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New Bisoxazoline Ligands Enable Enantioselective Electrocatalytic Cyanofunctionalization of Vinylarenes

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Abstract

In contrast to the rapid growth of synthetic electrochemistry in recent years, enantioselective catalytic methods powered by electricity remain rare. In this work, we report the development of a highly enantioselective method for the electrochemical cyanophosphinoylation of vinylarenes. A new family of serine-derived chiral bisoxazolines with ancillary coordination sites were identified as optimal ligands.

Owing to the prevalence of C=C bonds in feedstock chemicals and synthetic intermediates, the heterodifunctionalization of alkenes provides an efficient strategy for rapidly increasing the complexity of molecules in organic synthesis.[1] In this context, enantioselective methods that provide optically active compounds are particularly valuable in synthetic and medicinal applications.[2] We[3] and others[4] have recently demonstrated electrocatalysis as a viable and potentially general approach for the difunctionalization of alkenes. Gifted by the many unique attributes of electrochemistry,[5] these reactions are frequently highly efficient, selective, operationally simple, and environmentally friendly. Despite these advances, electro-synthetic methods that enable asymmetric alkene functionalization remain elusive.[6] In this report, we describe our development of highly enantioselective cyanophosphinoylation of alkenes through the rational design of ligands and optimization of electrolysis conditions.

In our previous studies, we have demonstrated the use of anodically coupled electrolysis (Scheme 1A) for the chlorotrifluoromethylation[7] and chloroalkylation[8] of alkenes. This strategy combines two distinct anodic events occurring in parallel to generate two radical intermediates simultaneously. Regulated by a redox-active catalyst, the addition of these radicals across the alkene π-bond takes place chemo- and regioselectively. Given the hypothesized mechanism, it is plausible to render these processes enantioselective when an appropriate chiral ligand is used. We set out to investigate this notion in the context of alkene

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Procedures and characterization data (PDF)

cyanophosphinoylation by means of electrochemical generation of cyano- and phosphinoyl radical equivalents (Scheme 1B). Organophosphorous groups are prevalent in medicine, agrochemicals, and molecular catalysts;[9] nitriles are versatile functional groups in organic synthesis. The envisioned reaction would install two useful functional handles to the alkene in a single step, providing unique structural patterns[10] that can be further elaborated to useful products (*vide infra*).

In the envisioned transformation, a secondary phosphine oxide[11] is oxidized on the anode to form the corresponding P-centered radical (Scheme 1A, $X^{\bullet}$).[12] This step can be direct or mediated by a catalyst. Meanwhile, CN^{-} is converted to $CN^{\bullet}$ in the form of a metal–cyano complex (cat^{OX}–Y). In this context, it has been established that Cu^{II}–CN complexes can behave as a latent $CN^{\bullet}$ in radical cyanation reactions.[13] We envision, upon the addition of the transient P-centered radical to the alkene, the nascent carbon-centered radical will further react with the persistent metal–cyano complex to furnish the C–CN bond and deliver the desired difunctionalized product.[14] We reasoned that judicious choice of chiral ligands could render this C–CN bond formation enantioselective, and this hypothesis is supported in the seminal work by Liu et al. in a series of elegant chemical cyanation reactions.[15]

A major challenge of implementing this reaction design lies in the reconciliation of multiple oxidation and reduction processes in the same electrochemical system. In particular, the electrochemical compatibility and behavior of copper complexes with common ligand scaffolds that can be readily made chiral [e.g., bisoxazoline (BOX), bisphosphine] have not been systematically studied.[16] In addition, for practical reasons, preparative-scale electrochemical reactions are ideally conducted in undivided vessels (e.g., common reaction flasks) using feedstock chemicals as the terminal oxidant or reductant (e.g., H^{+} as oxidant). This requirement creates a challenge, as Cu ions are substantially easier to reduce than H^{+} and would plate out on the cathode,[17] losing catalytic activity. Therefore, the choice of solvent, proton source, and ligand is critical.

We set out to investigate the feasibility of our reaction design in the difunctionalization of 4-methoxystyrene (**1**) using TMSCN and diphenylphosphine oxide (**2**) in the presence of Cu(BOX)-type complexes (Table 1). Using conditions that we previously established for electrochemical alkene difunctionalization in combination with Cu(**L4**), no desired product **3** was observed (entry 1). The Pt cathode was visibly covered with metallic Cu postelectrolysis. A survey of polar solvents that are ideal for electrochemistry revealed that DMF is optimal, providing **3** in 20% yield with 79% ee (entry 2). However, the Cu catalyst was again irreversibly reduced on Pt and the alkene was fully consumed to form various side products. Replacing HOAc with trifluoroethanol (TFE) as the proton source provided a solution to the product selectivity issue (entry 3). Although the reaction resulted in marginally lower yield and ee, little side product was observed and the remaining styrene was recovered. Finally, screening different electrolytes led to the discovery of the optimal conditions using ligand **L4,** providing **3** in 51% yield with 84% ee after passing 2 F of charge (entry 4).[18]

To further improve the reaction enantioselectivity, we surveyed a large number (>20) of chiral ligands (e.g., BOX, PyBOX, BiOX, PyrOX, and BINAP; see Table 1, entry 5 and the

SI), including those that are frequently used in Cu-catalyzed enantioselective radical reactions (Scheme 2A).[19] However, the optimal ee remained 84% (11:1 er). We reasoned substantial modification to the ligand scaffold would be necessary in order to break the selectivity ceiling that we encountered.

In a mechanistically related work by Stahl and Liu (Scheme 2A, eq 1),[15d] the C–CN bond formation via reductive elimination from a Cu^{III} intermediate was postulated as the enantioselectivity determining step. In their computational model, this key Cu^{III} intermediate adopts a pentacoordinated structure with two CN^- bound to the metal in addition to the C-centered radical and BOX ligand. Analogous pentacoordianted Cu^{III} complexes have been observed and proposed to undergo reductive elimination in several other reaction systems.[20]

Our cyanophosphinoylation reaction differs from the previous reports by Liu et al.[15] primarily in three ways. First, the phosphine oxide group in the key intermediate leading to reductive elimination could compete with the ligand or CN^- in binding to the Cu center. Second, DMF—a polar solvent that is used to ensure high solution conductivity—could also potentially replace a CN^- ligand in the cyanation transition state.[21] Finally, the transition state is considerably bulkier owing to the pendant phosphine oxide group.[22] All these factors could result in a less organized transition structure and induce unselective reaction pathways.

The above analysis led us to propose that the introduction of an ancillary ligand (e.g., an ester group) to the BOX scaffold would further stabilize the putative pentacoordinated Cu^{III} complex prior to reductive elimination (Scheme 2B). This modification would also increase the rigidity of the transition state and improve the stereochemical fidelity of the cyanation process. Moreover, we hypothesize that this multidentate ligand will further stabilize the Cu catalyst against cathodic demetalation and present a cationic intermediate (**I**) that is more susceptible to reductive elimination.[23]

Accordingly, we synthesized a series of bisoxazoline ligands with pendant ester groups derived from serine (sBOX). To the best of our knowledge, these ester-substituted BOX ligands have not been studied in asymmetric catalysis.[24] These ligands were then tested in the model reaction under otherwise identical conditions, and the difunctionalization product (**3**) was isolated in good yield and substantially improved ee (Scheme 3A). In particular, sBOX(^{i}Pr) and sBOX(^{t}Bu) provided 94% ee (32:1 er) and 95% ee (39:1 er), respectively. We also tested several other substituted styrenes, and sBOX outperformed **L4** across the board (Scheme 3B).

Owing to the ease of synthesis,[25] sBOX(^{i}Pr) was chosen instead of sBOX(^{t}Bu) to study the substrate scope. Styrenes with a variety of substituents proved to be suitable substrates. In particular, functionalities that are potentially sensitive to chemical oxidation, such as aldehyde (**21**) and sulfide (**24**), were preserved under the electrolysis conditions. These functional groups have not been shown to be compatible with previously reported cyanation conditions using chemical oxidants, such as $Mn(OAc)_3$[10] (see SI) and *N*-fluorobenzenesulfonimide.[15] Benzyl chloride (**27**), which could undergo nucleophilic substitution by CN^-, was also tolerated. Notably, a variety of electron-rich and electron-deficient *N*-heterocycles (**28, 29, 30, 31**) were converted to the corresponding products in high yield with excellent enantioselectivity. Substituted diaryl phosphine oxides took part in the difunctionalization smoothly, providing **32** and **33** with high ee. Dibutyl phosphine oxide also reacted (**34**) at elevated temperature (22 °C) to achieve synthetically useful yield and ee. Introduction of the phosphine oxide group significantly increases the crystallinity of the product, whose enantiomeric excess can be upgraded readily via ether washes with very little mass loss (e.g., **26, 28**). The current reaction conditions are not applicable to substrates that are intrinsically challenging to Cu-catalyzed cyanofunctionalization reactions,[10,15] such as dialkylphosphites (no desired product) and aliphatic alkenes (low enantioselectivity; see SI). Finally, we demonstrated the synthesis of **3** using ElectraSyn 2.0 instead of our custom-made electrochemical cell and obtained similar results (see SI).

We also extended this electrochemical protocol to the cyanosulfinylation of vinylarenes using sulfinic acids as nucleophiles to furnish product **35–38** in high efficiency and selectivity. To balance the pH of the medium and ensure the facile generation of sulfinyl radical, pyridine was added to the reaction.

The difunctionalized products contain two newly installed groups, granting access to various structurally diverse molecules upon further synthetic elaborations. For instance, thiourea-derived phosphine (**39**),[26] Schiff-based-derived phosphine oxide (**40**),[27] and aminophosphine (**41**)[28] constitute bifunctional scaffolds that resemble catalysts currently used in asymmetric synthesis (Scheme 4).

Finally, we propose an electrocatalytic cycle based on anodically coupled electrolysis (Figure 1A). Cyclic voltammetry (CV) data showed that the oxidation of Cu^{I}(sBOX)(OTf) catalyst to the corresponding Cu^{II} complex results in a feature at around 0.35 V (vs $Fc^{+/0}$; Figure 1B, black line). Upon the addition of TMSCN, however, this redox event takes place at a less positive potential of 0.15 V with an enhanced anodic current (red line). This result shows that ligand exchange leads to a complex—presumably Cu^{I}(sBOX)(CN)—that is both thermo-dynamically and kinetically more favorable to undergo oxidation. Importantly, the addition of phosphine oxide **2** further augmented the anodic current at 0.15 V (blue line), and this current improvement is more pronounced with a higher concentration of **2** (Figure S3). The observation of such catalytic current is indicative of Cu^{II}(sBOX)(CN) being capable of oxidizing **2** in a catalytic fashion,[29] likely resulting in a free P-centered radical while returning to the Cu^{I} state before anodic reoxidation. The direct oxidation of diphenylphosphine oxide on a carbon anode proved to be difficult (>0.3 V; see SI). Finally, we conducted controlled potential electrolysis with a constant anodic potential of 0.19 V and observed the formation of product **3** in 94% ee. These data together are consistent with an electrochemical difunctionalization reaction mediated by a $[Cu^{I/II}(sBOX)(CN)]^{0/+}$ redox couple.

Upon addition of the nascent P-centered radical to the alkene to form the C−P bond, the incipient carbon-centered radical undergoes single-electron oxidative addition to $[Cu^{II}(sBOX)(CN)]^{+}$. This event was followed by reductive elimination to furnish the chiral product. The resultant Cu^{I} picks up another molecule of CN^{-}—which becomes easier to oxidize according to CV data—before being turned over on the anode to Cu^{II}. The combination of appropriate reaction medium, proton donor, and chelating ligand allows the merger of Cu redox catalysis and electrochemistry without the necessity for an additional electron mediator.

Mechanism-informed ligand design enabled optimization of the enantioselectivity of the electrocatalytic difunctionalization reaction. In our aforementioned working hypothesis, an ester group in sBOX serves as an ancillary ligand to rigidify the key reduction elimination transition state toward high levels of enantioinduction. It is unlikely that these second-sphere groups provide merely steric repulsions to dictate the reaction enantioselectivity, as the ester groups are virtually planar, less bulky, and more flexible than the ^{i}Pr group in ligand **L4.** However, it is also possible that the ester groups exert electrostatic stabilization of the major reaction transition state by functioning as a Lewis base. The mechanism of enantioinduction by Cu(sBOX) complexes is a current topic of investigation.

From the perspective of green chemistry, the removal of a conventional chemical oxidant constitutes another attractive feature of our protocol. We anticipate that our electrocatalytic strategy and new bisoxazoline ligands will pave the way for the discovery of other synthetically useful transformations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(26). For use of chiral thiourea-derived phosphines, see: Fang Y-Q; Jacobsen EN Cooperative, Highly Enantioselective Phosphinothiourea Catalysis of Imine−Allene [3 + 2] Cycloadditions. J. Am. Chem. Soc 2008, 130, 5660–5661. [PubMed: 18393504] Fang Y-Q; Tadross PM; Jacobsen EN Highly Enantioselective, Intermolecular Hydroamination of Allenyl Esters Catalyzed by Bifunctional Phosphinothioureas. J. Am. Chem. Soc 2014, 136, 17966–17968. [PubMed: 25496451] Zhong F; Han X; Wang Y; Lu Y Highly Enantioselective [3 + 2] Annulation of Morita−Baylis−Hillman Adducts Mediated by L-Threonine-Derived Phosphines: Synthesis of 3-Spirocyclopentene-2-oxindoles Having Two Contiguous Quaternary Centers. Angew. Chem., Int. Ed 2011, 50, 7837–7841.

(27). For use of chiral Schiff base-derived phosphines and phosphine oxides, see: Dai H; Hu X; Chen H; Bai C; Zheng Z New efficient P,N,O-tridentate ligands for Ru-catalyzed asymmetric transfer hydrogenation. Tetrahedron: Asymmetry 2003, 14, 1467–1472.Kim T-J; Lee H-Y; Ryu E-S; Park D-K; Cho CS; Shim S-C; Jeong JH Asymmetric addition of diethylzinc to aromatic aldehydes by chiral ferrocene-based catalysts. J. Organomet. Chem 2002, 649, 258–267.Ye F; Zheng Z-J; Deng W-H; Zheng LS; Deng Y; Xia C-G; Xu L-W Modulation of Multifunctional N,O,P Ligands for Enantioselective Copper−Catalyzed Conjugate Addition of Diethylzinc and Trapping of the Zinc Enolate. Chem. -Asian J 2013, 8, 2242–2253. [PubMed: 23983068] Aleksanyan DV; Nelyubina YV; Dmitrienko AO; Bushmarinov IS; Klemenkova ZS; Kozlov VA Polyhedron 2015, 85, 295–301.

(28). For a review, see: Li W; Zhang J Recent developments in the synthesis and utilization of chiral b-aminophosphine derivatives as catalysts or ligands. Chem. Soc. Rev 2016, 45, 1657–1677. This precursor could also be readily elaborated to peptide-derived phophines for asymmetric catalysis:

[PubMed: 26776280] Wang T; Han X; Zhong F; Yao W; Lu Y Amino Acid-Derived Bifunctional Phosphines for Enantioselective Transformations. Acc. Chem. Res 2016, 49, 1369–1378. [PubMed: 27310293]

(29). Yi H; Yang D; Luo Y; Pao C-W; Lee J-F; Lei A Direct Observation of Reduction of Cu(II) to Cu(I) by P–H Compounds using XAS and EPR Spectroscopy. Organometallics 2016, 35, 1426–1429.

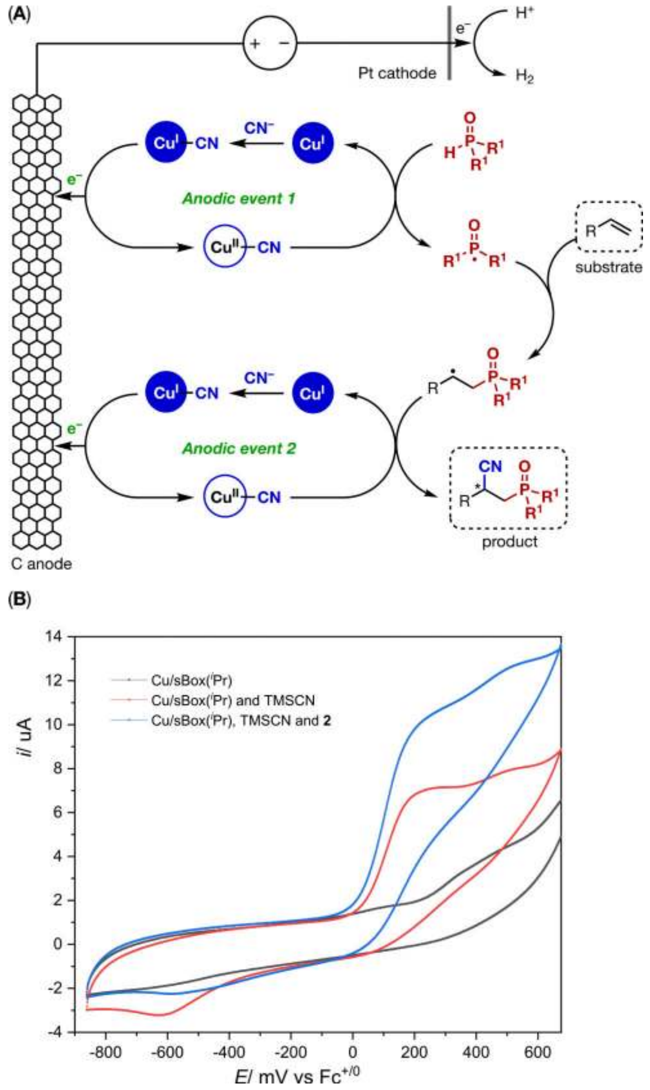
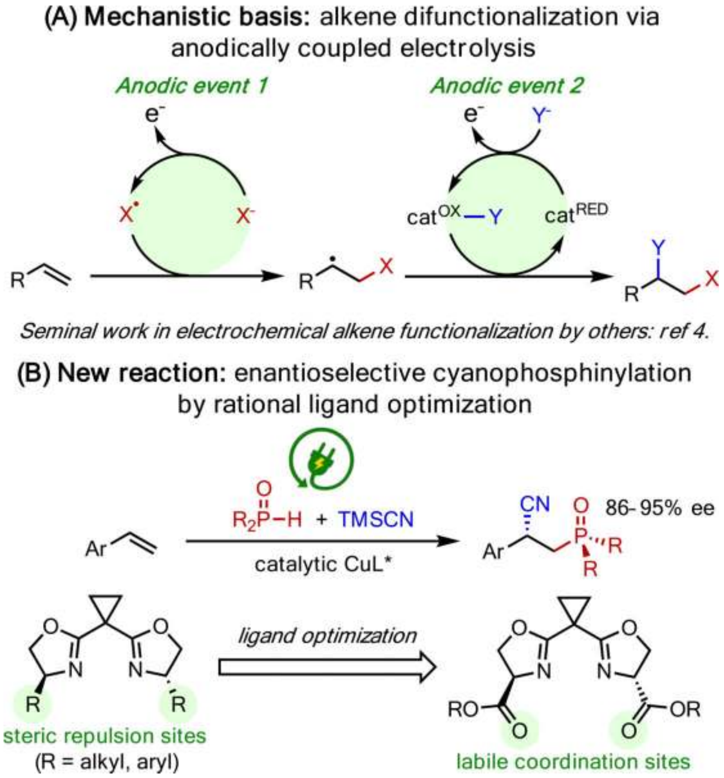
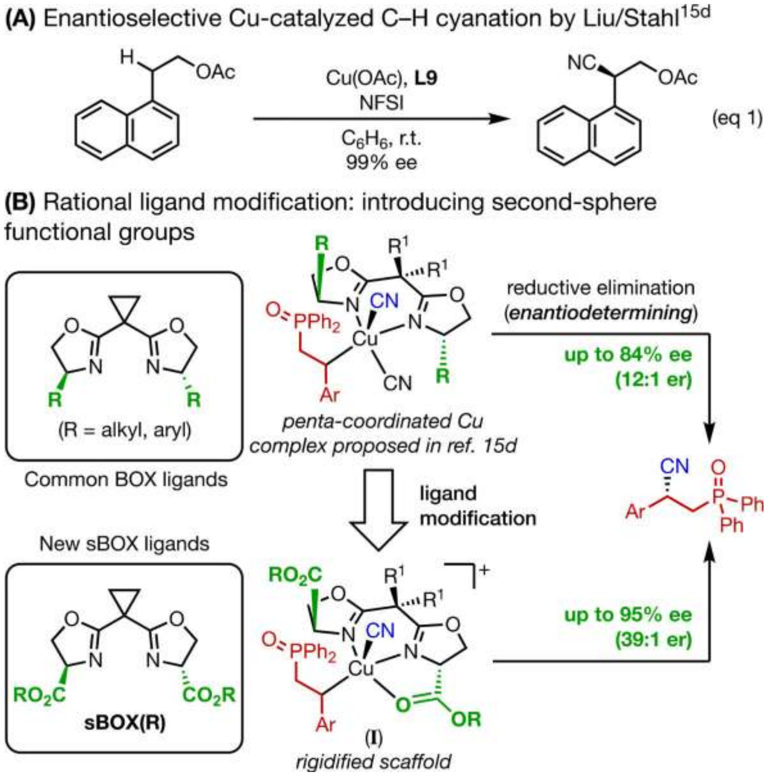


Figure 1.

(A) Proposed electrocatalytic cycle. (B) Cyclic voltammetry data.



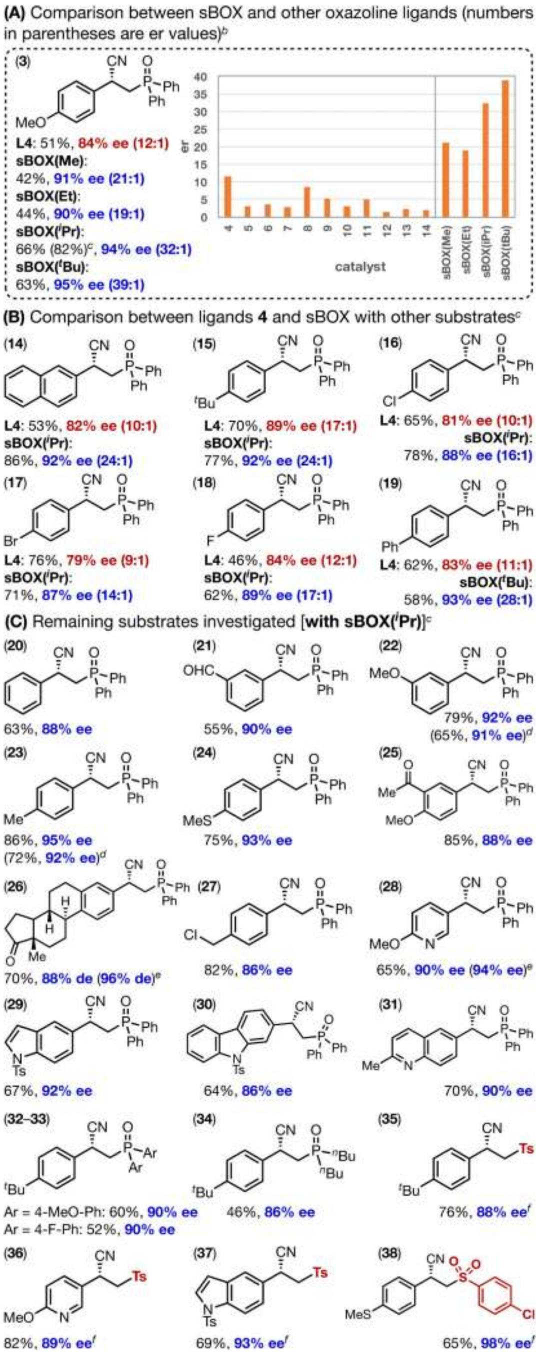
Scheme 1. Mechanistic Working Hypothesis



(A) Enantioselective Cu-catalyzed C–H cyanation by Liu/Stahl[15d]

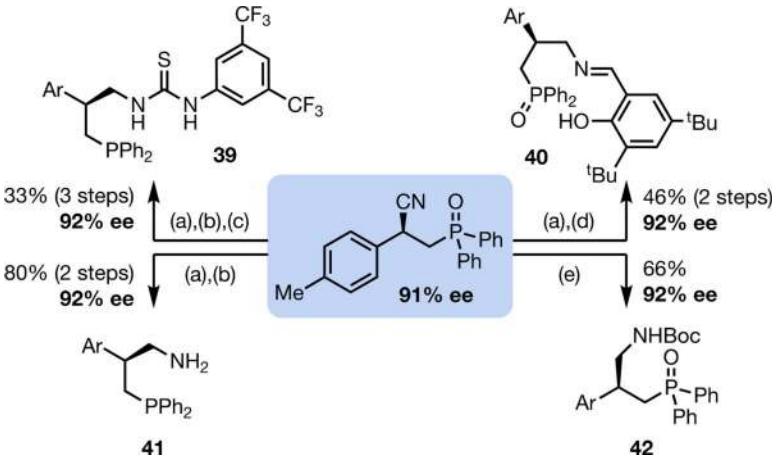
(B) Rational ligand modification: introducing second-sphere functional groups

Scheme 2. Development of Serine-Derived BOX Ligands



Scheme 3. Substrate Scope[a]

[a]Reaction conditions: alkene (0.2 mmol, 1 equiv), P source (1.5 equiv), TMSCN (2.0 equiv), $Cu(OTf)_2$ (3 mol %), ligand (6 mol %), $TBABF_4$ (2.0 equiv, 0.1 M), TFE (2.5 equiv), DMF (4.0 mL), C felt anode, Pt cathode, undivided cell, constant current $i = 3$ mA. [b]Total charge = 2 F, reaction time 3.5 h. [c]Total charge = 3–3.5 F, reaction time 5–6 h (see SI). [d]2.0 mmol scale. [e]Ee after ether washes. [f]Using *p*-toluenesulfinic acid or *p*-Cl-benzenesulfinic acid with pyridine (2 equiv).

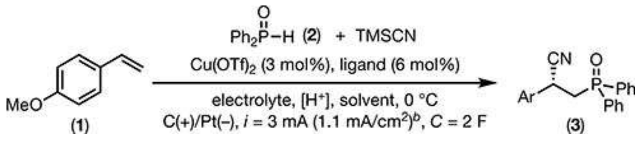


Scheme 4. Product Derivatization[a]

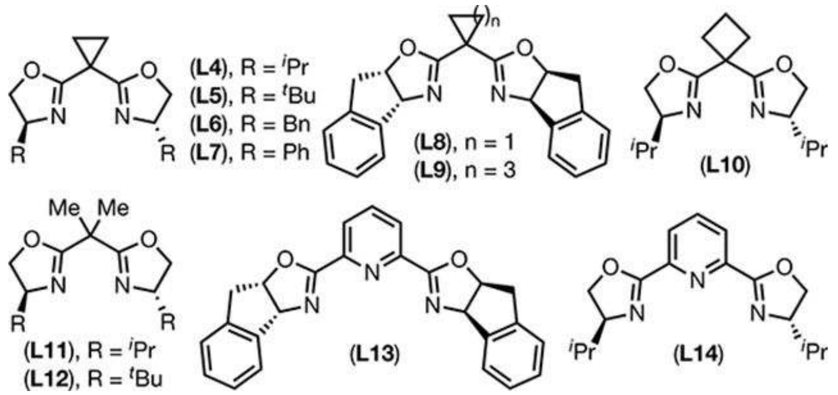
[a]Reaction conditions: (a) $CoCl_2$ (cat.), $NaBH_4$, MeOH, 0 °C, 83% yield; (b) $CeCl_3$, $LiAlH_4$, THF, 50 °C, 96% yield; (c) 3,5-Bistrifluoromethylphenyl isothiocyanate, DCM, 42% yield; (d) 3,5-Di-*tert*-butylsalicylaldehyde, EtOH, reflux, 55% yield. (e) $NiCl_2$ (cat.), $NaBH_4$, Boc_2O, MeOH, 66% yield.

Table 1.

Reaction Optimization[a]



Entry	Ligand	Electrolyte	[H+]	Solvent	Yield (%)	Ee (%)
1	**L4**	$LiClO_4$	HOAc	MeCN	<1	ND
2	**L4**	$LiClO_4$	HOAc	DMF	20	79
3	**L4**	$LiClO_4$	TFE	DMF	18	76
4	**L4**	**$TBABF_4$**	**TFE**	**DMF**	**51**	**84**
5	**L5–L14**	$TBABF_4$	TFE	DMF	<10–63	12–79



[a] Reaction conditions: **1** (0.2 mmol, 1 equiv), **2** (1.5 equiv), TMSCN (2.0 equiv), Cu(OTf)$_2$ (3 mol %), ligand (6 mol %), electrolyte (2.0 equiv, 0.1 M), [H$^+$] (2.5 equiv), solvent (4.0 mL), C felt anode, Pt cathode, undivided cell, constant current i = 3 mA, corresponding to anodic potential of 165–185 mV vs Fc$^{0/+}$.

[b] Based on geometrical surface area.