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Enantioselective Electroreductive Coupling of Alkenyl and Benzyl Halides via Nickel Catalysis

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Supporting Information Placeholder

ABSTRACT: An electrochemically-driven enantioselective nickel-catalyzed reductive cross-coupling of alkenyl bromides and benzyl chlorides is reported. The reaction forms products bearing allylic stereogenic centers with good enantioselectivity under mild conditions in an undivided cell. Electrochemical activation and turnover of the catalyst mitigate issues posed by metal powder reductants. This report demonstrates that enantioselective Ni-catalyzed cross-electrophile couplings can be driven electrochemically.

Nickel-catalyzed reductive cross-coupling reactions have emerged as powerful methods for the formation of carbon–carbon bonds.¹ Typically, these cross-electrophile couplings employ a superstoichiometric metal powder, often Mn⁰ or Zn⁰, as a reductant to turn over the Ni catalyst. Such methods enable the formation of valuable C(sp²)–C(sp³) bonds without pre-generation of sensitive organometallic reagents common to many traditional cross-coupling reactions. Reductive couplings can be rendered particularly useful when a chiral ligand is used to afford enantioenriched products. To this end, our lab has developed several asymmetric nickel-catalyzed reductive coupling reactions employing Mn⁰ or tetrakis(*N,N*-dimethylamino)ethylene (TDAE) as the stoichiometric reductant.^{2,3}

Reactions utilizing a heterogeneous metal reductant can suffer from capricious stirring effects, variability in metal activity based on source, batch,

and storage conditions, and the generation of excess waste. Several approaches have been reported for overcoming some of these inherent challenges. Most commonly, soluble organic reductants have been employed, though insoluble salts frequently precipitate from solution as the reactions progress.⁴ Metallaphotoredox reductive couplings have been reported by MacMillan,⁵ Lei,⁶ and Vannucci,⁷ with (Me₃Si)₃SiH, Et₃N, and triethanolamine serving as homogenous terminal reductants, respectively. In recent decades, electrochemistry has also been leveraged as a strategy for avoiding several of the issues associated with the use of superstoichiometric metal reductants.

Seminal reports from Durandetti, Nédélec, and Périchon describe the electroreductive nickel-catalyzed coupling of aryl bromides and iodides with a variety of activated alkyl electrophiles.⁸ An excess of alkyl halide was typically added slowly over the course of the reaction in order to minimize unproductive homocoupling. This reactivity was extended to the preparation of enantioenriched α -aryl carboxylic acids through the use of a chiral auxiliary, providing two enantioenriched acids in 82 and 85% enantiomeric excess (ee) after cleavage of the auxiliary.⁹ Recently, three additional electroreductive nickel-catalyzed couplings have been disclosed, all employing unactivated alkyl electrophiles. Hansen and coworkers reported the coupling of aryl bromides with alkyl bromides, using reticulated vitreous carbon foam (RVC) as the cathode and Zn as a sacrificial anode, in an undivided cell.¹⁰ Bio and coworkers reported an electrochemical reductive coupling of aryl iodides

with alkyl *N*-hydroxyphthalimide (NHP) esters in a divided cell, both in batch and in flow, with Et₃N as the terminal reductant.¹¹ Loren and coworkers reported an electroreductive decarboxylative coupling of carboxylate salts and aryl iodides, proceeding through *in situ* generation of NHP esters.¹² The photochemical and electrochemical methods reported to date all employ an excess of one of the electrophiles and form products that are either achiral or racemic – with the exception of the aforementioned auxiliary-based examples.

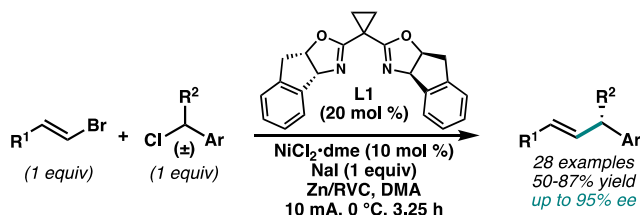


Figure 1. Nickel-catalyzed enantioselective electroreductive coupling. dme = 1,2-dimethoxyethane; DMA = *N,N*-dimethylacetamide.

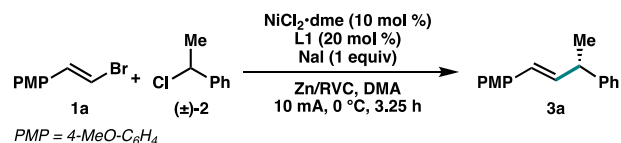
Recognizing the benefits of electrochemistry, we sought to demonstrate that the enantioselective Ni-catalyzed reductive alkenylation developed in our lab could be driven electrochemically. Whereas this transformation has been previously reported by our group with Mn⁰ as the terminal reductant,^{2b} an electroreductive manifold would allow for the formation of valuable enantioenriched products without some of the difficulties encountered when using superstoichiometric metal powder reductants. Herein we report the first asymmetric electrochemical reductive cross-coupling (Figure 1).

Electrolysis of a solution of alkenyl bromide **1a** (1 equiv), benzylic chloride **2** (1 equiv), NiCl₂·dme (10 mol %), indanyl-substituted bis(oxazoline) ligand **L1** (20 mol %), and NaI (1 equiv), in an undivided cell equipped with an RVC cathode and a sacrificial Zn anode, afforded **3a** in 84% yield and 94% ee (Table 1, entry 1).¹³ Electrolysis was highly efficient; the reaction was complete after application of the theoretically required amount of charge (2.0 F/mol). Judicious selection of electrode materials proved essential for this reaction. When graphite was used in place of RVC foam (entry 2), significant drops in conversion, yield, and enantioselectivity were observed, as well as reduced mass recovery – a

phenomenon previously observed by Baran and coworkers.¹⁴ Alternate sacrificial anode metals were also tested in place of Zn. The reaction stopped early due to voltage overload (12 V) when either Al or Mg were used (entries 3 and 4). Under the standard reaction conditions, an Fe anode afforded coupled product **3a** in 53% yield and 95% ee, with 28% remaining **2** (entry 5). When the reaction time was doubled (4 equiv e⁻), the Fe anode gave **3a** in 70% yield and 94% ee (entry 6).¹⁵ Given that tuning the current allows for control over the rate of catalyst turnover, it is unsurprising that modulating the current has a significant effect on the outcome of the reaction. Doubling the current (20 mA) and halving the reaction time (entry 7), as well as halving the current (5 mA) and doubling the reaction time (entry 8) both afforded product in lower yields and enantiomeric excesses (77% yield, 91% ee; and 61% yield, 93% ee, respectively).

Sodium iodide has been used by us and others as a reaction additive to increase yields in nickel-catalyzed reductive couplings.^{2b,16,17} In this reaction, NaI can serve a dual role as both reaction additive and electrolyte. Altering the identity of the electrolyte (TBAI, TBAPF₆, NaPF₆) resulted in reduced yields and enantioselectivities (entries 9–11). Lowering the loading of NaI or ligand, or increasing the temperature, were all detrimental to the reaction (entries 12–15).¹⁸ Control experiments confirmed that nickel and electrolyte were both essential (entries 16 and 17). Without ligand, the reaction afforded racemic product in 5% yield (entry 18). When no current was passed, product was produced in 2% yield, likely due to slow reduction by the Zn electrode (entry 19). Although this reaction is thermodynamically favorable, the use of an external power source is required to overcome the overpotential of the cell.¹⁹

Table 1. Effects of Reaction Parameters.^a



entry	deviation from standard conditions	yield (%) ^b	ee (%) ^c
1	None	84	94

2	graphite instead of RVC	14	41
3	Al instead of Zn	48 ^d	96
4	Mg instead of Zn	23 ^d	96
5	Fe instead of Zn	53	95
6	Fe instead of Zn, 6.5 h	70	94
7	20 mA, 1.6 h	77	91
8	5 mA, 6.5 h	61	93
9	TBAI instead of NaI	67	91
10	TBAPF ₆ instead of NaI	59	78
11	NaPF ₆ instead of NaI	24	76
12	0.5 equiv NaI	73	90
13	15 mol % ligand	80	91
14	10 mol % ligand	76	91
15	23 °C	49	89
16	no NiCl ₂ ·dme	0	–
17	no NaI	0 ^d	–
18	no ligand	5	0
19	no current	2	–

^aReactions conducted on 0.6 mmol scale.

^bDetermined by ¹H NMR integration versus Bn₂O as an internal standard. ^cDetermined by SFC using a chiral stationary phase. ^dReaction stopped early due to voltage overload. TBA = tetra-*N*-butylammonium.

Having established efficient reaction conditions, we sought to explore the scope of alkenyl bromide electrophiles that could serve as competent coupling partners. Both styrenyl and alkyl-substituted alkenyl bromides coupled in high yields and enantioselectivities (Figure 2). Aryl groups bearing both electron-withdrawing groups (**3c**) and electron-donating groups (**3a**) were well tolerated. Several heterocyclic substrates (**3d** and **3e**) react smoothly, as well as both benzyl- and benzoyl-protected alcohols (**3f**, **3g**). Aryl boronate **1b**, free alcohol **1h**, and primary alkyl chloride **1i** all coupled successfully to form products poised for direct elaboration (**3b**, **3h**, **3i**). Use of either (3*R*, 8*S*)-**L1** or (3*S*, 8*R*)-**L1** enabled the coupling of (–)-citronellal-derived alkenyl bromide **1k** to give either the (*S,S*)- or (*R,S*)-diastereomers of diene **3k**, each with good diastereoselectivity.

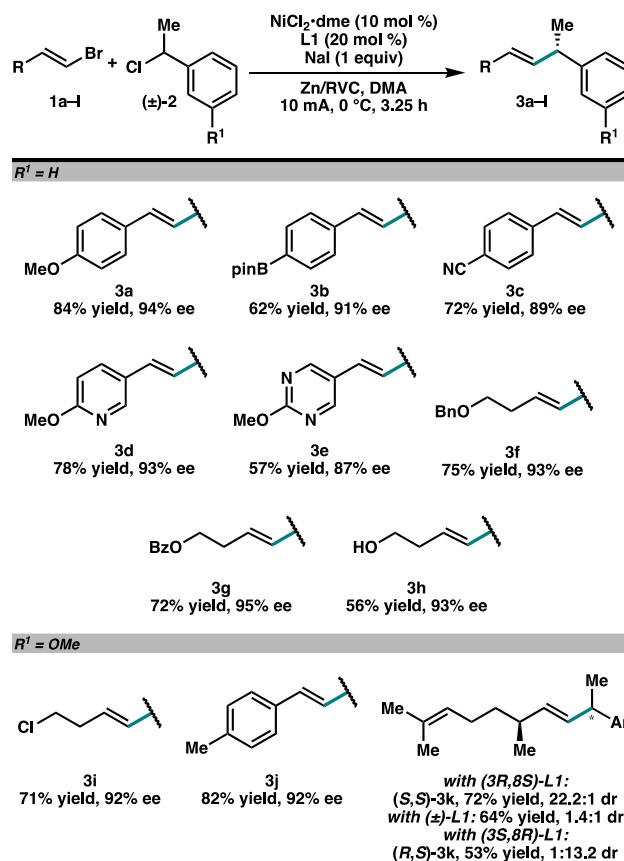


Figure 2. Scope of alkenyl bromides. Reactions conducted using 0.6 mmol alkenyl bromide and 0.6 mmol benzyl chloride.

A variety of benzylic chlorides also proved to be competent coupling partners (Figure 3). Several halogenated arenes (**4a–4d**) were tolerated; unfortunately, substrates possessing aryl bromides suffered from competitive iodination and hydrodebromination. Whereas the *o*-methyl product **5e** was obtained in lower yield and ee, the *o*-methoxy product was formed in good yield (**5n**). Extending the α -phenyl alkyl chain from methyl to ethyl gave product **5h** in comparable yield and excellent ee. Further increasing the steric bulk of this substituent resulted in a slight loss of ee (**5i**). The five- and six-membered ring products **5j** and **5k** were formed in good enantioselectivity, however a significant drop in selectivity was observed in the formation of 7-membered ring-containing product **5l**.

The starting benzylic chlorides were fully consumed after the reactions were run long enough to pass 2 F/mol, indicating excellent faradaic

efficiencies in all cases.²⁰ Construction of a larger reaction cell allowed for efficient scaleup of the reaction (0.6 mmol to 6.0 mmol), simply by increasing the current passed (10 mA to 100 mA), to afford **3a** on gram scale with only minor reductions in yield and enantioselectivity (83% yield, 91% ee).²¹

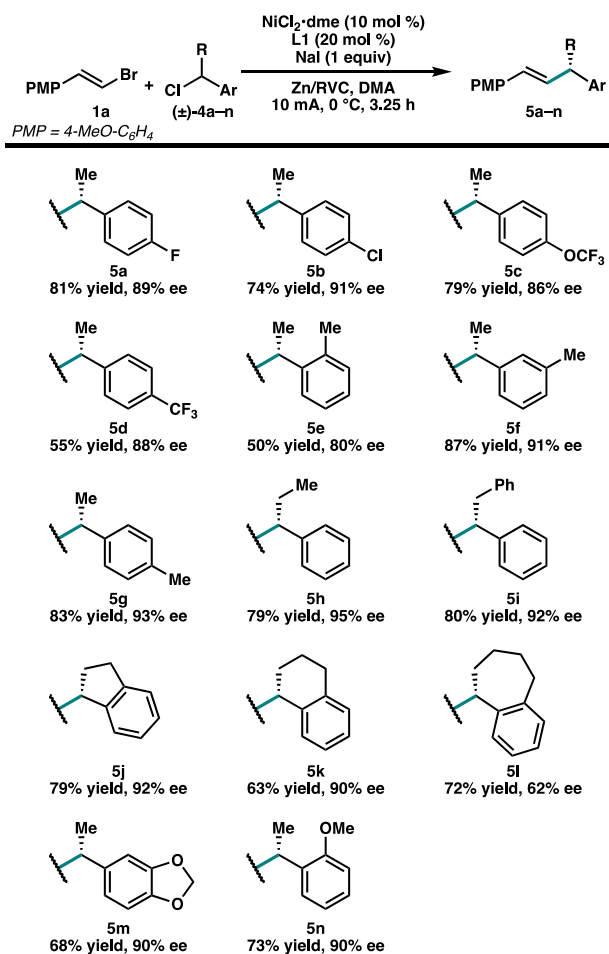


Figure 3. Scope of benzylic chlorides. Reactions conducted using 0.6 mmol alkenyl bromide and 0.6 mmol benzyl chloride.

In summary, an efficient, enantioselective, electroreductive coupling of alkenyl bromides and benzyl chlorides has been developed. The use of electric current to turn over the nickel catalyst eliminates the need for superstoichiometric metal powder reductants. This method provides stereoconvergent access to compounds with allylic stereogenic centers, under mild conditions and with good selectivity. Additionally, this method does not require an excess of either of the coupling partners. Studies are ongoing to expand the use of

electrochemical turnover in other nickel-catalyzed enantioselective reductive couplings.

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No competing financial interests have been declared.

ASSOCIATED CONTENT

Supporting Information. Available free of charge on the ACS Publications website. Experimental procedures, characterization data (¹H and ¹³C NMR, HRMS, FTIR) for all new compounds (pdf).

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KEYWORDS

Nickel, electrochemistry, enantioselective, cross-coupling, asymmetric catalysis

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 - Attempts to cool the reaction further presented issues with large amounts of water condensing on the exposed electrodes.
 - When the electrodes were connected directly with an ammeter between them, no current was observed with either an RVC or Ni foam cathode.
 - Full consumption of starting material was observed when 2 F/mol were passed; the Faradaic efficiency of each reported example is equal to its chemical yield.
 - See Supporting Information for details.

TOC Graphic:

