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 an electrocatalytic strategy. Electrochemistry allows for the seamless combination of two classic radical reactions—cobalt-mediated hydrogen-atom transfer and copper-promoted radical cyanation—to accomplish highly enantioselective hydrocyanation without the need for stoichiometric oxidant. We harness electrochemistry's unique feature of precise potential control to optimize the chemoselectivity of challenging substrates. Computational analysis sheds light on the origin of enantioinduction, for which the chiral catalyst imparts a combination of attractive and repulsive non-covalent interactions that direct the enantio-determining C–CN bond formation. This discovery demonstrates the power of electrochemistry in accessing new chemical space and providing solutions to pertinent challenges in synthetic chemistry.

Introduction

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 scale[6] 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 enantioselective hydrocyanation of 2-methoxy-6-vinylnaphthalene in the context of naproxen synthesis,[7-9] RajanBabu,[12] Schmalz,[13,14] and Vogt[14,15] have recently made seminal contributions using Ni catalysis (Figure 1B). To date, however, a general catalytic approach that meets the criteria of both broad reaction scope and high enantioselectivity remain 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[16-19] as a broadly applicable strategy for the difunctionalization of alkenes.[20] 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.[21,22] Further applying electrocatalysis to the *hydro*functionalization 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. To date, electrochemically driven hydrofunctionalization of alkenes is unknown, and electrosynthetic methods that enable asymmetric alkene functionalization remain elusive.[23-25] Against this backdrop, we describe an electrochemical approach for the enantioselective hydrocyanation of conjugated alkenes powered by a Co/Cu dual electrocatalytic process.
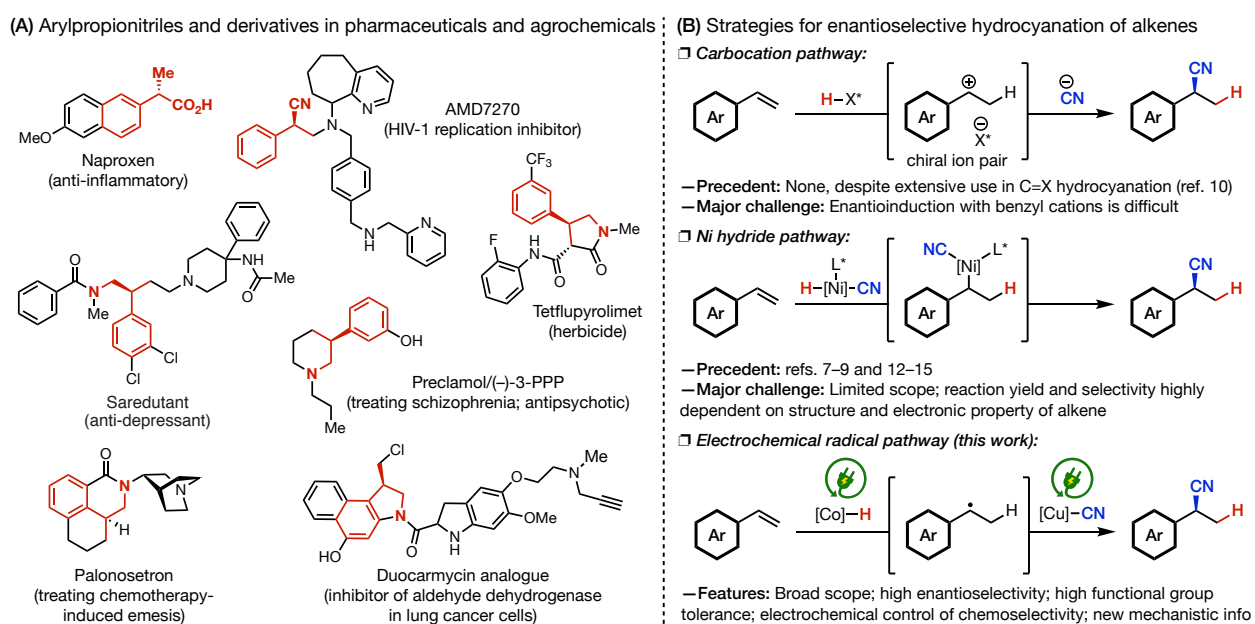

Figure 1. Enantioselective hydrocyanation: synthetic significance (A) and proposed strategy (B).

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,[26-30] reacts with an alkene substrate via hydrogen atom transfer (HAT) to produce carbon-centered radical (**I**).[31-33] 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.[34,35] This reaction design was inspired by Shenvi's seminal work showing that HAT-initiated alkene functionalization could intercept a second organometallic cycle in the context of Co/Ni-catalyzed, overall redox-neutral hydroarylation.[36] Critically, our 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. The key to successfully achieving this reaction thus relies on the identification of conditions that seamlessly accommodate both the Co HAT and Cu cyanation cycles.
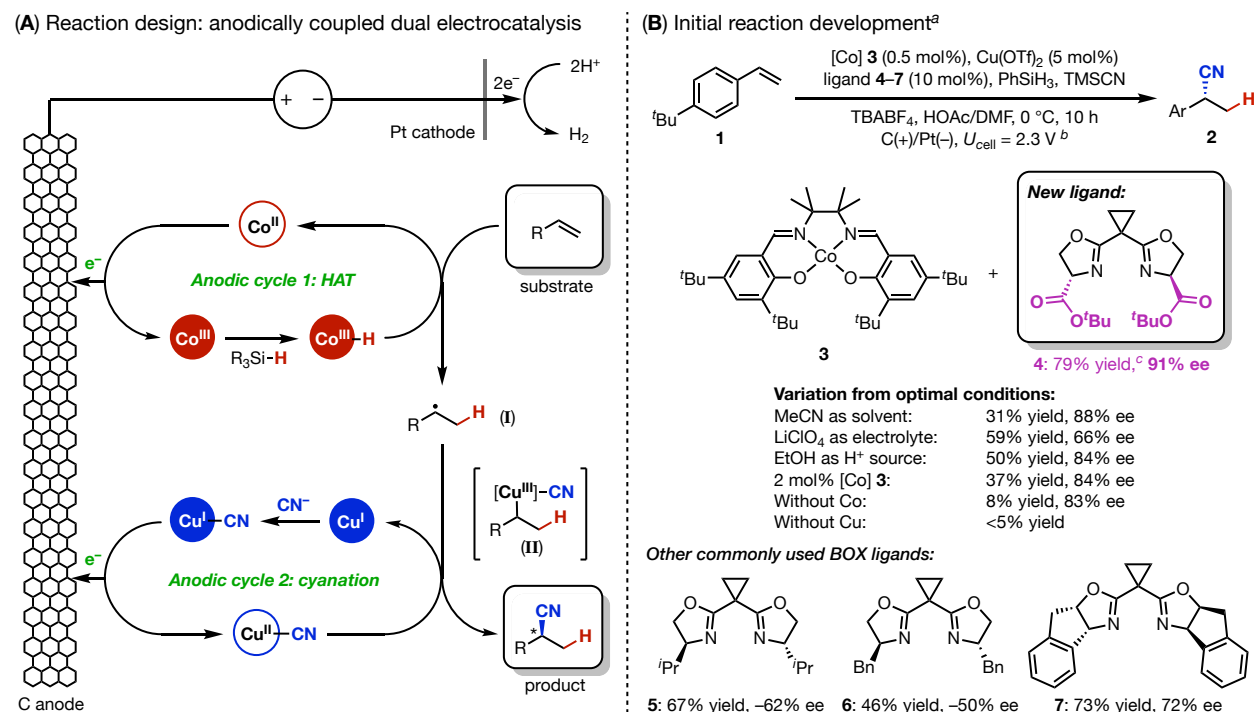
(A) Reaction design: anodically coupled dual electrocatalysis

(B) Initial reaction development^a

Figure 2. Reaction design (A), discovery, and optimization (B). ^{a}Yields determined by ^{1}H NMR. $^b U_{cell}$: cell voltage applied between the cathode and anode; $U_{cell} = 2.3$ V corresponds to *ca.* 0.24 V vs Fc$^{+/0}$ anodic potential (E_{anode}) and gives *ca.* 2 mA initial current. ^{c}Isolated yield.

We note that the attributes of electrochemistry render it uniquely capable of facilitating the merger of the two aforementioned catalytic processes into a broadly useful hydrocyanation protocol. Co-catalyzed hydrofunctionalization can encounter chemoselectivity issues with styrene-type substrates (*vide infra*), particularly in the presence of an oxidant, likely because the benzylic radical formed upon HAT is susceptible to over-oxidation to the benzyl cation[37] (except when the reaction between the benzylic radical and oxidant is desirable). Cu-catalyzed cyanation *requires* a potent chemical oxidant,[34,35] which can also limit the reaction scope to substrates lacking oxidatively labile functional groups. By contrast, electrochemical strategies, which allow one to dial in a minimally sufficient potential, circumvent the need for stoichiometric oxidants and eliminate formation of undesired side products.

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.[38] 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 [$E(Cu^{2+}/Cu^0) \approx -0.3$ V vs ferrocenium/ferrocene, Fc$^{+/0}$]. 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.[39] 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 PhSiH$_3$ and TMSCN promoted the conversion of 4-*tert*-butylstyrene (**1**) to the desired product (**2**) in good yield and moderate enantioselectivity (50–72% ee; Figure 2B). 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 ligands for Cu in enantioselective Lewis acid[40] or radical catalysis.[34,35,41,42] However, the optimal ee could not be improved above 72% (ligand **7**). During our reaction optimization, we discovered that ester-substituted bisoxazolines (e.g., **4**) are excellent ligands in the desired hydrocyanation reaction. These ligands are readily prepared from serine and have not been studied previously in asymmetric catalysis.[43] The use of ligand **4** under otherwise identical conditions drastically improved the reaction enantioselectivity to 91%. We therefore hypothesize that the second-sphere ester groups provide attractive noncovalent interactions to stabilize the enantio-determining transition state for the C–CN bond formation (*vide infra*).
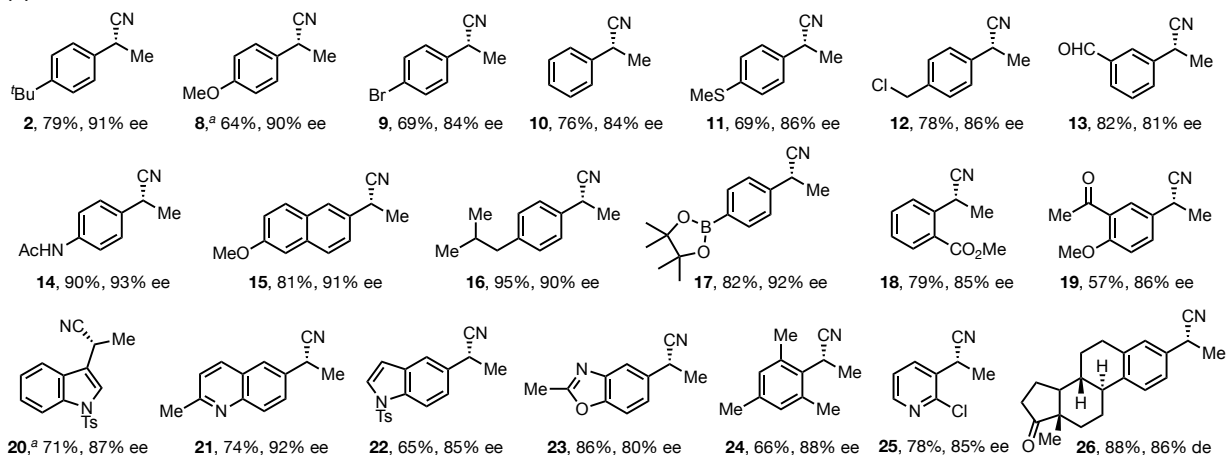
A number of control experiments serve to highlight the importance of each component of the reaction system. For example, using MeCN instead of DMF as the solvent, LiClO$_4$ instead of TBABF$_4$ as the electrolyte, or EtOH instead of HOAc as the proton source led to decreased product yield (Figure 2B). In each of these variations, we observed metallic Cu deposition on the cathode. Notably, the product was also formed in substantially lower ee in the presence of LiClO$_4$, showing that the polarity of the reaction medium influences the reaction 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.[33] 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. Under optimal conditions, a variety of vinylarenes underwent hydrocyanation to furnish desired arylpropionitriles with excellent enantioselectivity (Figure 3A). 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.
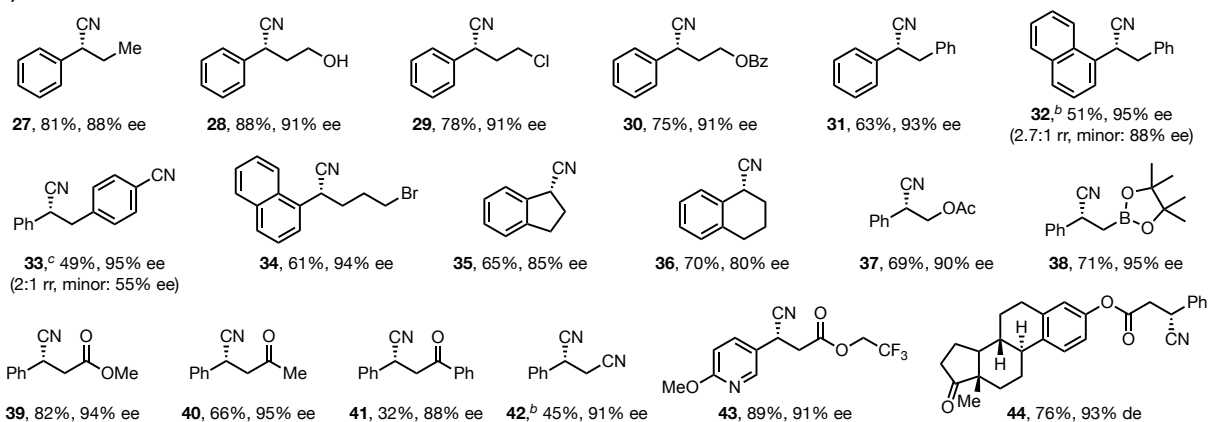
Importantly, our reaction is also applicable to internal alkenylarenes (Figure 3B), which are typically challenging substrates in previously reported enantioselective hydrocyanation reactions due to their low reactivity.[13] Our protocol shows very broad substrate generality, furnishing products with a variety of synthetically useful functional handles (**28**, **29**, **34**, **38**) and *N*-heterocyclic motifs (**43**). The stereochemistry of the starting alkenes is not important, and when applicable, we subject to the reaction a mixture of *E/Z*-isomers obtained directly from the olefination reaction. Both electron-rich (**37**) and electron-deficient alkenes (**39-44**) 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 potential medicinal chemistry studies.
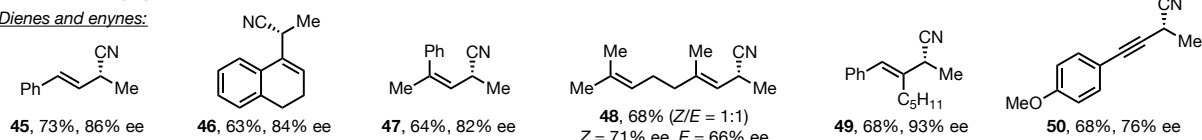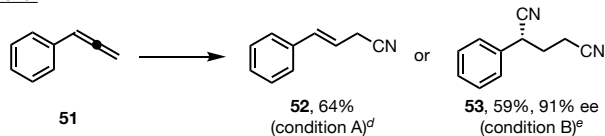
(A) Terminal alkenes:

2, 79%, 91% ee **8**,[a] 64%, 90% ee **9**, 69%, 84% ee **10**, 76%, 84% ee **11**, 69%, 86% ee **12**, 78%, 86% ee **13**, 82%, 81% ee

14, 90%, 93% ee **15**, 81%, 91% ee **16**, 95%, 90% ee **17**, 82%, 92% ee **18**, 79%, 85% ee **19**, 57%, 86% ee

20,[a] 71%, 87% ee **21**, 74%, 92% ee **22**, 65%, 85% ee **23**, 86%, 80% ee **24**, 66%, 88% ee **25**, 78%, 85% ee **26**, 88%, 86% de

(B) Internal alkenes:

27, 81%, 88% ee **28**, 88%, 91% ee **29**, 78%, 91% ee **30**, 75%, 91% ee **31**, 63%, 93% ee **32**,[b] 51%, 95% ee (2.7:1 rr, minor: 88% ee)

33,[c] 49%, 95% ee (2:1 rr, minor: 55% ee) **34**, 61%, 94% ee **35**, 65%, 85% ee **36**, 70%, 80% ee **37**, 69%, 90% ee **38**, 71%, 95% ee

39, 82%, 94% ee **40**, 66%, 95% ee **41**, 32%, 88% ee **42**,[b] 45%, 91% ee **43**, 89%, 91% ee **44**, 76%, 93% de

(C) Other conjugated alkenes:

Dienes and enynes:

45, 73%, 86% ee **46**, 63%, 84% ee **47**, 64%, 82% ee **48**, 68% (Z/E = 1:1) Z = 71% ee, E = 66% ee **49**, 68%, 93% ee **50**, 68%, 76% ee

Allene:

51 → **52**, 64% (condition A)[d] or **53**, 59%, 91% ee (condition B)[e]
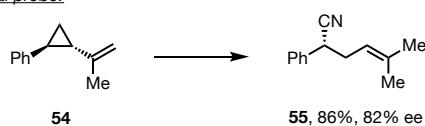
Radical probe:

54 → **55**, 86%, 82% ee

Figure 3. Reaction scope. Conditions: alkene (0.2 mmol, 1 equiv), PhSiH$_3$ (1.1 equiv), TMSCN (2.0 equiv), Co **3** (0.5 mol%), Cu(OTf)$_2$ (5 mol%), ligand **4** (10 mol%), TBABF$_4$ (2.0 equiv), HOAc (5.0 equiv), DMF (4.0 mL), C anode, Pt cathode, undivided cell, 0 °C, U_{cell} = 2.3 V. Isolated yields are reported, unless otherwise noted. [a]Optimal yield obtained at U_{cell} = 1.8 V (see discussion below). [b]With 1 mol% Co **3**. [c]With 2 mol% Co **3**. [d]Condition A: with 1.5 equiv TMSCN, 1.1 equiv PhSiH$_3$; yield determined by ^{1}H NMR. [e]Condition B: with 4.0 equiv TMSCN, 2.2 equiv PhSiH$_3$. Abbreviations: rr = regiomeric ratio, de = diastereomeric excess.

In addition to representing a conceptual advance, our electrochemical hydrocyanation—with its highly general reaction scope—is also synthetically valuable and provides a complementary route to existing methods for the synthesis of chiral nitriles. For examples, chiral arylpropionitriles of similar structures can, in theory, be constructed via a recently developed method that relies on Cu-catalyzed benzylic C–H cyanation using *N*-fluorobenzenesulfonimide (NFSI) as the terminal oxidant.[34] Although an elegant reaction design and a powerful method, this protocol employs strongly oxidizing NFSI and necessitates the intermediacy of an electrophilic N-centered radical as the H-atom abstractor. These requirements impose several limitations on the reaction scope. Our electrochemical approach provides an opportunity to overcome these limitations and makes accessible a complementary scope of enantioenriched nitriles. For example, substrates with oxidatively labile functional groups, such as sulfides (**11**) and electron-rich (hetero)arenes (e.g., **8**, **15**, **20**), can be converted to the corresponding nitriles without undesired oxidative degradation. In addition, our reaction design engages mild Co-mediated HAT to access the key benzylic radicals, thus circumventing the C–H abstraction pathway required for the chemical approach. As a result, substrates with multiple benzylic sites (e.g., **16**, **26**) can take part in the cyanation reaction in a site-specific manner. Furthermore, substrates with electron-deficient arenes (e.g., **13**, **18**, **21**), which are challenging in the chemical cyanation reaction likely because the benzylic C–H is acidic and polarity-mismatched with the NFSI-derived H-atom abstractor, can be readily engaged in our hydrocyanation reaction.

We further extended the scope of our reaction to other types of unsaturated substrates (Figure 3C). For example, dienes were converted to mono-hydrocyanated products in high efficiency and good to excellent enantioselectivity. In the case of linear dienes (**45–49**), the reaction selectively functionalizes the terminal C=C π-bond. Interestingly, in these transformations, enantioselective Cu-mediated C–CN bond formation is achieved via an allyl radical species, a process that is unknown in the literature. Structurally analogous enynes[44] also reacted chemoselectively in good ee (**50**). Finally, we expanded the reaction scope to allene substrates. The hydrocyanation of phenylallene (**51**) yielded cinnamyl cyanide (**52**) as the predominant product. This result suggests that the terminal C=C is more reactive and the HAT step preferentially generates a primary allyl radical intermediate.[45] 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 4). Product **15**, synthesized on a 2-mmol scale (~0.4 grams), was readily converted to either naproxen methyl ester **56** via methanolysis or to benzoindoline **57** via reduction followed by Pd-catalyzed C–H amination.[46] 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.
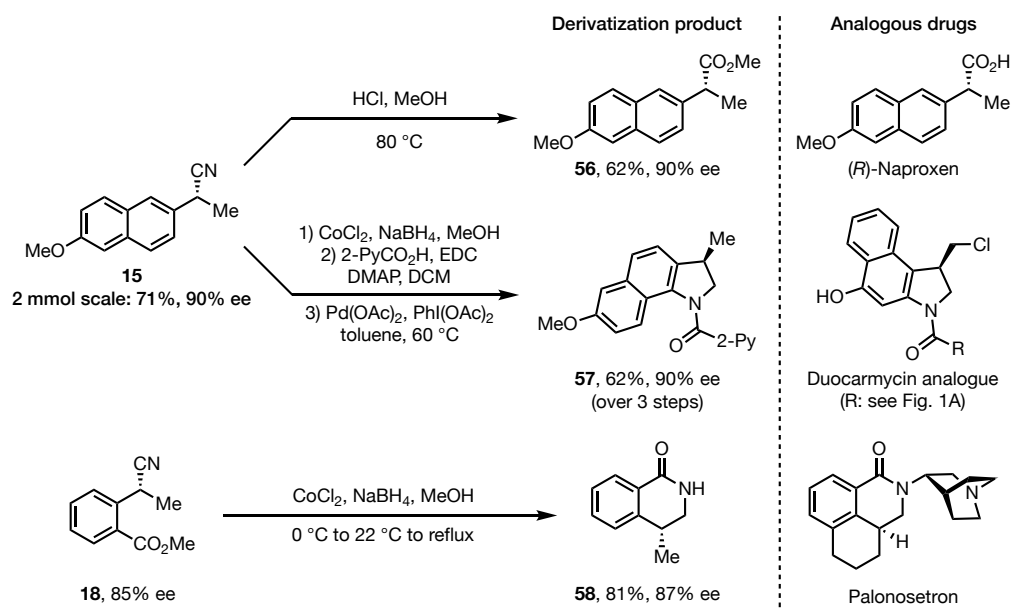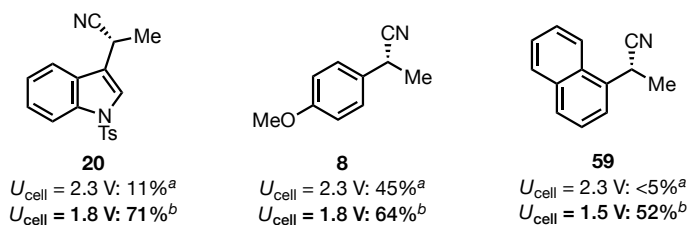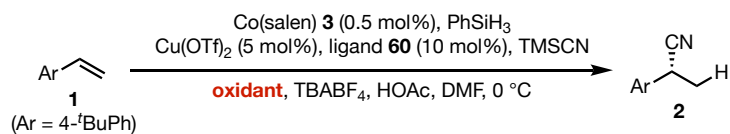
Figure 4. Product derivatization.

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 5A). 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 ($E_{anode} \sim 0.24$ V vs $Fc^{+/0}$), 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 aryl radical intermediate to the corresponding cation followed by nucleophilic trapping (e.g., formyl ester and ketone products). By lowering the voltage input from 2.3 V to 1.8 V ($E_{anode} \sim 0.08$ V), we successfully suppressed overoxidation 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 5B). In cases where a low yield of **2** was obtained (9-24%), the enantioselectivity was also substantially lower (40-68% ee). This erosion of ee 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.*

(A) Improving chemoselectivity by potential control

20
U_{cell} = 2.3 V: 11%[a]
U_{cell} = 1.8 V: 71%[b]

8
U_{cell} = 2.3 V: 45%[a]
U_{cell} = 1.8 V: 64%[b]

59
U_{cell} = 2.3 V: <5%[a]
U_{cell} = 1.5 V: 52%[b]

(B) Comparison with common chemical oxidants

Co(salen) **3** (0.5 mol%), PhSiH$_3$
Cu(OTf)$_2$ (5 mol%), ligand **60** (10 mol%), TMSCN
→
oxidant, TBABF$_4$, HOAc, DMF, 0 °C

Ar⟍ **1** (Ar = 4-^{t}BuPh) → Ar–CH(CN)–H **2**

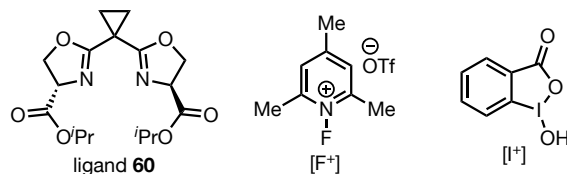| Entry	Oxidant	Conversion (%)[a]	Yield (%)[a]	Ee (%)
1	**anode**	**92**	**87**	**85**
2	NFSI	38	<5	—[c]
3	TBHP	85	15	68
4	[F$^+$]	78	24	63
5	PhI(OAc)$_2$	63	<5	—[c]
6	Mn(OAc)$_3$	86	9	40
7	Cu(OAc)$_2$	50	15	52
8	O$_2$ (balloon)	>95	<5	—[c]
9	[I$^+$]	79	14	62
10	CAN	75	<5	—[c]
11	Fc$^+$BF$_4^-$	8	<5	—[c]

ligand **60**

[F$^+$]

[I$^+$]

Figure 5. Electrochemical tuning of reaction chemoselectivity (A) and comparison with chemical methods (B). [a]Determined by ^{1}H NMR. [b]Isolated yield. [c]Not determined.

Stereochemical model. Finally, we enlisted theoretical methods to elucidate the role played by serine-derived BOX ligands in directing the highly enantioselective Cu-mediated cyanation. 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.[34] Traditionally, BOX-type ligands are thought to induce enantioselectivity through primarily *repulsive* steric interactions imparted by the bulky substituents α-to the N coordination sites. 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* electrostatic interactions with the substrate assembly in the key C–CN

forming transition state. Density functional theory computations are fully consistent with this hypothesis (Figure 6 and Supplementary Information). Using the reaction forming **10** as an example, the lowest energy transition state 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 α-to one of the ester groups and the aryl group on the substrate. This attractive non-covalent interaction dictates the geometry of both transition states by positioning the alkyl substituent on the substrate toward the ^{t}Bu-ester on the opposite half of the catalyst. However, this arrangement causes a more severe steric interaction between these two adjacent groups in TS$_S$ than TS$_R$. In fact, to mitigate this detrimental interaction in TS$_S$, the ester group deviates from its optimal planar geometry (dihedral angle $\theta = 22°$), therefore breaking conjugation. Based on these findings, we further hypothesize that this interplay between attractive and repulsive non-covalent interactions in the transition state determines the reaction enantioselectivity.
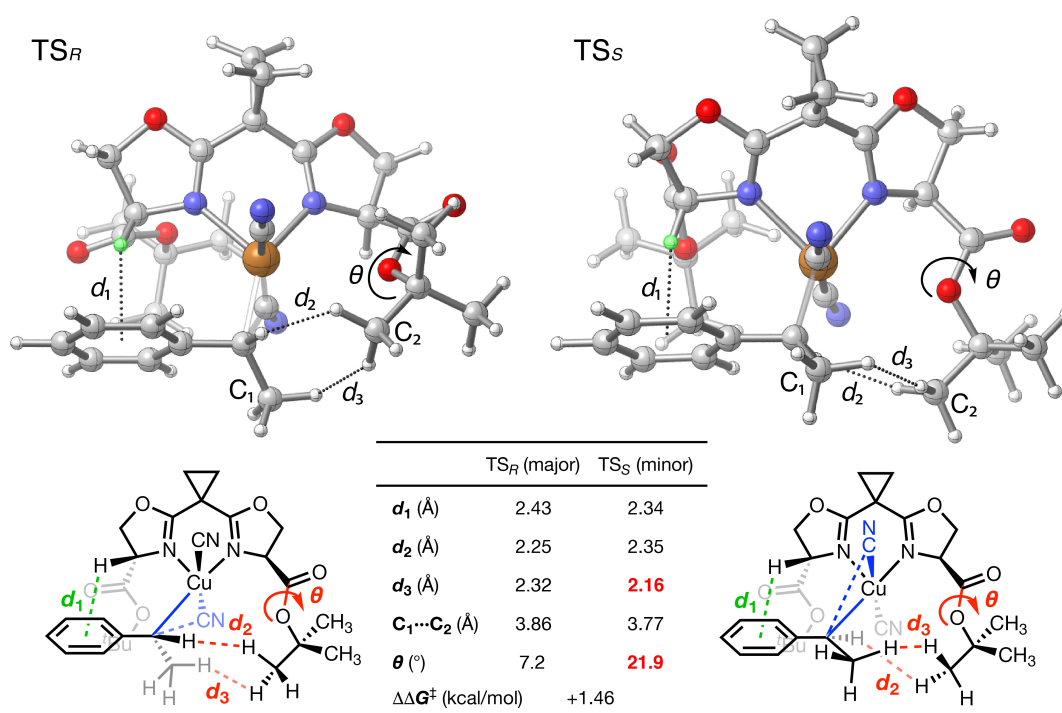

	TS$_R$ (major)	TS$_S$ (minor)
d_1 (Å)	2.43	2.34
d_2 (Å)	2.25	2.35
d_3 (Å)	2.32	**2.16**
C_1⋯C_2 (Å)	3.86	3.77
θ (°)	7.2	**21.9**
$\Delta\Delta G^{\ddagger}$ (kcal/mol)	+1.46	

Figure 6. Computational stereochemical model. Numbers in red indicate interatomic distances that are shorter than the sum of the van der Waals radii of the two atoms or dihedral angles that show significant deviation from their optimal values.

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, which can be explained by the increased steric interaction between the substrate alkyl group and the catalyst ester group in the minor TS 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 involving the aryl group.[47]

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.

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