Electrocatalytic Asymmetric Nozaki–Hiyama–Kishi Decarboxylative Coupling: Scope, Applications, and Mechanism

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ABSTRACT: The first general enantioselective alkyl-Nozaki-Hiyama-Kishi (NHK) coupling reactions are disclosed herein by employing a Cr-electrocatalytic decarboxylative approach. Using easily accessible aliphatic carboxylic acids (via redox-active esters) as alkyl nucleophile synthons, in combination with aldehydes and enabling additives, chiral secondary alcohols are produced in good yield and high enantioselectivity under mild reductive electrolysis. This reaction, which cannot be mimicked using stoichiometric metal or organic reductants, tolerates a broad range of functional groups, and is successfully applied to dramatically simplify the synthesis of multiple medicinally relevant structures and natural products. Mechanistic studies revealed that this asymmetric alkyl e-NHK reaction was enabled by using catalytic tetrakis(dimethylamino)ethylene (TDAE), which acts as a key reductive mediator to mediate the electroreduction of the Cr^{III}/chiral ligand complex.

INTRODUCTION

The synthesis of chiral secondary alcohols has been a subject of intense study for more than 40 years (Figure 1A).[1] Retrosynthetically, two main pathways to access aryl-alkyl substituted secondary alcohols employ either nucleophilic addition to an aldehyde[2] or asymmetric reduction[3] of the corresponding ketone. Early catalytic manifestations of the former process date back to the work of Noyori[4] on highly stereocontrolled organozinc additions to aldehydes whereas the latter strategy originated from the findings of Landor[5] ultimately leading to modern methods such as the venerable CBS[6] reduction. The Nozaki–Hiyama–Kishi (NHK) reaction, first discovered in 1977[7] and formalized in 1986[8] usually involves the cross-coupling of an alkenyl halide with an aldehyde through the use of stoichiometric Cr and catalytic Ni to afford an allylic alcohol product.[9] The corresponding alkyl-variant of this reaction is seldom employed with a variety of alkyl nucleophile surrogates being disclosed over the years such as alkyl iodides,[10] carboxylic acids [via redox-active esters (RAEs)],[11] olefins,[12] or even unactivated C–H bonds[13] (Figure 1B). Those variants, however, have not been employed in a catalytic, highly enantioselective fashion. In 2021, an electrocatalytic decarboxylative variant of the NHK reaction was disclosed by this team demonstrating a racemic proof of concept for such a bond forming strategy.[14] In this Article we disclose a broadly useful method that now achieves synthetically useful yields and enantiomeric excesses through a combination of fine-tuned electrochemical

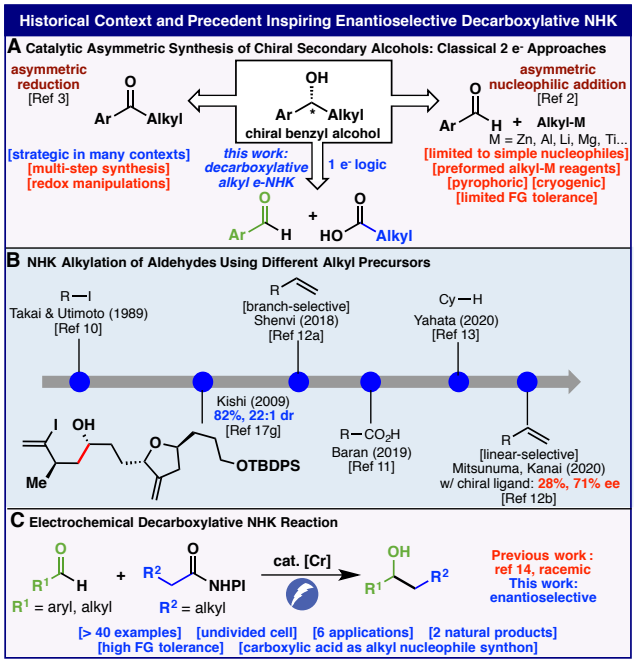
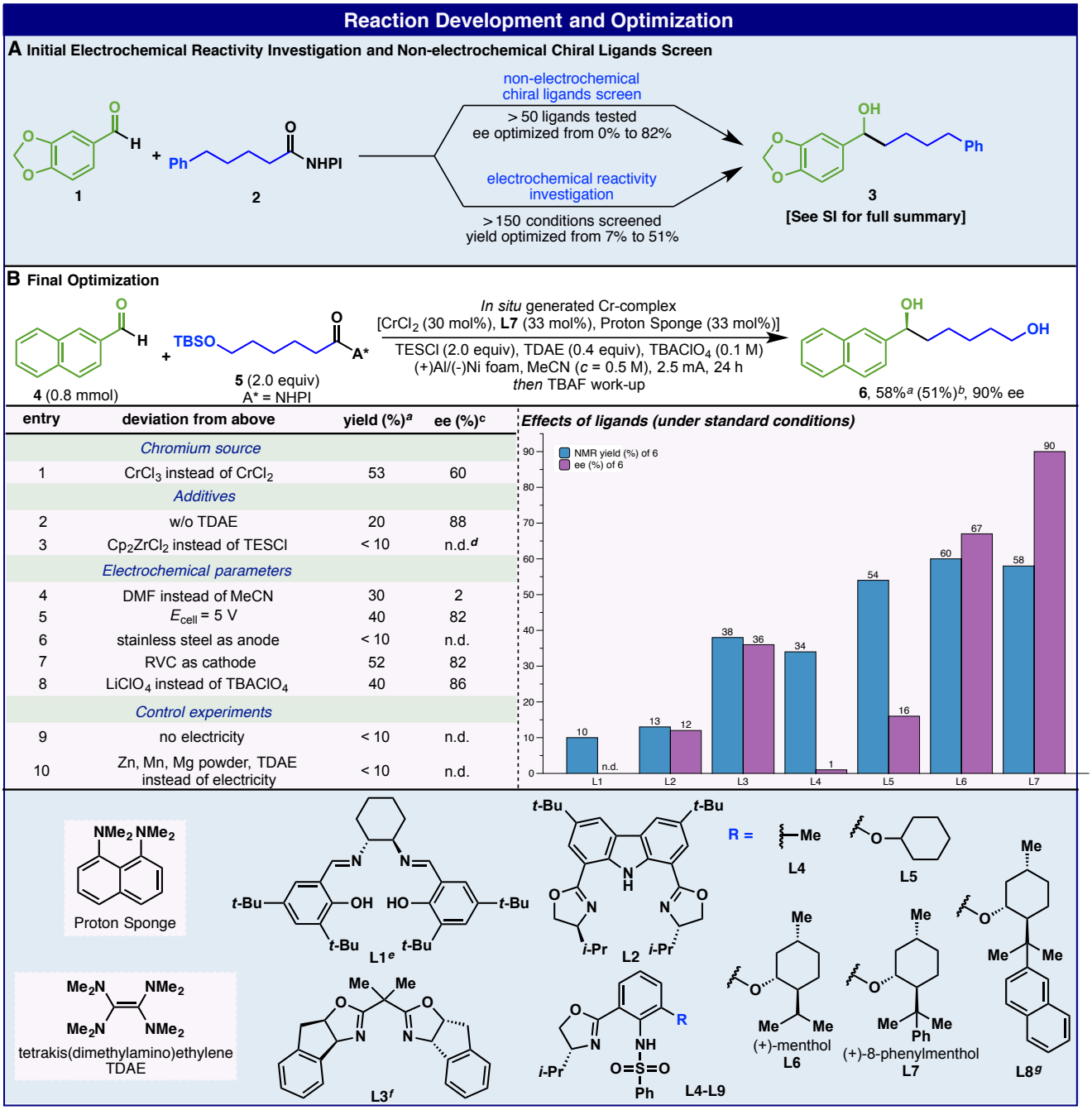


Figure 1. Historical context and precedent inspiring enantioselective decarboxylative NHK.

Table 1. Reaction Development and Optimization



entry	deviation from above	yield (%)[a]	ee (%)[c]
	Chromium source		
1	$CrCl_3$ instead of $CrCl_2$	53	60
	Additives		
2	w/o TDAE	20	88
3	Cp_2ZrCl_2 instead of TESCl	< 10	n.d.[d]
	Electrochemical parameters		
4	DMF instead of MeCN	30	2
5	E_{cell} = 5 V	40	82
6	stainless steel as anode	< 10	n.d.
7	RVC as cathode	52	82
8	$LiClO_4$ instead of $TBAClO_4$	40	86
	Control experiments		
9	no electricity	< 10	n.d.
10	Zn, Mn, Mg powder, TDAE instead of electricity	< 10	n.d.

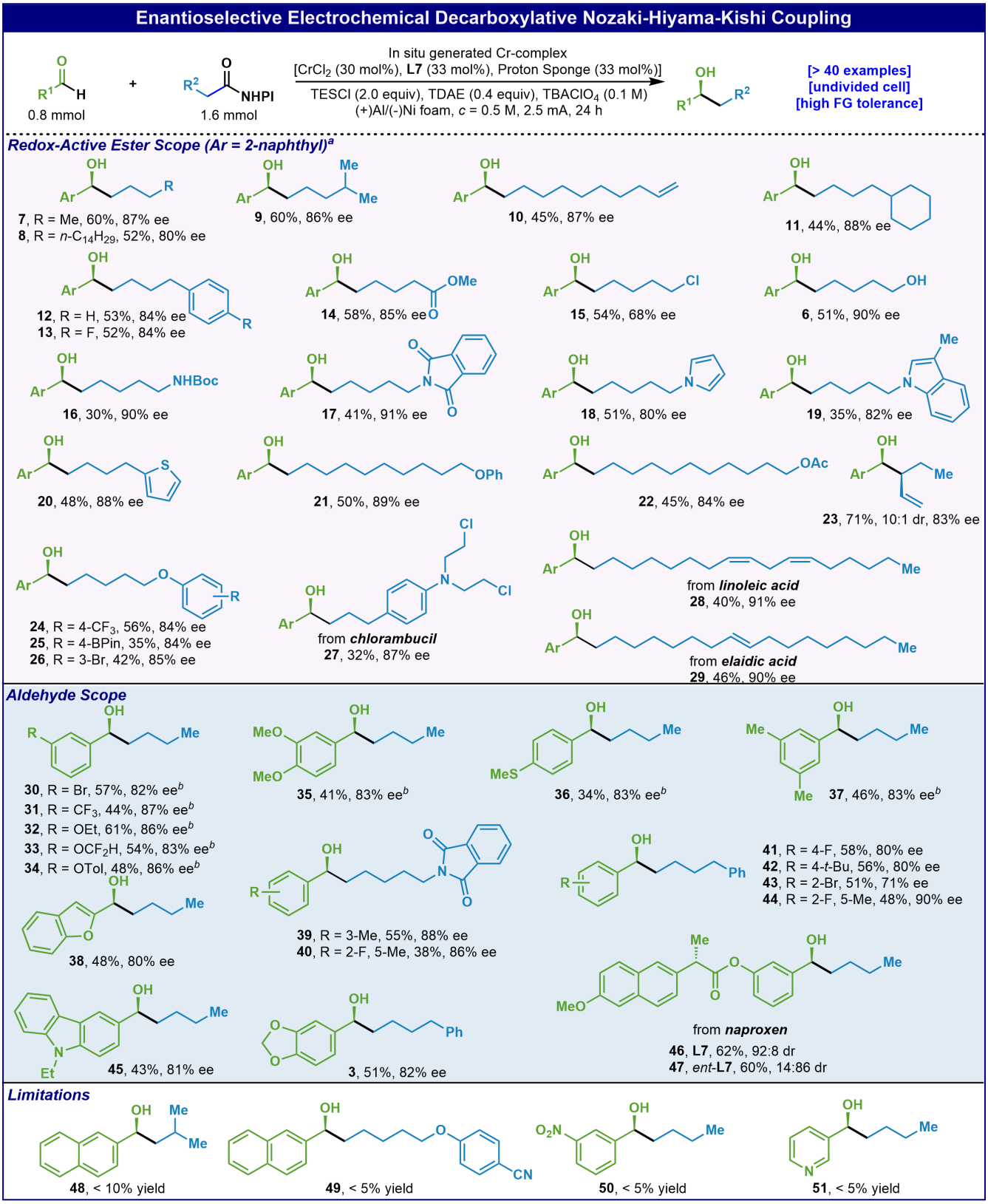
[a]Yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard. [b]Isolated yields after TBAF work-up. [c]Enantiomeric excess (ee) was determined by chiral SFC analysis. [d]Not determined. [e]2 equiv proton sponge was used. [f]Without proton sponge. [g]Cr(II)-**L8** complex not formed.

parameters, enabling additives, and an optimized chiral ligand.[15] The high functional group tolerance of this reaction combined with the versatility of using RAE-based alkyl donors can enable simplified access to enantioenriched alkyl-aryl alcohols in a variety of different contexts.

RESULTS AND DISCUSSION

The development of the asymmetric variant of decarboxylative electrocatalytic NHK took place in a bifurcated fashion as outlined in Table 1A on substrates **1** and **2**. Thus, parallel optimizations were carried out to maximize reactivity in an electrochemical setting and to maximize ee in a purely chemical system. By separating the challenges of maximizing electrochemical reactivity and ee, the research teams could cover ground more rapidly as it was practically simpler to explore >50 chiral ligands using superstoichiometric Cr loading under low yielding chemical conditions as only the ee measurement was relevant. At the same time, a variety of electrochemical parameters (>150 conditions screened) were explored such as solvent, electrolyte, additives, current density, concentration, and electrode material (see SI for complete summary of both endeavors). Early in

Table 2. Scope of Enantioselective Electrochemical Decarboxylative NHK coupling



[a]Isolated yields after TBAF work-up. [b]20 mol% $CrCl_2$, 22 mol% **L7**, and 22 mol% proton sponge were used.

those studies it was verified that the ee measurements observed using purely chemical conditions could be translated to non-optimized electrochemical conditions. With relatively optimized conditions and chiral ligand candidates identified, final reaction development commenced with alkyl aldehyde **3** and redox-active ester **4** (Table 1B). The extensive electrochemical screening campaign outlined above uncovered an optimal combination of chromium (II) chloride as the chromium source (along with catalytic proton sponge to enhance complex formation), TDAE[16]/TESCl

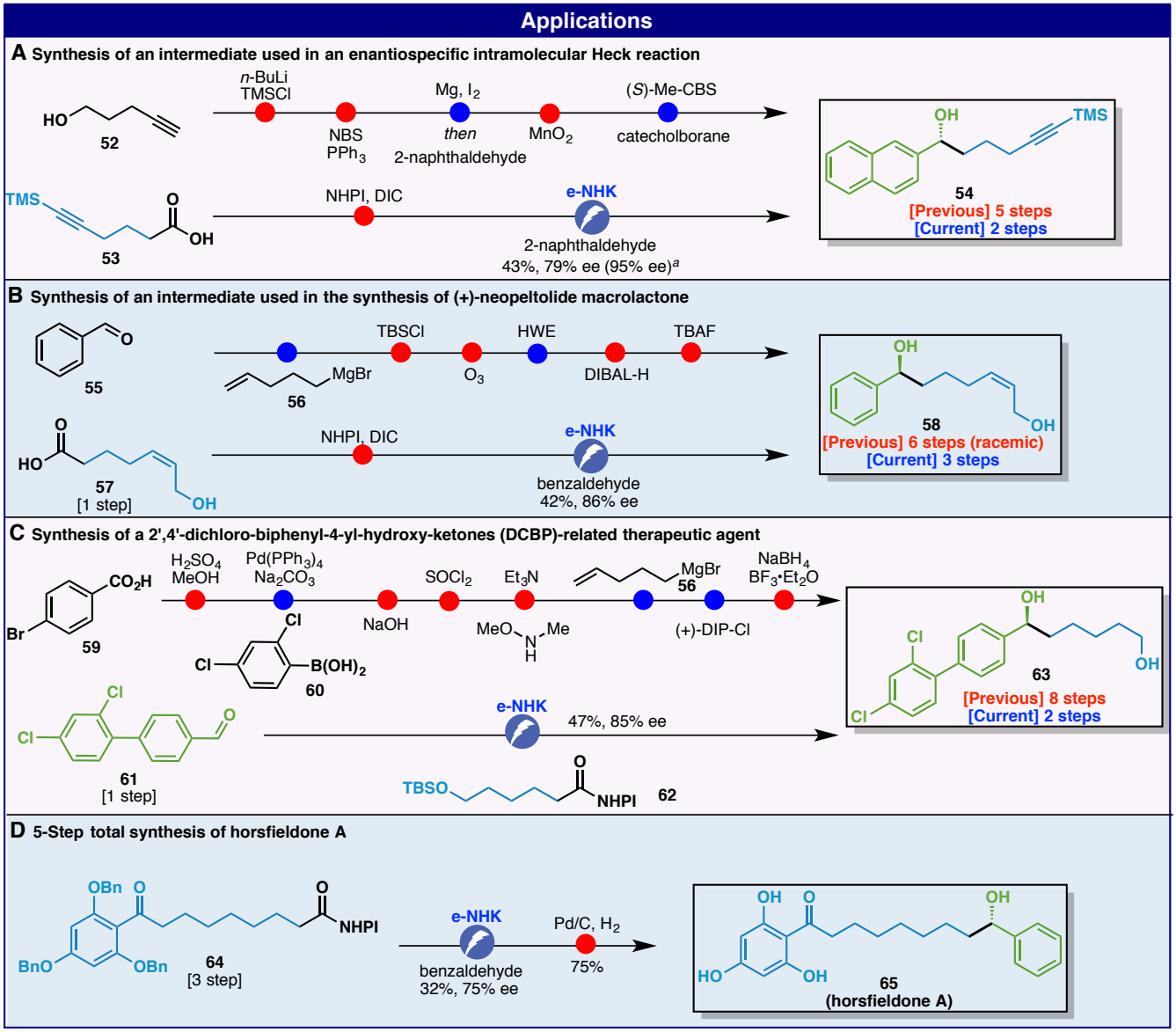


Figure 2. Applications: short synthesis of four bioactive aryl-alkyl substituted secondary alcohols. [a] After recrystallization.

as the additives, Al/Ni electrode materials, $TBAClO_4$ electrolyte, and a high concentration (0.5M) in CH_3CN. Of the chiral ligands explored, a unique sulfonamide-based structure (**L7**)[17] emerged as the optimum ligand. This final set of conditions provided a 51% isolated yield of benzylic alcohol **6** with 90% enantiomeric excess (Table 1B). Replacing $CrCl_2$ with air-stable $CrCl_3$ led to comparable yield but decreased enantio-selectivity (entry 1). The addition of TDAE significantly increased the reaction efficiency without impacting the enantioselectivity (entry 2). TESCl was found to be superior to Cp_2ZrCl_2 in terms of trapping the chromium alkoxides and regenerating the catalyst (entry 3). As for the electrochemical parameters, solvent choice was important wherein replacing CH_3CN with DMF (entry 4) lead to diminished enantioselectivity, presumably due to undesired competing coordination. Constant voltage (entry 5), alternative anode (entry 6) or cathode (entry 7) materials as well as the identity of the electrolyte (entry 8) decreased the observed reaction yield. Notably, classic batch conditions with or without external reducing agents (entries 9 and 10) displayed far lower reactivity for this transformation.

A wide variety of chiral ligands reported in asymmetric NHK reactions were evaluated (Table 1B, top right, see SI for full listing), including salen ligand **L1**,[18] Nakada's ligand **L2**[19] and BOX ligand **L3**.[20] We were pleased to determine that the chiral sulfonamide ligands (**L4**-**L9**) initially introduced by Kishi *et al.*, gave the most promising asymmetric induction. As a result of extensive screening of Kishi-type ligands (>40 ligands, See SI), the R substituent on the aniline was found to play a crucial role wherein the (+)-menthol substituent (**L6**) enhanced the ee value to 67% compared to a simple methyl group (**L4**, 1% ee) or a cyclohexyl group (**L5**, 16% ee). Thus, we evaluated several larger substituents at this position including (+)-8-phenylmenthol[21] (**L7**), which dramatically improved the ee value to 90%. However, an even more hindered variant containing a 2-naphthyl substituent (**L8**) did not form the required complex presumably due to its inability to coordinate to the Cr(II) center.

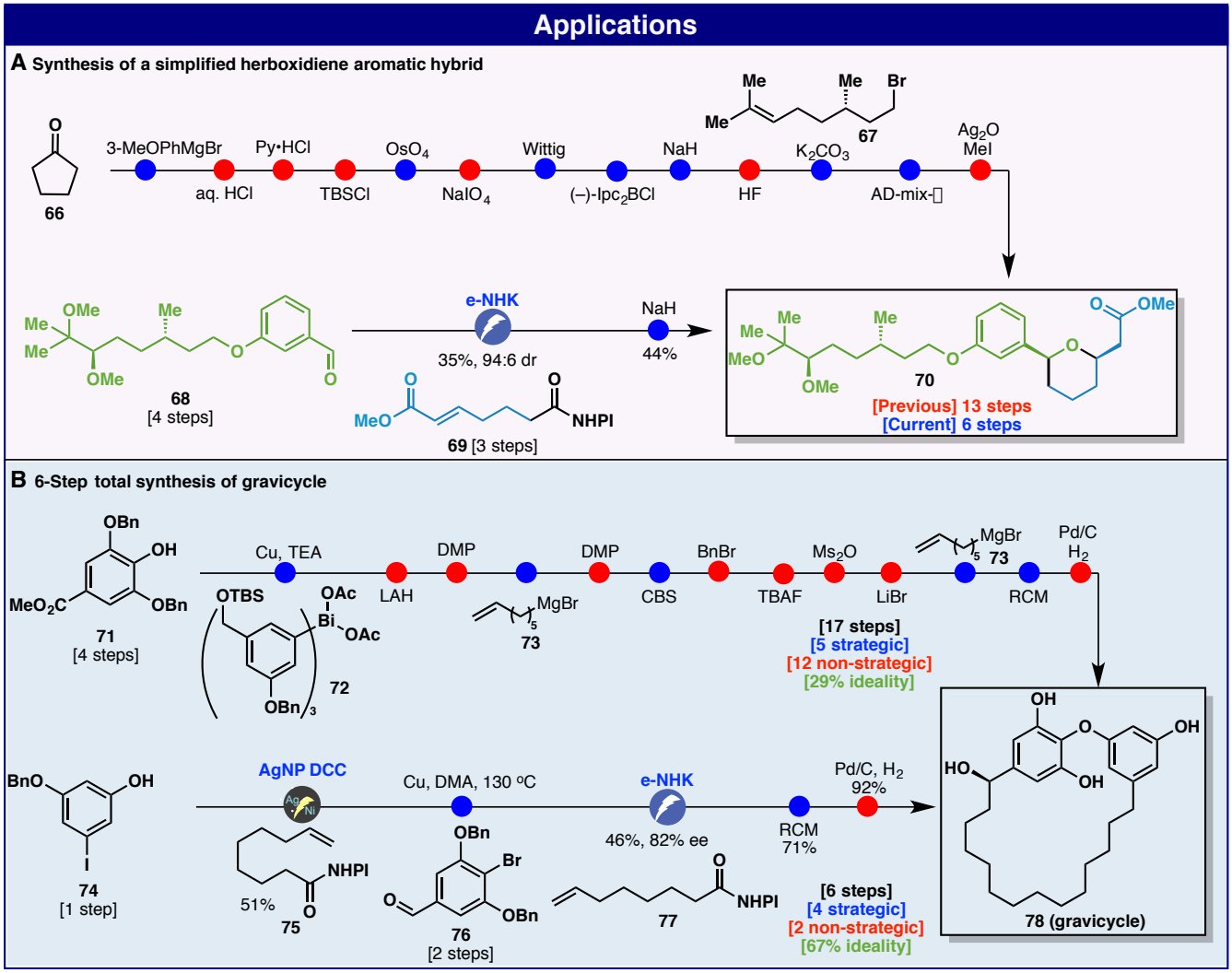


Figure 3. Applications: simplifying the synthesis of a herboxidiene aromatic hybrid and gravicycle.

With the optimal conditions in hand, the scope of this electrocatalytic enantioselective NHK decarboxylative coupling was explored as summarized in Table 2. With regard to the redox-active esters, which were derived from readily available aliphatic carboxylic acids, we were pleased to find that aside from simple alkyl chains (**7**, **8**, **9**, **11**), a wide variety of function groups could be tolerated, such as terminal alkenes (**10**), internal alkenes (**28**, **29**), aryl halides (**13**, **26**), esters (**14**), alkyl chlorides (**15**, **27**), silyl ethers (**6**), carbamates (**16**), imides (**17**), heterocycles (**18**, **19**, **20**), ethers (**21**, **24**, **25**, **26**), acetates (**22**), boronate ester (**25**), a trifluoromethyl group (**24**) and tertiary amines (**27**). An array of aromatic aldehydes proved to be suitable coupling partners, providing synthetically useful yields and enantioselectivity. The main byproducts are decarboxylative reduction products from the RAEs and benzyl alcohols derived from direct reduction of aromatic aldehydes. In general, substituents at the *meta*-position of the aromatic aldehydes give higher enantioselectivity than *ortho*-, and *para*-substituents, and the electronic properties of substituents have little impact on both yields and ee values. The functional group tolerance is also broad with respect to the aldehyde coupling partner, including aryl halides (**30**, **40**, **41**, **43**, **44**), ethers (**32**, **33**, **34**, **35**, **3**, **46**, **47**), thioethers (**36**), heterocycles (**38**, **45**), and esters (**46**, **47**). It is worth noting that in the case of a substrate bearing a remote stereocenter, the stereochemistry in the products was fully controlled by the stereochemistry of ligands (**L7**, *ent*-**L7**) rather than that of the substrate (**46**, **47**).

Of all the compounds listed in Table 1, only **7** has been previously prepared in an enantioselective fashion, all of which require pyrophoric nucleophiles (alkyl lithium and Grignard species).[22] Alcohols **30**, **35**, and **38** have been previously prepared in racemic fashion through Grignard additions.[23] It is advantageous in many cases to use carboxylic acid inputs from both a chemoselectivity standpoint and synthetic simplicity as several of the requisite alkyl halides would need to be derived either from alcohol halogenation or Hunsdiecker decarboxylation[24] (i.e. compounds **27**, **28**, and **29**).

Regarding the limitations of this method, nitro groups, benzonitriles, and pyridine-containing aldehydes are not suitable coupling partners (**49**-**51**). Beta-branched primary RAEs such as **48** also lead to poor yield. In addition, RAEs derived from secondary and tertiary aliphatic carboxylic acids failed to give any desired coupling products (see SI for details). Utilizing aliphatic aldehydes instead of aromatic ones led to significant loss in both yields and enantioselectivities (see SI for details).

APPLICATIONS

The electrocatalytic asymmetric NHK decarboxylative coupling disclosed herein, when applied strategically, can have a dramatically simplifying impact on synthesis as outlined in Figures 2 and 3. This is due to the radical retrosynthetic logic[25] employed that departs from the conventional 2e$^-$ strategies that are universally employed to access such substrates. For instance, alkyne **54**, which previously[26] required five steps involving non-strategic redox fluctuations, functional group interconversions, and pyrophoric nucleophiles could be prepared in only two steps commencing from **53** (Figure 2A). Diol **58**, an intermediate previously prepared as a racemic mixture (six steps) in a natural product total synthesis,[27] could be prepared in only three steps in high ee (Figure 2B). The medicinally relevant diol **63**[28] that required an 8-step route could be truncated to only two steps (Figure 2C). The first total synthesis of horsfieldone A[29] (**65**) was completed in 2 simple steps from the easily accessed RAE **64** (Figure 2D). Even more complex applications were designed and implemented as documented in Figure 3. For example, the herboxidiene analog **70**, previously required a 13-step route with many concession steps.[30] In contrast, starting from aldehyde **68** (four steps), an e-NHK coupling followed by cyclization led to the same compound in only 6 total steps. As a testament to the chemoselectivity of this reaction, RAE **69**, bearing an electrophilic acrylate moiety could be employed. Finally, a substantially truncated route to gravicycle[31] (**78**) was developed using a series of enabling electrocatalytic couplings. The prior route[32] to this natural product relied on an inefficient Bi-based *O*-arylation, pyrophoric reagents, numerous redox-fluctuations and functional group manipulations as part of a 17-step route. In contrast, the simple aryl iodide **74** could be subjected to electrocatalytic DCC-arylation[33] with RAE **75**, Ullman coupling with **76**,[34] e-NHK with RAE **77**, RCM, and deprotection to furnish **78** in only six steps.

MECHANISTIC STUDIES

Given that addition of TDAE proved important for obtaining good yields in the enantioselective e-NHK, mechanistic studies were carried out to determine the role of this additive. During the optimization process, a stoichiometric condition utilizing excess Cr(II) complex was found to give ee values comparable to the electrocatalytic system (Figure 4B). Addition of an acidic deuterium source to this reaction mixture led to formation of deuterated alkane **79** consistent with other reports of alkylative NHK-type reactions.[35] The consistent ee between the stoichiometric system and the electrochemical system suggests that both the stoichiometric and catalytic conditions involve formation of the same putative alkylchromium species, and that TDAE is not required for formation of this intermediate. We hypothesized that in the electrochemical system, TDAE mediates the reduction of the **L7**·Cr^{III}. This process might be more important with **L7**-coordinated Cr if the sterically encumbered chiral ligand imposes an additional kinetic barrier to reduction at the electrode surface.

To investigate the key electron transfer steps in the electrochemical system, cyclic voltammetry (CV) was performed (Figure 4C). To simplify the experimental setup, the **L7**·Cr^{III} complex was independently synthesized by treatment of **L7** with NaH (1.0 equiv) in THF followed by direct addition of solid $CrCl_3$·3THF to give a purple-green solid.[17a] **L7**·Cr^{III} exhibited quasireversible behavior with a large peak-to-peak separation (1.84V) and a cathodic peak potential of –1.53V at 100 mV/s (compared to ~–1.42V for the unligated $CrCl_3$·3THF complex) (Figure 4C, i). Both $CrCl_3$ and **L7**·Cr^{III} exhibited scan-rate dependent shifts in the cathodic peak potential with large half-peak to peak separation, suggesting that reduction at the cathode is kinetically slow. When compared to $CrCl_3$, the cathodic peak current of the **L7**·Cr^{III} catalyst is approximately 110 mV more negative, with an onset potential that is 150 mV more cathodic, suggesting the ligand increases the reduction potential of the complex or that it imposes an increased overpotential. Finite element simulation of the CV supported sluggish kinetics for the direct reduction of **L7**·Cr^{III} , as the voltammetry was best fit with low heterogeneous electron transfer rate constant of $1x10^{-5}$ cm s^{-1} (for comparison, fast reversible redox couples typically exhibit rate constants near 0.1 cm s^{-1}).[36] RAE **2** has a peak potential of –1.63V vs Fc/Fc^+ under the same CV conditions (Figure 4C, iii). This value lies close to the peak potential of **L7**·Cr^{III} (–1.53V), which could result in direct reduction of **2** at the cathode competing with reduction of **L7**·Cr^{III} given the challenging nature of the direct reduction of the Cr^{III} species. Thus, TDAE-mediated reduction of **L7**·Cr^{III} could allow the reaction to proceed more rapidly and at less-negative potentials, which could then avoid possible deleterious direct reduction of RAE **2**.

To investigate the ability of TDAE to serve as a mediator, $TDAE^{2+}(PF_6^-)_2$ was prepared by aerobic oxidation of TDAE in the presence of TMSBr (see SI). CV of $TDAE^{2+}(PF_6^-)_2$ in MeCN revealed two freely-diffusing reversible single-electron redox features at –1.05 V and –1.13V, consistent with previous literature reports (Figure 4C, ii).[37] Upon addition of **L7**·Cr^{III}, the cathodic peaks corresponding to $TDAE^{2+}$ reduction increase in current and there is concomitant loss of the anodic features associated with the $TDAE^0$/ $TDAE^{+\cdot}$ and $TDAE^{+\cdot}$/ $TDAE^{2+}$ oxidations, consistent with loss of $TDAE^{+\cdot}$ by chemical reaction with **L7**·Cr^{III} (EC mechanism) (Figure 4C, iv, v). The reduction of $TDAE^{2+}$ is less cathodic than both substrates (**1** and **2**) and **L7**·Cr^{III}, consistent with a scenario where $TDAE^{2+}$ undergoes preferential cathodic reduction. Additional CV studies were carried out to evaluate whether TDAE can also mediate reduction of either RAE **2** or aldehyde **1**. Addition of up to 10 equivalents of RAE **2** to $TDAE^{2+}(PF_6^-)_2$ in the absence of TESCl led to a negligible current increase (Figure 4C, vi). An increase in current was observed in the presence of TESCl (Figure 4C, vii); however, this feature disappeared after the first scan in a manner consistent with a trace impurity in the TESCl, which we ascribe to HCl. In a recent review, Waldvogel notes challenges of CV studies of silyl halides to due to their facile hydrolysis to generate HCl.[38] We have previously reported that the combination of TDAE and silyl halides induces reductive decarboxylation of NHP esters, but that TDAE/TESCl was determined to reduce benzylic NHP esters at rates that are slow relative to other silyl halides.[39] No significant current increase were observed upon addition of aldehyde **1** (100 equiv) to $TDAE^{2+}(PF_6^-)_2$ (Figure 4C, viii). This mechanistic scheme was further supported by finite element simulations of the voltammetry (Figure 4C, ix). Simulations of both

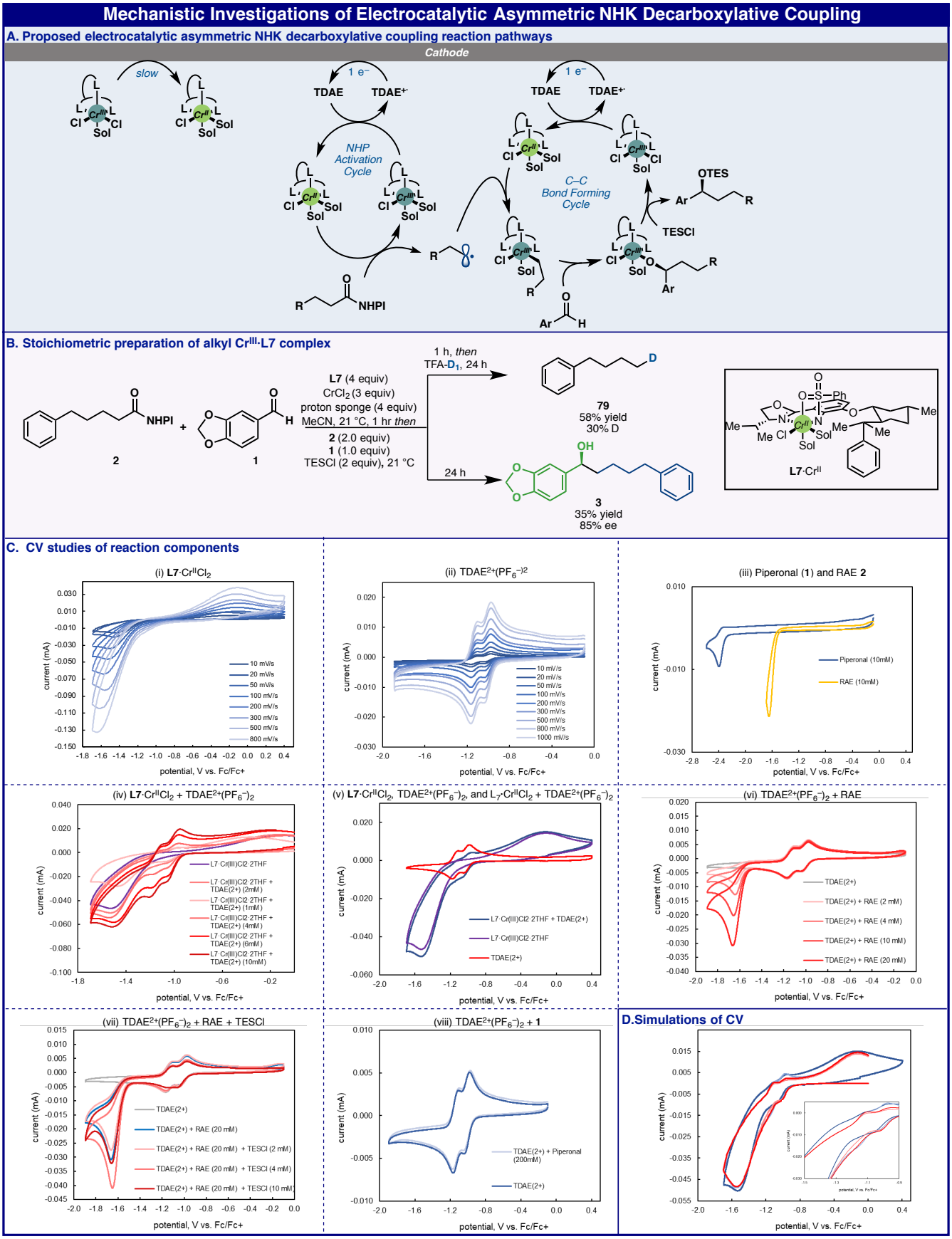


Figure 4. Mechanistic investigations. A. Proposed electrocatalytic cycle. B. Stoichiometric Cr-mediated reaction between **1** and **2** in the presence and absence of TFA-D_1. C. CV studies. All CVs were acquired in MeCN using 0.1 M $TBAClO_4$ supporting electrolyte. Unless otherwise noted, experiment was carried out with 100 mV/s scan rate. (i) [**L7**·$Cr^{III}Cl_2$·2 THF] = 8.55 mM. (ii) [$TDAE^{2+}(PF_6^-)_2$] = 0.001 M. (iii)[**1**] = 0.01 M, [**2**] = 0.01 M. (iv) [**L7**·$Cr^{III}Cl_2$·2 THF] = 8.55 mM. [$TDAE^{2+}(PF_6^-)_2$] varied from 0.002 to 0.01 M. (v)

L7·$Cr^{III}Cl_2$·2 THF [X M], $TDAE^{2+}(PF_6^-)_2$ [0.01 M], and **L7**·$Cr^{III}Cl_2$·2 THF [8.55 mM] and $TDAE^{2+}(PF_6^-)_2$ [0.002 M]. (vi) [$TDAE^{2+}(PF_6^-)_2$]= 0.002 M, [**2**] varied from 0.002 to 0.02 M. (vii) [$TDAE^{2+}(PF_6^-)_2$]= 0.002 M, [**2**] varied from 0.002 to 0.02 M, [TESCl] varied from 0.002 to 0.02 M. (viii) [$TDAE^{2+}(PF_6^-)_2$]= X M in the presence and absence of **1** [0.2 M]. D. Finite element simulation of CV of [**L7**·$Cr^{III}Cl_2$·2 THF] = 8.55 mM. [$TDAE^{2+}(PF_6^-)_2$] = 0.002 M. Dark blue trace: experimental CV. Light blue trace: simulation of no interaction between $TDAE^{+\cdot}$ and **L7**·$Cr^{III}Cl_2$·2 THF. Red trace: simulation of $TDAE^{+\cdot}$ complexation with [**L7**·$Cr^{III}Cl_2$·2 THF]. Pink trace: simulation of $TDAE^{+\cdot}$ complexation with [**L7**·$Cr^{III}Cl_2$·2 THF] followed by chemical regeneration of $TDAE^{2+}$.

$TDAE^{2+}$ and **L7**·Cr^{III} in solution with no mediation step provided a simulated CV with a clear shoulder at -1.13 V corresponding to the $TDAE^{+}/TDAE^{0}$ couple, a feature completely absent in the experimental CVs. Incorporation of an association step between $TDAE^{+}$ and **L7**·Cr^{III} into the simulation provided a voltammogram with no associated $TDAE^{+}/TDAE^{0}$ wave, providing evidence of a reaction between the reduced $TDAE^{+}$ and the Cr complex. Finally, incorporation of a turnover step (generating the reduced **L7**·Cr^{II} and regenerating $TDAE^{2+}$) once again resulted in the $TDAE^{+}/TDAE^{0}$ wave, leading to the conclusion that dissociation of $TDAE^{+}$ is slow, but still orders of magnitude faster than the direct reduction of **L7**·Cr^{III} (full simulation details can be found in the SI). TDAE is known to form charge-transfer complexes with organic molecules and metal surfaces.[40] Collectively, these results are consistent with TDAE serving as an electrochemical mediator to reduce **L7**·Cr^{III}. It is also possible that TDAE can scavenge trace impurities such as HCl or O_2 that could decompose intermediates in the catalytic cycle.[41] The latter observation is corroborated by the generally improved performance of TDAE over $TDAE^{2+}$ in the reaction, which may result from the capability of TDAE to scavenge trace impurities before electrolysis is commenced.

In principle, if TDAE mediates reduction of **L7**·Cr^{III}, then it should be possible to use stoichiometric TDAE to drive the reaction **L7**·Cr^{II} in the absence of current. Indeed, TDAE has been used as the stoichiometric reductant for Cr-catalyzed addition of alkenyl bromides and allyl bromides to aldehydes.[42] However, during the optimization process, <10% yield **3** was observed using stoichiometric TDAE and no electricity (see Table 1, entry 10). Based on a recent report by Wenger and coworkers in which $TDAE^{+\cdot}$ was invoked as an H-atom source, we hypothesized that with high concentrations of $TDAE^{+\cdot}$ (as under the stoichiometric conditions), hydrogen atom transfer (HAT) to the primary alkyl radical derived from **2** outcompetes addition of this species to **L7**·Cr^{II} to generate the alkyl Cr^{III} species.[43] In contrast, prior work from the Reisman lab showed that benzylic radicals undergo radical-radical dimerization faster than HAT in the presence of $TDAE^{+\cdot}$.[39] We ascribed this difference in reactivity to the difference in stability of the primary and benzylic radicals. This also highlights the enabling nature of using catalytic TDAE under electrochemical conditions: while $TDAE^{+\cdot}$ can mediate reduction of **L7**·Cr^{III}, its presence in high concentrations can intercept the radical generated from the RAE and prevent productive coupling. This is a distinct challenge for the alkyl NHK, which proceeds via formation of highly reactive alkyl radicals, relative to prior work.

CONCLUSION

In summary, an enantioselective alkyl e-NHK has been developed. This reaction allows the addition of simple, primary alkyl substrates to aldehydes to give secondary alcohols in high enantioselectivity. This class of substrates has not previously been rendered enantioselective for NHK reactions driven by canonical metal dust reductants. This asymmetric alkyl e-NHK was enabled by using TDAE as a key reductive mediator. CV studies and stoichiometric experiments suggest that the role of TDAE is to mediate reduction of the **L7**·Cr^{III} complex, which in the previous, non-asymmetric alkyl e-NHK, was found to be the rate determining step. This is especially beneficial for the asymmetric reaction, in which the chiral ligand is proposed to kinetically slow reduction of the catalyst at the electrode. The ability to use catalytic TDAE mediator is critical to avoid competing HAT processes between the alkyl radical and $TDAE^{+\cdot}$. The usefulness of this method is demonstrated by multiple synthetic campaigns, which highlight the strategic deployment of the asymmetric alkyl e-NHK to increase synthetic ideality and reduce step count.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. The Supporting Information contains all experimental procedures, analysis, and com-pound characterization data.

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ACKNOWLEDGMENT

This work was supported by the NSF Center for Synthetic Organic Electrochemistry, CHE-2002158 (the discovery and optimization effort). NIGMS (GM-118176) supported the scope and application study. A.C.H. was supported by an NSF Ascend fellowship (award number: 2138035). Authors are grateful to Dr. Laura Pasternack (Scripps Research) for assistance with nuclear magnetic resonance (NMR) spectroscopy, to Dr. Jason Chen, Brittany Sanchez and Quynh Nguyen Wong (Scripps Automated Synthesis Facility) for assistance with HRMS and chiral SFC analysis. Elemental analysis data were obtained from the CENTC Elemental Analysis Facility at the University of Rochester, funded by NSF CHE-0650456. Mass spectral data were acquired by Field Desorption Ionization mass spectrometry (FD-MS) using an JMS-T2000 AccuTOF GC-Alpha (JEOL, Inc). The purchase of the instrument was enabled by funds from DOW Next Generation Instrumentation (CCEC.DOWINSTR-1-GRANT.DOWINSTR). The authors would like to thank Jay Winkler for assistance with CV experiments and Mona Shahgoli for assistance with HRMS experiments, as well as the Caltech CCE NMR facility and Multiuser Mass Spectrometry Laboratory, which is also supported by the NSF CRIF program (CHE-0541745).

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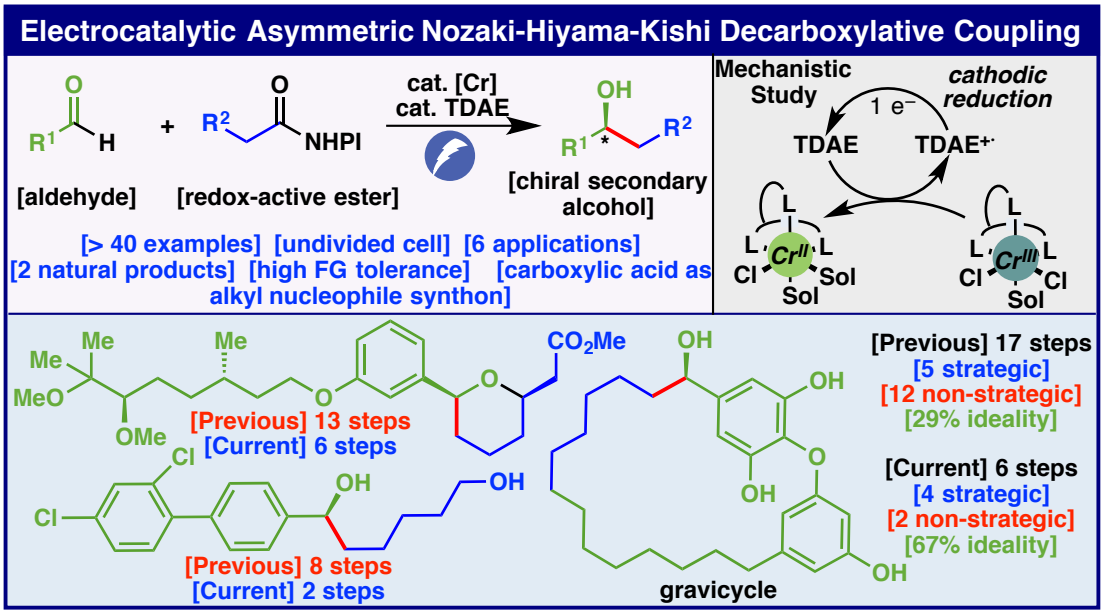
GRAPHICAL ABSTRACT (TOC)


Electrocatalytic Asymmetric Nozaki-Hiyama-Kishi Decarboxylative Coupling
cat. [Cr]
cat. TDAE
[aldehyde]
[redox-active ester]
[chiral secondary alcohol]
[> 40 examples] [undivided cell] [6 applications]
[2 natural products] [high FG tolerance] [carboxylic acid as alkyl nucleophile synthon]
Mechanistic Study
cathodic reduction
1 e⁻
TDAE
TDAE+·
[Previous] 13 steps
[Current] 6 steps
[Previous] 8 steps
[Current] 2 steps
gravicycle
[Previous] 17 steps
[5 strategic]
[12 non-strategic]
[29% ideality]
[Current] 6 steps
[4 strategic]
[2 non-strategic]
[67% ideality]