Nickel-Catalyzed Electro-Reductive Cross-Coupling of Aliphatic Amides with Alkyl Halides as a Strategy for Dialkyl Ketone Synthesis: Scope and Mechanistic Investigations

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ABSTRACT: The development and in-depth study of a novel catalytic method relying on the combination of nickel catalysis and electrochemistry for the cross-electrophile coupling of alkyl amides with alkyl halides is described. This methodology takes advantages of the stability and simple access of *N*-acyl imides as coupling partners for the selective synthesis of dissymmetric dialkyl ketones. Noteworthy, the developed electrochemical protocol affords selective access to linear alkyl ketones when using primary alkyl bromides featuring different chain length. Mechanistic studies including cyclic voltammetry, stoichiometric reactions, and isolation of catalytic intermediates provide a set of fundamental insights into monovalent (bpy)nickel-mediated activation of alkyl halides and alkyl amides. Alkyl bromides react with electrogenerated (bpy)Ni(I) species via single-electron oxidation to give alkyl radicals. *N*-acyl imides are shown to undergo spontaneous C-N bond oxidative addition at both (bpy)Ni(0) and (bpy)Ni(I) species leading to Ni(II) acyl intermediates. A stable nickel(II) acyl complex has also been isolated and fully characterized, and its catalytic competency is demonstrated. Finally, electrogenerated (bpy)Ni(I)-acyl species are shown to react with both alkyl bromide and alkyl amides. Overall, these investigations allowed for a comprehensive mechanistic picture of this selective cross-electrophile coupling to be assembled.

1. Introduction

Dialkyl ketones are an essential class of organic molecules found in abundance in nature as well as in many pharmaceuticals, fragrances and fine chemicals. They are also versatile building blocks for the construction of complex organic structures and offer multiple opportunities for functional group interconversion and late-stage derivatization of drug- and natural product-like molecules.[1] The rich and diverse chemical structures provided by dialkyl ketones still challenge the synthetic chemist to develop new practical and flexible methods for their efficient preparation. While nucleophilic acyl substitution reactions of activated carboxylic acid derivatives stand as the most versatile approaches to unsymmetrical dialkyl ketones,[2] today the development of new strategies that circumvent the classical need for premade sensitive and basic aliphatic organometallic reagents has become a fertile area of research. Consequently, exciting new advances have been made in terms of diversity of coupling partners, chemoselectivity issues, and functional group tolerance.

Modern organonickel chemistry has significantly contributed to this area with the emergence of new and highly efficient radical pathways to forge C(acyl)–C(sp^3) bonds under very mild conditions.[3] Nickel-catalyzed reductive coupling reactions of acyl-transfer reagents (typically acyl halides, anhydrides, and (thio)esters) with C(sp^3) electrophiles including alkyl halides, alkyl carboxylic acid-derived redox active esters, and Katritzky reagents, have been recently highlighted as very powerful strategies to achieve this goal.[4] By coupling two reactive, yet highly accessible and bench-stable electrophiles, they provide a practical and versatile access to a variety of dialkyl ketones with unique functional group tolerance.[5] However, the excess amounts of heterogeneous metal reductants that are typically used to generate a reactive alkyl radical and sustain the nickel catalytic redox cycle inevitably thwarts potential large-scale applications. On the other hand, electrochemistry, in addition to its innate scalability, sustainability, and tunability has often

been valued for the redox advantages it offers compared to purely chemical reactions. Under electrochemical conditions, oxidative and/or reductive events can be finely controlled. Therefore, it is not surprising that the number of electrochemically driven nickel-catalyzed cross-coupling methods started flourishing in the literature.[6] Under electrolytic conditions, alkyl halides as well as redox active esters have been successfully involved in reductive cross-coupling reactions for $C(sp^2)$–$C(sp^3)$ bond formation.[7] However, general methods enabling electroreductive acylation of $C(sp^3)$ centers remain elusive. In 1989, Périchon and co-workers reported the first nickel-catalyzed electro-reductive cross-coupling (ERCC) reaction between acyl chlorides and benzyl bromides providing only a few successful examples of alkyl benzyl ketones in moderate to good yields (Figure 1A).[8] More recently, in 2021, the group of Mei ingeniously reacted anhydrides - generated *in situ* from ubiquitous carboxylic acids – with phenethyl bromides that can undergo a chain-walking mechanistic event to selectively afford the corresponding α-branched benzylic ketones.[9,10] Despite their potential synthetic value, those methods suffer from undeniable limitations. The use of unstable activated acyl coupling partners does not allow such compounds to be employed in a multiple-step synthetic sequence. More importantly, these protocols suffer from a restrictive scope of alkyl halides, which only deliver benzyl ketones.

Conversely, bench stable amides have been shown to be very promising acyl-transfer reagents in transition metal-catalyzed acylation processes.[11] Indeed, amides offer the advantage to be unreactive under a variety of reaction conditions, which allows their use at the end of a multi-step synthetic sequences in a late-stage functionalization fashion. Several key reports have demonstrated the use of *aryl amides,* as acyl-transfer reagents in various cross coupling reactions.[11,12] However, as recently reported by Garg[13] and Szostak,[14]catalytic methods to forge C-C bonds from *aliphatic amides* remain challenging. Furthermore, nickel-catalyzed reductive cross-electrophile coupling reactions of amides are still underdeveloped, and *no electrochemical method has been so far documented regarding the use of amide electrophiles in cross-coupling reactions*.[15] Therefore, there are large areas of hitherto unexplored chemical space to satisfy these challenges and overcome current limitations in dialkyl ketone synthesis via Ni-catalyzed ERCC reactions.

Herein, we report the first electro-reductive cross-coupling of amides with alkyl halides that takes advantage of an inexpensive nickel(II) catalyst and provides the corresponding ketones with high efficiency (Fig 1B). The optimized electrochemical protocol is simple and robust. It opens access to a large scope of linear as well as α-branched aliphatic ketones under mild cell conditions. We also provide a mechanistic rationale for the coupling reaction based on in-depth mechanistic investigations including cyclic voltammetry (CV) studies, isolation of catalytic intermediates and stoichiometric organometallic experiments. This study also documents the reactivity of monovalent (bpy)Ni(I) species towards both alkyl halide and alkyl amide coupling partners.

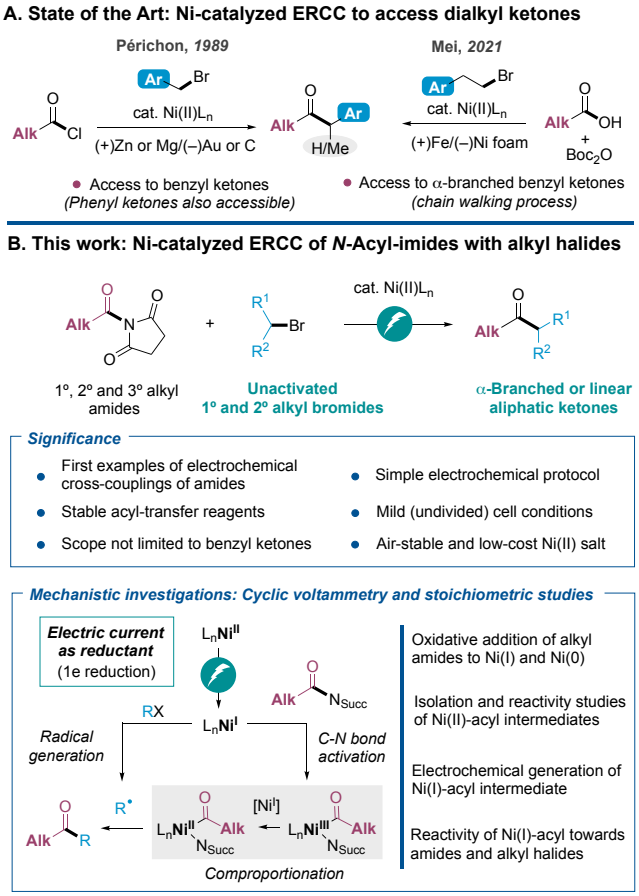


Figure 1. Introduction to Ni-catalyzed Electro-Reductive Cross-Coupling (ERCC) for the synthesis of dialkyl ketones from amides. (A) State of the Art and (B) This work: Ni-catalyzed ERCC of alkyl *N*-acylimides with alkyl halides.

2. Results and discussion

2.1. Optimization

We started our investigation with the cross-coupling of 1-(cyclohexanecarbonyl)pyrrolidine-2,5-dione **1a** with 4-bromotetrahydro-2*H*-pyran (THP-Br) as a model reaction to afford dialkyl ketone **2**. Extensive optimization experiments led to a general set of reaction conditions employing $Ni(OAc)_2{\cdot}4H_2O$ (10 mol%) as catalyst, 2,2'-bipyridine (10 mol%) as ligand, and KPF_6 (2 equiv) as the electrolyte. A standard cross-coupling protocol consisted of a DMF solution of **1a** (0.07 M) charged with the alkyl bromide (1.5 equiv), the catalyst system and electrolyte under an argon atmosphere, and electrolyzed at room temperature using an undivided cell equipped with a zinc anode and a nickel foam cathode and a current of 8 mA for 4 F/mol. Under these optimized conditions, **2** was obtained in 57% isolated yield.

Table 1 summarizes the influence of both chemical and electrochemical parameters that govern the reaction. First, the choice of solvent dramatically impacted the reaction efficiency (Table 1A). While similar yields were observed by replacing DMF with DMSO, only small amounts of **2** (5% yield) were obtained when using MeCN as the solvent. Regarding the catalyst system (Table 1B), the nature and oxidation state of nickel sources were also found to considerably alter the

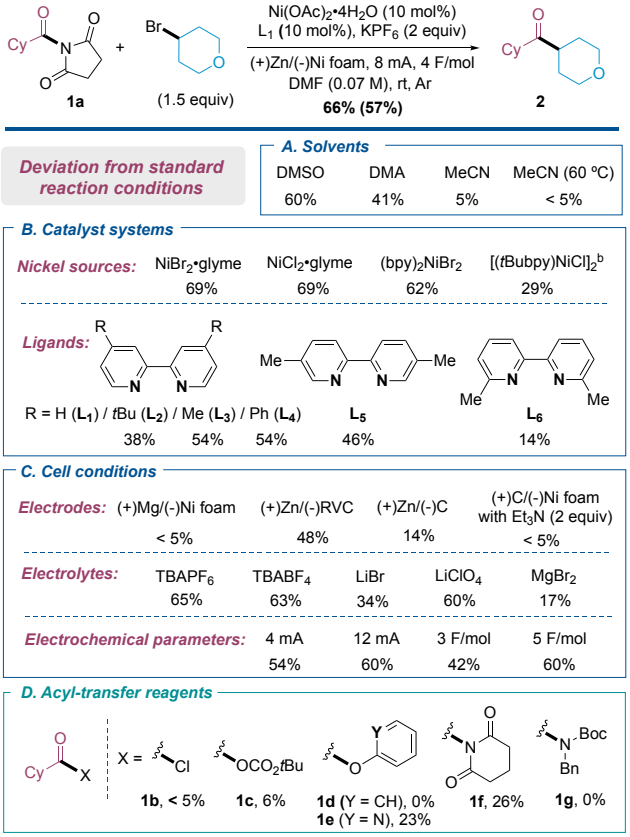
efficiency of the electrochemical process. While nickel(II) halides, e.g. $NiBr_2$•glyme and $NiCl_2$•glyme afforded results comparable to $Ni(OAc)_2$•$4H_2O$, pseudo-Ni(I) catalyst $[(t\text{Bubpy})NiCl]_2$[16] significantly diminished the yield of the reaction. Therefore, nickel acetate was selected for cost-effectiveness and toxicity reasons. The performance of the catalytic system was impacted by ligand substitution with sterically constrained 6,6'-dimethylbipyridine (L_6) affording lower yield of the dialkyl ketone compared to 5,5'-dimethyl-(L_5) and 4,4'-dialkylbipyridines (L_1-L_4). Excess of bpy ligand L_1 (up to 20 mol% with respect to nickel) slightly lowered the yield of the reaction from 66% to 46% (Table S4).

Regarding the cell conditions (Table 1C), the choice of electrode materials significantly influenced the reaction effectiveness. Replacing zinc sacrificial anode by magnesium totally shut down the catalytic process with less than 5% yield of dialkyl ketone **2** being observed. Trying to replace nickel foam cathode by RVC or graphite lowered the yield from 66% to 48% and 14%, respectively. Unfortunately, attempts to replace zinc sacrificial anode by a graphite electrode in the presence of triethylamine as a sacrificial reductant proved unsuccessful. Various electrolytes were also screened. $TBAPF_6$, $TBABF_4$ and $LiClO_4$ afforded comparable yields to KPF_6, whereas LiCl and $MgBr_2$ proved less efficient. KPF_6 was selected as it offers several advantages: low molecular weight, inexpensive, non-toxic, and non-explosive. Notably, halide salts and bases including NaI, $MgCl_2$, LiBr, and K_2CO_3 which are generally required as additives to achieve good yields in cross-electrophile coupling were screened.[4] The presence of such additional coordinating anion is proposed to enhance the stability of the monovalent nickel catalytic intermediates.[17] In our case, these additives did not increase the yield of the reaction,[18] suggesting that the succinimidate anion provides enhanced stability to the nickel intermediate (*vide infra*).[19]

Both the current and the amount of Faraday per mole of substrate were shown to slightly affect the yield of the reaction. Interestingly, lowering or increasing the value of both parameters led to a decrease of the coupling efficiency highlighting the presence of an optimum value. A range of other frequently used acylating reagents that are known to engage in reductive cross-coupling reactions were also evaluated under the standard conditions (Table 1D). Highly activated acyl chloride and anhydride derivatives (**1b-c**) – generated *in situ* from the corresponding carboxylic acid and Boc_2O – only afforded traces of compound **2**.[20] The phenyl- and 2-pyridyl ester derivatives, **1d** and **1e** respectively, proved also ineffective despite further optimization experiments. Finally, *N*-acyl-glutarimide **1f** delivered the desired ketone in only 26% yield, whereas *N*-Boc-amide **1g** proved unsuccessful thus highlighting the superior reactivity of cyclic *N*-acyl-imides in this process.

This preliminary study reveals, for the first time, that amides are indeed competent acyl-transfer reagents for electrochemically-driven cross-coupling reactions. Ni-catalyzed ERCC reactions of *N*-acyl-succinimides should provide a good balance of efficiency, cost-effectiveness, practicability, and mild reaction conditions that seem to be ideal for the synthesis of dialkyl ketones.

Table 1. Ni-catalyzed electrochemical acylation of THP-Br with *N*-acylimide **1a**: Standard reaction and selected optimization experiments.[a]



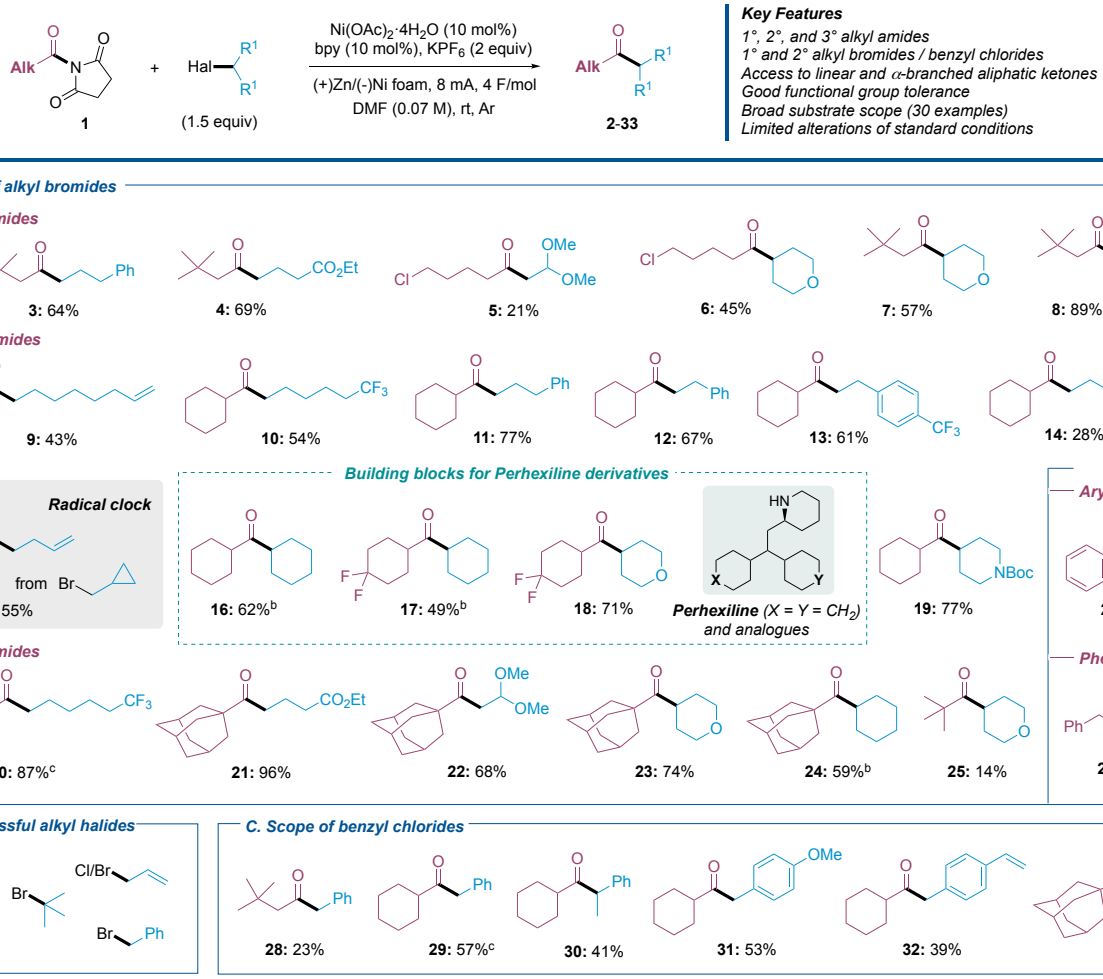
[a] Reactions performed on 0.25 mmol scale. Yields were determined by GC-MS using benzophenone as an internal standard. Yields in parentheses refer to isolated yields. [b] No extra bpy ligand added.

2.2. Scope and limitations

With the optimized conditions in hand, the scope of the nickel-catalyzed ERCC was examined with a variety of stable amides and commercially available alkyl halides (Scheme 1A). Pleasingly, primary (**3-8**), secondary (**9-19**) as well as tertiary alkyl amides (**20-25**) were suitable substrates under the reaction conditions affording the desired products in moderate to excellent yields. Notably, aliphatic amides bearing a chlorine atom attached to the carbon chain (**5** and **6**) that can act as an effective chemical handle for further derivatization was tolerated under the reaction conditions. In addition, amides bearing a difluoromethylene functional group (**17** and **18**), a valuable motif in drug discovery, were successfully coupled. Moreover, adamantyl amides performed particularly well, which is of importance given the well-documented value of the adamantly group in drug design.[21] In contrast, phenyl and phenethyl amides afforded low yield of the desired products (**26** and **27**, respectively).

The standard electrochemical procedure was applicable to both primary (**3-5**, **9-15**, and **20-22**) and secondary (**6-8, 16-19**, and **23-25**) alkyl bromides bearing a large variety of functional groups, e.g. trifluoromethyl (**10**, **20**), carboxylic ester (**4**, **21**), Boc-protected amines (**8**, **19**), including also sensitive functionalities like acetals (**5**, **22**), and unsaturated moieties (**9**).

Scheme 1. Scope of the Ni-catalyzed ERCC of alkyl *N*-acylimides with alkyl and benzyl halides[a]



[a] Reactions performed on 0.25 mmol scale. Isolated yields are given. [b] Reaction performed in DMSO. [c] 3 equivalents of alkyl halide were used, and 8 F/mol were applied. [d] GC-MS yield.

Interestingly, cyclopropylmethyl bromide underwent cyclopropane ring opening as a radical clock substrate to afford product **15** in 55% yield, thus providing support for the formation of alkyl radicals as intermediate species in the coupling process. Of note, phenethyl bromide derivatives delivered the corresponding phenethyl ketones (**12-14)** as the sole reaction products, with no α-branched benzylic ketone being formed. This result nicely differentiates our method from the one recently reported by Mei and co-workers.[9] Moreover, our protocol provides linear alkyl ketones selectively with various primary alkyl bromides. No regioisomeric branched alkyl ketones that could have resulted from a chain walking process were observed.

Unexpectedly, while the high number of cross amide/alkyl bromide examples demonstrated the robustness of the developed protocol, only trace amount of bis-cyclohexyl ketone (**16**) could be observed when trying to couple bromocyclohexane with amide **1a**. However, simply switching the solvent from DMF to DMSO allowed the formation of the desired product in 62% yield. The same modification of standard conditions also allowed the synthesis of 4,4-difluorocyclohexyl ketone **17** in 49% yield. It is interesting to note that bis-cycloalkyl ketones such as **2** and **16-18** represent valuable building blocks for the synthesis of Perhexiline, an anti-anginal drug, and some of its fluorinated analogues of high potential for the treatment of a variety of cardiovascular disorders.[22]

Nevertheless, some limitations remain in the scope of alkyl halides (Scheme 1B). Alkyl chlorides and iodides were not suitable coupling partners as illustrated with unsuccessful couplings of cyclohexyl chloride and iodide. The sterically hindered *tert*-butyl bromide also failed in affording the desired product.[23] The participation of activated halides in the coupling process, such as the allyl or benzyl bromides, proved also problematic. However, the more desirable and readily available benzylic chlorides proved better coupling partners. Thus, primary and secondary benzyl chlorides were smoothly coupled with primary, secondary, and tertiary alkyl amides to provide an array of benzyl ketones (**28-33**) in acceptable to good yields reinforcing the broad applicability of the developed methodology (Scheme 1C).

2.3. Mechanistic investigations

Besides its synthetic application, we were also very interested to gain more insight into the mechanism of the Ni-catalyzed ERCC reaction of *N*-acyl-succinimides. It is interesting to note that different mechanistic scenarios have been proposed for nickel-catalyzed electrochemical cross-coupling reactions

reported so far. For instance, the activation of C(sp^2) or C(sp^3) halides has been proposed to proceed either at ligated Ni(I)[7f,24] or Ni(0) species[7e,8,25] depending on the nature of the nickel precursor or the ligand or even the ligand to nickel ratio. We were thus particularly interested to delineate the parameters governing the cross-selectivity for the reaction of alkyl amides with alkyl bromides. Therefore, a series of cyclic voltammetry (CV) studies and stoichiometric reactions were undertaken.

We first confirmed that both substrates, *N*-acylimide **1a** and THP-Br, undergo reduction at much lower potential than the ligated nickel precatalysts (Figure S5). We then examined the cyclic voltammogram of the [$Ni(OAc)_2(H_2O)_4$]/*t*Bubpy ligand mixture with different Ni to ligand ratios. The CV with an excess of ligand exhibited one quasi-reversible reduction peak corresponding to Ni(II)/N(0) reduction (Figure S6).[26,27] In contrast, when a 1:1 ligand to Ni ratio is used (ratio used for catalysis), two reduction waves are observed (Figures 2A, S6 and S7). A first partially reversible reduction wave R_1 was observed at –1.82 V (*vs.* Ag/$AgNO_3$) with a corresponding oxidation peak O_1 at –1.67 V. The second reduction wave R_2 at –1.94 V is irreversible (Figure S7).[18] The two processes were associated to Ni(II)/N(I) and Ni(I)/Ni(0) reductions.[28] When the electrochemical reduction is carried out with a 1:1 mixture of $Ni(OAc)_2(H_2O)_4$/*t*Bubpy in the presence of THP-Br (15 equivalents) an increase of current is observed at the first reduction peak R_1 (Figure 2A and S8) associated with a significant decrease of the oxidation peak O_1. The reduction peak at R_2 is still observed under these conditions, but it completely disappears when the cyclic voltammetry is conducted at lower scan rate (0.02 V s^{-1} instead of 0.2 V s^{-1}, (Figure S9). These observations indicate that a chemical reaction occurred between THP-Br and Ni(I) species. The reaction most probably involves a bromide abstraction to give Ni(II) species and alkyl radicals.[29]

When the electrochemical reduction of $Ni(OAc)_2(H_2O)_4$/*t*Bubpy is carried out in the presence of *N*-acyl-succinimide **1a** (10 equivalents), an increase of the current intensity is observed at R_1 indicating that Ni(I) also reacts with **1a**, albeit at slightly lower extent than THP-Br (Figures 2B and S10-12). Interestingly, the reduction peak R_2 assigned to a Ni(I)/Ni(0) reduction is still observed. Based on these CV data, we hypothesized that the electrogenerated Ni(I) species reacts with amide **1a** to give the corresponding Ni(III)-acyl succinimidate complex, this intermediate could then undergo rapid comproportionation with remaining Ni(I) species[30] or be directly reduced at the electrode to give a Ni(II)-acyl intermediate (Figure 2C). Thus, the second reduction peak R_2 may correspond to the Ni(I)/Ni(0) reduction of this nickel acyl intermediate (*vide infra*).

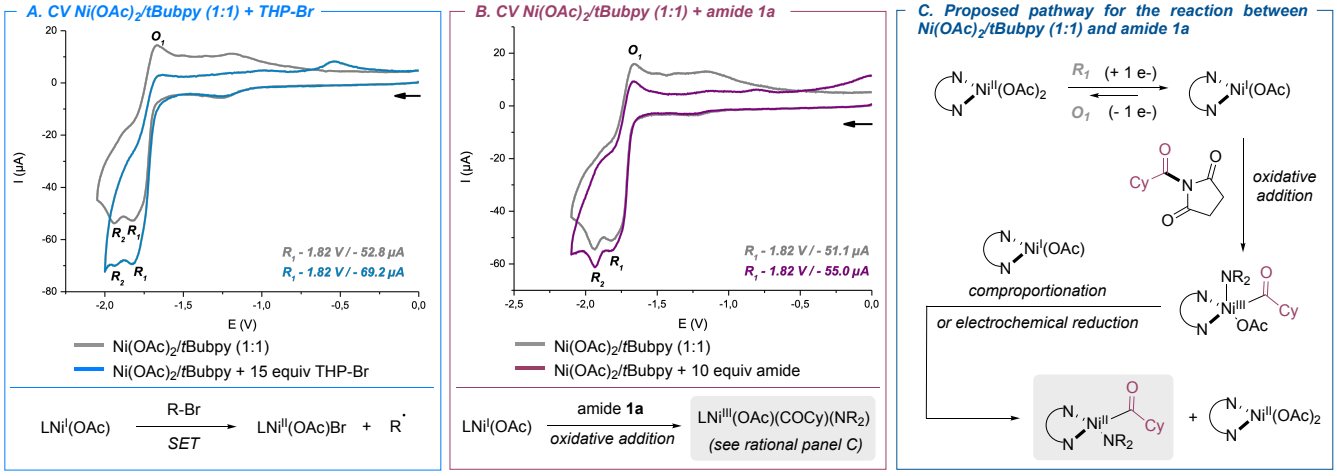


Figure 2. (A) Cyclic voltammetry of $Ni(OAc)_2$/*t*Bubpy (3mM in DMF in 1:1 ratio) in the presence of 15 equivalents of THP-Br.; (B) Cyclic voltammetry of $Ni(OAc)_2$/*t*Bubpy (3mM in DMF in 1:1 ratio) in the presence of 10 equivalents of *N*-acylsuccinimide **1a**; CVs measured with KPF_6 (0.1 M) as supporting electrolyte, with a scan rate of 0.2 V s^{-1} (C) Proposed pathway for the reaction of $Ni(OAc)_2$/*t*Bubpy (1:1) with **1a** under electroreduction**.**

To gain further insights into the putative formation of nickel acyl intermediates, we sought to prepare Ni(II)-acyl succinimidate complex **I** and to examine its reactivity. Satisfyingly, the stoichiometric reaction between *t*Bubpy/$Ni(COD)_2$ and **1a** proceeded smoothly at room temperature to give the desired Ni(II)-acyl succinimidate complex **I** which was isolated and fully characterized in solution and at the solid state (Figure 3A, left). Interestingly, complex **I** is stable in solution (THF, DMF) for long period. The stability of complex **I** contrasts with that of related Ni(II)-acyl halide derivatives which have been shown to be prone to rapid decomposition.[25b,31] The molecular structure of complex **I** was confirmed by single crystal X-ray diffraction analysis. The nickel center adopts a square planar environment and the succinimidate ligand is oriented perpendicular to the coordination plane, providing high steric shielding to the Ni center. This may account for the enhanced stability of the Ni(II)-acyl succinimidate intermediate compared with the halide counterpart.[19]

Notably, complex **I** represents the first example of structurally characterized Ni(II) acyl succinimidate ensuing from C-N bond oxidative addition.[32,33] While aliphatic amides are reputed to be challenging substrates in cross-coupling reactions,[13,14] we provide direct evidence that the C_{acyl}–N bond oxidative addition of aliphatic amides to Ni(0) is a very favorable process.

The cyclic voltammogram of complex **I** carried out in DMF displays two quasi-reversible reduction waves assigned to single electron reduction to Ni(I) at –1.74 V (R_1) and Ni(0) at –1.96 V (R_2) species (see Figure 3 and Figure S13).

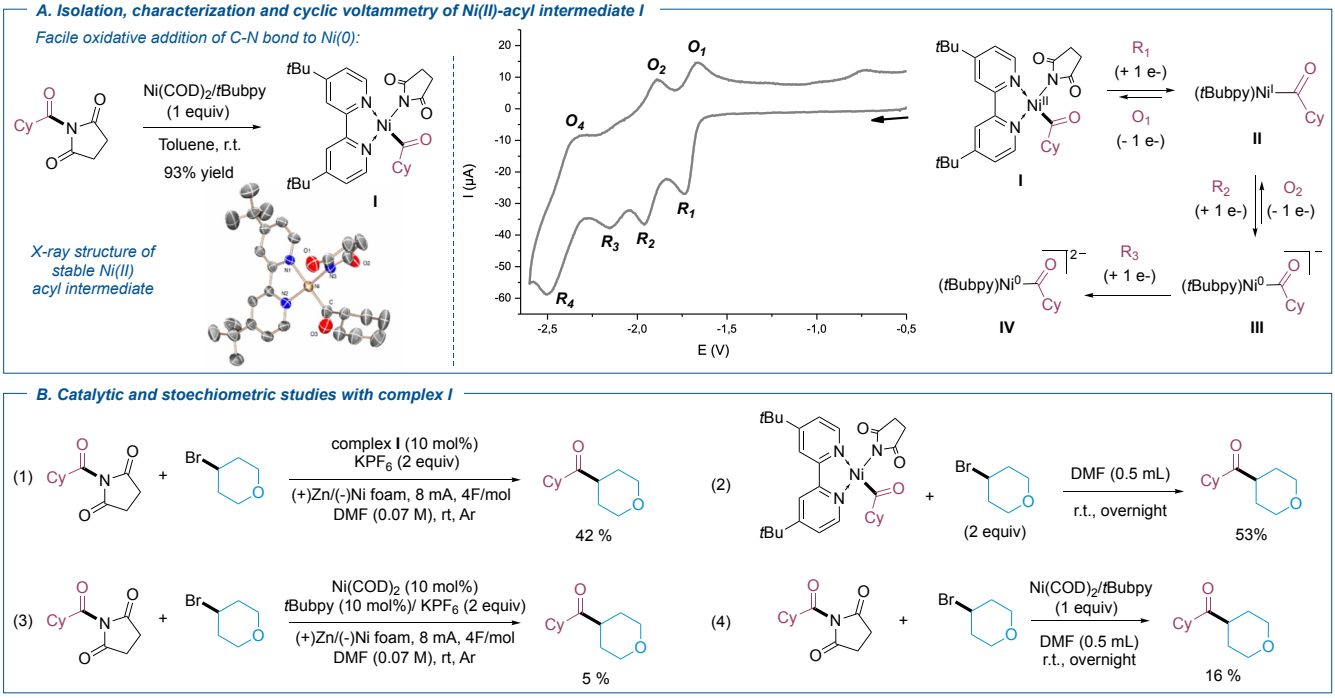


Figure 3. (A) Isolation, characterization, and cyclic voltammetry of Ni(II)-acyl intermediate **I.** CV measured with KPF_6 (0.1 M) as supporting electrolyte, with a scan rate of 0.2 V s^{-1}; (B) Catalytic and stoichiometric studies with complex **I** and Ni(0) precursors.

A third reduction wave (R_3) is also observed at –2.16 V and assigned to the reduction of the ligand coordinated to Ni(0). Finally, a fourth quasi-reversible reduction peak at –2.50 V (R_4) assigned to the free *t*Bubpy ligand is observed at lower potential. Complex **I** was also found to be oxidized at +0.10 V (Figure S14). The CV of complex **I** compares well to that observed when 10 equivalents of **1a** are added to the $Ni(OAc)_2(H_2O)_4$/*t*Bubpy (Figure S15). Therefore, this experiment endorses that these Ni-acyl complexes are potentially formed during the electrochemical reduction of $Ni(OAc)_2(H_2O)_4$/*t*Bubpy in the presence of **1a**.

Accordingly, electrolysis of catalytic amount of **I** in the presence of **1a** and THP-Br resulted in the formation of the desired ketone **2** in 42 % yield (Figure 3B, Eq 1), confirming that complex **I** is a catalytically relevant intermediate. Furthermore, the stoichiometric reaction of complex **I** with THP-Br also afforded **2** in 53% yield (Figure 3B, Eq 2). The same result is obtained in the presence of 2 equivalents of Zn as reductant.[18] This experiment indicates that the alkyl radical readily reacts with Ni(II)-acyl complex **I**, its reduction is not required to achieve the desired C-C bond formation.

At this stage, our experiments suggest that two pathways may account for the formation of the key Ni(II)-acyl intermediate **I**: *(i) via* oxidative addition of **1a** to Ni(0) species or *(ii) via* a sequence of oxidative addition of **1a** to Ni(I) followed by rapid comproportionation[30] or direct reduction at the electrode. However, when $Ni(COD)_2$ was used as precursor instead of Ni(II) salts, only small amount of the cross-coupling product was detected under catalytic and stoichiometric conditions (Figure 3B, Eqs 3 and 4).[18] These experiments indicate that, under electrolysis conditions, the formation of the Ni(II)-acyl intermediate **I** from the oxidative addition of **1a** to Ni(0) is not the main pathway. Altogether, these results suggest that the activation of **1a** and THP-Br most likely proceeds at Ni(I) species.

Finally, we thought that the stability of Ni(II)-acyl complex **I** would provide an interesting opportunity to get further insights into the reactivity of electroreduced monovalent Ni-acyl complex towards alkyl and acyl electrophiles (Figure 4). In particular, Ni(I) intermediates have been recently proposed to be the most relevant catalytically active species in cross-coupling reactions under reductive conditions, but very few mechanistic information have been gained on the electrophile activation step at Ni(I).[17,24,30,34,35]

We were thus eager to study the reactivity of electro-generated Ni(I)-acyl intermediates. Interestingly, the CV of the electrochemical reduction of complex **I** in the presence of 15 equivalents of THP-Br displays a significant increase of the current at the first reduction peak R_1, while the Ni(I)/Ni(0) reduction peak R_2 disappears (Figures 4A and S16). The reverse Ni(I)/Ni(II) oxidation peak O_1 almost vanishes because the electro-generated Ni(I)-acyl intermediate at the cathode is rapidly oxidized by THP-Br.[18]

A different CV response is observed when the electrochemical reduction of complex **I** is carried out in the presence of 10 equivalents of **1a** (Figure 4B). An increase of the current intensity is also observed at the Ni(II)/Ni(I) reduction peak R_1. In this case, the current intensity significantly increased with number of equivalents of **1a** (Figures S17 and 4B), and the reverse Ni(I)/Ni(II) oxidation peak O_1 is still observed suggesting that the reaction of Ni(I) acyl complex with **1a** is not complete under the CV conditions. In addition, the Ni(0)/Ni(I) oxidation peak O_2 is still observed. A possible reaction pathway that may account for the observed CV is proposed in Figure 4D. The electro-generated Ni(I) acyl intermediate would undergo oxidative addition of **1a** to give a Ni(III) bis-acyl intermediate that is spontaneously reduced at this potential to give a Ni(II)

bis acyl complex. This intermediate would undergo decarbonylative coupling reactions to give Ni(0) species[36,37] and side products that are classically observed during electrosynthesis. Notably, in the presence of both substrates, both oxidation peaks significantly decrease indicating that the Ni(I) acyl species is consumed (most probably by SET with Alk-Br) and that much less Ni(0) species ensuing from the side homocoupling reaction are formed (Figure 4C and S18).

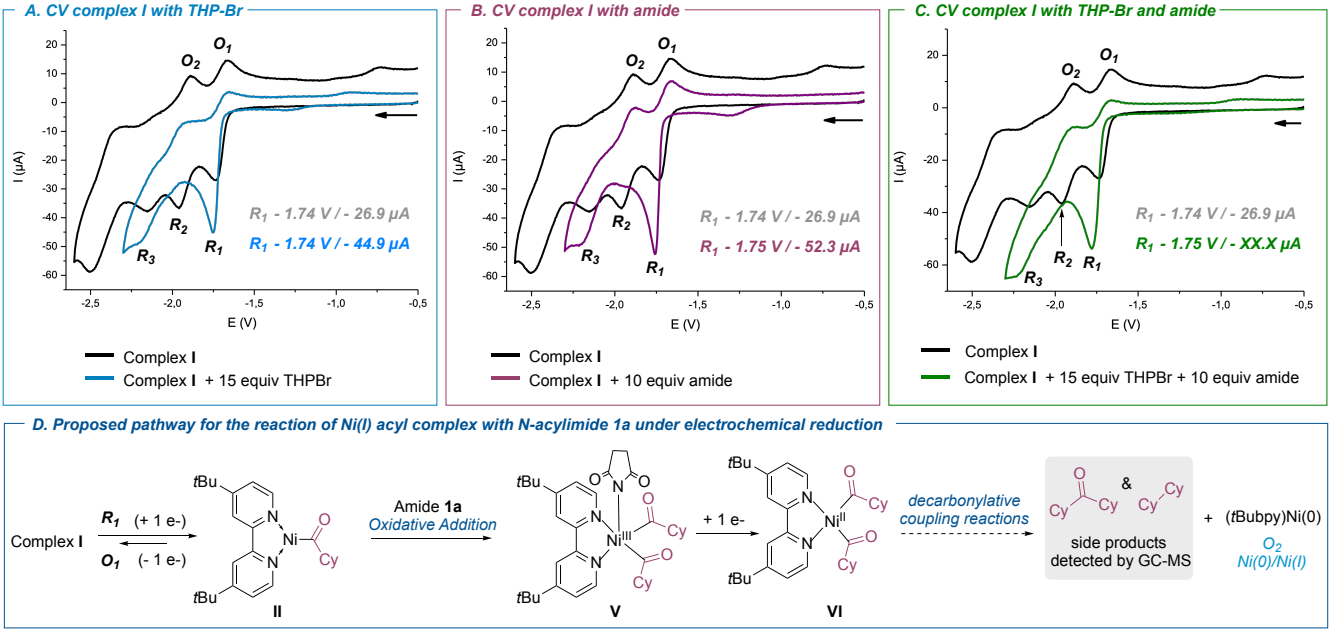
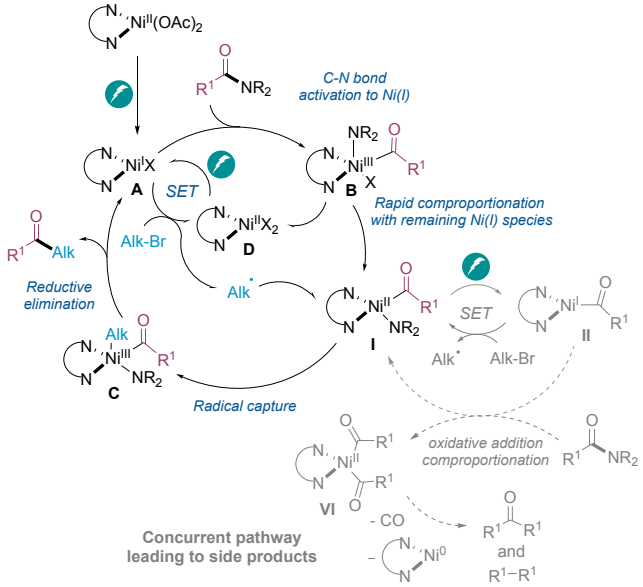


Figure 4. (A) Cyclic voltammetry for the reaction of Ni(II)-acyl complex **I** with THP-Br; (B) Cyclic voltammetry for the reaction of Ni(II)-acyl complex **I** with *N*-acylimide **1a**; (C) Cyclic voltammetry for the reaction of Ni(II)acyl complex **I** with THP-Br and amide **1a**; (D) Proposed pathway for the reaction of Ni(I) acyl complex with *N*-acylimide **1a** under electrochemical reduction. CVs measured with KPF_6 (0.1 M) as supporting electrolyte, with a scan rate of 0.2 V s^{-1}.

2.4. Proposed mechanism

Based on these electrochemical and organometallic studies and on recent mechanistic reports,[17,30] we propose a comprehensive mechanistic picture that accounts for the Ni-catalyzed electrochemical reductive cross-coupling of alkyl bromides and alkyl amides but also for the concurrent pathway leading to homocoupling byproducts (Scheme 2). First, the ligated Ni(II)$(OAc)_2$ complex is electro-reduced to Ni(I) species **A**. The electro-generated Ni(I) can undergo two competitive reactions with alkyl bromides and with alkyl amides. On the one hand, the reaction with alkyl bromide proceeds via single electron oxidation to give the corresponding alkyl radical and Ni(II) species **D**. On the other hand, the Ni(I) species can activate N-acyl imides *via* C-N bond oxidative addition to give a Ni(III) acyl intermediate **B** that spontaneously comproportionates with remaining Ni(I) species leading to a key Ni(II) acyl intermediate **I** and Ni(II) species **D**. It is noteworthy to mention that both processes would regenerate LNi(II)X_2 species that could be reduced again at the cathode allowing catalytic turnover. Then, the Ni(II) acyl intermediate **I** could directly capture the alkyl radical to give a Ni(III)(alkyl)(acyl) intermediate **C**.[38] The radical chain mechanism has been confirmed experimentally.[18] The Ni(III) intermediate undergoes spontaneous reductive elimination to afford the desired cross-coupled product and a Ni(I) species.

Scheme 2. Proposed catalytic pathway for the reductive cross-coupling of alkyl bromides and *N*-acyl imides.



Alternatively, cyclic voltammetry studies showed that Ni(II)-acyl complex **I** can be reduced at very close potential to Ni(I)-acyl intermediate. However, stoichiometric experiments indicated that this reduction step is not mandatory to achieve cross-coupling reaction. Instead, this competitive step may account for the formation of homocoupling side-products. Indeed, the electrogenerated Ni(I) acyl intermediate **II** was

shown to react with **1a** to give Ni(0) species along with symmetric dialkyl ketones and $C(sp^3)$-$C(sp^3)$ homocoupling products, which are systematically detected as minor byproducts under catalytic conditions. Based on our mechanistic work, we propose a sequence of oxidative addition of **1a** to complex **II** followed to rapid comproportionation leading to a Ni(II) bis acyl intermediate **VI** that would undergo (decarbonylative) reductive elimination.

3. Conclusions

The first electro-reductive cross-electrophile coupling reaction between amides and alkyl halides was successfully developed providing an efficient methodology to access dialkyl ketones. Our system uses very practical operating conditions with air-stable and economical nickel catalytic platform and a standardized electrochemical set-up. This study highlights the advantage of using *N*-acyl imides as coupling partners under electroreductive conditions as they allow the synthesis of dialkyl ketones that are hardly accessible with other acylating agents.

Thorough mechanistic studies have been carried out to delineate the reactivity of key nickel intermediates for the activation of alkyl bromides and *N*-acyl imides. A series of important mechanistic insights, highly relevant in the field of nickel catalyzed cross-coupling reactions, have been collected: *(i)* cyclic voltammetry studies indicate that electro-generated monovalent Ni(I) species activate both alkyl bromides via single-electron oxidation to give alkyl radicals and *N*-acyl imides *via* C-N bond oxidative addition. This has been substantiated with electro-generated Ni(I)-OAc and Ni(I)-acyl intermediates; (*ii*) stoichiometric studies have shown that C-N bond oxidative addition of alkyl amides also readily proceeds at Ni(0) species to give isolable Ni(II)-acyl imidate species. The succinimidate ligand was shown to provide enhanced stability to the Ni(II)-acyl intermediate, allowing us to evidence its catalytic relevance; *(iii)* under reductive electrolysis of (tBubpy)$Ni(OAc)_2$ the predominant species responsible for the activation of both electrophiles are Ni(I).[34]

Overall, this work has allowed us to provide a comprehensive mechanistic pathway leading to the desired cross-electrophile coupling product but also to the by-products. The fundamental information gained in this study provide useful insights into the reactivity of key nickel catalytic intermediates often involved in reductive cross-electrophile coupling reactions. Further mechanistic investigations on the reactivity of monovalent Ni(I) acyl complexes for the oxidative addition of acyl electrophiles are underway.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information contains experimental procedures and graphical abstracts for the electrochemical reaction, optimization of the reaction conditions, mechanistic experiments, analysis, and compound characterization data.

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Graphical Abstract: