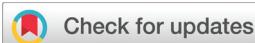


RESEARCH ARTICLE

[View Article Online](#)
[View Journal](#) | [View Issue](#)



Cite this: *Org. Chem. Front.*, 2021, **8**, 6603

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}

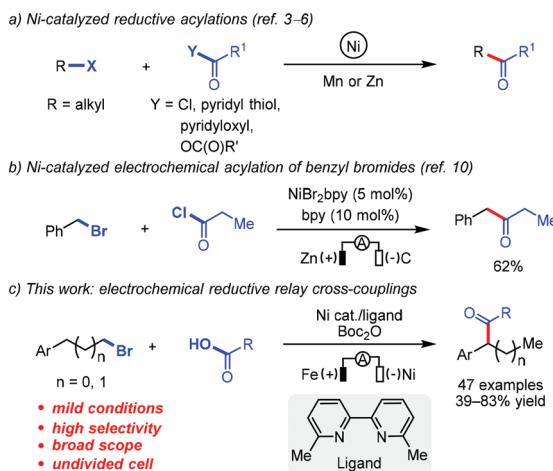
Received 16th August 2021,
Accepted 7th October 2021
DOI: 10.1039/d1qo01219c
rsc.li/frontiers-organic

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 $C(sp^3)$ -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.

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-



Scheme 1 Reductive cross-coupling reactions.

^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@sio.ac.cn

† Electronic supplementary information (ESI) available: Experimental procedures, product characterization, copies of NMR spectra. See DOI: 10.1039/d1qo01219c

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 $\text{NiCl}_2\text{-glyme}$ as the precatalyst, 6,6'-dimethyl-2,2'-bipyridine (ligand **1**) as the ligand, MgBr_2 as the electrolyte, $(\text{Boc})_2\text{O}$ 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 $\text{NiBr}_2\text{-glyme}$ or NiCl_2 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 Mg^{2+} 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 $(\text{Boc})_2\text{O}$ 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**).

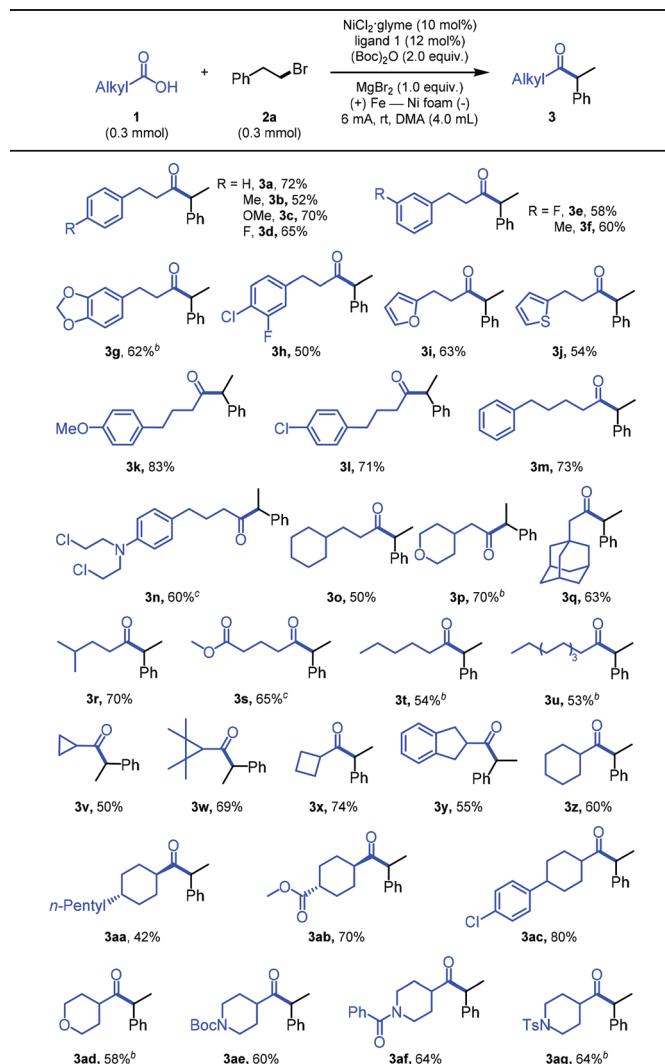
To gain insight into the reaction mechanism, we conducted a series of cyclic voltammetric analyses (Fig. 1 and 2, as well as S2–S5 in the ESI†). Compared to the reactants, the nickel catalyst is more easily reduced to a lower valency (Fig. S2†). When the nickel catalyst and ligand were added in an equal amount, the resulting complex exhibits two quasi-reversible peaks at -1.39 V and -1.90 V *versus* Ag/AgNO_3 in dimethyl-

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

Entry	Variation from the above conditions ^a	F/mol	Yield of 3a ^b (%)		
				ligand 1	ligand 2
1	None	4.5	77 (72) ^c		
2	$\text{NiBr}_2\text{-glyme}$ 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	$n\text{-Bu}_4\text{NBr}$ in lieu of MgBr_2	4.5	NP		
9	$(\text{Boc})_2\text{O}$ (1.0 equiv.)	4.5	40		
10	$(\text{Boc})_2\text{O}$ (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), $\text{NiBr}_2\text{-glyme}$ (10 mol%), ligand **1** (12 mol%), $(\text{Boc})_2\text{O}$ (2.0 equiv.), MgBr_2 (1.0 equiv.), and DMA (4 mL) in an undivided cell with iron ($1.5 \times 0.5 \text{ cm}^2$) and Ni foam ($2.5 \times 1.5 \text{ cm}^2$) as electrodes at rt and 6.0 mA for 6 h.

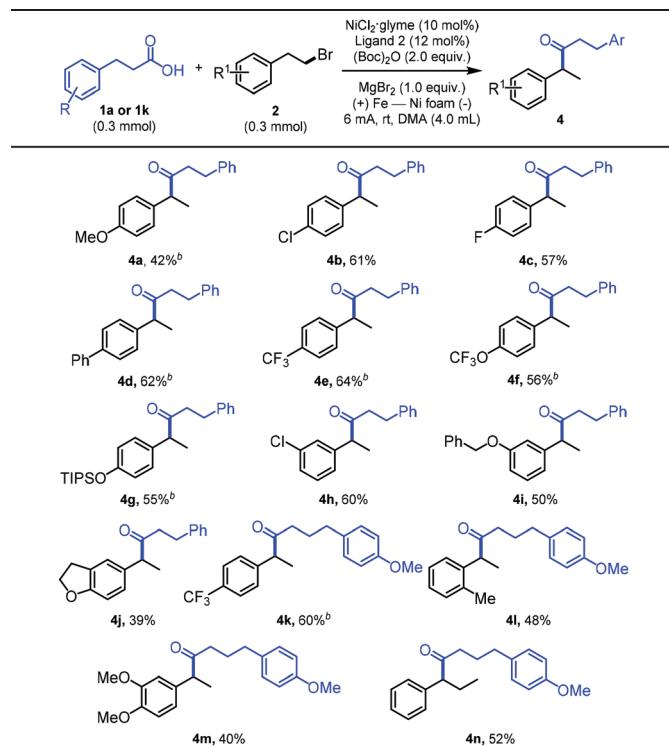
^b Yields were determined by ¹H NMR using CH_2Br_2 as an internal standard. ^c Isolated yield of **3a**. ^d NET_3 (1.0 equiv.) was added.

Table 2 Evaluation of scope of carboxylic acid^a

^a Standard conditions: **1** (0.3 mmol), **2a** (0.3 mmol), $\text{NiCl}_2\text{-glyme}$ (10 mol%), ligand 1 (12 mol%), $(\text{Boc})_2\text{O}$ (2.0 equiv.), MgBr_2 (1.0 equiv.), and DMA (4 mL) in an undivided cell with iron ($1.5 \times 0.5 \text{ cm}^2$) and Ni foam ($2.5 \times 1.5 \text{ cm}^2$) 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 $\text{Ni}(\text{II})/\text{Ni}(\text{I})$ and $\text{Ni}(\text{I})/\text{Ni}(\text{0})$, respectively. In addition, in the absence of electricity, the stoichiometric reaction with $\text{Ni}(\text{cod})_2$ as the catalyst afforded the desired product in 65% yield (Scheme 2). This result indicated that the $\text{Ni}(\text{0})$ 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), $\text{NiCl}_2\text{-glyme}$ (10 mol%), Ligand 2 (12 mol%), $(\text{Boc})_2\text{O}$ (2.0 equiv.), MgBr_2 (1.0 equiv.), and DMA (4 mL) in an undivided cell with iron ($1.5 \times 0.5 \text{ cm}^2$) and Ni foam ($2.5 \times 1.5 \text{ cm}^2$) as electrodes, rt, 6.0 mA, 6 h. ^b 8.0 mA, 6 h.

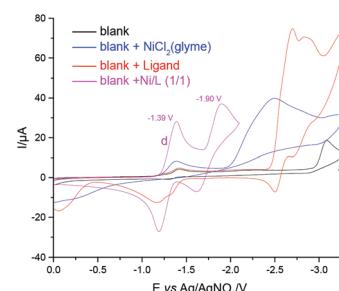


Fig. 1 Cyclic voltammograms recorded on a glassy carbon electrode at 100 mV s^{-1} . (a) blank solution, $0.1 \text{ M } n\text{-Bu}_4\text{NBr}$ in DMA; (b) solution (a) with 7.5 mM $\text{NiCl}_2\text{-glyme}$ added; (c) solution (a) with 7.5 mM 2,9-dimethyl-1,10-phenanthroline added; and (d) solution (a) with 7.5 mM $\text{NiCl}_2\text{-glyme}$ and 2,9-dimethyl-1,10-phenanthroline ($\text{Ni}/\text{L} = 1/1$) 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 $\text{Ni}(\text{0})$ 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 $\text{Ni}(\text{II})$ catalyst is reduced to Ni

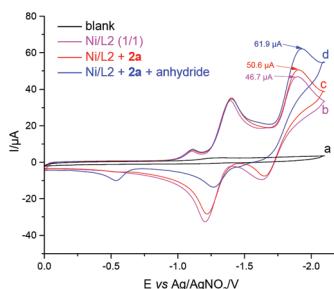
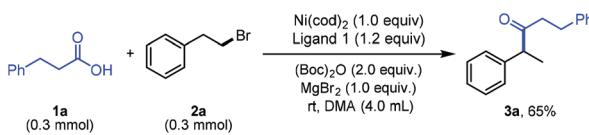
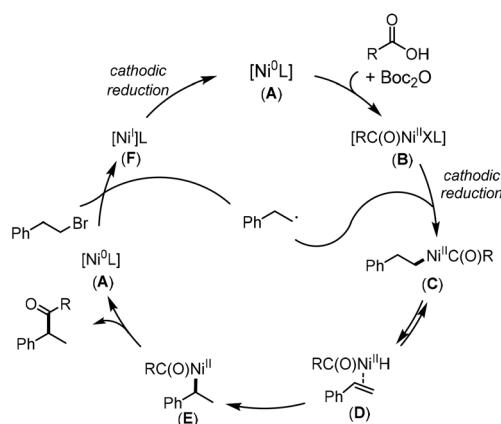


Fig. 2 Cyclic voltammograms recorded on a glassy carbon electrode at 100 mV s^{-1} : (a) blank solution, $0.1 \text{ M } n\text{-Bu}_4\text{NBr}$ in DMA; (b) solution (a) with $7.5 \text{ mM } \text{NiCl}_2\text{-glyme}$ and ligand 2 added; (c) solution (b) with $10 \text{ mM } 2\text{a}$ added; and (d) solution (c) with $10 \text{ mM } 3\text{-phenylpropanoic anhydride}$ added.



Scheme 2 Stoichiometric reaction without electric current.

(0) (A) *via* cathodic reduction. After the oxidative addition of the anhydride to $\text{Ni}(0)$, acyl $\text{Ni}(\text{II})$ species (B) is formed. After the cathodic reduction of B, the resulting acyl $\text{Ni}(\text{I})$ species reacted with an alkyl radical to generate the $\text{Ni}(\text{II})$ 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 $\text{Ni}(\text{II})$ intermediate, *via* β -hydride elimination to D and reinsertion. Upon reductive elimination, the desired cross-coupling product and the $\text{Ni}(0)$ species (A) are formed. A reacted with an alkyl bromide, affording an alkyl radical species and the $\text{Ni}(\text{I})$ species (F). Upon cathodic reduction, the active $\text{Ni}(0)$ is then regenerated. At this early stage, we cannot rule out other possible pathways, such as the one wherein a $\text{Ni}(\text{I})/\text{Ni}(\text{III})$ 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.

Acknowledgements

This work was financially supported by the Strategic Priority Research Program of the Chinese Academy of Sciences (Grant XDB20000000), the NSF of China (Grants 21821002, 21772222, and 91956112), and the S&TCSM of Shanghai (Grants 18JC1415600 and 20JC1417100).

References

- (a) R. K. Dieter, Reaction of Acyl Chlorides with Organometallic Reagents: A Banquet Table of Metals for Ketone Synthesis, *Tetrahedron*, 1999, **55**, 4177–4236; (b) N. J. Lawrence, Aldehydes and ketones, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1739–1749.
- (a) D. Mistein and J. K. Stille, A General, Selective, and Facile Method for Ketone Synthesis from Acid Chlorides and Organotin Compounds Catalyzed by Palladium, *J. Am. Chem. Soc.*, 1978, **100**, 3636–3638; (b) M. Asaoka, A. Kosaka, M. Tanaka, T. Ueda, T. Houkawa and H. Takei, Chelation controlled *cis*-selective acylation of 2-(alkoxycarbonyl)-cyclopentylzinc iodides, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2949–2950; (c) D. Wang and Z. Zhang, Palladium-Catalyzed Cross-Coupling Reactions of Carboxylic Anhydrides with Organozinc Reagents, *Org. Lett.*, 2003, **5**, 4645–4648; (d) Y. Zhang and T. Rovis, A Unique Catalyst Effects the Rapid Room-Temperature Cross-Coupling of Organozinc Reagents with Carboxylic Acid Fluorides, Chlorides, Anhydrides, and Thioesters, *J. Am. Chem. Soc.*, 2004, **126**, 15964–15965; (e) H. Tatamidani, F. Kakiuchi and N. Chatani, A New Ketone Synthesis by Palladium-Catalyzed Cross-Coupling Reactions of Esters with Organoboron Compounds, *Org. Lett.*, 2004, **6**, 3597–3599; (f) Y. Yu and L. S. Liebeskind, Copper-Mediated, Palladium-Catalyzed Coupling of Thiol Esters with Aliphatic Organoboron Reagents, *J. Org. Chem.*, 2004, **69**, 3554–3557; (g) N. A. Weires, E. L. Baker and N. K. Garg, Nickel-catalysed Suzuki–Miyaura coupling of amides, *Nat. Chem.*, 2016, **8**, 75–79; (h) B. J. Simmons, N. A. Weires,

J. E. Dander and N. K. Garg, Nickel-Catalyzed Alkylation of Amide Derivatives, *ACS Catal.*, 2016, **6**, 3176–3179.

3 (a) M. Onaka, Y. Matsuoka and T. Mukaiyama, A Convenient Method for the Direct Preparation of Ketones from 2-(6-(2-methoxyethyl)pyridyl) Carboxylates and Alkyl Iodides by Use of Zinc Dust and A Catalytic Amount of Nickel Dichloride, *Chem. Lett.*, 1981, **10**, 531–534; (b) A. C. Wotal and D. J. Weix, Synthesis of Functionalized Dialkyl Ketones from Carboxylic Acid Derivatives and Alkyl Halides, *Org. Lett.*, 2012, **14**, 1476–1479; (c) H. Yin, C. Zhao, H. You, K. Lin and H. Gong, Mild ketone formation via Ni-catalyzed reductive coupling of unactivated alkyl halides with acid anhydrides, *Chem. Commun.*, 2012, **48**, 7034–7036.

4 (a) A. C. Wotal, R. D. Ribson and D. J. Weix, Stoichiometric Reactions of Acylnickel(II) Complexes with Electrophiles and the Catalytic Synthesis of Ketones, *Organometallics*, 2014, **33**, 5874–5881; (b) J. Wang, B. P. Cary, P. D. Beyer, S. H. Gellman and D. J. Weix, Ketones from Nickel-Catalyzed Decarboxylative, Non-Symmetric Cross-Electrophile Coupling of Carboxylic Acid Esters, *Angew. Chem., Int. Ed.*, 2019, **58**, 12081–12085; (c) J. Wang, M. E. Hoerrner, M. P. Watson and D. J. Weix, Nickel-Catalyzed Synthesis of Dialkyl Ketones from the Coupling of N-Alkyl Pyridinium Salts with Activated Carboxylic Acids, *Angew. Chem., Int. Ed.*, 2020, **59**, 13484–13489; (d) F. Wu, W. Lu, Q. Qian, Q. Ren and H. Gong, Ketone Formation via Mild Nickel-Catalyzed Reductive Coupling of Alkyl Halides with Aryl Acid Chlorides, *Org. Lett.*, 2012, **14**, 3044–3047; (e) C. Zhao, X. Jia, X. Wang and H. Gong, Ni-Catalyzed Reductive Coupling of Alkyl Acids with Unactivated Tertiary Alkyl and Glycosyl Halides, *J. Am. Chem. Soc.*, 2014, **136**, 17645–17651; (f) X. Jia, X. Zhang, Q. Qian and H. Gong, Alkyl-aryl ketone synthesis via nickel-catalyzed reductive coupling of alkyl halides with aryl acids and anhydrides, *Chem. Commun.*, 2015, **51**, 10302–10305; (g) M. Zheng, W. Xue, T. Xue and H. Gong, Ester Formation via Nickel-Catalyzed Reductive Coupling of Alkyl Halides with Chloroformates, *Org. Lett.*, 2016, **18**, 6152–6155; (h) Y. Ai, N. Ye, Q. Wang, K. Yahata and Y. Kishi, Zirconium/Nickel-Mediated One-Pot Ketone Synthesis, *Angew. Chem., Int. Ed.*, 2017, **56**, 10791–10795.

5 A. H. Cherney, N. T. Kadunce and S. E. Reisman, Catalytic Asymmetric Reductive Acyl Cross-Coupling: Synthesis of Enantioenriched Acyclic α,α -Disubstituted Ketones, *J. Am. Chem. Soc.*, 2013, **135**, 7442–7445.

6 J. He, P. Song, X. Xu, S. Zhu and Y. Wang, Migratory Reductive Acylation between Alkyl Halides or Alkenes and Alkyl Carboxylic Acids by Nickel Catalysis, *ACS Catal.*, 2019, **9**, 3253–3259.

7 (a) D. A. Everson, B. A. Jones and D. J. Weix, Replacing Conventional Carbon Nucleophiles with Electrophiles: Nickel-Catalyzed Reductive Alkylation of Aryl Bromides and Chlorides, *J. Am. Chem. Soc.*, 2012, **134**, 6146–6159; (b) K. A. Johnson, S. Biswas and D. J. Weix, Cross-Electrophile Coupling of Vinyl Halides with Alkyl Halides, *Chem. – Eur. J.*, 2016, **22**, 7399–7402; (c) K. E. Poremba, N. T. Kadunce, N. Suzuki, A. H. Cherney and S. E. Reisman, Nickel-Catalyzed Asymmetric Reductive Cross-Coupling To Access 1,1-Diarylalkanes, *J. Am. Chem. Soc.*, 2017, **139**, 5684–5687.

8 (a) T. J. DeLano and S. E. Reisman, Enantioselective Electroreductive Coupling of Alkenyl and Benzyl Halides via Nickel Catalysis, *ACS Catal.*, 2019, **9**, 6751–6754; (b) R. J. Perkins, A. J. Hughes, D. J. Weix and E. C. Hansen, Metal-Reductant-Free Electrochemical Nickel-Catalyzed Couplings of Aryl and Alkyl Bromides in Acetonitrile, *Org. Process Res. Dev.*, 2019, **23**, 1746–1751; (c) H. Li, C. P. Breen, H. Seo, T. F. Jamison, Y.-Q. Fang and M. M. Bio, Ni-Catalyzed Electro-chemical Decarboxylative C–C Couplings in Batch and Continuous Flow, *Org. Lett.*, 2018, **20**, 1338–1341; (d) F. Lian, K. Xu, W. Meng, H. Zhang, Z. Tan and C. Zeng, Nickel-catalyzed electrochemical reductive decarboxylative coupling of N-hydroxyphthalimide esters with quinoxalinones, *Chem. Commun.*, 2019, **55**, 14685–14688; (e) T. Koyanagi, A. Herath, A. Chong, M. Ratnikov, A. Valiere, J. Chang, V. Molteni and J. Loren, One-Pot Electrochemical Nickel-Catalyzed Decarboxylative Sp^2 – Sp^3 Cross-Coupling, *Org. Lett.*, 2019, **21**, 816–820; (f) C. Li, Y. Kawamata, H. Nakamura, J. C. Vantourout, Z. Liu, Q. Hou, D. Bao, J. T. Starr, J. Chen, M. Yan and P. S. Baran, Electrochemically Enabled, Nickel-Catalyzed Amination, *Angew. Chem., Int. Ed.*, 2017, **56**, 13088–13093; (g) Y. Kawamata, J. C. Vantourout, D. P. Hickey, P. Bai, L. Chen, Q. Hou, W. Qiao, K. Barman, M. A. Edwards, A. F. Garrido-Castro, J. N. deGruyter, H. Nakamura, K. Knouse, C. Qin, K. J. Clay, D. Bao, C. Li, J. T. Starr, C. Garcia-Irizarry, N. Sach, H. S. White, M. Neurock, S. D. Minteer and P. S. Baran, Electrochemically Driven, Ni-Catalyzed Aryl Amination: Scope, Mechanism, and Applications, *J. Am. Chem. Soc.*, 2019, **141**, 6392–6402; (h) Y. Wang, L. Deng, X. Wang, Z. Wu, Y. Wang and Y. Pan, Electrochemically Promoted Nickel-Catalyzed Carbon–Sulfur Bond Formation, *ACS Catal.*, 2019, **9**, 1630–1634; (i) B. L. Truesdell, T. B. Hamby and C. S. Sevov, General $C(sp^2)$ – $C(sp^3)$ Cross-Electrophile Coupling Reactions Enabled by Overcharge Protection of Homogeneous Electrocatalysts, *J. Am. Chem. Soc.*, 2020, **142**, 5884–5893.

9 (a) M. Yan, Y. Kawamata and P. S. Baran, Synthetic Organic Electrochemical Methods Since 2000: On the Verge of a Renaissance, *Chem. Rev.*, 2017, **117**, 13230–13319; (b) J.-Y. Nédélec, J. Périchon and M. Troupel, Organic Electroreductive Coupling Reactions Using Transition Metal Complexes as Catalysts, *Top. Curr. Chem.*, 1997, **185**, 141–173; (c) J. Chaussard, J.-C. Folest, J.-Y. Nédélec, J. Périchon, S. Sibille and M. Troupel, Use of Sacrificial Anodes in Electrochemical Functionalization of Organic Halides, *Synthesis*, 1990, 369–381.

10 H. Marzouk, Y. Rollin, J. C. Folest, J.-Y. Nédélec and J. Périchon, Electrochemical synthesis of ketones from acid chlorides and alkyl and aryl halides catalysed by nickel complexes, *J. Organomet. Chem.*, 1989, **369**, C47–C50.

11 (a) K.-J. Jiao, Z.-M. Li, X.-T. Xu, L.-P. Zhang, Y.-Q. Li, K. Zhang and T.-S. Mei, Palladium-catalyzed reductive electrocarboxylation of allyl esters with carbon dioxide, *Org. Chem. Front.*, 2018, **5**, 2244–2248; (b) D. Liu, H.-X. Ma, P. Fang and T.-S. Mei, Nickel-Catalyzed Thiolation of Aryl Halides and Heteroaryl Halides through Electrochemistry, *Angew. Chem., Int. Ed.*, 2019, **58**, 5033–5037; (c) H. Qiu, B. Shuai, Y.-Z. Wang, D. Liu, Y.-G. Chen, P.-S. Gao, H.-X. Ma, S. Chen and T.-S. Mei, Enantioselective Ni-Catalyzed Electrochemical Synthesis of Biaryl Atropisomers, *J. Am. Chem. Soc.*, 2020, **142**, 9872–9878; (d) P.-S. Gao, X.-J. Weng, Z.-H. Wang, C. Zheng, B. Sun, Z.-H. Chen, S.-L. You and T.-S. Mei, Cu(II)/TEMPO-Catalyzed Enanti-selective C(sp³)-H Alkynylation of Tertiary Cyclic Amines via Shono-type Oxidation, *Angew. Chem., Int. Ed.*, 2020, **59**, 15245–15259.

12 K.-J. Jiao, D. Liu, H.-X. Ma, H. Qiu, P. Fang and T.-S. Mei, Nickel-Catalyzed Electrochemical Reductive Relay Cross-Coupling of Alkyl Halides to Aryl Halides, *Angew. Chem., Int. Ed.*, 2020, **59**, 6520–6524.

13 G. S. Kumar, A. Peshkov, A. Brzozowska, P. Nikolaienko, C. Zhu and M. Rueping, Nickel-Catalyzed Chain-Walking Cross-Electrophile Coupling of Alkyl and Aryl Halides and Olefin Hydroarylation Enabled by Electrochemical Reduction, *Angew. Chem., Int. Ed.*, 2020, **59**, 6513–6519.

14 (a) B. J. Stokes, S. M. Opra and M. S. Sigman, Palladium-Catalyzed Allylic Cross-Coupling Reactions of Primary and Secondary Homoallylic Electrophiles, *J. Am. Chem. Soc.*, 2012, **134**, 11408–11411; (b) B. J. Stokes, A. J. Bischoff and M. S. Sigman, Pd(quinox)-catalyzed allylic relay Suzuki reactions of secondary homostyrenyl tosylates via alkene-assisted oxidative addition, *Chem. Sci.*, 2014, **5**, 2336–2339.

15 (a) H. Sommer, F. Juliá-Hernández, R. Martin and I. Marek, Walking Metals for Remote Functionalization, *ACS Cent. Sci.*, 2018, **4**, 153–165; (b) A. Vassuer, J. Bruffaerts and I. Marek, Remote functionalization through alkene isomerization, *Nat. Chem.*, 2016, **8**, 209–219.

16 (a) F. Zhou, Y. Zhang, X. Xu and S. Zhu, NiH-Catalyzed Remote Asymmetric Hydroalkylation of Alkenes with Racemic α -Bromo Amides, *Angew. Chem., Int. Ed.*, 2019, **58**, 1754–1758; (b) W. Wang, C. Ding, Y. Li, Z. Li, Y. Li, L. Peng and G. Yin, Migratory Arylboration of Unactivated Alkenes Enabled by Nickel Catalysis, *Angew. Chem., Int. Ed.*, 2019, **58**, 4612–4616; (c) S.-Z. Sun, M. Börjesson, R. Martin-Montero and R. Martin, Site-Selective Ni-Catalyzed Reductive Coupling of α -Haloboranes with Unactivated Olefins, *J. Am. Chem. Soc.*, 2018, **140**, 12765–12769; (d) F. Juliá-Hernández, T. Moragas, J. Cornellà and R. Martin, Remote carboxylation of halogenated aliphatic hydrocarbons with carbon dioxide, *Nature*, 2017, **545**, 84–88; (e) Y. He, Y. Cai and S. Zhu, Mild and Regioselective Benzylidic C–H Functionalization: Ni-Catalyzed Reductive Arylation of Remote and Proximal Olefin, *J. Am. Chem. Soc.*, 2017, **139**, 1061–1064; (f) I. Buslov, F. Song and X. Hu, An Easily Accessed Nickel Nanoparticle Catalyst for Alkene Hydroarylation with Tertiary Silanes, *Angew. Chem., Int. Ed.*, 2016, **55**, 12295–12299; (g) J. S. Bair, Y. Schramm, A. G. Sergeev, E. Clot, O. Eisenstein and J. F. Hartwig, Linear-Selective Hydroarylation of Unactivated Terminal and Internal Olefins with Trifluoromethyl-Substituted Arenes, *J. Am. Chem. Soc.*, 2014, **136**, 13098–13101; (h) W.-C. Lee, C.-H. Wang, Y.-H. Lin, W.-C. Shih and T.-G. Ong, Tandem Isomerization and C–H Activation: Regioselective Hydroheteroarylation of Allylarenes, *Org. Lett.*, 2013, **15**, 5358–5361; (i) L. K. Johnson, C. M. Killian and M. Brookhart, New Pd(II)- and Ni(II)-Based Catalysts for Polymerization of Ethylene and α -Olefins, *J. Am. Chem. Soc.*, 1995, **117**, 6414–6415.

17 (a) Y. He, C. Liu, L. Yu and S. Zhu, Ligand-Enabled Nickel-Catalyzed Redox-Relay Migratory Hydroarylation of Alkenes with Arylborons, *Angew. Chem., Int. Ed.*, 2020, **59**, 9186–9191; (b) L. Peng, Y. Li, Y. Li, W. Wang, H. Pang and G. Yin, Ligand-Controlled Nickel-Catalyzed Reductive Relay Cross-Coupling of Alkyl Bromides and Aryl Bromides, *ACS Catal.*, 2018, **8**, 310–313; (c) L. Peng, Z. Li and G. Yin, Photochemical Nickel-Catalyzed Reductive Migratory Cross-Coupling of Alkyl Bromides with Aryl Bromides, *Org. Lett.*, 2018, **20**, 1880–1883; (d) F. Chen, K. Chen, Y. Zhang, Y. He, Y.-M. Wang and S. Zhu, Remote Migratory Cross-Electrophile Coupling and Olefin Hydroarylation Reactions Enabled by in Situ Generation of NiH, *J. Am. Chem. Soc.*, 2017, **139**, 13929–13935; (e) F. Chen, X. Xu, Y. He, G. Huang and S. Zhu, NiH-Catalyzed Migratory Defluorinative Olefin Cross-Coupling: Trifluoromethyl-Substituted Alkenes as Acceptor Olefins to Form gem-Difluoroalkenes, *Angew. Chem., Int. Ed.*, 2020, **59**, 5398–5402; (f) Y. Zhang, X. Xu and S. Zhu, Nickel-catalysed selective migratory hydrothiolation of alkenes and alkynes with thiols, *Nat. Commun.*, 2019, **10**, 1752–1760; (g) Y. Zhang, B. Han and S. Zhu, Rapid Access to Highly Functionalized Alkyl Boronates by NiH-Catalyzed Remote Hydroarylation of Boron-Containing Alkenes, *Angew. Chem., Int. Ed.*, 2019, **58**, 13860–13864; (h) Y. Li, D. Wu, H.-G. Cheng and G. Yin, Difunctionalization of Alkenes Involving Metal Migration, *Angew. Chem., Int. Ed.*, 2020, **59**, 7990–8003; (i) Y. Li, Y. Li, L. Peng, D. Wu, L. Zhu and G. Yin, Nickel-catalyzed migratory alkyl–alkyl cross-coupling reaction, *Chem. Sci.*, 2020, **11**, 10461–10464; (j) W. Wang, C. Ding and G. Yin, Catalyst-controlled enantioselective 1,1-arylboration of unactivated olefins, *Nat. Catal.*, 2020, **3**, 951–958.

18 Md. C. Sheikh, S. Takagi, T. Yoshimura and H. Morita, Mechanistic studies of DCC/HOBt-mediated reaction of 3-phenylpropionic acid with benzyl alcohol and studies on the reactivities of ‘active ester’ and the related derivatives with nucleophiles, *Tetrahedron*, 2010, **66**, 7272–7278.

19 C. Amatore, A. Jutand, J. Périchon and Y. Rollin, Mechanism of the Nickel-Catalyzed Electrosynthesis of Ketones by Heterocoupling of Acyl and Benzyl Halides, *Monatsh. Chem.*, 2000, **131**, 1293–1304.