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Dual Electrocatalysis Enables Enantioselective Hydrocyanation of Conjugated Alkenes

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Abstract

Chiral nitriles and their derivatives are prevalent in pharmaceuticals and bioactive compounds. Enantioselective alkene hydrocyanation represents a convenient and efficient approach for synthesizing these molecules. However, a generally applicable method featuring a broad substrate scope and high functional group tolerance remains elusive. Here, we address this long-standing synthetic problem using dual electrocatalysis. Using this strategy, we leverage electrochemistry to seamlessly combine two canonical radical reactions—cobalt-mediated hydrogen-atom transfer and copper-promoted radical cyanation—to accomplish highly enantioselective hydrocyanation without the need for stoichiometric oxidants. We also harness electrochemistry's unique feature of precise potential control to optimize the chemoselectivity of challenging substrates. Computational analysis uncovers the origin of enantio-induction, for which the chiral catalyst imparts a combination of attractive and repulsive non-covalent interactions to direct the enantio-determining C–CN bond formation. This work demonstrates the power of electrochemistry in accessing new chemical space and providing solutions to pertinent challenges in synthetic chemistry.

Alkene hydrocyanation, in which H and CN groups are added across a C=C π -bond, is a highly useful transformation,^{1–4} as it provides versatile nitriles that are key intermediates in the synthesis of polymers, agrochemicals, cosmetics, and pharmaceuticals (Figure 1a).⁵ This reaction is used in the industrial production of adiponitrile on a million-ton annual scale⁶ and has been explored by scientists at DuPont in the synthesis of naproxen, a top-selling anti-inflammatory medicine.^{7–9} The development of a general catalytic alkene hydrocyanation method with broad substrate scope, precise chemoselectivity, and high stereochemical control would have significant impact on synthetic organic chemistry across both academia and industry. Despite extensive studies on the enantioselective hydrocyanation of polar π -bonds (e.g., C=O and C=N),¹⁰ analogous methods for the hydrocyanation of alkenes remain underdeveloped.¹¹ Following early examples of highly

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enantioselective hydrocyanation of 2-methoxy-6-vinylnaphthalene by RajanBabu *et al.* in the context of naproxen synthesis,^{7–9} seminal contributions have been made using transition metal catalysis (e.g., Ni catalysis; Figure 1b).^{12–17} To date, however, a general catalytic approach that meets the criteria of both broad reaction scope and high enantioselectivity remains elusive. In particular, internal alkenes, which would lead to a substantially wider range of useful products, have proven to be challenging substrates.

Recently, we have established electrocatalysis^{18–21} as a broadly applicable strategy for the difunctionalization of alkenes.²² This approach merges the electrochemical generation of radical intermediates with catalyst-controlled radical addition to the alkene. Specifically, we devised anodically coupled electrolysis—a process that combines two anodic events to form two distinct radical intermediates—for the synthesis of a diverse suite of vicinally heterodifunctionalized structures.^{23,24} Further applying electrocatalysis to the hydrofunctionalization of alkenes, such as hydrocyanation, would substantially expand the scope of electrosynthesis. Such transformations would enable direct access to a specific monofunctionalized product in one step from the alkene precursor, and are therefore complementary to difunctionalization reactions in the context of target-oriented synthesis. Achieving this reaction enantioselectively would further increase its synthetic value and grant access to valuable chiral targets for applications in organic synthesis and medicinal chemistry. Early studies in electroorganic synthesis demonstrated the feasibility of electrochemical hydrofunctionalization of alkenes. However, known examples are primarily limited to intramolecular cyclizations²⁵ or reactions using activated alkenes (e.g., Michael acceptors)²⁶ with limited examples of intermolecular hydrofunctionalization of unactivated alkenes.²⁷ In addition, no enantioselective variants are currently available. In general, electrosynthetic methods that enable asymmetric alkene functionalization remain elusive.^{28–30} Against this backdrop, we describe an electrochemical approach for the enantioselective hydrocyanation of conjugated alkenes powered by a Co/Cu dual electrocatalytic process.

Results and Discussion

Reaction design

Achieving the desired hydrocyanation using our electrocatalytic strategy would require the parallel generation of two open-shell species that serve as H• and CN• equivalents. Toward this goal, we envisioned combining two metal-mediated elementary radical reactions in an anodically coupled electrocatalytic system (Figure 2a). In the proposed catalytic cycle, [Co^{III}]-H (formally), generated from a Co^{III} precursor and a hydrosilane,^{31–35} reacts with an alkene substrate via hydrogen atom transfer (HAT) to produce carbon-centered radical **I**.^{36–38} This intermediate then enters the cyanation cycle and undergoes single-electron oxidative addition to [Cu^{II}]-CN to form **II**, a formally Cu^{III} intermediate. Subsequent reductive elimination completes the hydrocyanation reaction.^{39–41}

This reaction design has garnered inspiration from two key discoveries in the area of metal-mediated radical chemistry. For one, metal hydride hydrogen-atom transfer (MHAT) has recently been established as a versatile approach for the hydrofunctionalization of alkenes.³¹ Directly related to this work, Carreira reported a racemic version of Co-catalyzed alkene

hydrocyanation using TsCN as the CN source.³ Recently, Shenvi showed for the first time that HAT-initiated alkene functionalization could intercept a second organometallic cycle in the context of Co/Ni-catalyzed hydroarylation.⁴² Nevertheless, there have been very few applications of MHAT to asymmetric catalysis,⁴³ and no study has been performed to date in the context of MHAT-mediated electrocatalysis. Secondly, our mechanistic design was also inspired by recent advances in enantioselective Cu-catalyzed radical cyanation. For example, Liu reported a series of elegant methods for the enantioselective cyanofunctionalization of styrenes promoted by chemical oxidants.⁴⁰ Harnessing this reactivity, we have recently established the viability of Cu-mediated asymmetric electrocatalysis in the context of cyanophosphinoylation of alkenes by replacing chemical oxidants⁴⁴ with an anode.⁴⁵ However, the scope of this cyanophosphinoylation reaction was limited to terminal styrenes. More importantly, Cu catalysis alone is not amenable to the development of a highly enantioselective hydrocyanation reaction, which is a synthetically more valuable transformation. In this work, we investigate a dual catalytic strategy that harnesses the synergistic combination of Co HAT and Cu cyanation, thereby providing a unique solution to this synthetic challenge.

The desired hydrocyanation reaction is an overall oxidative transformation, which requires the turnover of both catalysts via a pair of single-electron oxidation events to return the resultant Co^{II} and Cu^I species back to their reactive Co^{III} and Cu^{II} oxidation states (Figure 2a). The key to successfully achieving this reaction therefore relies on the identification of oxidative conditions that seamlessly accommodate both the Co HAT and Cu cyanation cycles. We note that the attributes of electrochemistry render it uniquely capable of facilitating the merger of these two catalytic processes into a broadly useful hydrocyanation protocol. On one hand, Co-catalyzed hydrofunctionalization can encounter chemoselectivity issues with styrene-type substrates (vide infra), particularly in the presence of an oxidant; this is likely due to the formation of a benzylic radical that is susceptible to over-oxidation to a benzyl cation.⁴⁶ On the other hand, Cu-catalyzed cyanation requires a potent chemical oxidant,^{39,40} which can also limit the reaction scope to substrates lacking oxidatively labile functional groups. By contrast, electrochemical strategies allow one to dial in a minimally sufficient potential, thereby circumventing the need for stoichiometric oxidants and addressing the incompatibility issues potentially associated with our Co/Cu dual catalytic process.

Reaction discovery and development

We set out to evaluate various combinations of Co and Cu catalysts. The electrochemical properties of many Co complexes have been well-documented.⁴⁷ However, the electrochemical compatibility and behavior of Cu complexes with common chiral ligands are largely unknown. In addition, Cu ions are highly susceptible to electroplating on the cathode (complete reduction of Cu(OTf)₂ observed at ~ -0.5 V vs ferrocenium/ferrocene, Fc⁺⁰, in DMF; see Supplementary Fig. 8). In an undivided electrochemical cell (e.g., a standard laboratory flask), an ideal vessel for preparative-scale electrochemical reactions, Cu complexes could be readily reduced at the cathode and lose catalytic activity.⁴⁸ Through systematic optimization, we found that Co(salen) complex **3** (0.5 mol%) and Cu(OTf)₂ (5 mol%) together with bisoxazoline (BOX) type ligands (**5–7**; 10 mol%) in the presence of

PhSiH₃ and TMSCN promoted the conversion of 4-*tert*-butylstyrene (**1**) to the desired product (**2**) in good yield and moderate enantioselectivity (50–72% e.e.; Figure 2b). Cyclic voltammetry studies revealed that both the BOX ligand and CN⁻ are important in keeping the Cu catalyst in solution presumably through the formation of [Cu(BOX)(CN)_n]-type complexes, avoiding detrimental cathodic deposition during electrolysis (see Supplementary Fig. 9). In addition, the combination of Pt as the cathode and HOAc as the terminal oxidant is important to ensure facile proton reduction at a relatively low overpotential, which outcompetes the undesired Cu reduction.

To further optimize enantioselectivity, we surveyed a catalog of chiral bidentate *N,N*- and *P,P*-ligands, including several that are known to be excellent Cu ligands for enantioselective Lewis acid⁴⁹ or radical catalysis.^{39,40,50,51} However, the optimal e.e. could not be improved above 72% (ligand **7**). During our reaction optimization, we discovered that serine-derived bisoxazolines (sBOXs; e.g., **4**) are excellent ligands in the desired hydrocyanation reaction. These ligands are readily prepared from serine,⁵² and were recently shown by us to be effective ligands in the cyanophosphinoylation reaction as well.⁴⁵ As shown in Figure 2b, the use of ligand **4** drastically improved the reaction enantioselectivity to 91% e.e. and also increased the yield to 79%. Using computational methods, we show that such high reaction enantioselectivity arises from a complex interplay between attractive and repulsive non-covalent interactions due to the second-sphere ester groups in these sBOX ligands (vide infra).

A number of control experiments serve to highlight the importance of each component of our reaction system. For example, using MeCN instead of DMF as the solvent, LiClO₄ instead of TBABF₄ as the electrolyte, or EtOH instead of HOAc as the proton source, led to decreased product yield (Figure 2b). Notably, the product was also formed in substantially lower e.e. in the presence of LiClO₄. Previous work showed that the identity of the electrolyte can significantly affect the polarity of the electrical double layer (EDL).⁵³ As such, we hypothesize that TBABF₄ creates a significantly less polar EDL on the anode than LiClO₄, which is responsible for the improved enantioselectivity. When Co loading was increased from 0.5 to 2 mol%, the yield of **2** was dramatically decreased and a large amount of hydrogenated side product was observed.³⁸ This result highlights the importance of balancing the rates of the HAT and cyanation events to ensure optimal product selectivity. Finally, the reaction requires both Cu and Co to operate, as excluding either catalyst led to minimal conversion to the hydrocyanation product.

Reaction scope and application

In addition to representing a conceptual advance, our electrochemical hydrocyanation is also synthetically valuable and provides a complementary route to existing methods for the synthesis of chiral nitriles. Under optimal conditions, a variety of vinylarenes underwent hydrocyanation to furnish desired arylpropionitriles with excellent enantioselectivity (Table 1). The efficiency of the transformation was found to be relatively independent of the electronic properties of the aryl substituents. Importantly, the very mild reaction conditions imparted by the combination of electrochemistry and a radical mechanism made accessible a broad scope of enantioenriched nitriles with a diverse range of functional groups. In

particular, functionalities that are susceptible to oxidative degradation under chemical conditions, such as electron-rich arenes (e.g., **8**, **15**, **20**), sulfides (**11**), and aldehydes (**13**), can be readily engaged in the hydrocyanation. Furthermore, groups including benzyl chlorides (**12**), aryl halides (**9**, **25**), and aryl boronates (**17**), which might induce catalyst promiscuity under Ni-promoted conditions, were well tolerated in our reaction. Alkenes with various heterocycles (**20-23**, **25**) also proved excellent substrates. The scalability of the reaction was demonstrated in the synthesis of products **2** and **15** on 2–5 mmol scales (10–25 times scale-up), which were isolated in comparable but marginally decreased yield and e.e. We attribute the reduction in yield and e.e. to inefficient mass and heat transport due to the heterogeneous nature of electrode reactions, which may be addressed via reactor engineering.

Importantly, our reaction is also applicable to internal alkenylarenes (Table 1), which are typically challenging substrates in previously reported enantioselective hydrocyanation reactions due to their low reactivity.¹³ Our protocol shows very broad substrate generality, furnishing products with a variety of synthetically useful functional handles (**28**, **29**, **34**, **38**) and *N*-heterocyclic motifs (**43**). Since the stereochemistry of the starting alkene does not affect the yield or enantioselectivity, a mixture of *E/Z*-isomers can be used directly in this reaction. Both electron-rich (**37**) and electron-deficient (**39-44**) alkenes proved suitable substrates. In particular, hydrocyanation was achieved for cinnamoyl-type structures including esters (**39**, **43**, **44**), ketones (**40**, **41**), and nitriles (**42**). These results demonstrate that our reaction can serve as a more general alternative to the enantioselective Michael addition en route to similar products. Considering that numerous bioactive natural products and their synthetic precursors contain cinnamoyl side chains (e.g., taxol, phyllanthocin), our method provides a convenient means to derivatize these compounds for medicinal chemistry studies.

We further extended the scope of our reaction to other types of unsaturated substrates (Table 1). For example, dienes were converted to mono-hydrocyanated products in high efficiency and enantioselectivity. In the case of linear dienes (**45-49**), the reaction selectively functionalizes the terminal C=C π -bond. Structurally analogous enynes also reacted chemoselectively in good e.e. (**50**). Interestingly, in these transformations, enantioselective Cu-mediated C–CN bond formation is achieved via an allyl or propargyl radical species.⁵⁴ Finally, we expanded the reaction scope to allenes. The hydrocyanation of phenylallene (**51**) yielded cinnamyl cyanide (**52**) as the predominant product. Based on density functional theory (DFT) calculations, we believe that this product arose from regioselective HAT at the central allene carbon to form an allyl radical (24.3 kcal/mol more stable than the corresponding vinyl radical; see Supplementary Fig. 13) followed by Cu-promoted regioselective cyanation at the primary carbon to maintain the conjugated styrene motif (4.1 kcal/mol lower barrier than cyanation at the benzylic carbon; see Supplementary Fig. 13). This selectivity allowed us to achieve double hydrocyanation through the use of an excess of reagents to generate 1,3-dinitrile **53** with high enantioselectivity. A radical rearrangement experiment provided key support for the intermediacy of the organic radical species. Exposure of cyclopropane-derived alkene **54** to the reaction conditions led to the expected ring opening, furnishing alkene-containing nitrile **55** in high yield and enantioselectivity.

Alkyl nitriles are highly versatile synthetic intermediates that can be readily transformed to a variety of useful functional groups, such as aldehydes, alcohols, carboxylic acids, esters, amines, and heterocycles. Here we showcase the synthetic value of our reaction products through three examples (Figure 3). Product **15** was readily converted to either naproxen methyl ester **56** via methanolysis or to benzoindoline **57** via reduction followed by Pd-catalyzed C–H amination.⁵⁵ Both derivatizations occurred with complete retention of stereochemistry. Nitrile **18** was subjected to reduction and subsequent cyclization to yield dihydroisoquinolone **58**. These products bear structural resemblance to high-value drug molecules, again highlighting the significance of the enantioselective hydrocyanation reaction.

Electrochemical control of reaction chemoselectivity

A key advantage of electrochemistry is the ability to achieve external control over the electrode potential input. This feature allowed us to regulate the hydrocyanation chemoselectivity of electron-rich vinylarenes (Figure 4a). For example, using 3-vinyl-*N*-Ts-indole as the substrate, under our standard conditions with the application of a cell voltage of 2.3 V ($E_{\text{anode}} \sim 0.24$ V vs $\text{Fc}^{+/0}$), we observed full conversion of the alkene but minimal formation of desired nitrile **20**. Instead, several side products were formed, including those that arose from over-oxidation of the benzyl radical intermediate⁵⁶ to the corresponding cation followed by nucleophilic trapping (e.g., formate and ketone products). By lowering the voltage input from 2.3 V to 1.8 V ($E_{\text{anode}} \sim 0.08$ V), we successfully suppressed over-oxidation and obtained hydrocyanation product **20** in 71% yield. This principle was also applied to the optimization of reactions forming **8** and **59**.

For comparative purposes, we examined the hydrocyanation of alkene **1** under traditional chemical conditions without an electrical input. None of the chemical oxidants we surveyed promoted the reaction with efficiencies or enantioselectivities comparable to our protocol (Figure 4b). In cases where a low yield of **2** was obtained (9–24%), the enantioselectivity was also substantially lower (40–68% e.e.). This erosion of e.e. is likely a result of a racemic carbocation pathway caused by over-oxidation of the key benzylic radical intermediate. We note that, although these results could potentially be improved through extensive optimization of reaction conditions, such optimization studies would need to address the challenges associated with the use of a terminal chemical oxidant. Electrochemistry, with its ability to enable electron transfer with a minimally sufficient potential input, provides an ideal means to circumvent issues with chemical oxidation and harness multiple redox catalytic cycles for productive chemistry.

Stereochemical model

Finally, we enlisted theoretical methods to elucidate the role played by sBOX ligands in directing the highly enantioselective Cu-mediated hydrocyanation. A previous study showed that the radical combination to generate intermediate **II** (Figure 2) is facile, whereas reductive elimination to construct the C–CN bond is slow and thus enantio-determining.³⁹ Traditionally, BOX-type ligands are thought to induce enantioselectivity through primarily repulsive steric interactions imparted by the bulky substituents on the oxazoline groups.⁴⁹ Considering that the ester-derived ligands (**4**, **60**) perform substantially better than the

canonical BOX ligands with various steric profiles (e.g., **5-7**), we hypothesized that the ester groups must also provide attractive interactions with the substrate assembly in the key C–CN forming transition state (TS). DFT computations are fully consistent with this hypothesis (Figure 5 and Supplementary Section 7). Using the reaction forming **10** as an example, the lowest energy TS structures leading to the major (*R*) and minor (*S*) products (TS_{*R*} and TS_{*S*}, respectively) both display a favorable C–H⋯π interaction between the acidic proton at the α-position of one ester group and the substrate aryl group. This attractive non-covalent interaction dictates the TS geometry by positioning the substrate alkyl group towards the ester on the opposite half of the catalyst. However, this arrangement causes more severe steric interactions in TS_{*S*} than TS_{*R*}. In addition to having the closest catalyst-substrate contacts (*d*₃ in Figure 4), these exponentially repulsive steric interactions also force the bulky ^tBu-ester group to deviate more significantly from its optimal planar geometry in TS_{*S*} (both θ values in Figure 4), and this broken conjugation further destabilizes the minor TS. Based on these findings, we further hypothesize that this complex interplay between attractive and repulsive non-covalent interactions in the TS determines the reaction enantioselectivity. We note in passing that this computational analysis refutes our previous hypothesis⁴⁵ that direct coordination of the ester groups to the Cu center was responsible for stabilizing the major TS during enantioselective C–CN formation.

This stereochemical model is consistent with our experimental observations. For example, reactions with internal alkenes are in general more enantioselective than those with terminal alkenes. This can be explained by the increased steric interactions between the substrate alkyl group and the catalyst ester group in TS_{*S*} for the internal alkenes. In addition, substrates with more electron-rich aryl groups (e.g., **2**, **8**) in general lead to higher enantioselectivity than those with electron-deficient groups (e.g., **9**, **13**), which can be rationalized by an enhanced C–H⋯π interaction with the aryl group.⁵⁷

Conclusion

The electrocatalytic hydrocyanation described herein reveals the unique advantages of harnessing electrochemistry in exploring new chemical space and developing solutions to challenging synthetic problems. This new transformation will enhance chemists' access to a diverse array of enantioenriched nitriles. On a fundamental level, the realization of electrochemical hydrofunctionalization and demonstration of enantioselective electrocatalysis will improve the scope of electrosynthesis and its adoption in modern organic chemistry.

Methods

Method A

General procedure for the electrochemical hydrocyanation of alkenes using a custom-made cell⁵⁸ (0.20 mmol scale)—In a 2 dr vial, ligand **4** (7.6 mg, 0.02 mmol, 10 mol %) and Cu(OTf)₂ (3.6 mg, 0.01 mmol, 5 mol %) were dissolved in DMF (1.0 mL) under a N₂ atmosphere, and the mixture was stirred for 2 hours before use (Solution A). An oven-dried, 10 mL two-neck glass tube as equipped with a magnetic stir bar, a rubber septum, a threaded Teflon cap fitted with electrical feedthroughs, a carbon felt anode (1 ×

$0.5 \times 0.6 \text{ cm}^3$) (connected to the electrical feedthrough via a 9 cm in length, 2 mm in diameter graphite rod), and a platinum plate cathode ($1.0 \times 0.5 \text{ cm}^2$). To this reaction vessel, TBABF₄ (132 mg) was added. The cell was sealed and flushed with nitrogen gas for 5 min, followed by the sequential addition via syringe of the olefin substrate (0.2 mmol, 1.0 equiv, dissolved in 1 mL DMF) and HOAc (60 μL , 1 mmol, 5 equiv), Co(salen) **3** (0.6 mg, 0.001 mmol, 0.5 mol%, dissolved in 1 mL DMF), and Solution A. A nitrogen-filled balloon was adapted through the septum to sustain a nitrogen atmosphere. The reaction vessel was then cooled to 0 °C. PhSiH₃ (24 mg, 0.22 mmol, 1.1 equiv) and TMSCN (50 μL , 0.4 mmol, 2 equiv) were dissolved in DMF (1.0 mL) and the resulting solution was added to the glass tube via syringe. Electrolysis was initiated at a cell potential of 2.3 V at 0 °C. Upon full consumption of olefin starting material as determined by thin-layer chromatography analysis, the electrical input was removed. The mixture was diluted with ethyl acetate (60 mL) and then washed with water (40 mL), brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was subjected to flash column chromatography on silica gel (eluted with hexanes/ethyl acetate) to yield the desired product.

Method B

General procedure for the electrochemical hydrocyanation of alkenes using ElectraSyn 2.0 (0.30 mmol scale)—Remove the graphite plate from the ElectraSyn graphite electrode assembly to obtain the empty electrode holder and then cut a piece of carbon felt ($5.3 \times 0.8 \times 0.6 \text{ cm}^3$) and fixed it on the commercial graphite electrode using Pt wire as the working electrode. Pt foil was used as the counter electrode. In a dried sealed tube, sBOX(Pr) **60** (11.4 mg, 0.03 mmol) and Cu(OTf)₂ (5.4 mg, 0.015 mmol) were dissolved in DMF (1.0 mL) under a N₂ atmosphere, and the mixture was stirred for 2 hours before use. Charge the ElectraSyn vial (10 mL volume) with a Teflon-coated magnetic stir bar, TBABF₄ (198 mg, 0.6 mmol) and olefin (48.0 mg, 0.30 mmol). Cover the screw thread area of the vial with a rubber septum to ensure that the seal is airtight. Adapt the carbon felt and Pt foil electrodes on the ElectraSyn vial cap and screw the vial cap onto the vial to finger tight and flushed with nitrogen gas for 5 minutes. Using a syringe, add DMF (3.0 mL), HOAc (90 mg, 1.5 mmol), Co(salen) **3** (0.0015 mmol, 0.5 mol%, 0.9 mg dissolved in 1 mL DMF) and the copper catalyst solution (prepared as in Method A) through the rubber septum. A nitrogen-filled balloon was adapted through the septum to sustain a nitrogen atmosphere. Adapt the electrochemical cell onto the vial holder of ElectraSyn 2.0 and the reaction vessel was then cooled to 0 °C using an ice bath. After that, TMSCN (0.6 mmol, 75 μL) and PhSiH₃ (0.33 mmol, 35.7 mg) were dissolved in DMF (1.0 mL), which was added to the reaction solution via syringe. Select “new experiments” at “constant current” and adjust the current to 3.0 mA. Select “No” for “use of reference electrode” and adjust the reaction time to “10 h 43 min 35 sec”. Adjust “mmols substrate” to “0.3 mmol” and choose not to alternate the polarity. Review the parameters, remove the ice bath and start the experiment. After electrolysis, disconnect the reaction vial from ElectraSyn 2.0, gently remove the cap with electrodes from the vial and transfer the reaction media to a separatory funnel. Wash both electrodes with ethyl acetate (20 mL) to transfer any residual product. Add 30 mL ethyl acetate to the separatory funnel and wash the organic solution with water and brine. Dry the organic layer with anhydrous Na₂SO₄ and concentrated under reduced

pressure. The residue was subjected to flash column chromatography on silica gel (eluted with hexanes/ethyl acetate) to yield 32.0 mg of desired product (57% yield, 73% brsm, unoptimized) with 86% e.e.

Method C

Scale-up electrolysis using a commercial three-necked flask (2.0 mmol, 0.4 g scale)—In a dried sealed tube, sBOX(^tBu) **4** (76.0 mg, 0.2 mmol) and Cu(OTf)₂ (36.1 mg, 0.1 mmol) were dissolved in DMF (4.0 mL) under a N₂ atmosphere, and the mixture was stirred for 2 hours before use. To an oven-dried three neck round bottom flask (50 mL) equipped with a magnetic stir bar were added TBABF₄ (988 mg, 3 mmol) and olefin substrate (368.4 mg, 2 mmol). Each neck was fitted with a rubber septum. The septa on the side necks were fitted with a carbon felt anode (1.5 × 1.0 × 0.6 cm³, connected to a 9 cm in length, 2 mm in diameter graphite rod), and a platinum foil cathode (2.5 × 1.5 cm²), the lower (closest) ends of the electrodes was 0.5 cm apart. The cell was sealed and flushed with nitrogen gas for 5 minutes, followed by the addition via syringe of DMF (24 mL), HOAc (0.6 mL), Co(salen) **3** (0.01 mmol, 0.5 mol%, 6.0 mg dissolved in 1 mL DMF), and copper catalyst solution made in advance. A nitrogen-filled balloon was adapted through the septum to sustain a nitrogen atmosphere. The reaction vessel was then cooled to 0 °C. After that, TMSCN (4 mmol, 2 equiv, 500 uL) and PhSiH₃ (2.2 mmol, 1.1 equiv, 238 mg) were dissolved in DMF (1.0 mL) and added to the reaction solution via syringe. Electrolysis was initiated at a constant current of 7.0 mA at 0 °C. Reaction was stopped after 4.0 F/mol charge was passed (30 hours 38 min). The mixture was then diluted with ethyl acetate (200 mL) and then washed with water, brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was subjected to flash column chromatography on silica gel (eluted with hexanes/ethyl acetate) to yield 299.9 mg of desired product (71% yield) with 90% e.e.

Method D

Scale-up electrolysis using a commercial three-necked flask (5.0 mmol, 0.8 g scale)—In a dried sealed tube, sBOX(^tBu) **4** (190.0 mg, 0.5 mmol) and Cu(OTf)₂ (90.4 mg, 0.25 mmol) were dissolved in DMF (10.0 mL) under a N₂ atmosphere, and the mixture was stirred for 2 hours before use. To an oven-dried three neck round bottom flask (100 mL) equipped with a magnetic stir bar were added TBABF₄ (1.98 g, 6 mmol) and olefin substrate (800 mg, 5 mmol). Each neck was fitted with a rubber septum. The septa on the side necks were fitted with a carbon felt anode (1.8 × 1.8 × 0.6 cm³, connected to a 9 cm in length, 2 mm in diameter graphite rod), and a platinum foil cathode (2.0 × 3.0 cm²), the lower (closest) ends of the electrodes was 1.0 cm apart. The cell was sealed and flushed with nitrogen gas for 5 minutes, followed by the addition via syringe of DMF (35 mL), HOAc (1.5 mL), Co(salen) **3** (0.025 mmol, 0.5 mol%, 15 mg dissolved in 10 mL DMF), and copper catalyst solution made in advance. A nitrogen-filled balloon was adapted through the septum to sustain a nitrogen atmosphere. The reaction vessel was then cooled to 0 °C. After that, TMSCN (10 mmol, 2 equiv, 1250 uL) and PhSiH₃ (5.5 mmol, 1.1 equiv, 594 mg) were dissolved in DMF (5.0 mL) and added to the reaction solution via syringe. Electrolysis was initiated at a constant current of 10.0 mA at 0 °C. Reaction was stopped after 4.0 F/mol charge was passed (53 hours 37 min). The mixture was then diluted with ethyl acetate (300

mL) and then washed with water, brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was subjected to flash column chromatography on silica gel (eluted with hexanes/ethyl acetate) to yield 514.2 mg of desired product (55% yield) with 85% e.e.

Method E

General procedure for control experiments using chemical oxidants instead electrochemistry—In a 2 dr vial, sBOX(ⁱPr) (3.5 mg, 0.01 mmol, 10 mol %) and Cu(OTf)₂ (1.8 mg, 0.005 mmol, 5 mol %) were dissolved in DMF (1.0 mL) under a N₂ atmosphere, and the mixture was stirred for 2 hours before use. To a dried 2 dr vial, *tert*-butyl styrene (16.0 mg, 0.1 mmol, 1.0 equiv), the oxidant (0.1 mmol, 1.0 equiv) and HOAc (30.0 mg, 0.5 mmol, 5.0 equiv) were added under a N₂ atmosphere. After that, Co(salen) (0.0005 mmol, 0.5 mol%, 0.3 mg dissolved in 0.5 mL DMF) and the copper catalyst solution made in advance were added. A nitrogen-filled balloon was adapted through the septum to sustain a nitrogen atmosphere. The reaction vessel was then cooled to 0 °C. PhSiH₃ (0.11 mmol, 1.1 equiv, 12 mg) and TMSCN (0.2 mmol, 2 equiv, 25 uL) were dissolved in DMF (0.5 mL) and added to the reaction solution via syringe. After stirring at room temperature for 24 hours, the mixture was diluted with ethyl acetate (20 mL) and then washed with water, brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. Yields were determined with ¹H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. The enantiomeric excess value of the product was measured by HPLC analysis on a chiral stationary phase.

Method F

Product derivatization: nitrile methanolysis—In a dried sealed tube, (*R*)-2-(6-methoxynaphthalen-2-yl)propanenitrile **15** (21.1 mg, 0.10 mmol, 90% *ee*) and 37% HCl (1.0 mL) were dissolved in MeOH (1.0 mL) under a N₂ atmosphere. The mixture was then heated under 80 °C for 48 hours. After cooling to room temperature, the mixture was extracted with ethyl acetate (30 mL) 3 times. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. Column chromatography using silica gel was then applied to yield the desired product in 62% yield (15.1 mg) in 90% e.e. as a colorless oil.

Method G

Product derivatization: indoline formation

Step 1: A solution of (*R*)-2-(6-methoxynaphthalen-2-yl)propanenitrile **15** (0.3 mmol, 63.3 mg, 90% *ee*) and CoCl₂ (0.6 mmol, 2.0 equiv, 78 mg) in dry methanol (3.0 mL) was cooled to 0 °C under nitrogen atmosphere. NaBH₄ (3.0 mmol, 10 equiv, 114 mg) was added in portions. The resulting reaction mixture was then allowed to warm to room temperature and continued to stir for 2 hours. After that, the reaction mixture was poured into 100 mL of 2 M HCl at 0 °C and stirred till the black precipitate was dissolved. The mixture was washed with ethyl acetate (50 mL) 3 times and the aqueous layer was made alkaline with NaOH at 0 °C and then extracted with ethyl acetate (100 mL) twice. The organic layer was separated

and dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product with 84% yield was used directly for the next step.

Step 2: Under a N₂ atmosphere, a solution of **S1** (43.0 mg, 0.2 mmol), picolinic acid (29.5 mg, 1.2 equiv, 0.24 mmol), EDCI (57.5 mg, 1.5 equiv, 0.3 mmol) and DMAP (2.5 mg, 0.1 equiv, 0.02 mmol) in dry dichloromethane (2.0 mL) was stirred at room temperature overnight. After that, the reaction mixture was purified directly by flash column chromatography to give the desired product with 80% isolated yield.

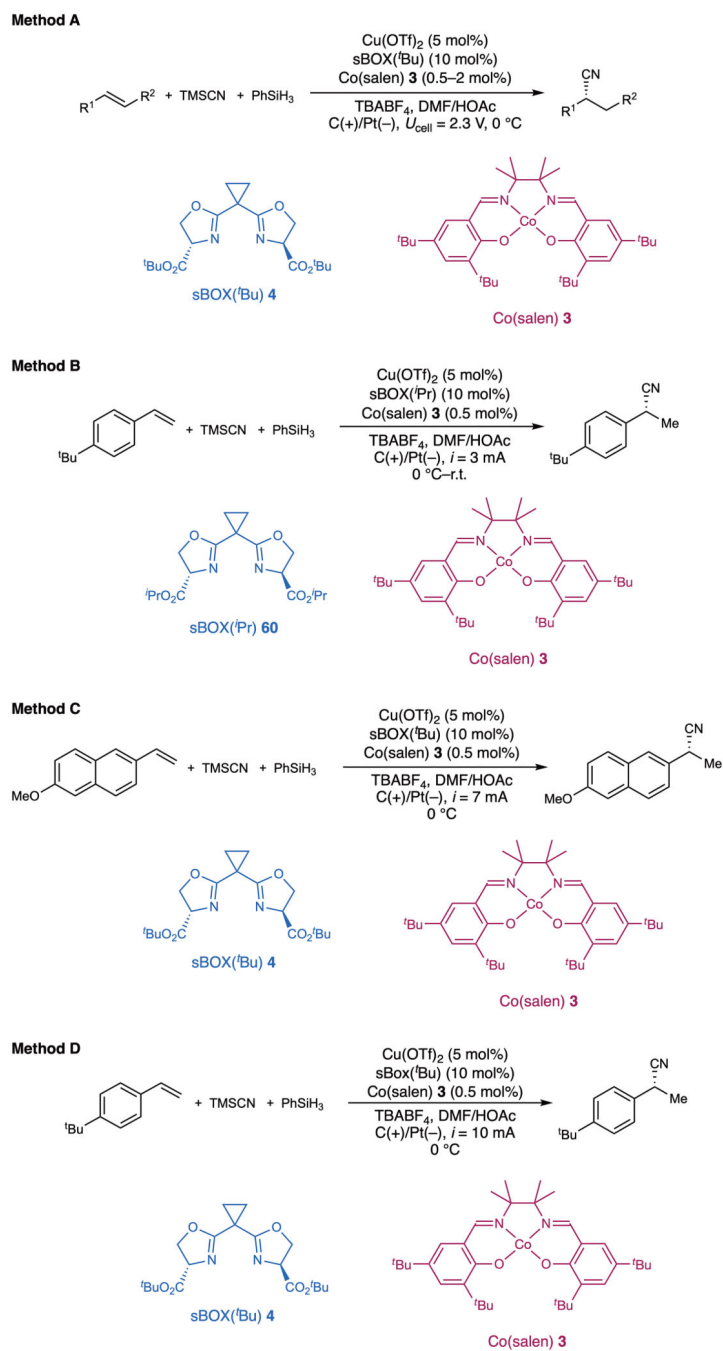
Step 3: Under a N₂ atmosphere, a mixture of **S2** (0.1 mmol, 1.0 equiv, 32 mg), Pd(OAc)₂ (0.005 mmol, 0.05 equiv, 1.2 mg), PhI(OAc)₂ (0.25 mmol, 2.5 equiv, 80.5 mg), and toluene (1 mL) in a sealed tube was heated at 60 °C for 24 hours. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was purified by silica gel flash chromatography to give the cyclized product with 92% isolated yield in 90% e.e.

Method H. Product derivatization: dihydroisoquinolinone formation—Under a N₂ atmosphere, solution of methyl (*R*)-2-(1-cyanoethyl)benzoate **18** (0.1 mmol, 18.9 mg, 85% ee) and CoCl₂ (0.2 mmol, 2.0 equiv, 26 mg) in dry methanol (1.0 mL) was cooled to 0 °C. NaBH₄ (1.0 mmol, 10 equiv, 38 mg) was added in portions. The resulting reaction mixture was then allowed to warm to room temperature and continued to stir for 2 hours. After that, the reaction mixture was heated to reflux for overnight. The resulting reaction mixture was extracted by ethyl acetate (20 mL) 3 times and the combined organic layers were dried over anhydrous Na₂SO₄. Purification by silica gel flash chromatography gave the cyclized product with 81% isolated yield in 87% e.e.

Data Availability Statement

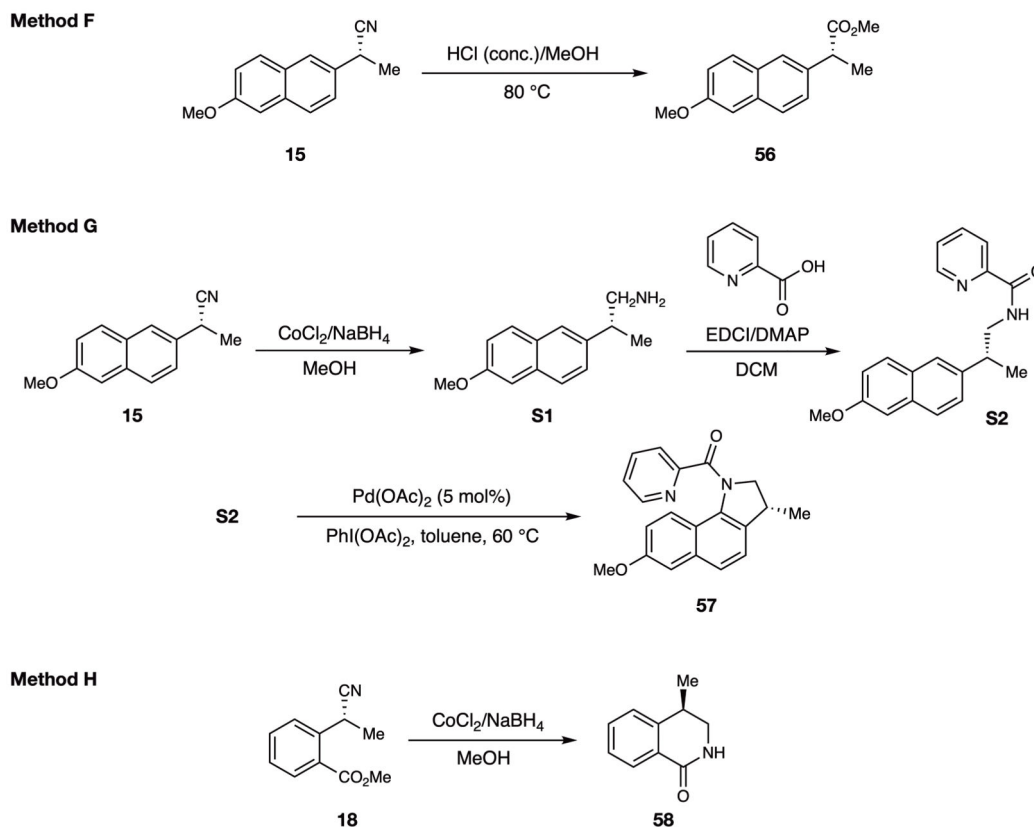
The data that support the findings of this study are included in this published article (and its supplementary information files) or available from the corresponding authors upon reasonable request. Crystallographic data for compound **4** have been deposited at the Cambridge Crystallographic Data Centre under deposition number 1978310 and can be obtained free of charge (http://www.ccdc.cam.ac.uk/data_request/cif).

Extended Data



Extended data figure 1 | Methods for electrochemical hydrocyanation of alkenes.

Method A, electrochemical hydrocyanation of alkenes using a custom-made cell⁵⁸ (0.20 mmol scale). **Method B**, electrochemical hydrocyanation of alkenes using ElectraSyn 2.0 (0.30 mmol scale). **Method C**, Scale-up electrolysis using a commercial three-necked flask (2.0 mmol, 0.4 g scale). Detailed experimental procedures can be found in Methods section.



Extended data figure 2 |. Methods for product derivatization.

Method F, Derivatization of product **15** to naproxen methyl ester **56** (analogous to naproxen). **Method G**, Derivatization of product **15** to benzindoline **57** (analogous to duocarmycin). **Method H**, Derivatization of product **18** to dihydroisoquinolone **58** (analogous to palonosetron). Detailed experimental procedures can be found in Methods section.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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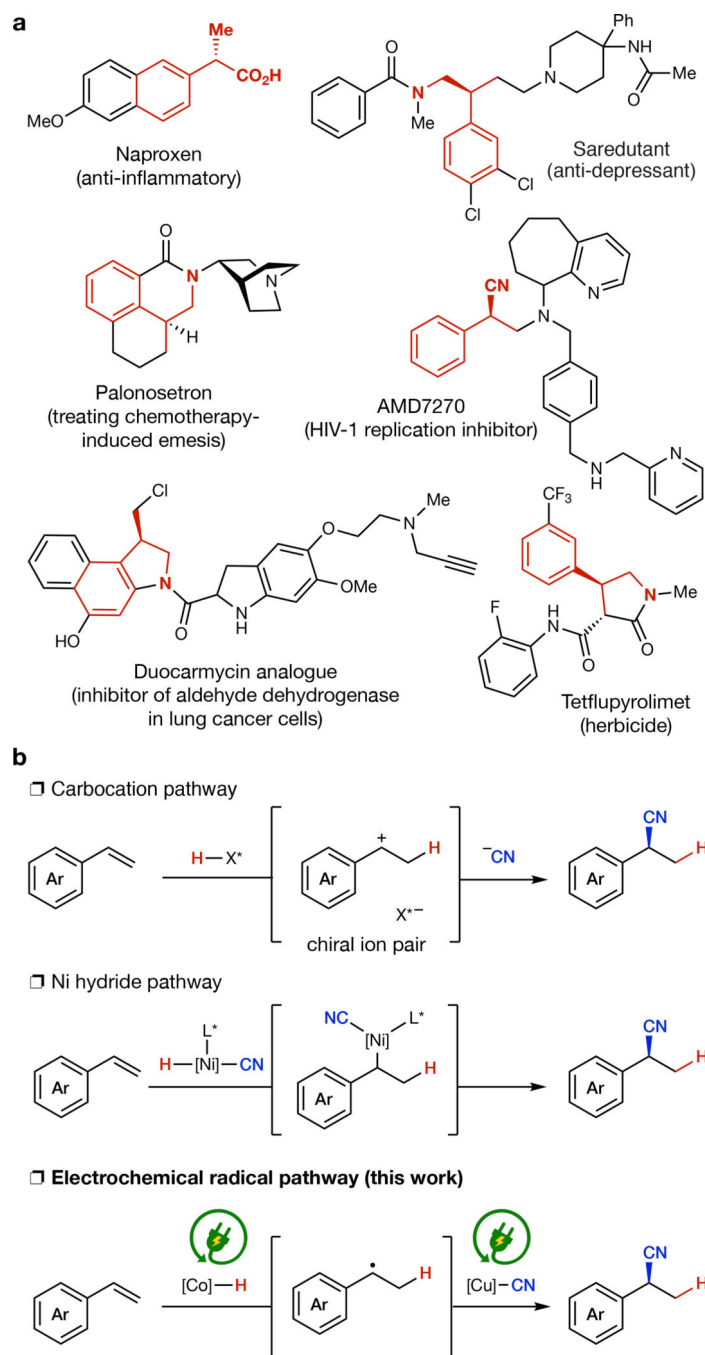


Fig. 1 | Enantioselective hydrocyanation: synthetic significance and proposed strategy.
a, Arylpropionitriles and derivatives in pharmaceuticals and agrochemicals. **b-d**, Strategies for enantioselective hydrocyanation of alkenes. **b**, The challenges for the carbocation pathway are that enantioinduction with benzyl cations is difficult. There is no current precedent, despite extensive use of this strategy in C=X hydrocyanation¹⁰. **c**, The challenges for the Ni hydride pathway are limited scope, and that reaction yield and selectivity are highly dependent on structure and electronic property of alkene. There is precedent for this pathway^{7-9, 12-15}. **d**, Features of electrochemical radical pathway (this work) include broad

scope; high enantioselectivity; high functional group tolerance; electrochemical control of chemoselectivity; new mechanistic information. asterisk implies possession of chiral information

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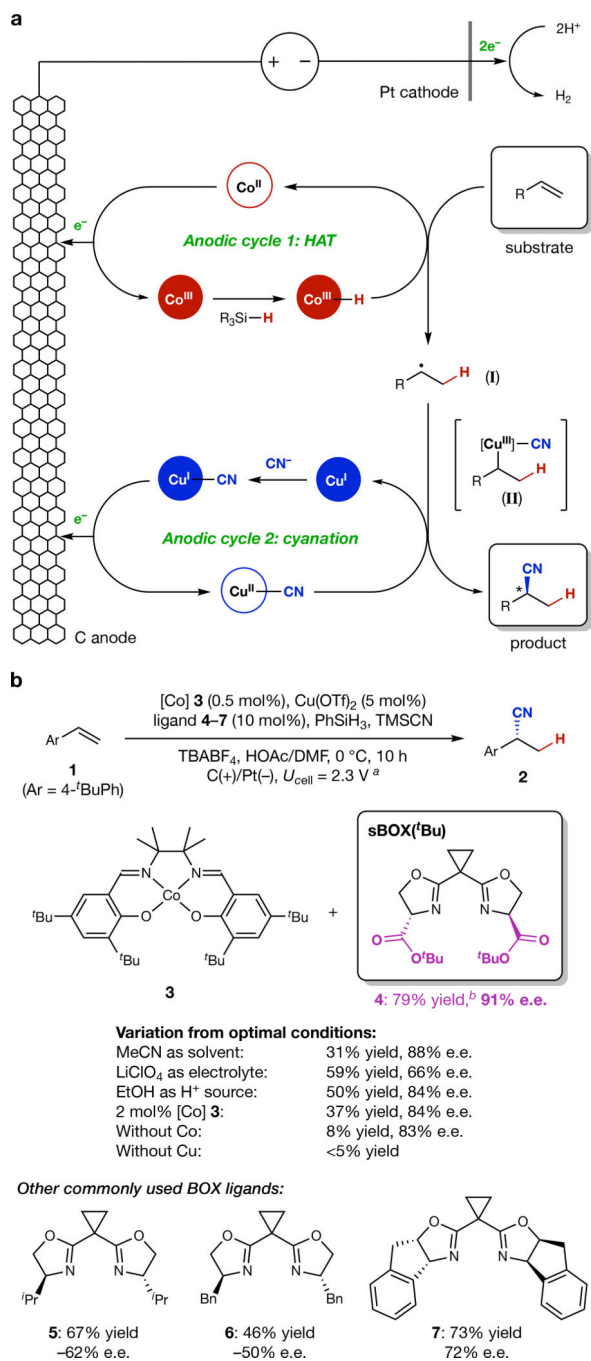


Fig. 2 | Reaction design, discovery and optimization.

a, Anodically coupled dual electrocatalysis is employed as reaction design. **b**, Development and optimization of the reaction. Yields were determined by ¹H NMR. ^a U_{cell} : cell voltage applied between the cathode and anode; $U_{\text{cell}} = 2.3 \text{ V}$ corresponds to *ca.* 0.24 V vs $\text{Fc}^{+/0}$ anodic potential (E_{anode}) and gives *ca.* 2 mA initial current. ^bIsolated yield. Abbreviations: e.e. = enantiomeric excess.

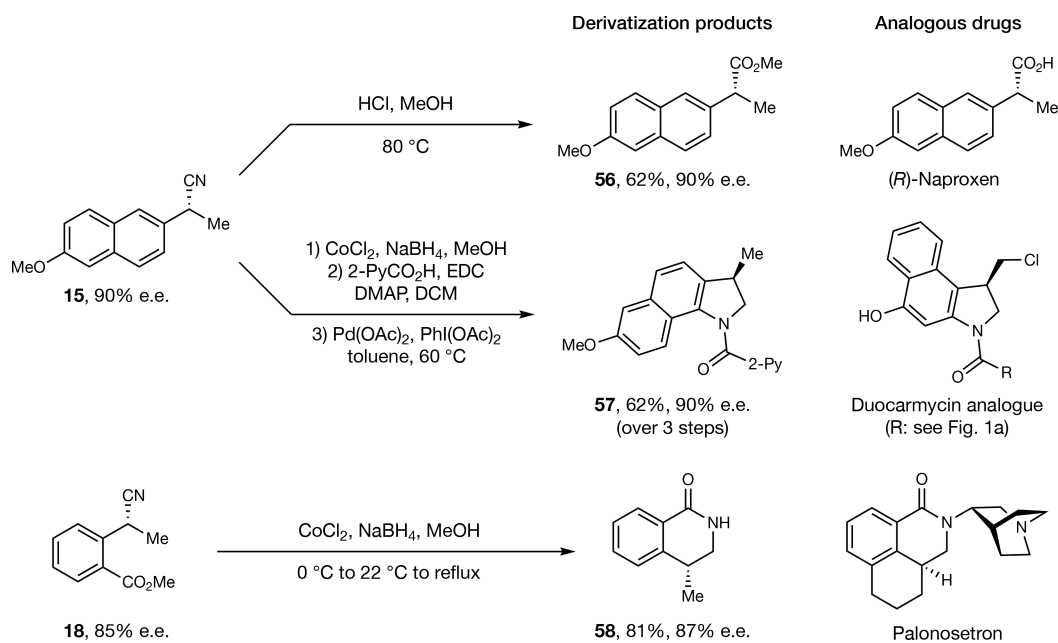


Fig. 3 |. Product derivatization.

a. Product **15** is derived to naproxen methyl ester **56** (analogous to naproxen) via methanolysis. **b.** Product **15** is derived to benzoinoline **57** (analogous to duocarmycin) via reduction followed by Pd-catalyzed C–H amination. **c.** Product **18** is derived to dihydroisoquinolone **58** (analogous to palonosetron) via reduction and subsequent cyclization. Detailed experimental procedures can be found in Supporting Information.

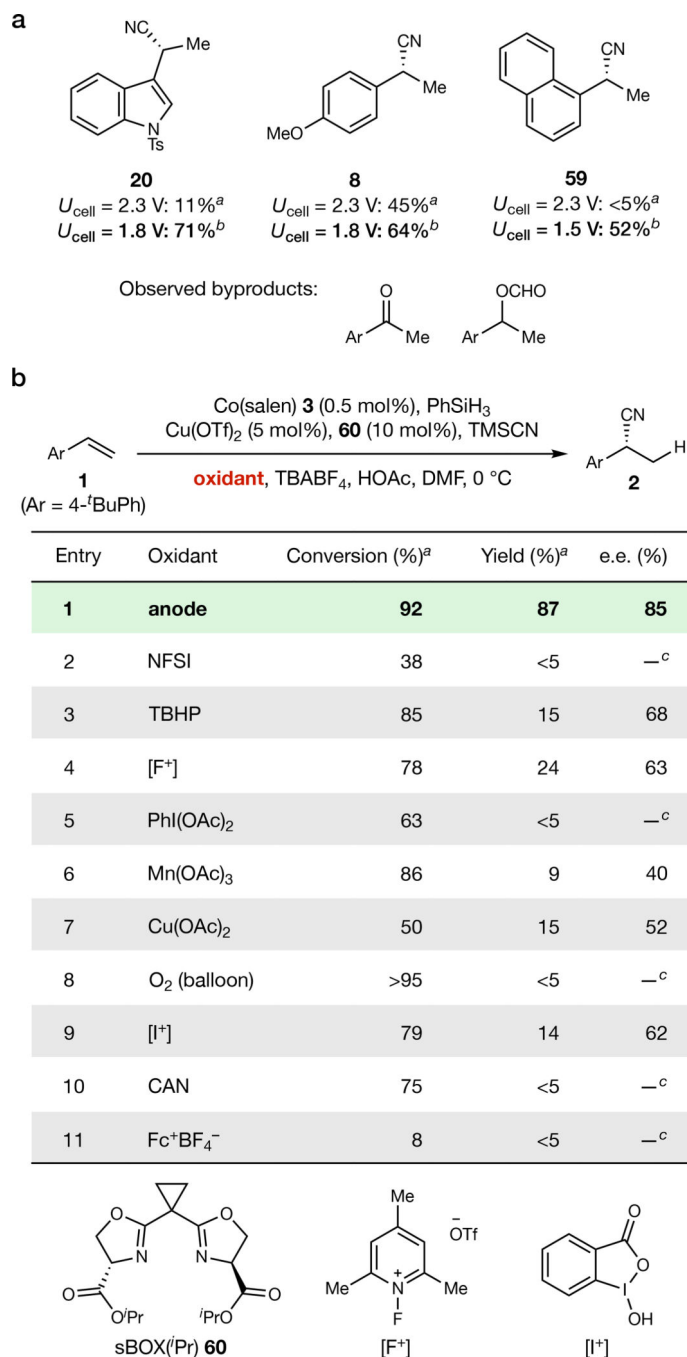


Fig. 4 |. Electrochemical tuning of reaction chemoselectivity and comparison with chemical methods.

a. Chemoselectivity thus product yield is easily improved by controlling applied potential, minimizing ketone and formate byproducts formed from overoxidation of electron-rich substrates. ^aDetermined by ¹H NMR. ^bIsolated yield. **b.** Comparison with common chemical oxidants shows that electrochemical method is superior to traditional chemical oxidants. The ability to provide minimal oxidation power in electrochemical method suppresses overoxidation which results in byproducts or racemic carbocation pathway. ^cNot determined.

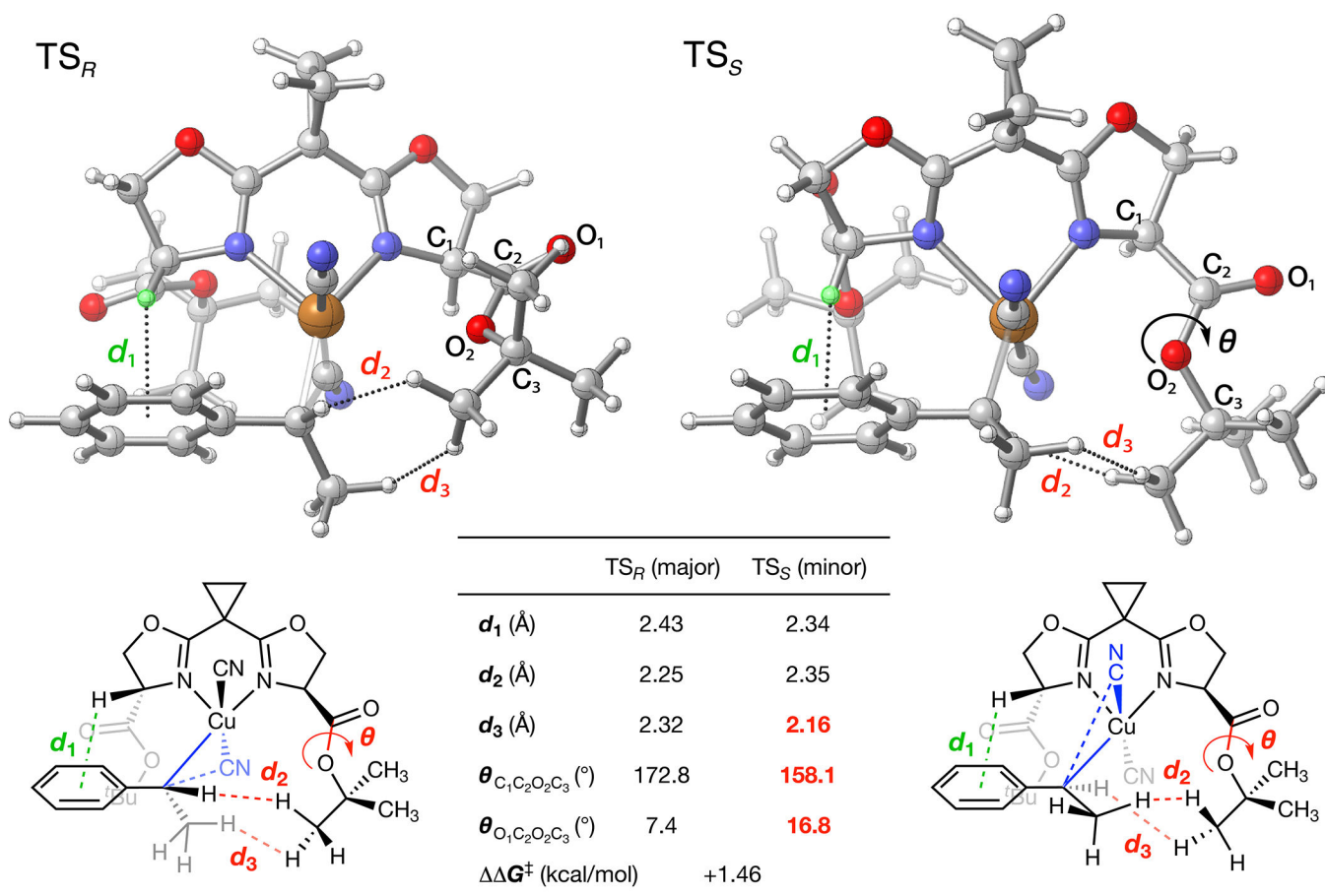


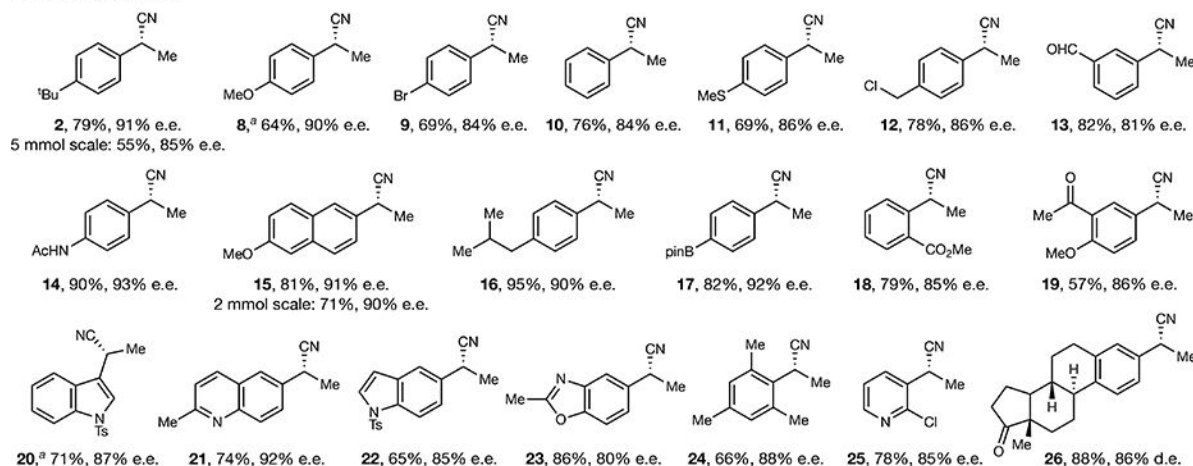
Fig. 5 |. Computational stereochemical model.

DFT calculation shows a favorable C–H π interaction between substrate and ligand, leading to a more organized transition state thus high e.e.. Numbers in red indicate closest catalyst–substrate contacts or dihedral angles which significantly deviate from their optimal values.

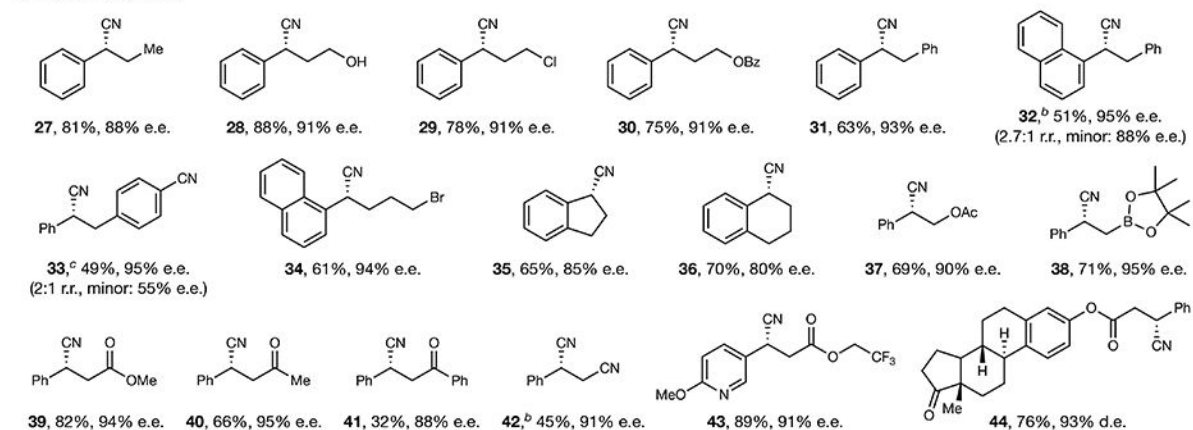
Table 1 |

Reaction scope.

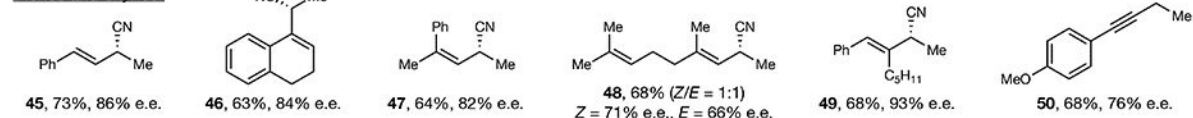
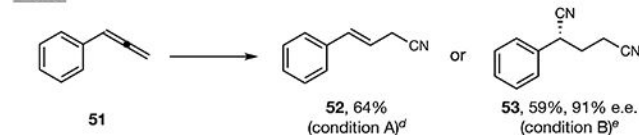
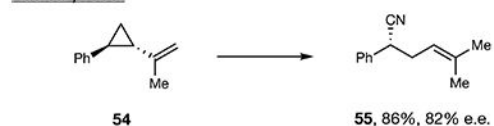
□ Terminal alkenes:



□ Internal alkenes:



□ Other conjugated alkenes:

Dienes and enynes:Allene:Radical probe:

Conditions: alkene (0.2 mmol, 1 equiv), PhSiH₃ (1.1 equiv), TMSCN (2.0 equiv), Co **3** (0.5 mol%), Cu(OTf)₂ (5 mol%), ligand **4** (10 mol%), TBABF₄ (2.0 equiv), HOAc (5.0 equiv), DMF (4.0 mL), C anode, Pt cathode, undivided cell, 0 °C, $U_{\text{cell}} = 2.3$ V. Isolated yields are reported, unless otherwise noted.

^aOptimal yield obtained at $U_{\text{cell}} = 1.8$ V (see discussion below about electrochemical control of reaction chemoselectivity).

^bWith 1 mol% Co **3**.

^cWith 2 mol% Co **3**.

^dCondition A: with 1.5 equiv TMSCN, 1.1 equiv PhSiH₃; yield determined by ¹H NMR.

^eCondition B: with 4.0 equiv TMSCN, 2.2 equiv PhSiH₃.

Abbreviations: r.r. = regiomeric ratio, d.e. = diastereomeric excess.

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