

# Dual-functional cobalt catalyst enables electrocatalytic allylic C–H alkylation

Ming Chen<sup>1</sup>, Zheng-Jian Wu<sup>1</sup>, Jinshuai Song<sup>2</sup> & Hai-Chao Xu<sup>1</sup>

<sup>1</sup>State Key Laboratory of Physical Chemistry of Solid Surfaces, Key Laboratory of Chemical Biology of Fujian Province, and College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, China

<sup>2</sup>Green Catalysis Center, College of Chemistry, Zhengzhou University, Zhengzhou 450001, China

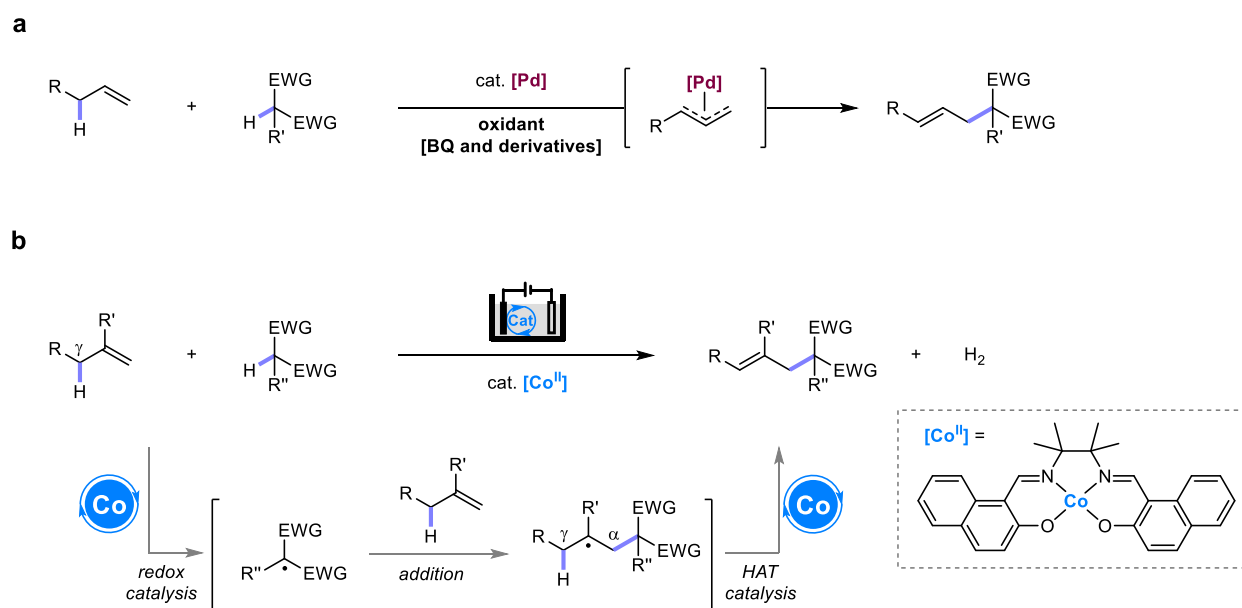
Correspondence: haichao.xu@xmu.edu.cn

**Abstract:** Transition metal-catalyzed allylic substitution reactions of pre-activated allylation agents with nucleophiles are extensively studied synthetic methods that have enjoyed widespread applications in organic synthesis. The direct alkylation of allylic C–H bonds with nucleophiles, which minimizes pre-functionalization and converts inexpensive, abundantly available materials to value-added alkenyl-substituted products, remains challenging. Current methods generally involve C–H activation, require the use of noble-metal catalysts and stoichiometric chemical oxidants, and often show limited scope. Here we report an electrocatalytic allylic C–H alkylation reaction with carbon nucleophiles employing an easily available cobalt-salen complex as the molecular catalyst. These C(sp<sup>3</sup>)–H/C(sp<sup>3</sup>)–H cross-coupling reactions proceed through H<sub>2</sub> evolution and require no external chemical oxidants. Importantly, the mild conditions and radical mechanism ensure excellent functional group tolerance and substrate compatibility with both linear and branched terminal alkenes. The synthetic utility of the electrochemical method is highlighted by its scalability (up to 200 mmol scale) and its successful application in the late-stage functionalization of complex structures.

## Introduction

The synthesis of three-dimensional organic molecules necessitates the efficient construction of C(sp<sup>3</sup>)–C(sp<sup>3</sup>) bonds. Among the various methods to access these chemical entities, noble metal-catalyzed allylic substitution of pre-activated allylation agents such as allylic carboxylates, carbonates, and halides with carbon nucleophiles have been extensively studied and widely used in organic synthesis over the past decades.<sup>1–3</sup> The allyl moiety in the product provides a versatile synthetic handle for further transformations. To minimize pre-functionalization and streamline the synthesis of complex molecules, recent efforts have been devoted to converting C(sp<sup>3</sup>)–H bonds directly to C(sp<sup>3</sup>)–C(sp<sup>3</sup>) bonds.<sup>4,5</sup> In this context, the groups of Shi<sup>6</sup> and White<sup>7</sup> have independently published in 2008 seminal work on Pd-catalyzed allylic C(sp<sup>3</sup>)–H alkylation of allyl arenes via  $\pi$ -allylpalladium intermediates (Fig. 1a). The substrate scope has since then been extended to unactivated  $\alpha$ -olefins and various carbon nucleophiles.<sup>8–10</sup> Notwithstanding the progress, these methods still require noble-metal catalysts and stoichiometric chemical oxidants.

A further limitation is that only  $\alpha$ -olefins without branches on the alkene or at the allylic position are amenable, likely due to the difficulty in activating weakly coordinating branched alkenes and achieving satisfactory regioselectivity.



**Fig. 1 Allylic C(sp<sup>3</sup>)-H alkylation.** **a**, Pd-catalyzed allylic C-H alkylation usually proceeds through C-H activation to form allyl-metal species. **b**, Electrocatalytic approach to allylic C-H alkylation with a cobalt salen complex as the molecular catalyst. This method proceeds through a radical mechanism involving the addition of a C-radical derived from the carbon nucleophile to the alkene. EWG, electron-withdrawing group. HAT, hydrogen atom transfer.

Cobalt represents an attractive alternative to noble metals for transition-metal catalysis due to its greater natural abundance and cost efficiency.<sup>11-19</sup> In view of the challenges associated with the selective functionalization allylic C-H bonds of unactivated alkenes through organometallic activation, we envision a radical-based electrocatalytic approach<sup>20-30</sup> to expand the scope of allylic C-H alkylation and eliminate the need for external chemical oxidants (Fig. 1b).<sup>31</sup> In the envisioned process, the acidic carbon nucleophile is oxidized electrocatalytically with a cobalt-based molecular catalyst to generate an electron-deficient carbon-centered radical,<sup>32-34</sup> which then adds to the alkene to afford an alkyl radical. The newly formed radical center significantly weakens the  $\gamma$ -C-H bond [bond dissociation energy (BDE) < 36 kcal mol<sup>-1</sup>],<sup>35</sup> enabling effective hydrogen atom transfer to the cobalt catalyst to furnish the alkene alkylation product.<sup>32,36</sup> In contrast to the organometallic C-H activation, the presence of substituents at the  $\beta$ - or  $\gamma$ -positions of the alkene substrate should not interfere with the radical reactions; in fact, they might even be beneficial, thus expanding the substrate scope to branched alkenes. The success of the electrocatalytic reaction hinges on the dual function of the cobalt catalyst as a redox mediator and a site-selective HAT catalyst. Reported studies have already established cobalt-salen complexes as effective HAT agent to convert carbon radicals to alkenes.<sup>32,36,37</sup> Our

previous work has shown that cobalt-salen complexes are competent electrocatalysts for promoting intramolecular cyclization,<sup>32</sup> paving the way for the more challenging intermolecular allylic C–H alkylation reactions.

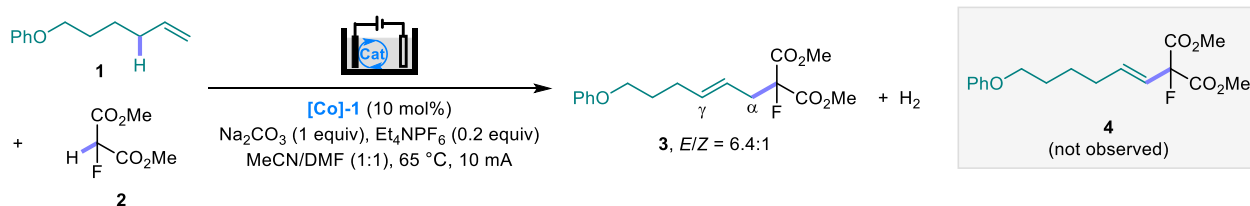
Herein we report an electrochemically enabled, cobalt-catalyzed allylic C–H alkylation reaction that shows exceptional functional group compatibility and tolerates various carbon nucleophiles as well as linear and branched unactivated  $\alpha$ -olefins (Fig. 1b). The electrocatalytic method employs a readily available cobalt-salen complex as the molecular catalyst, and proceeds through the designed radical mechanism, presenting a unique approach to allylic C–H functionalization.

## Results and discussion

**Reaction development.** Considering the importance of fluorinated small molecules in the fields of pharmaceuticals and agrochemicals<sup>38</sup> and the versatility of the fluoromalonate moiety in synthesis,<sup>39</sup> we first investigated the electrocatalytic fluoroalkylation of alkenes. The allylic alkylation of  $\alpha$ -olefin **1** with 2-fluoromalonate **2** was chosen as the model reaction for reaction optimization (Table 1). The desired alkylation product **3** was produced in an optimal yield of 80% when the electrolysis reaction was conducted in an undivided cell at 65 °C with cobalt salen complex [Co]-**1** as the catalyst, Na<sub>2</sub>CO<sub>3</sub> as the basic additive, and MeCN/DMF (1:1) as the solvent (entry 1). The alkylation reaction afforded **3** as the only regioisomer without the formation of **4**, which would arise from C–H cleavage at the sterically more hindered  $\alpha$ -position. The cobalt catalyst (entry 2), heating (entry 3), and Na<sub>2</sub>CO<sub>3</sub> (entry 4) were all critical for success. The yield of **3** was reduced if the reaction employed another base such as K<sub>2</sub>CO<sub>3</sub> (entry 5), Cs<sub>2</sub>CO<sub>3</sub> (entry 6) or NaOAc (entry 7), or an alternative cobalt catalyst such as [Co]-**2**, [Co]-**3**, or [Co]-**4** (entry 8). Changing the solvent to MeCN/MeOH (1:1) or DMF/MeOH (1:1) also led to significant yield loss (entries 9 and 10). The reaction can be conducted at a constant current of 3 mA or 6 mA (entry 11) instead of 10 mA without affecting the yield but showed a slight yield loss at 20 mA (entry 12) due to incomplete conversion.

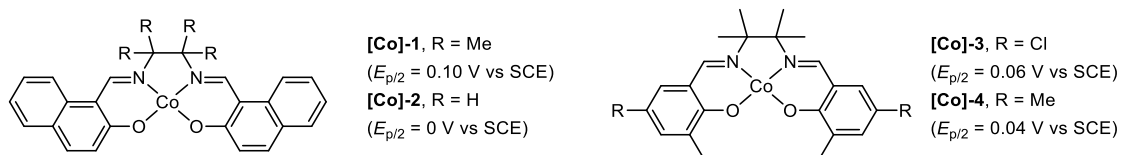
**Evaluation of substrate scope.** We then investigated the allylic C–H alkylation of various  $\alpha$ -olefins with 2-fluoromalonate **2** (Fig. 2, top). Monosubstituted alkenes bearing diverse substituents were tolerated, including i) electrophilic groups such as epoxide (**5**) and alkyl chloride (**6**), bromide (**7**) and sulfonates (**8**, **9**), ii) acid/base sensitive Boc-protected amino esters (**16**, **17**) and  $\beta,\gamma$ -unsaturated amides (**18**, **21**), as well as iii) oxidation-labile functionalities such as aldehyde (**19**), amine (**20**), anilide (**21**), and sulfonamide (**22**). The presence of a sterically bulky trimethylsilyl group at the  $\gamma$ -position resulted in a reduced yield of 35% (**23**) but did not affect the preference for the cleavage of the  $\gamma$ -C–H bond.

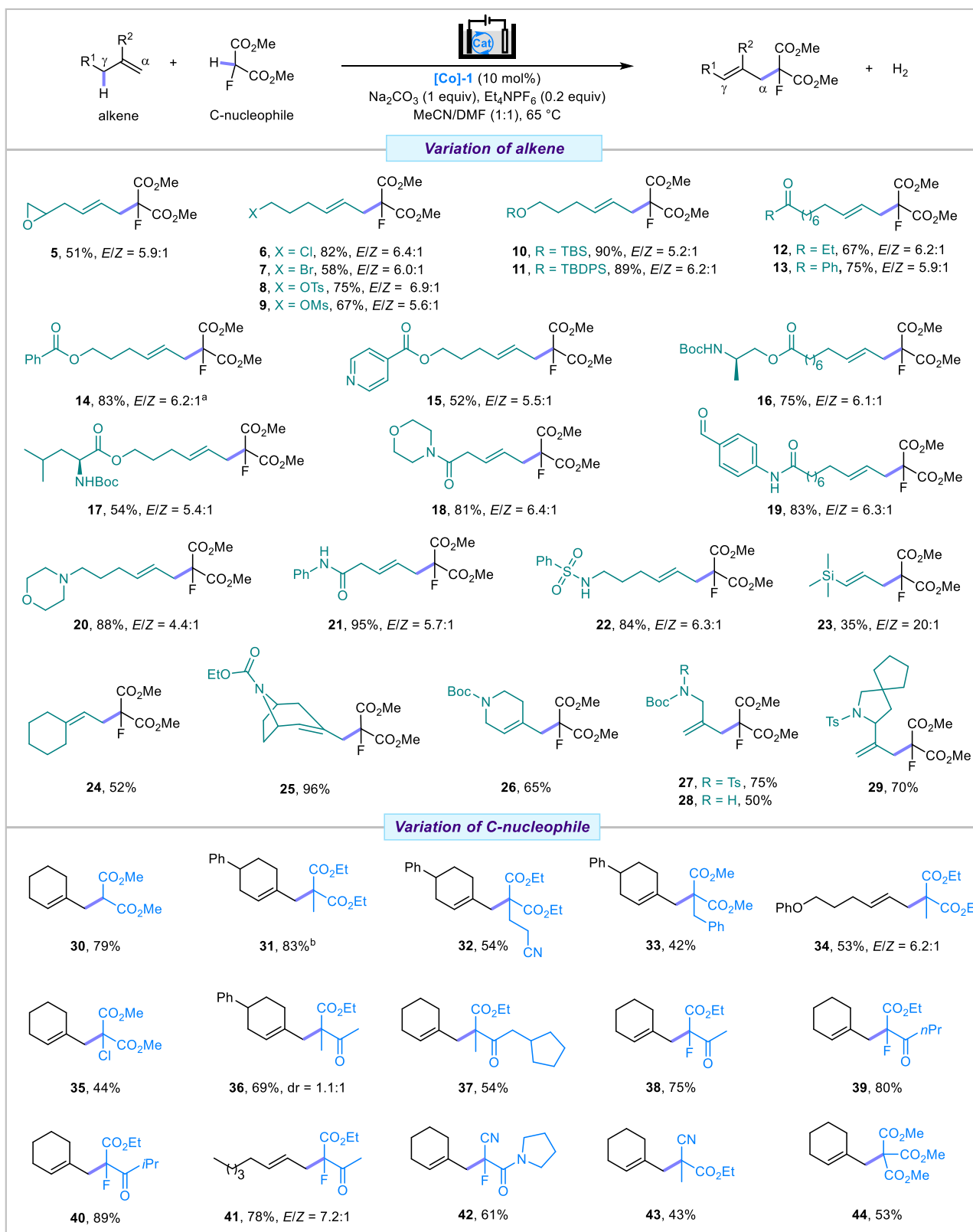
**Table 1 Optimization of reaction conditions for the electrocatalytic allylic C–H alkylation reaction<sup>a</sup>**



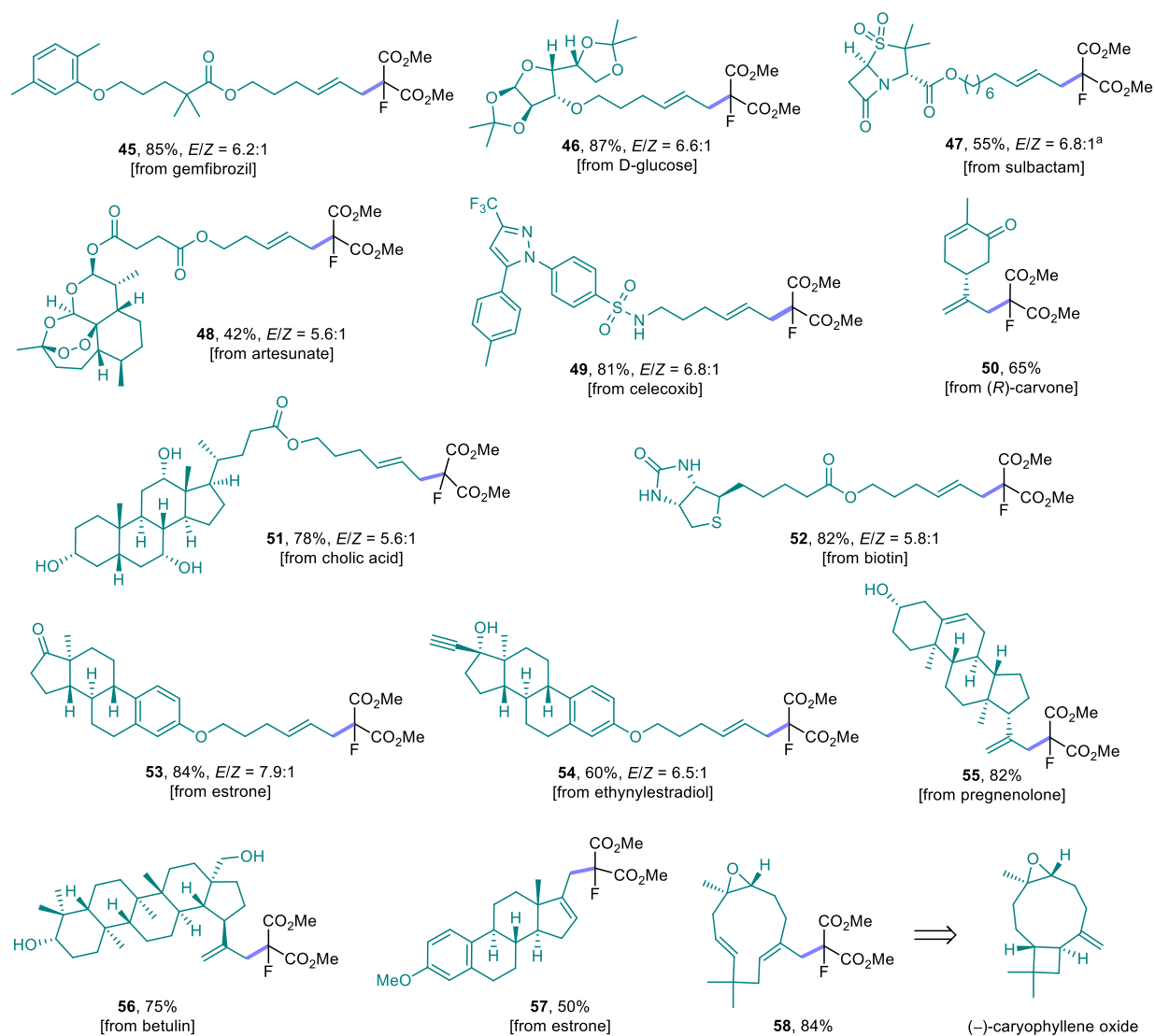
Entry	Deviation from standard conditions	Yield of <b>2</b> (%) <sup>b</sup>
1	None	80 <sup>c</sup>
2	No <b>[Co]-1</b>	0 (56)
3	Reaction at rt	18 (70)
4	No $\text{Na}_2\text{CO}_3$	15 (72)
5	$\text{K}_2\text{CO}_3$ instead of $\text{Na}_2\text{CO}_3$	43 (34)
6	$\text{Cs}_2\text{CO}_3$ instead of $\text{Na}_2\text{CO}_3$	20 (50)
7	$\text{NaOAc}$ instead of $\text{Na}_2\text{CO}_3$	44 (30)
8	<b>[Co]-2</b> , or <b>[Co]-3</b> , or <b>[Co]-4</b> as catalyst	20–73
9	MeCN/MeOH (1:1) as solvent	32 (45)
10	MeOH/DMF (1:1) as solvent	65 (16)
11	3 mA or 6 mA	82–83
12	20 mA	78 (6)

<sup>a</sup>Reaction conditions: RVC anode, Pt plate cathode, **1** (0.2 mmol), **2** (0.5 mmol, 2.5 equiv), MeCN (3 mL), DMF (3 mL), constant current (10 mA), 2.0 h ( $3.7 \text{ F mol}^{-1}$ ), undivided cell. <sup>b</sup>Determined by  $^1\text{H}$  NMR analysis using 1,3,5-trimethoxybenzene as the internal standard, unreacted **1** in brackets. <sup>c</sup>Isolated yield.





**Fig. 2 Scope of electrocatalytic allylic C–H alkylation.** Reaction conditions: alkene (0.2 mmol), carbon nucleophile (0.5 mmol, 2.5 equiv), MeCN (3 mL), DMF (3 mL), undivided cell, RVC anode, Pt cathode, 10 mA or 3 mA. All yields are isolated yields. <sup>a</sup>Reaction in MeCN/THF (1:1), 5 mA. <sup>b</sup>Reaction with NaOAc (1.0 equiv) instead of Na<sub>2</sub>CO<sub>3</sub>.

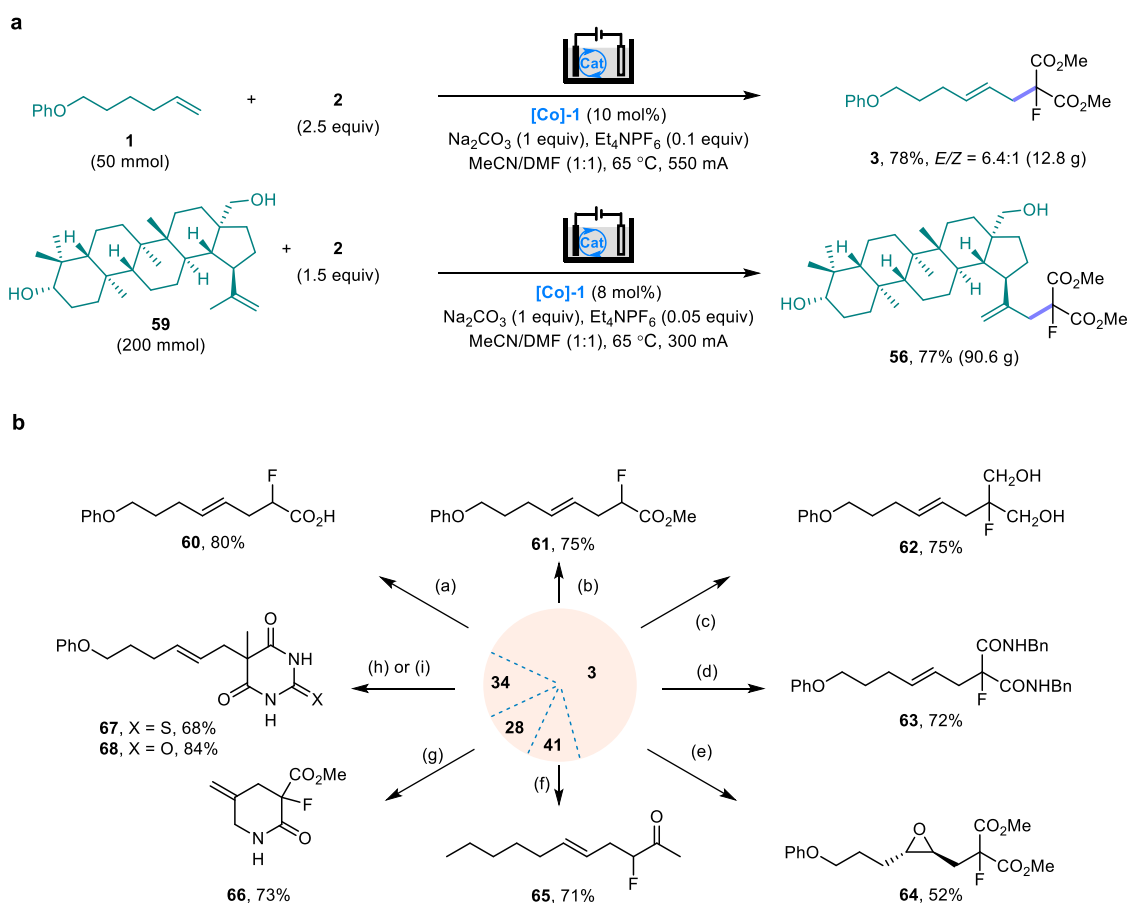


**Fig. 3** Late-stage functionalization of alkenes derived from natural products and drugs. Reaction conditions: alkene (0.2 mmol), **2** (0.5 mmol), [Co]-**1** (0.02 mmol), Na<sub>2</sub>CO<sub>3</sub> (0.2 mmol), Et<sub>4</sub>NPF<sub>6</sub> (0.04 mmol), MeCN (3 mL), DMF (3 mL), constant current (10 mA or 3 mA), undivided cell, 65 °C. All yields are isolated yields. <sup>a</sup>Reaction on 0.3 mmol scale.

Branched  $\alpha$ -olefins were also suitable substrates. Vinylcyclohexane, a  $\gamma$ -branched  $\alpha$ -olefin, reacted to give the trisubstituted alkene **24** as the only regioisomer. This preference for the cleavage of the 3°  $\gamma$ -C–H bond over the 2° C–H at the  $\alpha$ -position was likely caused by the relatively low BDE of the former. 1,1-Disubstituted alkenes also reacted exclusively via the cleavage of the  $\gamma$ -C–H bonds (**25–29**). In the cases of **27–29**, all of which contained two different types  $\gamma$ -C–H bonds, the reactions occurred exclusively at the more accessible Me group to give the contra-thermodynamic terminal alkenes instead of the more stable internal alkenes that would derive from reaction at the weaker 2° or 3° C–H bonds adjacent to the nitrogen substituents. These selectivities can be explained by a combination of steric control and a mismatch in polarity of the hydridic C–H bonds at the  $\alpha$ -position of the nitrogen

atoms with the electron-rich [Co<sup>II</sup>] salen complex.<sup>36</sup> Notably, the terminal alkenes **27–29** did not undergo further alkylation probably because the incorporation of the electron-withdrawing malonate group reduced their reactivity toward the electron-deficient carbon radical derived from **2**.

We next investigated the scope of the carbon nucleophile (Fig. 2, bottom). The electrocatalytic C–H alkylation reaction exhibited excellent compatibility with several types of acidic carbon nucleophiles, including dimethyl malonate (**30**) and malonates bearing a 2-alkyl (**31–34**) or chloro (**35**) group, β-ketoesters bearing at the α-positions a Me (**36** and **37**) or fluoro (**38–41**) group, β-cyanoamide (**42**), β-cyanoester (**43**), and trimethyl methanetricarboxylate (**44**). Notably, dimethyl malonate-derived product **30** did not undergo further alkylation because of its reduced acidity compared with dimethyl malonate.



**Fig. 4 Decagram scale synthesis and product transformations.** **a**, Decagram scale synthesis of **3** and **56**. **b**, Transformations of the C–H alkylation products. (a) AcOH/H<sub>2</sub>SO<sub>4</sub>/H<sub>2</sub>O (8:5:1), reflux. (b) LiCl, DMSO, H<sub>2</sub>O, 140 °C. (c) LiAlH<sub>4</sub>, THF, 0 °C to rt. (d) BnNH<sub>2</sub>, MeOH, 50 °C. (e) *meta*-Chloroperbenzoic acid, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt. (f) KOH, MeOH, H<sub>2</sub>O, rt. (g) TFA, DCM, 0 °C to rt. (h) thiourea, NaH, 0 °C to rt. (i) urea, NaH, 0 °C to rt.

The high reaction efficiency and functional group tolerance of the electrocatalytic method were further highlighted by its application in the late-stage functionalization of complex drug molecules and natural products (Fig.

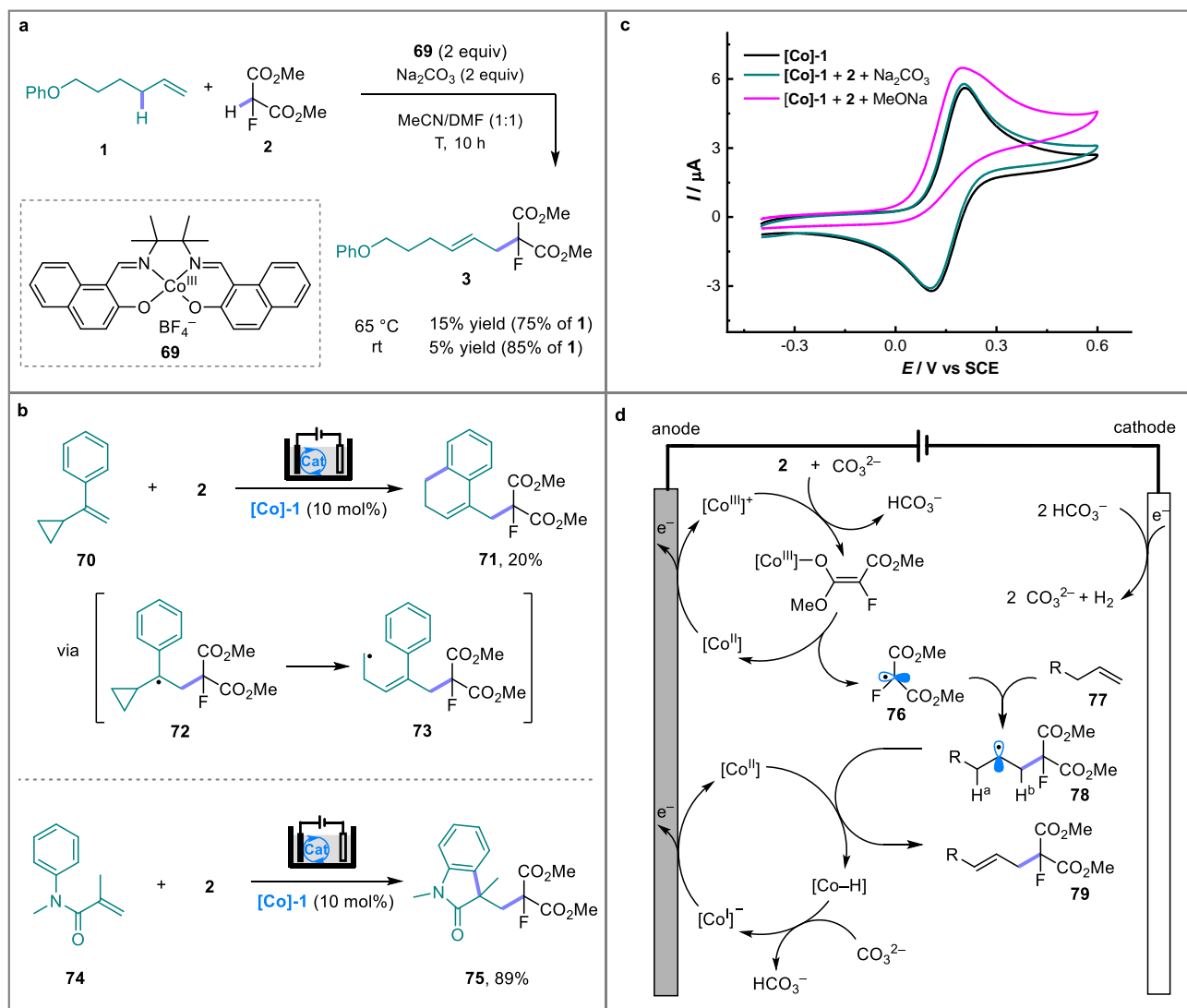
3). The reactions of (*R*)-carvone (**50**), pregnenolone (**55**), and betulin (**56**) occurred exclusively through cleavage of the C–H bond at the Me group instead of the sterically encumbered but weaker 3° allylic C–H bond, suggesting that the regioselectivity was controlled by steric effects. (–)-Caryophylle oxide that contained a four-membered ring at the allylic position underwent addition/ring opening to afford **58** as the final product, which is consistent with the envisioned radical mechanism.

The synthetic utility of the electrocatalytic method was further demonstrated by its scalability and the versatile transformations of the alkylation products (Fig. 4). The 50 mmol scale reaction of **1** and 200 mmol scale reaction of betulin (**59**) with malonate **2** proceeded smoothly to generate the expected products **3** (12.8 g, 78% yield) and **56** (90.6 g, 77% yield), respectively, with similar yields to the small-scale reactions. Notably, the large-scale reaction of betulin was conducted at an increased concentration of 0.22 M instead of 0.033 M, which thus required less solvent, cobalt catalyst (8 mol% instead of 10 mol%), reactant **2** (1.5 equiv instead of 2.5 equiv) and electrolyte (0.05 equiv instead of 0.2 equiv). On the other hand, the fluoroalkylation product **3** could undergo decarboxylation to furnish  $\alpha$ -fluorocarboxylic acid **60** or  $\alpha$ -fluorocarboxylic ester **61**, reduction to form fluorinated 1,3-diol **62**, amidation to produce malonate amide **63**, or epoxidation to afford epoxide **64**. Hydrolytic decarboxylation of ketoester **41** resulted in  $\alpha$ -fluoroketone **65**, whereas malonate **28** bearing a Boc-protected amino group cyclized upon deprotection into fluorinated  $\delta$ -lactam **66**. Finally, the annulation of malonate **34** with thiourea or urea afforded barbituric acid derivatives **67** and **68**, which are the key structural motifs in several drug molecules.

We next investigated the reaction mechanism by first testing the allylic C–H alkylation of alkene **1** with malonate **2** in the presence of 2 equiv of [Co<sup>III</sup>] complex **69**, which afforded the desired product **3** in 15% yield at 65 °C, or 5% yield at rt (Fig. 5a). The low conversion rates of both reactions with stoichiometric **69** could be attributed to the decomposition of the [Co<sup>III</sup>] oxidant. These results demonstrated that [Co<sup>III</sup>] could promote the allylic C–H alkylation. We next examined the reactions of malonate **2** with two radical probes, vinylcyclopropane **70** and N-phenyl acrylamide **74** (Fig. 5b). The reaction of **70** with **2** produced the cyclopropane ring-opening product **71** in 20% yield, suggesting the involvement of carbon radical **72**. Subsequent ring opening of **72** to **73**, followed by the intramolecular cyclization of the latter with the tethered phenyl ring and rearomatization led to the formation of the final product **71**. On the other hand, the reaction of **74** and **2** produced oxoindole **75** in 89% yield, further confirming that a radical mechanism was involved. The cyclic voltammograms of [Co]-**1** were obtained in the absence and presence of malonate **2** (Fig. 5c). While the voltammogram exhibited no change with the addition of **2** and Na<sub>2</sub>CO<sub>3</sub>, the reduction wave for [Co<sup>III</sup>]/[Co<sup>II</sup>] disappeared in the presence of **2** and NaOMe but without the observation of a catalytic current. These results suggested that the electrochemically produced [Co<sup>III</sup>] species reacted with **2** in the presence of a base



through inner-sphere electron transfer.<sup>32</sup> Na<sub>2</sub>CO<sub>3</sub> was barely soluble in the mixed solvent of DMF/MeCN (1:1), explaining its failure in promoting the reaction of [Co<sup>III</sup>] with **2** under the static conditions employed for the CV testing.



**Fig. 5 Mechanistic studies and proposal.** **a**, Allylic C–H alkylation with stoichiometric [Co<sup>III</sup>] complex **69** as the oxidant. **b**, Probing radical intermediates with vinylcyclopropane **70** and acrylamide **74**. **c**, Cyclic voltammograms of [Co]**I**-1 (3 mM) obtained in MeCN/DMF (1:1, 0.1 M Et<sub>4</sub>NPF<sub>6</sub>) at 50 °C. **2** (10 mM), Na<sub>2</sub>CO<sub>3</sub> (10 mM), NaOMe (5 mM). **d**, Proposed reaction mechanism for the electrocatalytic intermolecular allylic C–H alkylation.

Based on the results of this study and previous work,<sup>32,36</sup> a possible mechanism for the electrocatalytic allylic C–H alkylation reaction was proposed (Fig. 5d). Anodic oxidation of the [Co<sup>I</sup>] catalyst ( $E_{p/2} = 0.10$  V vs SCE) generates a [Co<sup>III</sup>] complex, which oxidizes the acidic carbon nucleophile with the assistance of a base through inner-sphere electron transfer to generate an electrophilic carbon-centered radical **76** and regenerates the [Co<sup>I</sup>] catalyst. Addition

of **76** onto alkene **77** produces a new carbon centered radical **78**. The [Co<sup>II</sup>] catalyst abstracts hydrogen H<sup>a</sup> of **78** to afford the final alkylation product **79** and the cobalt species [Co–H].<sup>37,40,41</sup> Computation studies revealed that HAT from H<sup>a</sup> of **78** was kinetically much more favored over H<sup>b</sup> (Supplementary Fig. 7). The latter is deprotonated<sup>36,42</sup> and oxidized anodically back to the [Co<sup>II</sup>] catalyst. At the cathode, protons are reduced to H<sub>2</sub>, which is detected by gas chromatography.

In summary, we have developed an electrocatalytic allylic C–H alkylation reaction with acidic carbon nucleophiles employing an easily available cobalt-salen complex as the molecular catalyst. The mild reaction conditions, coupled with the fact that the employed cobalt catalyst has a low oxidation potential but high efficiency, ensure exceptional functional group tolerance. The dehydrogenative cross-coupling retains the functionalities from the alkene and the carbon nucleophile, providing handles for further synthetic manipulations. The radical mechanism confers compatibility with both linear and branched  $\alpha$ -olefins, ultimately opening a new pathway for the development of allylic C–H functionalization reactions.

## Methods

**General procedure for electrocatalytic allylic C–H alkylation (0.2 mmol scale).** To a 10 mL Schlenk tube was added the alkene substrate (0.2 mmol), the carbon nucleophile (0.5 mmol), Et<sub>4</sub>NPF<sub>6</sub> (0.04 mmol), Na<sub>2</sub>CO<sub>3</sub> (0.2 mmol), and [Co]-**1** (0.02 mmol). The tube was equipped with a reticulated vitreous carbon (RVC) anode (100 PPI, 0.5 cm x 1.2 cm x 1.6 cm) and a platinum plate (1 cm x 1 cm x 0.1 cm) cathode. After three cycles of evacuation and backfilling with argon, 6 mL of degassed MeCN/DMF (1:1) was added. The electrolysis was carried out at 65 °C using a constant current (10 mA or 3 mA) until complete consumption of the alkene substrate. The reaction mixture was cooled to rt and concentrated under reduced pressure. The residue was chromatographed through silica gel eluting with petroleum ether/ethyl acetate to afford the product. All new compounds were fully characterized (see Supplementary Information for details).

**Data availability.** The data supporting the findings of this study are available within the article and its Supplementary Information file. Any further relevant data are available from the authors on request.

## References

- (1) Pàmies, O.; Margalef, J.; Cañellas, S.; James, J.; Judge, E.; Guiry, P. J.; Moberg, C.; Bäckvall, J.-E.; Pfaltz, A.; Pericàs, M. A.; Diéguez, M. Recent Advances in Enantioselective Pd-Catalyzed Allylic Substitution: From Design to Applications. *Chem. Rev.* **2021**, *121*, 4373-4505.
- (2) Trost, B. M.; Crawley, M. L. Asymmetric Transition-Metal-Catalyzed Allylic Alkylations: Applications in Total Synthesis. *Chem. Rev.* **2003**, *103*, 2921-2944.
- (3) Cheng, Q.; Tu, H.-F.; Zheng, C.; Qu, J.-P.; Helmchen, G.; You, S.-L. Iridium-Catalyzed Asymmetric Allylic

Substitution Reactions. *Chem. Rev.* **2019**, *119*, 1855-1969.

(4) Liu, G.; Wu, Y.: Palladium-Catalyzed Allylic C–H Bond Functionalization of Olefins. In *C-H Activation*; Yu, J.-Q., Shi, Z., Eds.; Springer Berlin Heidelberg: Berlin, Heidelberg, 2010; pp 195-209.

(5) Wang, R.; Luan, Y.; Ye, M. Transition Metal–Catalyzed Allylic C(sp<sup>3</sup>)–H Functionalization via  $\eta^3$ -Allylmetal Intermediate. *Chin. J. Chem.* **2019**, *37*, 720-743.

(6) Lin, S.; Song, C.-X.; Cai, G.-X.; Wang, W.-H.; Shi, Z.-J. Intra/Intermolecular Direct Allylic Alkylation via Pd(II)-Catalyzed Allylic C–H Activation. *J. Am. Chem. Soc.* **2008**, *130*, 12901-12903.

(7) Young, A. J.; White, M. C. Catalytic Intermolecular Allylic C–H Alkylation. *J. Am. Chem. Soc.* **2008**, *130*, 14090-14091.

(8) Young, A. J.; White, M. C. Allylic C-H Alkylation of Unactivated  $\alpha$ -Olefins: Serial Ligand Catalysis Resumed. *Angew. Chem. Int. Ed.* **2011**, *50*, 6824-6827.

(9) Trost, B. M.; Hansmann, M. M.; Thaisrivongs, D. A. Palladium-Catalyzed Alkylation of 1,4-Dienes by C H Activation. *Angew. Chem. Int. Ed.* **2012**, *51*, 4950-4953.

(10) Howell, J. M.; Liu, W.; Young, A. J.; White, M. C. General Allylic C–H Alkylation with Tertiary Nucleophiles. *J. Am. Chem. Soc.* **2014**, *136*, 5750-5754.

(11) Moselage, M.; Li, J.; Ackermann, L. Cobalt-Catalyzed C–H Activation. *ACS Catal.* **2016**, *6*, 498-525.

(12) Baccalini, A.; Vergura, S.; Dolui, P.; Zanoni, G.; Maiti, D. Recent advances in cobalt-catalysed C–H functionalizations. *Org. Biomol. Chem.* **2019**, *17*, 10119-10141.

(13) Dhawa, U.; Tian, C.; Li, W.; Ackermann, L. Cobalt-Electrocatalyzed C–H Allylation with Unactivated Alkenes. *ACS Catal.* **2020**, *10*, 6457-6462.

(14) Ackermann, L. Metalla-electrocatalyzed C–H Activation by Earth-Abundant 3d Metals and Beyond. *Acc. Chem. Res.* **2020**, *53*, 84-104.

(15) Gandeepan, P.; Finger, L. H.; Meyer, T. H.; Ackermann, L. 3d metallaelectrocatalysis for resource economical syntheses. *Chem. Soc. Rev.* **2020**, *49*, 4254-4272.

(16) Zhang, H.; Huang, J.; Meng, F. Cobalt-catalyzed diastereo- and enantioselective allyl addition to aldehydes and  $\alpha$ -ketoesters through allylic C–H functionalization. *Cell Rep. Phys. Sci.* **2021**, *2*, 100406.

(17) Michigami, K.; Mita, T.; Sato, Y. Cobalt-Catalyzed Allylic C(sp<sup>3</sup>)–H Carboxylation with CO<sub>2</sub>. *J. Am. Chem. Soc.* **2017**, *139*, 6094-6097.

(18) Maity, S.; Dolui, P.; Kancharla, R.; Maiti, D. Introducing unactivated acyclic internal aliphatic olefins into a cobalt catalyzed allylic selective dehydrogenative Heck reaction. *Chem. Sci.* **2017**, *8*, 5181-5185.

(19) Han, J.-F.; Guo, P.; Zhang, X.-G.; Liao, J.-B.; Ye, K.-Y. Recent advances in cobalt-catalyzed allylic functionalization. *Org. Biomol. Chem.* **2020**, *18*, 7740-7750.

(20) Novaes, L. F. T.; Liu, J.; Shen, Y.; Lu, L.; Meinhardt, J. M.; Lin, S. Electrocatalysis as an enabling technology for organic synthesis. *Chem. Soc. Rev.* **2021**, *50*, 7941-8002.

(21) Yuan, Y.; Yang, J.; Lei, A. Recent advances in electrochemical oxidative cross-coupling with hydrogen evolution involving radicals. *Chem. Soc. Rev.* **2021**.

(22) Siu, J. C.; Fu, N.; Lin, S. Catalyzing Electrosynthesis: A Homogeneous Electrocatalytic Approach to Reaction Discovery. *Acc. Chem. Res.* **2020**, *53*, 547-560.

(23) Francke, R.; Little, R. D. Redox catalysis in organic electrosynthesis: basic principles and recent developments. *Chem. Soc. Rev.* **2014**, *43*, 2492-2521.

(24) Yan, M.; Kawamata, Y.; Baran, P. S. Synthetic Organic Electrochemical Methods Since 2000: On the Verge of a Renaissance. *Chem. Rev.* **2017**, *117*, 13230-13319.

(25) Jiang, Y.; Xu, K.; Zeng, C. Use of Electrochemistry in the Synthesis of Heterocyclic Structures. *Chem. Rev.* **2018**, *118*, 4485-4540.

- (26) Kärkäs, M. D. Electrochemical strategies for C–H functionalization and C–N bond formation. *Chem. Soc. Rev.* **2018**, *47*, 5786-5865.
- (27) Moeller, K. D. Using Physical Organic Chemistry To Shape the Course of Electrochemical Reactions. *Chem. Rev.* **2018**, *118*, 4817-4833.
- (28) Waldvogel, S. R.; Lips, S.; Selt, M.; Riehl, B.; Kampf, C. J. Electrochemical Arylation Reaction. *Chem. Rev.* **2018**, *118*, 6706-6765.
- (29) Nutting, J. E.; Rafiee, M.; Stahl, S. S. Tetramethylpiperidine N-Oxyl (TEMPO), Phthalimide N-Oxyl (PINO), and Related N-Oxyl Species: Electrochemical Properties and Their Use in Electrocatalytic Reactions. *Chem. Rev.* **2018**, *118*, 4834-4885.
- (30) Jiao, K.-J.; Xing, Y.-K.; Yang, Q.-L.; Qiu, H.; Mei, T.-S. Site-Selective C–H Functionalization via Synergistic Use of Electrochemistry and Transition Metal Catalysis. *Acc. Chem. Res.* **2020**, *53*, 300-310.
- (31) Huang, H.-M.; Bellotti, P.; Glorius, F. Transition metal-catalysed allylic functionalization reactions involving radicals. *Chem. Soc. Rev.* **2020**, *49*, 6186-6197.
- (32) Cai, C.-Y.; Wu, Z.-J.; Liu, J.-Y.; Chen, M.; Song, J.; Xu, H.-C. Tailored cobalt-salen complexes enable electrocatalytic intramolecular allylic C–H functionalizations. *Nat. Commun.* **2021**, *12*, 3745.
- (33) Wu, Z.-J.; Xu, H.-C. Synthesis of C3-Fluorinated Oxindoles through Reagent-Free Cross-Dehydrogenative Coupling. *Angew. Chem. Int. Ed.* **2017**, *56*, 4734-4738.
- (34) Fu, N.; Shen, Y.; Allen, A. R.; Song, L.; Ozaki, A.; Lin, S. Mn-Catalyzed Electrochemical Chloroalkylation of Alkenes. *ACS Catal.* **2019**, *9*, 746-754.
- (35) Zhang, X.-M. Homolytic Bond Dissociation Enthalpies of the C–H Bonds Adjacent to Radical Centers. *J. Org. Chem.* **1998**, *63*, 1872-1877.
- (36) Ye, K.-Y.; McCallum, T.; Lin, S. Bimetallic Radical Redox-Relay Catalysis for the Isomerization of Epoxides to Allylic Alcohols. *J. Am. Chem. Soc.* **2019**, *141*, 9548-9554.
- (37) Crossley, S. W. M.; Barabé, F.; Shenvi, R. A. Simple, Chemoselective, Catalytic Olefin Isomerization. *J. Am. Chem. Soc.* **2014**, *136*, 16788-16791.
- (38) Zhou, Y.; Wang, J.; Gu, Z. N.; Wang, S. N.; Zhu, W.; Acena, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II-III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas. *Chem. Rev.* **2016**, *116*, 422-518.
- (39) Harsanyi, A.; Sandford, G. 2-Fluoromalonate Esters: Fluoroaliphatic Building Blocks for the Life Sciences. *Org. Process Res. Dev.* **2014**, *18*, 981-992.
- (40) Song, L.; Fu, N.; Ernst, B. G.; Lee, W. H.; Frederick, M. O.; DiStasio, R. A.; Lin, S. Dual electrocatalysis enables enantioselective hydrocyanation of conjugated alkenes. *Nat. Chem.* **2020**, *12*, 747-754.
- (41) Wiedner, E. S.; Bullock, R. M. Electrochemical Detection of Transient Cobalt Hydride Intermediates of Electrocatalytic Hydrogen Production. *J. Am. Chem. Soc.* **2016**, *138*, 8309-8318.
- (42) 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.* **2011**, *50*, 11125-11128.

## Acknowledgements

The authors acknowledge the financial support of this research from NSFC (No. 21971213) and Fundamental Research Funds for the Central Universities.

## Author contributions

M.C. and Z.J.W. performed the experiments and analyzed the data. J.S. conducted the computational studies.  
H.C.X. directed the project and wrote the manuscript.

**Additional information**

**Competing interests:** The authors declare no competing interests.

**Supplementary Information** is available.