

RESEARCH ARTICLE

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Nickel-catalyzed electrochemical reductive relay cross-coupling of alkyl halides with alkyl carboxylic acids†

Ke-Jin Jiao,^{a,b} Cong Ma,^b Dong Liu,^b Hui Qiu,^b Bin Cheng^{*a} and Tian-Sheng Mei^{ID *b}

A highly regioselective Ni-catalyzed electrochemical (undivided cell) reductive relay cross-coupling between alkyl carboxylic acids and alkyl bromides has been developed. This strategy allows the direct acylation of benzylic C(sp³)–H bonds in good yields from commercially available alkyl carboxylic acids, thus providing an alternative strategy for the synthesis of dialkyl ketones. Various functional groups are tolerated under mild reaction conditions.

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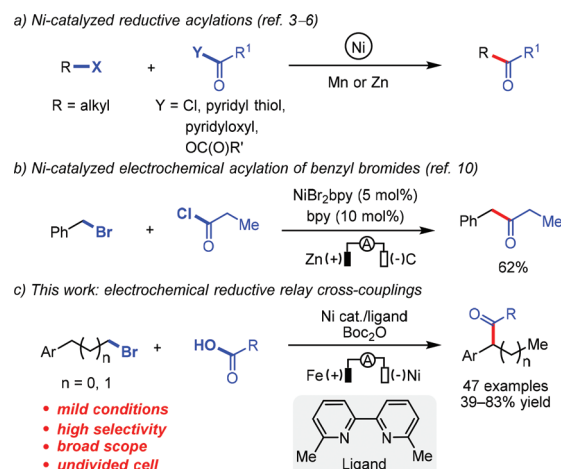
Introduction

Ketones are versatile and abundant building blocks in organic synthesis and are prevalent in agrochemicals, natural products, and pharmaceuticals.¹ The traditional transition metal-catalyzed cross-coupling of organometallics with carboxylic acids or their derivatives is one of the most useful methods for the preparation of ketones.² Alternatively, reductive Ni-catalyzed cross-coupling between alkyl halides and carboxylic acids or their derivatives has emerged as an appealing strategy for constructing unsymmetrical ketones as it avoids the involvement of organometallic reagents.³ For instance, in 1981 Mukaiyama and co-workers reported an elegant example of Ni-catalyzed acylation of alkyl iodides with substituted pyridyl carboxylates using zinc dust as the reductant, although the method requires extra steps for the synthesis of the substrates, as well as an excess of alkyl iodides.^{3a} In 2012 the groups of Weix and Gong independently developed efficient Ni-catalyzed reductive cross-couplings of alkyl iodides and alkyl carboxylic acid derivatives using Mn or Zn as the reductant (Scheme 1a).^{3b,c} Inspired by these seminal works, numerous Ni-catalyzed reductive cross-couplings between carboxylic acid derivatives and various electrophiles have been developed,⁴ including asymmetric variants.⁵ Recently, Wang, Zhu and co-

workers demonstrated a Ni-catalyzed migratory reductive acylation between alkyl bromides and alkyl carboxylic acids, although a long reaction time (24 h) was required.⁶ A common limitation associated with transition metal-catalyzed reductive cross-couplings between alkyl halides and carboxylic acids or their derivatives is their reliance on using stoichiometric amounts of Mn or Zn as reductants. These metals often require surface activation⁷ and some sensitive functional groups react readily with them. To circumvent such issues, electric current could be used directly to turn over the Ni catalyst.^{8,9} As early as 1989, Périchon and co-workers reported a Ni-catalyzed electrochemical cross-coupling of alkyl acyl chlorides and benzyl bromides, although Zn was used as a sacrificial anode (Scheme 1b).¹⁰ However, to the best of our knowledge, Ni-catalyzed electrochemical reductive relay cross-

^aInstitute of Marine Biomedicine, Shenzhen Polytechnic, Shenzhen, 518055, China. E-mail: chengbin@szpt.edu.cn^bState Key Laboratory of Organometallic Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China. E-mail: mei7900@sioc.ac.cn

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Scheme 1 Reductive cross-coupling reactions.

coupling of alkyl acids and alkyl bromides has not been disclosed.

As part of our ongoing interest in the merger of electrochemistry and transition metal catalysis,¹¹ we have recently reported a Ni-catalyzed electrochemical relay cross-coupling of aryl halides and alkyl bromides;¹² a very similar method was reported virtually simultaneously by Rueping and co-workers.¹³ We questioned whether a reductive relay cross-coupling strategy could be applied to the synthesis of ketones from commercially available carboxylic acids and alkyl bromides by taking advantage of “chain-walking” of an alkyl-nickel species.^{14–17} Herein, we demonstrate that an electrochemical relay cross-coupling of carboxylic acids and alkyl bromides can be executed efficiently at room temperature, affording unsymmetrical dialkyl ketones with good regioselectivity and yield (Scheme 1c).

Results and discussion

Initially, we selected 3-phenylpropionic acid (**1a**) and (2-bromoethyl)benzene (**2a**) as reaction partners. To our delight, upon using NiCl₂·glyme as the precatalyst, 6,6'-dimethyl-2,2'-bipyridine (ligand **1**) as the ligand, MgBr₂ as the electrolyte, Boc₂O as the acid activation reagent, and *N,N*-dimethylacetamide (DMA) as the solvent in an undivided cell with iron and Ni foam electrodes under 6 mA current for 6 hours at room temperature, the relay cross-coupling product was obtained in 72% isolated yield (Table 1, entry 1). Using NiBr₂·glyme or NiCl₂ as the catalyst resulted in lower yields

(entries 2 and 3). The efficiency of the reaction decreased precipitously when magnesium, aluminum, or reticulated vitreous carbon (RVC) was chosen as the anode (entries 4–6). It is worth noting that Mg²⁺ is crucial for the reaction (entries 7 and 8). We reasoned that the magnesium salt contributes to the oxidative addition of low-valent nickel species to the *in situ*-generated anhydride.^{3c,4e} Varying (higher and lower) the amount of Boc₂O did not improve the efficiency (entries 9 and 10). The replacement of L1 with L2 also diminished the yield (entry 11). In addition, the C6-alkyl substituents in the ligand backbone are crucial for the relay reaction (see Table S1 in the ESI† for details). Finally, a control experiment revealed that no coupling product was produced in the absence of the catalyst or ligand (entry 12).

With the optimized reaction conditions in hand, we next investigated the generality of this electrochemical reductive cross-coupling reaction. As shown in Table 2, the catalytic system exhibited good functional group tolerance. The carboxylic acids substituted with a variety of functional groups such as alkyl, ether, fluoro, chloro, amino, ketone, and ester groups were well tolerated. Arenes with electron-rich or electron-poor substituents also gave satisfactory results (**3a–3h**, **3k**, and **3l**). To our delight, heteroaromatic rings such as furan and thiophene were also tolerated under the standard conditions, affording acceptable yields (**3i** and **3j**). Furthermore, this protocol could also be applied to more simple alkyl acids with moderate yields (**3o–3u**). It is worth noting that cyclic carboxylic acids with high ring strain (**3v–3y**) or simple six-membered rings (**3z–3ac**) were also well-tolerated and the relay cross-coupling reactions proceeded smoothly with good yields. Encouragingly, for piperidine or amylene oxide carboxylic acids, the reaction afforded the corresponding acylation products in good yields (**3ad–3ag**). Finally, commercially available pharmaceuticals such as chlorambucil and chrysanthemum acid smoothly underwent electrochemical reductive coupling, affording the indicated product in only a slightly diminished comparative yield (**3n** and **3w**).

Next, we examined the breadth of the competent alkyl bromides. As shown in Table 3, alkyl bromides substituted with a variety of functional groups such as ether, chloro, fluoro, trifluoromethyl, trifluoromethoxy, and OTIPS groups were well tolerated under the standard reaction conditions, affording the relay products in good yields (**4a–4i** and **4k**). For alkyl bromide substrates with polysubstituted aromatic rings, the reaction efficiency was not less-satisfying and the relay cross-coupled products (**4j** and **4m**) were obtained with 39% and 40% yield, respectively. To our delight, this relay process can proceed along three carbon-long alkyl chains with only a slightly diminished yield (**4n**).

To gain insight into the reaction mechanism, we conducted a series of cyclic voltammetric analyses (Fig. 1 and 2, as well as S2–S5 in the ESI†). Compared to the reactants, the nickel catalyst is more easily reduced to a lower valency (Fig. S2†). When the nickel catalyst and ligand were added in an equal amount, the resulting complex exhibits two quasi-reversible reductive peaks at –1.39 V and –1.90 V *versus* Ag/AgNO₃ in dimethyl-

Table 1 Reaction optimization with substrate **1a**^a

Entry	Variation from the above conditions ^a	F/ mol	Yield of 3a ^b (%)
1	None	4.5	77 (72) ^c
2	NiBr ₂ ·glyme as the catalyst	4.5	64
3	NiCl ₂ as the catalyst	4.5	47
4	Mg as the anode	4.5	37
5	Al as the anode	4.5	55
6 ^d	RVC as the anode	4.5	31
7	MgI ₂ in lieu of MgBr ₂	4.5	31
8	<i>n</i> -Bu ₄ NBr in lieu of MgBr ₂	4.5	NP
9	(Boc) ₂ O (1.0 equiv.)	4.5	40
10	(Boc) ₂ O (3.0 equiv.)	4.5	40
11	Ligand 2 as the ligand	4.5	42
12	Without Ni or ligand	4.5	0

^a Standard conditions: **1a** (0.3 mmol), **2a** (0.3 mmol), NiBr₂·glyme (10 mol%), ligand **1** (12 mol%), (Boc)₂O (2.0 equiv.), MgBr₂ (1.0 equiv.), and DMA (4 mL) in an undivided cell with iron (1.5 × 0.5 cm²) and Ni foam (2.5 × 1.5 cm²) as electrodes at rt and 6.0 mA for 6 h. ^b Yields were determined by ¹H NMR using CH₂Br₂ as an internal standard. ^c Isolated yield of **3a**. ^d NEt₃ (1.0 equiv.) was added.

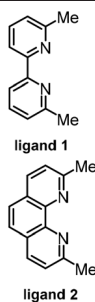
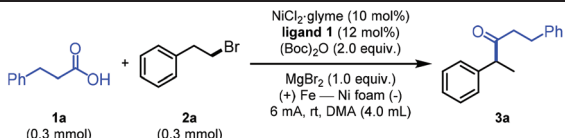
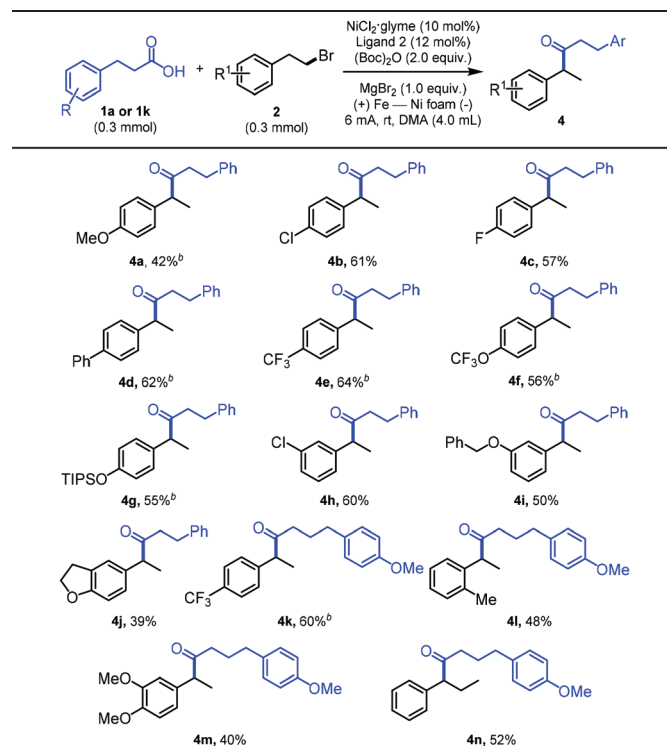


Table 2 Evaluation of scope of carboxylic acid^a

^a Standard conditions: **1** (0.3 mmol), **2a** (0.3 mmol), NiCl₂·glyme (10 mol%), ligand 1 (12 mol%), (Boc)₂O (2.0 equiv.), MgBr₂ (1.0 equiv.), and DMA (4 mL) in an undivided cell with iron (1.5 × 0.5 cm²) and Ni foam (2.5 × 1.5 cm²) as electrodes, rt, 6.0 mA, 6 h. ^b 8.0 mA, 6 h. ^c 7.0 mA, 6 h.

acetamide (curve d, Fig. 1), which may be attributed to the reduction potential of Ni(II)/Ni(I) and Ni(I)/Ni(0), respectively. In addition, in the absence of electricity, the stoichiometric reaction with Ni(cod)₂ as the catalyst afforded the desired product in 65% yield (Scheme 2). This result indicated that the Ni(0) species generated at the cathode may act as the active catalyst.

Next, we sought to understand which reactant the catalyst prefers to react with. 3-Phenylpropanoic anhydride was prepared according to a literature report.¹⁸ When the alkyl bromide (**2a**) was added first, the catalytic current was slightly increased whereas the catalytic current was significantly increased upon the addition of 3-phenylpropanoic anhydride (Fig. 2). Furthermore, when the anhydride was added first, the

Table 3 Evaluation of alkyl halides^a

^a Standard conditions: **1a** or **1k** (0.3 mmol), **2** (0.3 mmol), NiCl₂·glyme (10 mol%), ligand 1 (12 mol%), (Boc)₂O (2.0 equiv.), MgBr₂ (1.0 equiv.), and DMA (4 mL) in an undivided cell with iron (1.5 × 0.5 cm²) and Ni foam (2.5 × 1.5 cm²) as electrodes, rt, 6.0 mA, 6 h. ^b 8.0 mA, 6 h.

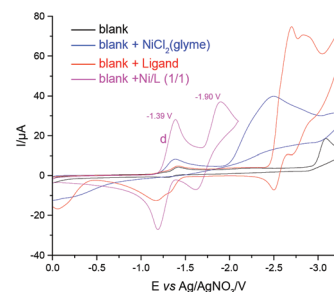


Fig. 1 Cyclic voltammograms recorded on a glassy carbon electrode at 100 mV s⁻¹: (a) blank solution, 0.1 M *n*-Bu₄NBr in DMA; (b) solution (a) with 7.5 mM NiCl₂·glyme added; (c) solution (a) with 7.5 mM 2,9-dimethyl-1,10-phenanthroline added; and (d) solution (a) with 7.5 mM NiCl₂·glyme and 2,9-dimethyl-1,10-phenanthroline (Ni/L = 1/1) added.

catalytic current was significantly increased whereas the catalytic current was almost unchanged following the subsequent addition of alkyl bromide (**2a**) (Fig. S5†). Based on the above cyclic voltammetric (CV) studies, it was found that the putative Ni(0) complex reacts more readily with the anhydride.

Based on literature reports^{3c,4a,e,19} and our mechanistic studies (see the ESI† for more details), a plausible mechanism is presented for the Ni-catalyzed electrochemical reductive couplings (Scheme 3). First, the Ni(II) catalyst is reduced to Ni

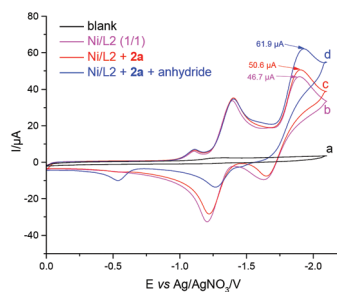
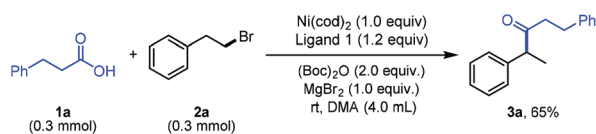
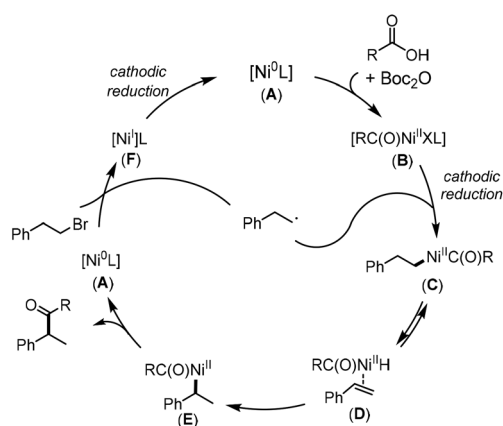


Fig. 2 Cyclic voltammograms recorded on a glassy carbon electrode at 100 mV s⁻¹: (a) blank solution, 0.1 M *n*-Bu₄NBr in DMA; (b) solution (a) with 7.5 mM NiCl₂·glyme and ligand 2 added; (c) solution (b) with 10 mM **2a** added; and (d) solution (c) with 10 mM 3-phenylpropanoic anhydride added.



Scheme 2 Stoichiometric reaction without electric current.

(0) (A) *via* cathodic reduction. After the oxidative addition of the anhydride to Ni(0), acyl Ni(II) species (B) is formed. After the cathodic reduction of B, the resulting acyl Ni(I) species reacted with an alkyl radical to generate the Ni(II) species (C). The direct reductive elimination from C generated a linear by-product, and C is also converted into species E, a more thermodynamically stable benzylic Ni(II) intermediate, *via* β -hydride elimination to D and reinsertion. Upon reductive elimination, the desired cross-coupling product and the Ni(0) species (A) are formed. A reacted with an alkyl bromide, affording an alkyl radical species and the Ni(I) species (F). Upon cathodic reduction, the active Ni(0) is then regenerated. At this early stage, we cannot rule out other possible pathways, such as the one wherein a Ni(I)/Ni(III) coupling is involved.



Scheme 3 Plausible catalytic cycle.

Conclusions

In summary, we have demonstrated the first example of a Ni-catalyzed electrochemical reductive relay cross-coupling of alkyl acids to alkyl bromides in an undivided cell, affording 1,1-dialkyl ketones in good yields and regioselectivities. The protocol is operationally simple and robust. Further research on exploring the mechanism and developing more transition metal-catalyzed electrochemical reductive relay cross-couplings is currently underway in our laboratory.

Conflicts of interest

The authors declare no competing financial interest.

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