Coupling of Alternating Current to Transition-Metal Catalysis: Examples of Nickel-Catalyzed Cross-Coupling

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Abstract

The coupling of transition-metal to photoredox catalytic cycles through single-electron transfer steps has become a powerful tool in the development of catalytic processes. In this work we demonstrated that transition-metal catalysis can be coupled to alternating current (AC) through electron transfer steps that occur periodically at the same electrode. AC-assisted Ni-catalyzed amination, etherification, and esterification of aromatic bromides showed higher yields and selectivity compared to observed in the control experiments with direct current (DC). Our mechanistic studies suggested the importance of both reduction and oxidation processes in the maintenance of the AC-assisted catalytic reactions. As in presented examples, the AC assistance should be well-suited for catalytic cycles involving reductive elimination or oxidative addition as a limiting step.
**Introduction**

Ni-based catalysis has attracted much attention as an effective tool for forming the C(aryl)-Heteroatom bond,¹ which is frequently found in drug-like molecules, dyes, and conjugated polymers. However, Ni-catalytic systems are often inferior to more prevalent but expensive Pd-catalytic systems. Unfavorable reductive elimination from Ni(II) species and the instability of the Ni(I) species are among the factors causing this inferiority. Nevertheless, Ni-catalysis is susceptible to facilitation by energy inputs from light or electricity because of the availability of redox states of nickel ranging from 0 to +4 (Figure 1A-B).

![Diagram of Ni-catalytic cycles](image)

**Figure 1.** Some methods for activating Ni-based catalytic cycles by sequential oxidation and reduction: (A) Photoredox-assisted; (B) DC-assisted; (C) AC-assisted couplings. (D) Working hypothesis of the mechanism underlying the coupling of alternating current (AC) to the nickel catalytic cycle for cross-coupling reactions.
By merging photoredox and nickel catalysis, MacMillan and others enabled previously elusive Ni-catalyzed C-C, C-N, and C-O coupling reactions. In most situations, the coupling between photoredox and nickel catalysis involves single-electron oxidation and reduction of nickel catalytic species by a photoredox catalyst (Figure 1A). Thus, oxidation to Ni(III) species enables reductive elimination, whereas reduction to Ni(0) species accelerates oxidative addition. Later, Baran’s group, regarding the example of C-N coupling, showed that the photocatalytic approach might be successfully replaced with assistance by direct current (DC) electrolysis. Here, nickel species are oxidized on one electrode, enabling reductive elimination, and reduced on another electrode, accelerating oxidative addition (Figure 1B); the current-assisted catalytic cycle involving nickel species in oxidation states +1, +2, and +3 was suggested. This approach was effective for the C-S, C-P, Heck, and C-O coupling reactions.

Although some disagreements exist regarding key reaction intermediates, mechanistic studies of both electrochemically and photochemically enabled nickel cross-coupling suggest that both oxidation and reduction processes are essential for maintaining the sustainable catalytic pathway. These mechanistic considerations led us to the idea of merging alternating current (AC) with Ni-catalyzed cross-coupling reactions (Figure 1C). AC authentically fits the idea of a catalytic cycle assisted by a pair of redox processes. Because of the periodical polarity switch, both redox steps can successfully occur at the same electrode with a tunable delay between them (Figure 1D). In this work, we performed AC-assisted Ni-catalyzed amination, etherification, and esterification of aromatic bromides. For all reactions, AC displayed advantages over DC in our electrochemical cell.

Currently, AC has a significantly more modest application in organic synthesis compared with DC – generally, it is used for preventing electrode fouling. Notable works showed that AC can be successfully applied in the electrosynthesis of phenol, trifluoromethylated arenes, or in accelerating S-S bond metathesis through reversible redox steps.
Results and discussion

We performed reactions in an electrochemical cell equipped with two glassy carbon (GC) rod electrodes. A commercial waveform generator supplied sinusoidal voltage to the electrodes; we used an oscilloscope to measure both the voltage and current in our experiments (Figure 2A, Figure S3). The combinations of NiBr$_2$·DME (DME – dimethoxyethane) with 2,2’-Dipyridyl (Bipy) or 4,4’-Di-tert-butyl-2,2’-dipyridyl (di-$^t$BuBipy) were chosen as catalysts because they were successfully employed in various catalytic systems.$^{2d,5}$

To perform the catalytic cycle based on both reduction and oxidation of the catalyst, the voltage should be sufficient to perform the reduction on one of the electrodes, whereas the oxidation occurs on another electrode. We proposed that reduction of [Ni(Bipy)$_x$I$^{2+}$ to [Ni(Bipy)$_x$I$^0$ (for $x = 3$, -1.25 V vs saturated calomel electrode (SCE) in CH$_3$CN) is most likely to be a process that would favor oxidative addition.$^{14}$ Similarly, oxidation of [NiL(Ar)(Nu)] to [NiL(Ar)(Nu)]$^+$ (L – ligand, Ar – aryl, Nu – nucleophile) would favor the reductive elimination of Ar-Nu.$^{15}$ Considering that the potential for oxidation of [Ni(C$_6$H$_3$(CF$_3$)$_2$)(OCH$_2$CF$_3$)] to [Ni(C$_6$H$_3$(CF$_3$)$_2$)(OCH$_2$CF$_3$)]$^+$ is 0.83 V vs SCE in CH$_3$CN, which is at the high end of the expected oxidation potentials for the [NiL(Ar)(Nu)] species,$^{2d}$ a voltage higher than ~ 2.1 V is required to simultaneously perform the desired oxidation and reduction of nickel species. We found a peak voltage of 3V to be effective in most of our experiments; in such conditions the peak value of current varied from 10 mA to 20 mA in different experiments.

In the initial screening, we aimed to optimize the conditions for amination, etherification, and esterification of aryl bromides (Figure 2B-D and Tables S1-3). We used the reaction between bromobenzene (1) (50 mM) and morpholine (150 mM) for optimization of the amination conditions because 1 being a less reactive substrate than 4-bromobenzotrifluoride (3) offered more room for the optimization (Figure 2B). Different combinations of ligands (di-$^t$BuBipy and Bipy) and solvents (dimethylformamide (DMF) and dimethylacetamide (DMA)) worked, but combining DMA with di-$^t$BuBipy provided better stability of the nickel complex in the solution and more reproducible results than the other systems did. The fre-
quency of the applied voltage is a unique parameter for AC-assisted catalysis. Interestingly, the dependency of yield on frequency has a maximum of around 2 Hz (87%). The increase in frequency to 25 Hz caused a steep drop in yield, most likely because of the increased contribution of charging and discharging of the electrical double layer (see Figure S5 for the quantitative analysis) and of nonproductive reversible Ni(II)/Ni(I) and Ni(II)/Ni(0) oxidation/reduction cycles to the current at high frequencies. At the same time, the decrease in frequency as well as the use of DC also led to diminished yields. We can speculate at this point that in case of the use of AC assistance some optimum “resonance” frequency exists which is defined by the complex combination of the parameters such as rates of chemical and electron-transfer steps, rate of diffusion of the catalytic and non-catalytic species from and to the surface of the electrodes, and stirring rate. Yet, we expect that under specific conditions the value of “resonance” frequency may provide valuable data related to the kinetics of the discussed reactions.

In contrast to amination, the base is an essential component in esterification (Figure 2C). We achieved the best results using a suspension of potassium carbonate as in photo-activated esterification; organic bases were found to be less effective. The increase of the ligand concentration or the use of more sterically hindered ligands than bipyridine resulted in diminished yields. The choice of NBu4PF6 as a supporting electrolyte was instrumental for getting good yields of esters; we suggest two possible reasons for that. First, carboxylate is a relatively weak ligand; thus, eliminating the competition of carboxylate with bromide at the nickel center increases the efficiency of a catalytic cycle. Second, carboxylate is a more electronegative group than amine or alcoholate; thus, the oxidation potential of the [NiL(Ar)(RCOO)] species (e.g., 0.9 V vs SCE for [Ni(C6H3(CF3)2)(OAc)]) is expected to be higher than that of [NiL(Ar)(OR)] and the [NiL(Ar)(NHR2)] species. Avoiding excessive anodic oxidation of Br− allows one to achieve higher oxidation potentials in experiments with NBu4PF6 than with LiBr (Figure S18), which might be necessary for the oxidation of the [NiL(Ar)(RCOO)] species. The optimum frequency for esterification reaction was 2 Hz.
Figure 2. (A) Experimental set-up for the AC-assisted cross-coupling reactions. (B–D) Optimization of conditions for AC-assisted amination, esterification, and etherification reactions, respectively. The comparison of the results of the experiments with AC-assistance (using optimized conditions) and DC-assistance (using potentiostatic and galvanostatic conditions) is given in red boxes.
The control DC experiments at potentiostatic (2.8 V) and galvanostatic (2, 4, and 6 mA) conditions demonstrated low yields (13-26 %) and high amount (22-53%) of biaryl side product (see Table S2). As esterification, etherification also requires the addition of a base (Figure 2D); we tested 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,4-diazabicyclo[2.2.2]octane (DABCO) as bases; however, the best results were achieved with quinuclidine, analogously to photoredox-assisted etherification.2d Interestingly, the use of non-cyclic tertiary amines led to the formation of the homocoupling product in considerable amounts (Table S3) – presumably, they serve as sacrificial reductants in this case. Comparing the results of AC- and DC-assisted (both in the potentiostatic and galvanostatic modes) etherification further highlights that AC-assistance demonstrates higher selectivity towards the formation of cross-coupling products vs homocoupling products than DC-assistance. Moreover, the decrease in the amount of the biaryl product occurs gradually with an increase in the frequency. Two hypotheses could explain these observations: (i) the shorter lifetime of [NiL(Ar)(Nu)] species in the AC than in the DC experiments; (ii) fewer chances for the second oxidative addition in the AC than in the DC experiments. With a short lifetime, [NiL(Ar)(Nu)] does not have time to disproportionate appreciably to the [NiL(Ar)₂] intermediate with two aryl groups at one nickel center, which affords diaryl coupling products by reductive elimination.17 In the DC experiments, a continuous strongly reducing environment near the cathode increases chances that the oxidative addition product [NiL(Ar)Br] will undergo reduction to Ni(I) species and subsequently a second oxidative addition, resulting in [NiL(Ar)₂Br] intermediates that eliminate diaryl products.17-18

Next, we studied the substrate scope of the discussed coupling reactions (Figure 3). Amination appears to be the most robust reaction in relation to the activity of the substrates – couplings with non-activated (1), sterically hindered aryl halides (o-bromotoluene), and halides bearing electron-donor groups (m-bromoanisole) exhibited good yields (61-74%) (Figure 3A). The amine scope is not limited only to secondary and primary amines – the hydrochlorides of amines successfully reacted in the presence of the suspension of K₂CO₃.
Figure 3. The scope of AC-assisted nickel-catalyzed amination (A), esterification (B), and etherification (C). Isolated yields are shown. NMR yields are shown in parentheses. For details of the experimental protocols, see the Supporting information. Boc – tertbutyloxycarbonyl. \(^\text{a}\)A mixture of the corresponding amine hydrochloride (3 eq.) and \(\text{K}_2\text{CO}_3\) (5 eq.) was used instead of amine. \(^\text{b}\)Sodium acetate (5 eq.) was used instead of a mixture of carboxylic acid and \(\text{K}_2\text{CO}_3\).
Esterification of 3 resulted in 48-75% yields for aliphatic, aromatic, and Boc (tert-Butyloxy carbonyl) protected amino acids (Figure 3B). Other electron-deficient aryl bromides (i.e., 4-bromobenzonitrile and methyl 4-bromobenzoate) and 2-bromonaphtalene also reacted smoothly with Boc-L-proline with 45-79% yields. As expected, the highest yields (66-79%) in etherification were achieved in reactions with electron-deficient aryl bromides and primary alcohols (Figure 3C). The reactions with secondary alcohols - cyclohexanol and isopropanol – gave 50% and 62% yield, respectively, but required a 6-fold instead of a 3-fold excess of alcohol and a prolonged reaction time.

It is worth mentioning that additional control DC-assisted experiments of amination, esterification and etherification, performed using potentiostatic mode (for substrates 7, 24, and 29), demonstrated lower NMR yields (66%, 4%, and 29%, respectively) (see Supporting information for details) compared to the NMR yields in identical AC-assisted reactions (98%, 79%, and 66%, respectively) (Figure 3).

Overall, the advantage of AC over DC assistance is the most pronounced for esterification and etherification and, to a less extent, for amination. This observation is in agreement with literature data: while a very broad scope was demonstrated for DC-assisted amination, only humble scope with 32-43% yields was shown for etherification. DC-assisted esterification was enabled only using a specific microfluidic cell with a narrow (≤0.5 mm) gap between the electrodes. This close distance between the electrodes allowed to perform reactions that involve short-living intermediates existing between reduction and oxidation steps. AC provides an alternative way to conduct reactions that require a short interval between reduction and oxidation.

To better understand the basic mechanistic features of AC-assisted nickel-catalyzed cross-coupling, we performed electrochemical studies of the discussed reactions. First, we measured the potentials of the electrodes (the glassy carbon rods) relatively standard nonaqueous silver electrode (Ag+/Ag) in typical amination, etherification, and esterification experiments. As Figure 4A shows, the potential changes from 0.8 to -2.2 V (vs Ag+/Ag) in the amination reaction. This interval remains the same for the etherifi-
cation (Figure S19); however, for esterification, it is shifted to slightly higher potentials because of the absence of Br− in the electrolyte.

**Figure 4.** Mechanistic studies of the cross-coupling reactions. (A) GC electrode potential vs Ag+/Ag in a typical amination experiment (3 (50 mM), morpholine (150 mM), NiBr₂·DME (5 mM), di-tBuBipy (7.5 mM) in LiBr (0.2M) DMA solution. (B) CV curve of a NiBr₂·DME (2mM) and a Bipy (2mM) solution before (blue) and after (gray) the addition of 3 (2mM) (0.1M TBAPF₆, DMA). (C) Amination in the divided cell without stirring. The concentrations of the reagents are identical to A. (D) Control experiment of amination with DC and Zn sacrificial anode. The concentrations of the reagents are identical to A. (E) Kinetics of the amination reaction between 3 (50 mM) and morpholine (150 mM) (NiBr₂·DME (5 mM), Bipy (7.5 mM) in LiBr (0.2M) DMA solution) with ON/OFF cycles of AC. Conversion of 3 to 7 was determined by HPLC. See Supporting information for details.
To better understand what electrochemical processes occur within these potentials in the reactions under investigation, we performed cyclic voltammetry (CV) studies (Figure 4B and Supporting information). The voltammogram of Ni(DME)Br$_2$ (2 mM) and Bipy (2 mM) showed two partially separated quasi-reversible reduction waves with peaks at -1.42 and -1.57 V (Figure 4B). The coulometric studies$^{19}$ and the combination of the voltammograms for [Ni(Bipy)$_3$]$^{2+}$ and Ni(Bipy)Br$_2$$^{17,19b,20}$ strongly indicate that these waves represent the sequential reduction of Ni(II) to Ni(0) through a Ni(I) intermediate. When 3 (2 mM) was added to a solution of Ni(Bipy)Br$_2$, the original reduction waves could still be detected, but they became less resolved and fully irreversible; two new reduction waves appeared with peak potentials of -1.71 and -1.89 V. We hypothesized that oxidative addition occurs after the reduction of nickel to a zero oxidation state, making the reduction waves irreversible, and that these additional waves (-1.71 and -1.89 V) correspond to the sequential reduction of the [NiL(Ar)Br] species.$^{21}$ Nevertheless, the voltammetry under conditions as close as possible to the synthetic experiments (GC rods as working and counter electrodes, scan rate of 24 V/s, and the concentrations of reagents as in synthesis) indicated that in synthetic experiments the reduction of the [NiL(Ar)Br] species might be less significant than in analytical CV because of the higher surface area of the electrode, the higher concentration of nickel ions, and the higher scan rate (Figs. S8, 12, 16). These data imply that NiL(Ar)Br is the most probable species to undergo further ligand exchange and oxidation to afford the product of cross-coupling (Figure 1D). The anodic area of the CV curves of the amination and etherification reaction mixtures is dominated by the oxidation of Br$^{-}$ (Figs. S18); therefore, Br$_3^{-}$ and Br$_2$ are probably mediators of the electrochemical oxidation of nickel species in these experiments.

To confirm that processes at one electrode are sufficient to perform the reactions, we conducted the AC-assisted reaction between 3 and morpholine in a divided cell without stirring (Figure 4C). This experiment resulted in a 77% yield, confirming that the transfer of intermediates between electrodes is unnecessary for this reaction to proceed. To probe the possibility that only the reduction phase of the AC cycle is essential for the coupling, we performed DC amination and etherification of 3 with a Zn
sacrificial anode and set the potential of the GC cathode equal to the peak negative potential in AC experiments (-2.2 V vs Ag+/Ag) (Figure 4D, Figure S22). Both experiments resulted in the formation of the biaryl product (30) with 60-70% yields and only minor quantities (2-8%) of the coupling products 7 and 5, thus indicating the essential role of the oxidation phase of the AC cycle in forming the coupling products. To probe the role of the self-sustainable catalysis by Ni(I) species in bulk solution (Figure 5A), we performed kinetic experiments with the ON/OFF cycles of AC (Figure 4E, Figure S23, 24). The kinetics of the amination reaction between 3 and morpholine as well as the data for similar esterification and etherification experiments indicate that the reactions stop almost immediately when AC is OFF and start again when AC is ON, demonstrating that the contribution of the long-living (minutes timescale) self-sustainable Ni(III)/Ni(I) cycles to the formation of the products (7, 5, 18) is insignificant; short-living Ni(III)/Ni(I) cycles that require constant regeneration of Ni(I) remain possible.

Figure 5. Possible catalytic cycles involving oxidative addition to Ni(I) species. (A) Self-sustainable Ni(III)/Ni(I) cycle. (B) Current-assisted Ni(III)/Ni(I) cycle.5

Overall, our mechanistic studies are consistent with the proposal in Figure 1D. Likely, the catalytic cycle is initiated by the reduction of Ni(II), which is abundant in the solution, to the Ni(0) species, which undergo oxidative addition. During the low-voltage phase, when neither oxidation nor reduction processes are expected, the oxidative addition product undergoes ligand exchange. The further oxidation of [NiL(Ar)Nu] species to a Ni(III) state favors reductive elimination, which would furnish the desired
coupling product and release Ni(I) species. There are at least two ways by which Ni(I) could be reduced to Ni(0): (i) direct reduction at the electrode, and (ii) reversible disproportionation to Ni(II) and Ni(0) with the subsequent reduction of Ni(II) to Ni(0) at the electrode. At the same time, current-assisted catalytic cycles involving oxidative addition to Ni(I) species (Figure 5B) may coexist with the proposed cycle (Figure 1D).

**Conclusion**

To summarize, we demonstrated the coupling of AC to transition metal catalysis using three examples of related nickel-catalyzed coupling reactions, but the idea of enabling new catalytic cycles by periodically oxidizing and reducing catalytic intermediates by AC could be applied to various catalytic systems, especially to ones that involve oxidative addition or reductive elimination as a rate-limiting step. The use of AC provides two important advantages: (i) the absence of the need to transfer reactive intermediates between electrodes, which prevents their dilution and allows working with short-living intermediates; (ii) the frequency and the waveform of AC are easily tunable experimental parameters that can be used to achieve the selectivity of reactions. Moreover, side electrochemical reactions might be tolerated in experiments with AC if they are fully reversible. We hope that further development of synthetic methods based on the coupling of transition metal catalysis to AC will enable new efficient transformations.

In addition, this work demonstrates well how external oscillations (not necessarily electrochemical ones) could couple to catalytic cycles to perform otherwise unfavorable chemical transformations. The oscillator pumps energy into the catalytic cycle by periodically modifying its intermediates. This point of view might be relevant for development of catalytic processes enabled by various oscillatory fields.

**ASSOCIATED CONTENT**

**Supporting Information.** Experimental procedures, electrochemical analysis data and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.
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This work demonstrates that periodic oxidation and reduction of a catalyst by alternating current enable otherwise unfavorable catalytic cycles. Nickel catalyzed amination, etherification, and esterification were universally enabled by alternating current with yields and selectivity strongly exciding these in the experiments with direct current (DC).