further synthetic transformations.¹⁹ However, direct dehydrogenation of carboxamide²⁰ to construct enamide is more



Table 3 Synthesis of methylene- γ -lactam derivatives^a

^a Reaction conditions: on 0.1 mmol scale, [Co] (0.015 mmol), *i*Pr₂NEt (0.3 mmol), DMF (2 mL), blue LEDs ($\lambda = 450\text{--}460$ nm), 40 °C and under an Ar atmosphere. Isolated yield.

difficult and more inert N-benzoyl amides usually give poor yields.^{20a,b} On the basis of the above optimized conditions, we next focused on the synthesis of enamide with diverse 2-iodobenzamides. As illustrated in Table 4, a wide range of aliphatic amine derivatives was examined, giving rise to the corresponding enamide products efficiently. First, transformation of

Table 4 Carboxamide α,β -dehydrogenation^a

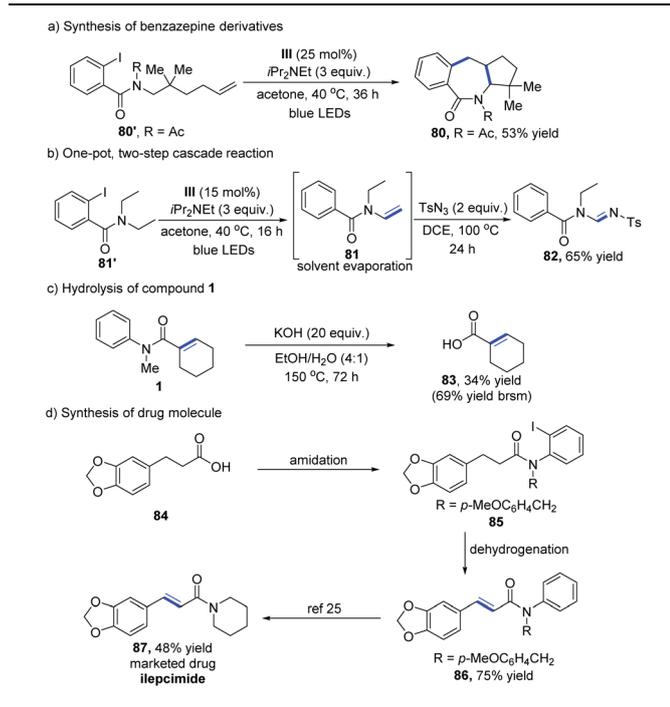
^a Reaction conditions: on 0.1 mmol scale, [Co] (0.015 mmol), *i*Pr₂NEt (0.3 mmol), acetone (2 mL), blue LEDs ($\lambda = 450\text{--}460$ nm), 40 °C and under an Ar atmosphere. Isolated yield. ^b [Co] (0.025 mmol). ^c Reaction was carried out at room temperature. Boc = *tert*-butyloxycarbonyl. Ac = acetyl.

endocyclic aliphatic amines produced the desired compounds in excellent yields (48–50). Spirocyclic (51 and 52) and piperazine-derived enamides (53) were readily synthesized in high yields. Remarkably, norlaudanosine, a dopamine metabolite, also reacted well (54). Encouraged by the study of secondary aliphatic amines, we started to investigate primary aliphatic amines, which were still not broadly explored in previous reports with low yields and limited substrate scope. To our delight, the formation of the desired enamide product 55 was observed when Boc was employed as the N-protecting group. It was found that a striking feature of this reaction was the exclusive formation of α,β -dehydrogenation products without any undesired isomer and isoindolin-1-one byproducts. Primary amines with a 2° α -C–H bond such as butylamine and octylamine, *etc.* were amenable, producing the desired enamides in reasonable yields (56–60). Likewise, dehydrogenation of primary amines with a 3° α -C–H bond containing different functionalities, including the methyl group (61), the phenyl group (62), the steric hindrance 1-adamantlyl group (63), and ester (64) proceeded well. 1-Ethylpropylamine reacted to provide the corresponding product in 64% yield, although as a mixture of stereoisomers (65). The dehydrogenative selectivity of 3-methyl-2-butanamine was conformed to Hofmann's elimination rule, leading to the expected product 66 in 68% yield with excellent regioselectivity (r.r > 20 : 1). Additionally, cyclopentylamine derivatives reacted smoothly to produce enamides in moderate yield (67–69). Tetrahydrofuran-3-amine could lead to the formation of a separable mixture of regioisomers, with 4,5-dihydrofuran being the major product (70). This result showed that the polar effect favored elimination of the hydridic H at the β -position rather than the neutral H. Moreover, cyclobutylamine derivatives were found to be competent substrates as well, producing the corresponding products in moderate yields (71–73). Next, we tested this method using an acetyl group as the N-protecting group. Some functional groups were found to be well tolerated under these conditions, including cycloalkyl (74–76), 2-cyclopentylethylamine (77) and 4-phenyl-1-butylamine (78). Lastly, this protocol also worked efficiently for α,β -dehydrogenation of cyclohexanol with a 2-iodophenylsilyl starting material (79).²¹

We next applied this methodology to the concise synthesis of a benzazepine derivative, which contains an important seven-membered nitrogenous heterocyclic skeleton for a wide range of biorelevant molecules. 2-Iodobenzamide substrates without a H atom at the β -position could be converted into the desired product 80 in moderate yield (Table 5a).²² The structure of 80 has been determined by X-ray crystal structure analysis. With the success of the dehydrogenative reaction for the direct construction of α,β -unsaturated systems, we continued to study the further transformations of the reaction products. Amide 81' could be readily converted to the enamide intermediate, which was engaged in 1,3-dipolar cycloaddition with sulfonylazide for the assembly of amidine (Table 5b).²³ To verify the practicability of this cobalt-catalyzed dehydrogenation process, a scale-up (4 mmol) experiment was performed, which provided α,β -unsaturated amide 1 in 83% yield (see the ESI†). On treatment of 1 under strong basic conditions, the carboxylic acid 83 was

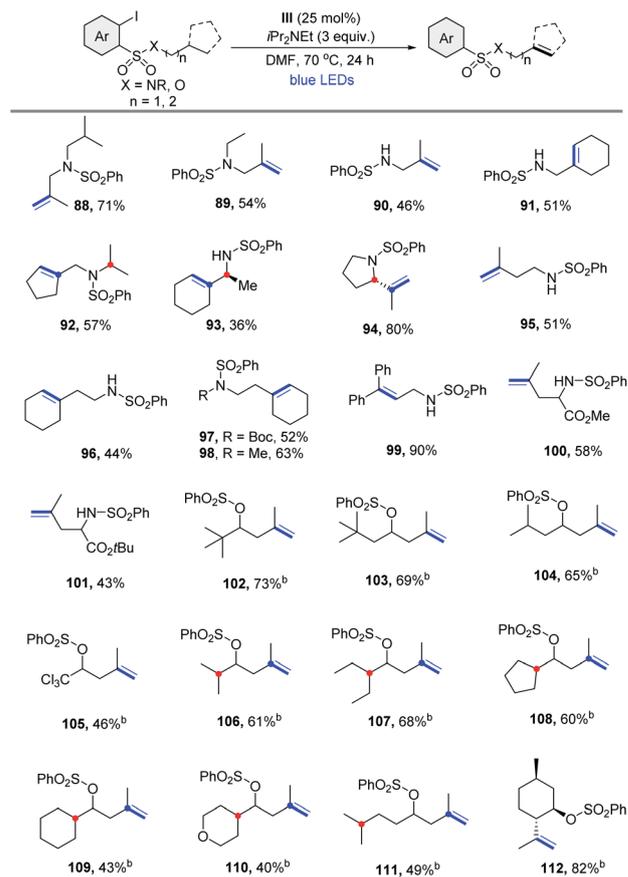


Table 5 Further applications of the method



afforded with a 69% yield based on recovered starting material (Table 5c). Furthermore, this method was utilized in the synthesis of the drug ilepcimide (ICM).²⁴ As shown in Table 5d, the dehydrogenation strategy enabled us to access the key compound **86** from commercially available carboxylic acid **84**, which was then subjected to transamidation²⁵ to provide ilepcimide **87**.

Having demonstrated the feasibility of α,β -dehydrogenation *via* the 1,5-HAT reaction, we next investigated the $\beta,\gamma/\gamma,\delta$ -dehydrogenation of distant C–H sites *via* the higher order 1,*n*-HAT ($n > 5$) pathway.²⁶ The 2-iodobenzenesulfonyl group was selected as an ideal supporting group. 1,6- or 1,7-HAT mode could be reached more easily because the longer C–S bond can readily accommodate quasi-linear geometry.²⁷ As shown in Table 6, 2-iodobenzenesulfonyl chloride derived sulfonamides are effective substrates for remote dehydrogenation. However, the yield of the desired β,γ -dehydrogenation product **88** was poor at 40 °C. A better result was obtained when the reaction was performed at 70 °C in *N,N*-dimethylformamide. It was found that both the secondary and primary amines bearing an isopropyl or cycloalkyl unit, which have a 3° β -H site, underwent efficient 1,6-HAT to produce allylic sulfonamides in moderate to good yields with high regiocontrols (**88–91**). Substrates that possessed 3° β -H, along with competitive 3° α -H sites, reacted selectively at the β -H sites, thus producing **92** and **93** with high regioselectivities. A heterocyclic (*S*)-2-isopropylpyrrolidine reacted smoothly to afford **94** in 80% yield. Encouraged by the results described above, we aimed at extending this protocol to the formation of homoallylic compounds *via* the γ,δ -dehydrogenation process involving 1,7-HAT. For substrates with a 3° γ -H site, a series of homoallylic sulfonamide derivatives were

Table 6 Scope of β,γ - and γ,δ -dehydrogenation^a

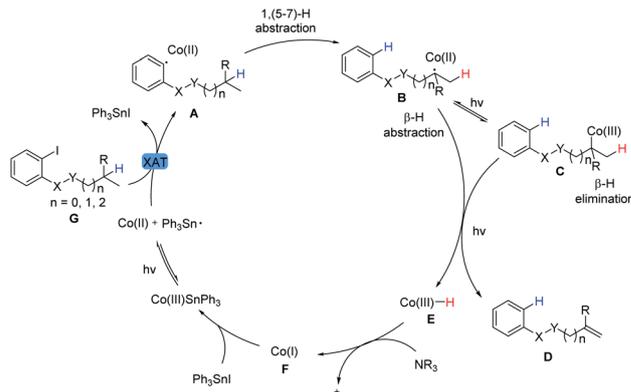
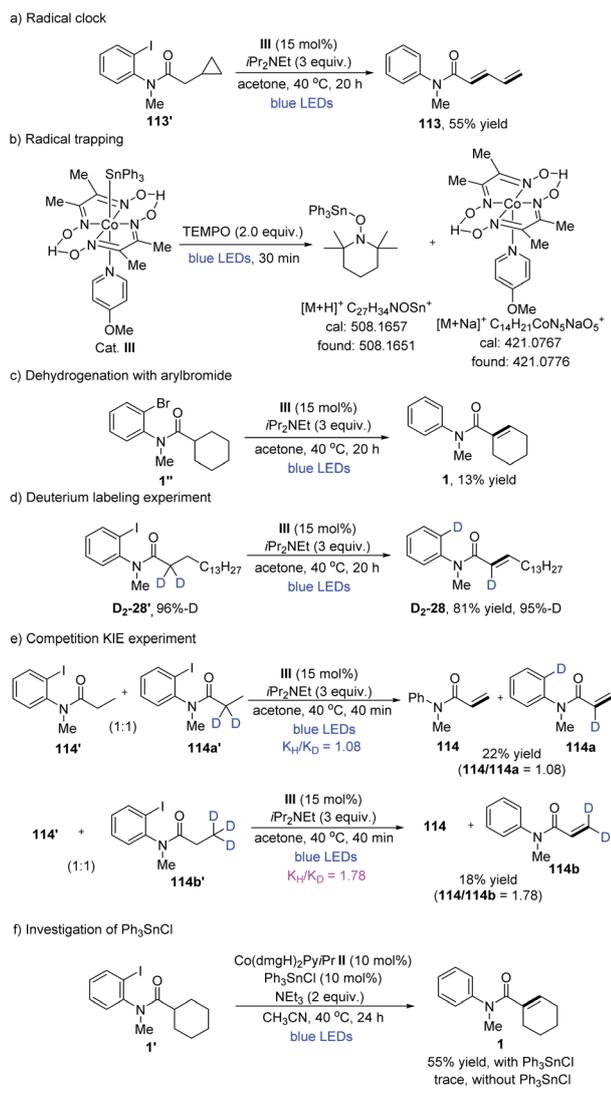
^a Reaction conditions: on 0.1 mmol scale, [Co] (0.025 mmol), *iPr*₂NET (0.3 mmol), DMF (2 mL), blue LEDs ($\lambda = 450\text{--}460$ nm), 70 °C and under an Ar atmosphere. Isolated yield. ^b Reaction was carried out at 40 °C. Boc = *tert*-butyloxycarbonyl.

prepared in moderate yields (**95–98**). The substrate bearing the benzylic C–H afforded the corresponding product in a relatively high yield (**99**). Reactions of leucine esters also proceeded well (**100**, **101**). As expected, remote dehydrogenation was also effective with secondary alcohols, producing homoallylic sulfonate derivatives at 40 °C in moderate yields (**102–105**). Obviously, compared with 1,6- or 1,8-HAT, the regioselectivity for 1,7-HAT was very high (**106–111**). Finally, a natural menthol derivative gave isopulegol sulfonate in 82% yield (**112**), convincingly demonstrating the potential of this method.

Next, some mechanistic experiments were performed. The radical nature of this transformation was preliminarily confirmed by a radical-clock experiment producing the ring-opened compound **113** in 55% yield (Table 7a). Moreover, a radical trapping experiment was performed under the irradiation of cobalt catalyst **III** with the addition of TEMPO. As a result, the related triphenyltin-TEMPO adduct and Co(II) species were confirmed through HRMS (Table 7b). These observations demonstrated the possibility of visible light promoting the homolysis of the Co(III)–Sn bond. The substitution of aryl iodide for aryl bromide derivatives led to a significant



Table 7 Mechanistic studies



Scheme 2 Proposed reaction mechanism.

alkyl cobaloximes with or without Ph_3SnCl . When only $\text{Co}(\text{dmgh})_2\text{PyPr}$ or $\text{Co}(\text{dmgh})_2\text{Py}(\text{pentyl})$ was used, it appeared that only a trace of **1** was produced. Obviously, with the addition of 10 mol% Ph_3SnCl , reactions proceed smoothly (Table 7f and S7†). The observation showed that the source of tin radicals was critical to the reaction for the C–I bond activation, since nucleophilic $\text{Co}(\text{i})$ species would react with Ph_3SnCl or Ph_3SnI to generate $\text{Co}(\text{dmgh})_2\text{PySnPh}_3$, which might facilitate iodine abstraction from aryl iodide to produce an aryl radical through halogen-atom transfer.

Therefore, on the basis of the experimental results and previous reports,³¹ a plausible mechanistic pathway was proposed and shown in Scheme 2. Visible light irradiation of $\text{Co}(\text{III})\text{SnPh}_3$ promotes the homolysis of the $\text{Co}(\text{III})\text{–Sn}$ bond to facilitate iodine abstraction from aryl iodide to produce the aryl radical **A** and $\text{Co}(\text{II})$ metalloradical. This highly activated intermediate **A** undergoes a fast intramolecular 1,*n*-hydrogen atom transfer process leading to the alkyl radical **B**. Then, $\text{Co}(\text{II})$ metalloradical species can reversibly accept the radical to afford the $\text{Co}(\text{III})$ -alkyl adduct **C** ($\text{BDE} < 30 \text{ kcal mol}^{-1}$). With irradiation, formal β -hydride elimination or direct β -hydrogen abstraction by $\text{Co}(\text{II})$ species will furnish the final dehydrogenative product **D** and $\text{Co}(\text{III})\text{–H}$ (cobalt hydride equivalent) **E**.³² The latter is deprotonated by an amine base to generate $\text{Co}(\text{i})$ species **F**.^{7a} Subsequently, nucleophilic $\text{Co}(\text{i})$ species **F** would react with Ph_3SnI to regenerate $\text{Co}(\text{III})\text{SnPh}_3$ along with the completion of the catalytic cycle.³³ Given the short lifetime of photoexcited $\text{Co}(\text{i})^*$ species as well as the control experiment performed in Table 7f, it was not a major pathway that $\text{Co}(\text{i})^*$ might undergo a single electron reduction of aryl halide **G**^{11,34,35} to generate aryl radical **A** in this system.

Conclusions

In summary, we have described a visible-light-induced chemo-selective dehydrogenation for the synthesis of a range of alkene derivatives under extremely mild reaction conditions by using inexpensive and easily accessible cobaloxime complexes. Importantly, this strategy used highly reactive aryl radical intermediates as controlling elements to mediate

drop in yield (Table 7c). In a deuterium labeling experiment, deuterated substrate **D**₂-28' was prepared and subjected to the standard reaction conditions for the formation of **D**₂-28 in 81% yield with one D atom shifted to the benzene ring (Table 7d). This experiment supported the assumption of an intramolecular 1,5-HAT process. In addition, UV-vis absorption spectra showed that $\text{Co}(\text{dmgh})_2(4\text{-OMe-Py})\text{SnPh}_3$ absorbs visible light with an absorption maximum at 439 nm. Further monitoring the reaction system of Co cat., **1** and $i\text{Pr}_2\text{NEt}$ revealed that an absorption band at 550–650 nm quickly appeared upon irradiation, which was consistent with the formation of Co^{I} species (ESI Fig. S6†).²⁸ Kinetic isotope effect (KIE) experiments were also performed. When the α -hydrogen atoms were deuterated, the intermolecular competitive reaction isotopic value ($K_{\text{H}}/K_{\text{D}}$) between **114'** and **114a'** was determined to be 1.08.²⁹ Thereafter, when the β -hydrogen atoms were deuterated, a higher kinetic isotopic effect value ($K_{\text{H}}/K_{\text{D}}$) between **114'** and **114b'** was determined to be 1.78 (Table 7e).³⁰ In addition, the control experiments were carried out to test



intramolecular 1,*n*-hydrogen atom transfer processes. In addition, Co-assisted efficient and selective dehydrogenation avoided competitive byproducts from radical cyclization and double bond isomerization, which showed unprecedented practicality and generality. The excellent photocatalytic activity of the cobaloxime system does not require any external photosensitizers and oxidants, which further demonstrates the potential of this method to access pharmaceutical compounds and perform late-stage functionalization.

Data availability

All experimental data associated with this work are available in the ESI†.

Author contributions

W.-L. Y. planned and conducted most of the experiments; Z.-G. R., K.-X. M., J.-J. Y. conducted the synthetic experiments and analyzed the experimental data. H.-Q. Y. conducted theoretical calculations; W. W. revised the manuscript; P.-F. X., H. Z. and W.-L. Y. directed the projects and wrote the manuscript. All authors contributed to the discussion.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

- 1 K. Weissermel and H.-J. Arpe, *Olefins, Industrial Organic Chemistry*, Wiley-VCH, Weinheim, 2008, p. 59.
- 2 (a) C. Kim, Y. Dong and L. Que, *J. Am. Chem. Soc.*, 1997, **119**, 3635–3636; (b) P. H. Buist, *Nat. Prod. Rep.*, 2004, **21**, 249–262; (c) M. A. Bigi, S. A. Reed and M. C. White, *Nat. Chem.*, 2011, **3**, 216–222.
- 3 (a) R. Breslow, B. B. Snider and R. J. Corcoran, *J. Am. Chem. Soc.*, 1974, **96**, 6792–6794; (b) A.-F. Voica, A. Mendoza, W. R. Gutekunst, J. O. Fraga and P. S. Baran, *Nat. Chem.*, 2012, **4**, 629–635; (c) M. Parasram, P. Chuentragool, D. Sarkar and V. Gevorgyan, *J. Am. Chem. Soc.*, 2016, **138**, 6340–6343; (d) M. Parasram, P. Chuentragool, Y. Wang, Y. Shi and V. Gevorgyan, *J. Am. Chem. Soc.*, 2017, **139**, 14857–14860; (e) P. Chuentragool, M. Parasram, Y. Shi and V. Gevorgyan, *J. Am. Chem. Soc.*, 2018, **140**, 2465–2468; (f) Y. Xia, K. Jana and A. Studer, *Chem.–Eur. J.*, 2021, **27**, 16621–16625; (g) L. M. Stateman, R. M. Dare, A. N. Paneque and D. A. Nagib, *Chem*, 2022, **8**, 210–224.
- 4 (a) M.-J. Zhou, L. Zhang, G. Liu, C. Xu and Z. Huang, *J. Am. Chem. Soc.*, 2021, **143**, 16470–16485; (b) J. G. West, D. Huang and E. J. Sorensen, *Nat. Commun.*, 2015, **6**, 10093–10099; (c) L. Huang, A. Bismuto, S. A. Rath, N. Trapp and B. Morandi, *Angew. Chem., Int. Ed.*, 2021, **60**, 7290–7296.
- 5 (a) W.-M. Cheng and R. Shang, *ACS Catal.*, 2020, **10**, 9170–9196; (b) K. Pak, S. Cheung, S. Sarkar and V. Gevorgyan, *Chem. Rev.*, 2022, **122**, 1543–1625.
- 6 (a) V. Artero, M. Chavarot-Kerlidou and M. Fontecave, *Angew. Chem., Int. Ed.*, 2011, **50**, 7238–7266; (b) J. L. Dempsey, B. S. Brunschwig, J. R. Winkler and H. B. Gray, *Acc. Chem. Res.*, 2009, **42**, 1995–2004; (c) L.-Z. Wu, B. Chen, Z.-J. Li and C.-H. Tung, *Acc. Chem. Res.*, 2014, **47**, 2177–2185; (d) B. Chen, L.-Z. Wu and C.-H. Tung, *Acc. Chem. Res.*, 2018, **51**, 2512–2523.
- 7 (a) M. E. Weiss, L. M. Kreis, A. Lauber and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2011, **50**, 11125–11128; (b) M. E. Weiss and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2011, **50**, 11501–11505; (c) L. M. Kreis, S. Krautwald, N. Pfeiffer, R. E. Martin and E. M. Carreira, *Org. Lett.*, 2013, **15**, 1634–1637; (d) M. Balkenhohl, S. Kölbl, T. Georgiev and E. M. Carreira, *JACS Au*, 2021, **1**, 919–924; (e) B. Morandi, B. Mariampillai and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2011, **50**, 1101–1104; (f) B. Gaspar and E. M. Carreira, *J. Am. Chem. Soc.*, 2009, **131**, 13214–13215.
- 8 (a) W.-Q. Liu, T. Lei, S. Zhou, X.-L. Yang, J. Li, B. Chen, J. Sivaguru, C.-H. Tung and L.-Z. Wu, *J. Am. Chem. Soc.*, 2019, **141**, 13941–13947; (b) T. Lei, G. Liang, Y. Y. Cheng, B. Chen, C.-H. Tung and L.-Z. Wu, *Org. Lett.*, 2020, **22**, 5385–5389; (c) Y.-W. Zheng, B. Chen, P. Ye, K. Feng, W. Wang, Q.-Y. Meng, L.-Z. Wu and C.-H. Tung, *J. Am. Chem. Soc.*, 2016, **138**, 10080–10083; (d) Q.-Y. Meng, J.-J. Zhong, Q. Liu, X.-W. Gao, H.-H. Zhang, T. Lei, Z.-J. Li, K. Feng, B. Chen, C.-H. Tung and L.-Z. Wu, *J. Am. Chem. Soc.*, 2013, **135**, 19052–19055; (e) G. Zhang, C. Liu, H. Yi, Q.-Y. Meng, C. Bian, H. Chen, J.-X. Jian, L.-Z. Wu and A. Lei, *J. Am. Chem. Soc.*, 2015, **137**, 9273–9280; (f) G. Zhang, X. Hu, C.-W. Chiang, H. Yi, P. Pei, A. K. Singh and A. Lei, *J. Am. Chem. Soc.*, 2016, **138**, 12037–12040; (g) G. Zhang, Y. Lin, X. Luo, X. Hu, C. Chen and A. Lei, *Nat. Commun.*, 2018, **9**, 1225–1231.
- 9 (a) R. Bam, A. S. Pollatos, A. J. Moser and J. G. West, *Chem. Sci.*, 2021, **12**, 1736–1744; (b) M. Giedyk, K. Goliszewska and D. Gryko, *Chem. Soc. Rev.*, 2015, **44**, 3391–3404; (c) S. Busato, O. Tinembart, Z.-D. Zhang and R. Scheffold, *Tetrahedron*, 1990, **46**, 3155–3166; (d) B. Giese, J. Hartung, J. He, O. Hüter and A. Koch, *Angew. Chem., Int. Ed.*, 1989, **28**, 325–327; (e) G. N. Schrauzer, L. P. Lee and J. W. Sibert, *J. Am. Chem. Soc.*, 1970, **92**, 2997–3005; (f) D. N. Ramakrishna, R. Symons and M. Symons, *J. Chem. Soc., Faraday Trans. 1*, 1984, **80**, 423–434.
- 10 (a) H. Zhao, A. J. McMillan, T. Constantin, R. C. Mykura, F. Juliá and D. Leonori, *J. Am. Chem. Soc.*, 2021, **143**, 14806–14813; (b) T. Constantin, M. Zanini, A. Regni, N. S. Sheikh, F. Juliá and D. Leonori, *Science*, 2020, **367**, 1021–1026; (c) F. Juliá, T. Constantin and D. Leonori, *Chem. Rev.*, 2022, **122**, 2292–2352.



- 11 (a) K. L. Brown and R. Legates, *J. Organomet. Chem.*, 1982, **233**, 259–265; (b) D. Lenoir, H. Dauner, I. Ugi, A. Gieren, R. Hübner and V. Lamm, *J. Organomet. Chem.*, 1980, **198**, C39–C42; (c) V. F. Patel and G. Pattenden, *J. Chem. Soc., Chem. Commun.*, 1987, 871–872.
- 12 W.-L. Yu, Y.-C. Luo, L. Yan, D. Liu, Z.-Y. Wang and P.-F. Xu, *Angew. Chem., Int. Ed.*, 2019, **58**, 10941–10945.
- 13 (a) G. N. Schrauzer and G. Kratel, *Chem. Ber.*, 1969, **102**, 2392–2407; (b) M. Tada and K. Kaneko, *J. Org. Chem.*, 1995, **60**, 6635–6636.
- 14 J. Robertson, J. Pillaia and R. K. Lusha, *Chem. Soc. Rev.*, 2001, **30**, 94–103.
- 15 Tin radicals might act as halogen-atom transfer (XAT) agents for activation of aryl C–I bonds (see Table 7f and S7†).
- 16 (a) B. Giese, P. Erdmann, T. Gobel and R. Springer, *Tetrahedron Lett.*, 1992, **33**, 4545–4548; (b) B. P. Branchaud and W. D. Detlefsen, *Tetrahedron Lett.*, 1991, **32**, 6273–6276; (c) W. Affo, H. Ohmiya, T. Fujioka, Y. Ikeda, T. Nakamura, H. Yorimitsu, K. Oshima, Y. Imamura, T. Mizuta and K. Miyoshi, *J. Am. Chem. Soc.*, 2006, **128**, 8068–8077.
- 17 (a) Y. Chen, A. Turlik and T. R. Newhouse, *J. Am. Chem. Soc.*, 2016, **138**, 1166–1169; (b) D. Huang, S. M. Szewczyk, P. Zhang and T. R. Newhouse, *J. Am. Chem. Soc.*, 2019, **141**, 5669–5674; (c) M. Chen and G. Dong, *J. Am. Chem. Soc.*, 2017, **139**, 7757–7760; (d) Z. Wang, Z. He, L. Zhang and Y. Huang, *J. Am. Chem. Soc.*, 2018, **140**, 735–740; (e) C. J. Teskey, P. Adler, C. R. Gonçalves and N. Maulide, *Angew. Chem., Int. Ed.*, 2019, **58**, 447–451; (f) S. Gnaim, J. C. Vantourout, F. Serpier, P.-G. Echeverria and P. S. Baran, *ACS Catal.*, 2021, **11**, 883–892; (g) Z. Wang, L. Hu, N. Chekshin, Z. Zhuang, S. Qian, J. X. Qiao and J.-Q. Yu, *Science*, 2021, **374**, 1281–1285.
- 18 J. Caruano, G. G. Muccioli and R. Robiette, *Org. Biomol. Chem.*, 2016, **14**, 10134–10156.
- 19 (a) K. Gopalaiah and H. B. Kagan, *Chem. Rev.*, 2011, **111**, 4599–4657; (b) F. Beltran and L. Miesch, *Synthesis*, 2020, **52**, 2497–2511.
- 20 (a) G. Li, P. A. Kates, A. K. Dilger, P. T. Cheng, W. R. Ewing and J. T. Groves, *ACS Catal.*, 2019, **9**, 9513–9517; (b) N. Holmberg-Douglas, Y. Choi, B. Aquila, H. Huynh and D. A. Nicewicz, *ACS Catal.*, 2021, **11**, 3153–3158; (c) T. Shono, Y. Matsumura, K. Tsubata, Y. Sugihara, S. Yamane, T. Kanazawa and T. Aoki, *J. Am. Chem. Soc.*, 1982, **104**, 6697–6703; (d) P. Spieß, M. Berger, D. Kaiser and N. Maulide, *J. Am. Chem. Soc.*, 2021, **143**, 10524–10529.
- 21 D. P. Curran, D. H. Kim, T. Liu and W. Shen, *J. Am. Chem. Soc.*, 1988, **110**, 5900–5902.
- 22 D. P. Curran, A. C. Abraham and H. Liu, *J. Org. Chem.*, 1991, **56**, 4335–4337.
- 23 X. Xu, X. Li, L. Ma, N. Ye and B. Wang, *J. Am. Chem. Soc.*, 2008, **130**, 14048–14049.
- 24 (a) S. Li, C. Wang, W. Li, K. Koike, T. Nikaido and M.-W. Wang, *J. Asian Nat. Prod. Res.*, 2007, **9**, 421–430; (b) Y. Zeng, B. Qin, Y.-W. Shi, Y.-S. Long, W.-Y. Deng, B.-M. Li, B. Tang, Q.-H. Zhao, M.-M. Gao, N. He and W.-P. Liao, *Epilepsy Res.*, 2021, **170**, 106533–106538.
- 25 Z. Wang, A. Matsumoto and K. Maruoka, *Chem. Sci.*, 2020, **11**, 12323–12328.
- 26 (a) K. A. Hollister, E. S. Conner, M. L. Mark, L. Spell, K. Deveaux, L. Maneval, M. W. Beal and J. R. Ragains, *Angew. Chem., Int. Ed.*, 2015, **54**, 7837–7841; (b) F. W. Friese, C. Mück-Lichtenfeld and A. Studer, *Nat. Commun.*, 2018, **9**, 2808–2816; (c) N. Radhoff and A. Studer, *Angew. Chem., Int. Ed.*, 2021, **60**, 3561–3565.
- 27 M. Nechab, S. Mondal and M. Bertrand, *Chem.–Eur. J.*, 2014, **20**, 16034–16059.
- 28 P. Du, K. Knowles and R. Eisenberg, *J. Am. Chem. Soc.*, 2008, **130**, 12576–12577.
- 29 The rate constant of 1,5-HAT, see: D. P. Curran and A. C. Abraham, *Tetrahedron*, 1993, **49**, 4821–4840.
- 30 (a) E. M. Simmons and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2012, **51**, 3066–3072; (b) K. C. Cartwright, E. Joseph, C. G. Comadoll and J. A. Tunge, *Chem.–Eur. J.*, 2020, **26**, 12454–12471.
- 31 (a) G. N. Schrauzer, J. W. Sibert and R. J. Windgassen, *J. Am. Chem. Soc.*, 1968, **90**, 6681–6688; (b) C. D. Garr and R. G. Finke, *J. Am. Chem. Soc.*, 1992, **114**, 10440–10445; (c) J. Halpern, *Acc. Chem. Res.*, 1982, **15**, 238–244; (d) X. Sun, J. Chen and T. Ritter, *Nat. Chem.*, 2018, **10**, 1229–1233; (e) H. Cao, H. Jiang, H. Feng, J. M. C. Kwan, X. Liu and J. Wu, *J. Am. Chem. Soc.*, 2018, **140**, 16360–16367.
- 32 The hypothesis for intermediate **E** is a Co(I) center with a protonated glyoxime ligand, serving as a cobalt hydride equivalent, see: (a) D. P. Estes, D. C. Grills and J. R. Norton, *J. Am. Chem. Soc.*, 2014, **136**, 17362–17365; (b) D. C. Lacy, G. M. Roberts and J. C. Peters, *J. Am. Chem. Soc.*, 2015, **137**, 4860–4864.
- 33 Compared with other bases unable to form aminoalkyl radicals, *i*Pr₂NEt gave the best result. It is also possible that aminoalkyl radicals perform halogen atom transfer (XAT) from Ph₃SnI to generate tin radicals (see the ESI†).
- 34 (a) L. Pause, M. Robert and J.-M. Savéant, *J. Am. Chem. Soc.*, 1999, **121**, 7158–7159; (b) A. J. Fry and R. L. Krieger, *J. Org. Chem.*, 1976, **41**, 54–57.
- 35 The synthesis of aryl-cobaloxime intermediates failed. And the computational experiments showed that the aryl Co–C bond had a higher BDE than the alkyl Co–C bond (see the ESI†), previous reports on aryl-cobalt, see: (a) N. A. Miller, T. E. Wiley, K. G. Spears, M. Ruetz, C. Kieninger, B. Kräutler and R. J. Sension, *J. Am. Chem. Soc.*, 2016, **138**, 14250–14256; (b) M. Ruetz, C. Gherasim, K. Gruber, S. Fedosov, R. Banerjee and B. Kräutler, *Angew. Chem., Int. Ed.*, 2013, **52**, 2606–2610.

