

Peer Review File

Manuscript Title: Electrochemically Driven Cross-Electrophile Coupling of Alkyl Halides

Editorial Note: Parts of this Peer Review File have been redacted as indicated to maintain the confidentiality of unpublished data.

Reviewer #1 was unable to review and subsequently withdrawn.

Reviewer Comments & Author Rebuttals

Reviewer Reports on the Initial Version:

Referee #2 (Remarks to the Author):

The manuscript submitted by Lin and co-workers reports an elegant electrochemical synthetic method to forming C(sp³)-C(sp³) bonds through reductive coupling reactions. The method does not require the use of transition metals, which is of significant value from a sustainability perspective. The novelty of the work lies in the full mechanistic understanding of the reaction in relation to relative reduction potentials using both computational (DFT) and experimental (CV) studies. This has enabled the method to be applied to a broad range of substrates.

The data and methodology is of a high quality, with a large supporting information file that fully details all experimental and analytical data. The robustness, validity and reliability are therefore of high calibre.

The only drawback of this work is in the scale-up experiment and the passivation layer formed on the cathode that increases resistance. Whilst this has been addressed by using an ethereal co-solvent, 1g of material is not a huge scale-up. It would be great to see a larger increase in scale to assess if this is possible or if the passivation layer again becomes problematic. In relation to this, further comment on the use of Mg as the anode would be valuable. Electrode screening of the cathode electrode material has been conducted, but limited information and rationale on the anode. Then in relation to passivation, could an alternating current (probably requiring a divided cell) help to address this?

As a very minor comment, it would be useful to have the structure of each compound on the cyclic voltammogram as well as the compound number (similar to that seen on NMR spectra), to save flicking back and forth. Also, why does the current in the CV of compound 2 continue to increase?

Referee #3 (Remarks to the Author):

See, Lin and co-workers report electrochemical driven transition-metal-free cross electrophile coupling of alkyl halides. Various electrophiles such as alpha-bromoalkylboronic esters, benzylic chlorides, allylic chlorides, propargylic chlorides, alpha-chloroalkylsilanes were chemoselectively cross coupled with a large series of electrophiles (primary alkyl bromides, chlorosilanes, TsOMe, CO₂, ClGeMe₃) to give the corresponding cross-coupled products in moderate to very good yields. The functional group tolerance was well documented. Reductive cross-coupling is achieved upon using electrochemistry. The selectivity is based on the difference of the potentials of the two electrophiles, allowing for selective reduction of one halide over the other. Mechanistic studies are provided and also a larger scale setup was developed. The substrate scope is amazingly broad and cross coupling of more complex biologically relevant compounds was documented. Considering the magic methyl effect, authors also provided examples on the MeOTs cross coupling (even D3COTs). I am very much impressed by this nice contribution and recommend publication in Nature subject to modifications as noted below:

1) Considering the alpha-haloalkylboronic esters as substrates, authors should also discuss the classical Matteson rearrangement. Most of the primary bromides used as coupling partners can be readily transferred to the corresponding Grignard-reagents and directly be used in the Matteson rearrangement to give the same products (also under transition-metal-free conditions; maybe easier in scale up?). I therefore ask authors to run 2-3 reactions under Matteson conditions and compare yields. Likely, compound 45 cannot be prepared via the classical Matteson approach since the Grignard would not be stable, yet also the electrochemical approach provides a low yield. It would be important if authors can discuss the advantages: maybe pick one or two examples where

Matteson would fail.

2) Authors discuss the potential of the first reduction to generate the C-radical. However, no information is provided for the reduction of the C-radical to the corresponding anion. Please comment on that.

3) I am wondering whether CD₃OD can be used as the electrophile to get the deuterated product. Would be a valuable extension of the method.

4) Obvious coupling partners are aryl halides. They are generally easy to reduce (in particular the iodides) and the aryl anions are also rather stabilized. Please comment on the coupling of iodobenzene (even better bromobenzene and chlorobenzene) with an alkyl bromide.

5) Minor "Matteson" is misspelled in the main text.

Reviewer: 2**Comments:**

1. “The manuscript submitted by Lin and co-workers reports an elegant electrochemical synthetic method to forming C(sp³)-C(sp³) bonds through reductive coupling reactions. The method does not require the use of transition metals, which is of significant value from a sustainability perspective. The novelty of the work lies in the full mechanistic understanding of the reaction in relation to relative reduction potentials using both computational (DFT) and experimental (CV) studies. This has enabled the method to be applied to a broad range of substrates.”
 “The data and methodology is of a high quality, with a large supporting information file that fully details all experimental and analytical data. The robustness, validity and reliability are therefore of high calibre.”

Response: We thank the reviewer for their positive comments and constructive suggestions on our work. These comments and suggestions have helped us further improve the manuscript.

2. “The only drawback of this work is in the scale-up experiment and the passivation layer formed on the cathode that increases resistance. Whilst this has been addressed by using an ethereal co-solvent, 1g of material is not a huge scale-up. It would be great to see a larger increase in scale to assess if this is possible or if the passivation layer again becomes problematic.”

Response: According to the reviewer’s suggestion, we have scaled up the reaction to 20 mmol using two different reaction vessels (Figure C1~2). Both reactions gave the product in excellent yield (>90% yield, >3 g product) and the electrolyte can be recovered by simple wash and extraction process, which suggests that our method is robust and practical. The formation of a black solid layer was observed on the Mg electrode surface. However, in the presence of DME as a co-solvent, the cell voltage remained relatively stable during electrolysis. Therefore, the anode passivation is not a major concern for even larger scale reactions in the mixed solvent system. These new data have been included in the revised manuscript and SI.

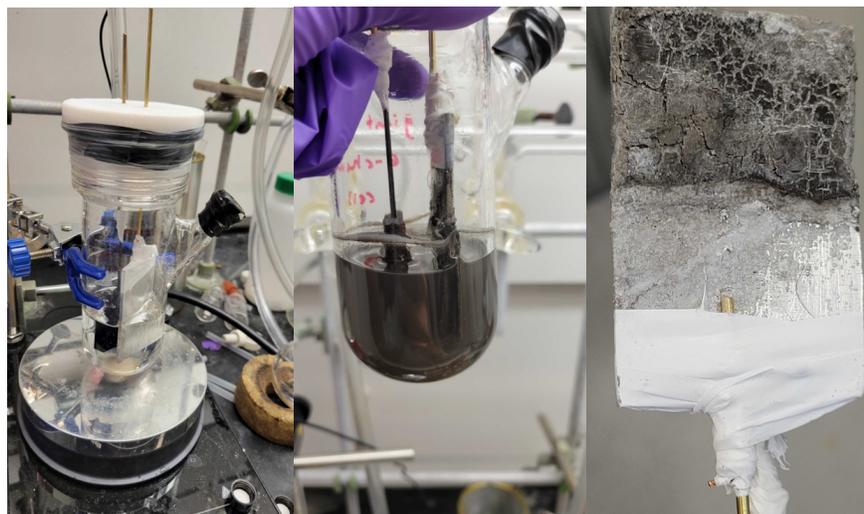
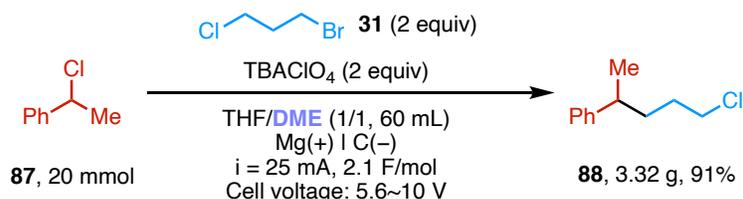


Figure C1: Electrolysis setup using a custom-made electrolysis cell (left), reaction mixture after electrolysis (middle), Mg electrode after electrolysis (right).

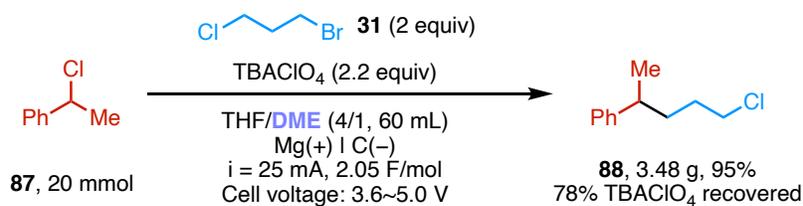


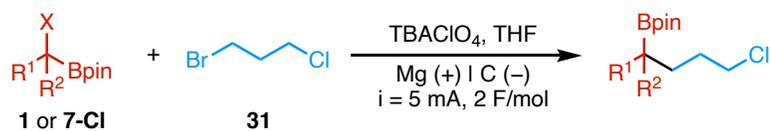
Figure C2: Electrolysis setup using a commercial three-necked RBF (left), reaction mixture after electrolysis (middle), Mg electrode after electrolysis (right).

3. “*In relation to this, further comment on the use of Mg as the anode would be valuable. Electrode screening of the cathode electrode material has been conducted, but limited information and rationale on the anode.*”
 “*Then in relation to passivation, could an alternating current (probably requiring a divided cell) help to address this*”

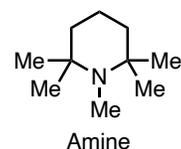
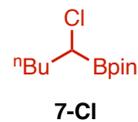
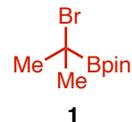
Response: Per the reviewer’s suggestion, we have further surveyed several different types of anodes for this reaction (Scheme C1). Using an undivided cell (standard conditions), Mg remains the optimal anode material. When using an Al anode, after passing about 0.5 F/mol of charge, the cell voltage increased drastically (>30 V; entry 2). This is due to the generation of a white passivation layer on the Al anode (likely aluminum oxide), and adding TMEDA as a ligand for Al ion did not help. As for other metal anodes (Zn, Fe, Ni, Sn), the *in situ* generated metal ions are more easily reduced on the cathode, and this competing reaction results in very low conversion of the alkyl halide (entries 3-6). We have also tried graphite anode together with 1,2,2,6,6-pentamethylpiperidine as a sacrificial reductant but the reaction only gave the product in 16% yield (entry 7). The low yield is likely caused by competitive reduction of anodically generated amine radical cation. *In situ* generated Mg^{2+} is harder to be reduced than the alkyl halide substrate (see Figure S13 in SI). Therefore, Mg plate is the optimal anode for the undivided cell reaction.

Previously, we found that the e-XEC can also be conducted in a divided cell (72% yield; entry 9) when using a Mg plate anode. During revision, we substituted Mg with graphite anode along with 1,2,2,6,6-pentamethylpiperidine as the sacrificial reductant. Promisingly, this combination afforded the product in 75% yield (entry 10). Thus, for divided cell reactions, the anode material is not limited to Mg. Notably, the Mg plate remains clean after electrolysis without significant passivation (Figure C3). Nevertheless, owing to the low conductivity of THF, the cell voltages of divided cell reactions were high.

According to the reviewer’s suggestion, we also tried alternating polarity electrolysis with different frequencies in a divided cell. However, neither reaction provided the product (entries 11-12).



Entry	Variation from above conditions	Conversion	Yield
1	standard condition with 7-Cl	95%	70%
2	Al(+) instead of Mg(+)	25%	15%
3	Zn(+) instead of Mg(+)	6%	0%
4	Fe (+) instead of Mg(+)	5%	0%
5	Ni (+) instead of Mg(+)	16%	0%
6	Sn (+) instead of Mg(+)	3%	0%
7	C (+) + Amine instead of Mg(+)	67%	16%
8	standard condition with 1	100%	86%
9	Mg (+), divided cell, <i>i</i> = 2.5 mA	90%	72%
10	C (+)+ Amine, divided cell, <i>i</i> = 2.5 mA	95%	75%
11	Mg (+), divided cell, <i>i</i> = 2.5 mA, Alternating electrode polarity per 1s	70%	0%
12	Mg (+), divided cell, <i>i</i> = 2.5 mA, Alternating electrode polarity per 5s	36%	0%



Scheme C1: Anode material screening and divided cell experiments.



Figure C3: Divided cell before electrolysis (left), reaction mixture after electrolysis (middle), electrode after electrolysis (right).

5. “As a very minor comment, it would be useful to have the structure of each compound on the cyclic voltammogram as well as the compound number (similar to that seen on NMR spectra), to save flicking back and forth.”

Response: We thank the reviewer for their suggestion. We have added structures in the revised SI.

6. *“Also, why does the current in the CV of compound 2 continue to increase?”*

Response: We reasoned that the reduction of compound **2** is thermodynamically challenging. The reduction peak of **2** may lie outside the solvent window. In addition, the reduction kinetics of **2** is sluggish. In our CV potential window, the reduction rate of **2** on the working electrode is slower than the diffusion rate of **2** from the bulk solution to the electrode surface. Therefore, the current in the CV continuously increases.

Reviewer: 3

Comments:

1. “*See, Lin and co-workers report electrochemical driven transition-metal-free cross electrophile coupling of alkyl halides. Various electrophiles such as alpha-bromoalkylboronic esters, benzylic chlorides, allylic chlorides, propargylic chlorides, alpha-chloroalkylsilanes were chemoselectively cross coupled with a large series of electrophiles (primary alkyl bromides, chlorosilanes, TsOMe, CO₂, ClGeMe₃) to give the corresponding cross-coupled products in moderate to very good yields. The functional group tolerance was well documented. Reductive cross-coupling is achieved upon using electrochemistry. The selectivity is based on the difference of the potentials of the two electrophiles, allowing for selective reduction of one halide over the other. Mechanistic studies are provided and also a larger scale setup was developed. The substrate scope is amazingly broad and cross coupling of more complex biologically relevant compounds was documented. Considering the magic methyl effect, authors also provided examples on the MeOTs cross coupling (even D₃COTs). I am very much impressed by this nice contribution and recommend publication in Nature subject to modifications as noted below.*”

Response: We thank reviewer for supporting publication of this work in *Nature* after revision and for their constructive review comments. These comments have helped us further improve the manuscript.

1. “*1) Considering the alpha-haloalkylboronic esters as substrates, authors should also discuss the classical Matteson rearrangement. Most of the primary bromides used as coupling partners can be readily transferred to the corresponding Grignard-reagents and directly be used in the Matteson rearrangement to give the same products (also under transition-metal-free conditions; maybe easier in scale up?). I therefore ask authors to run 2-3 reactions under Matteson conditions and compare yields. Likely, compound 45 cannot be prepared via the classical Matteson approach since the Grignard would not be stable, yet also the electrochemical approach provides a low yield. It would be important if authors can discuss the advantages: maybe pick one or two examples where Matteson would fail.*”

Response: According to the reviewer’s suggestion, we have conducted several control experiments to compare our method with the Matteson reaction. This comparison helped to make a stronger case for the significance of our new method. We think our method is complementary and more favorable in the following scenarios. First, the Matteson reaction can only be used to synthesize alkylboronic esters. In contrast, our method can also cross couple alkyl halides without an alpha-Bpin group such as benzyl-, allyl-, and propargyl chloride as well as *alpha*-haloalkylsilanes. In addition, other electrophiles such as chlorosilanes, chlorogermanes, and CO₂ are also suitable electrophiles.

Second, our method could be applied to synthesize alkyboronic esters that cannot be obtained using the Matteson reaction. In general, alkyl halides that could be easily transformed into Grignard reagents can readily undergo Matteson reaction to give the desire product (e.g., **19**, **89**, **93**, **97**) in comparable yields to our method. However, several other types of alkyl halides are not compatible with the Matteson reaction due to instability of their corresponding Grignard reagents (e.g., prone to intramolecular S_N2 reaction, E1cB reaction, or radical dimerization; Scheme C2, eq 1-4). In contrast, these alkyl bromides suitable substrates for the e-XEC.

Finally, our method can couple *alpha*-haloalkylboronic esters with chlorosilane to synthesize *gem*-silylboryl products. To the best of our knowledge, the Matteson reaction has not been explored in this context. Our preliminary trials showed only less than 15% desired product can be obtained (Scheme C2, eq 5-7). We also note that using our method, the carbanion nucleophile is *in situ* generated via electrochemistry, thus circumventing the preparation of Grignard reagents that is necessary prior to the Matteson reaction. These data have been included in the revised SI, and a sentence has been added to the main text.

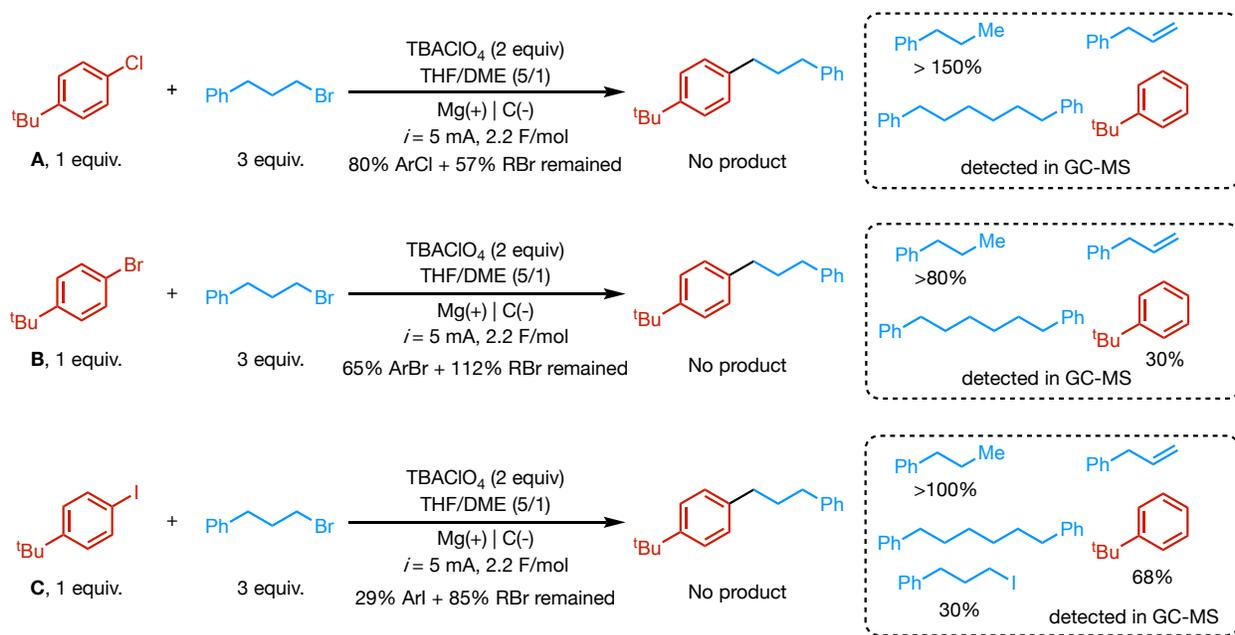
Response: Due to the transient nature of C-centered radicals generated from alkyl halide reduction, experimental determination of the potentials required for their reduction to the carbanions is difficult. One can imagine very facile side reactions such as dimerization, disproportionation, and HAT with the solvent can take place upon radical generation. Nevertheless, Saveant and coworkers reported a combined experimental and theoretical approach (*J. Am. Chem. Soc.* 1989, 111, 1620) to provide an estimate of the thermodynamic potentials of alkyl radical reduction in DMF. In our work, we have performed DFT calculations to help understand the reduction of different types of alkyl halides and the corresponding radicals. Our calculation results revealed that the second electron reduction, thermodynamically, is more difficult than the first reduction, which is consistent with what is observed in the literature (see: *J. Am. Chem. Soc.* 1986, 108, 638 and *J. Am. Chem. Soc.* 1989, 111, 1620). Introducing activation groups, such as, Bpin, aryl, alkenyl, alkynyl, and silyl, could reduce the reduction potential of corresponding alkyl halides and radical. These data have been included in revised SI (Part 8).

3. *“I am wondering whether CD₃OD can be used as the electrophile to get the deuterated product. Would be a valuable extension of the method.”*

[REDACTED]

4. *“Obvious coupling partners are aryl halides. They are generally easy to reduce (in particular the iodides) and the aryl anions are also rather stabilized. Please comment on the coupling of iodobenzene (even better bromobenzene and chlorobenzene) with an alkyl bromide.”*

Response: According to the reviewer’s suggestion, we have tried to couple aryl chloride, bromide, and iodide with alkyl bromide. However, under similar conditions, no desired XEC product was formed (Scheme C4). Due to its very negative reduction potential, aryl chloride **A** was mostly recovered, and protodehalogenation of the alkyl bromide was the major side product. With aryl bromide **B** or aryl iodide **C**, protodehalogenation of the aryl halide was observed (30% and 68%, respectively). Although we did not observe sp²-sp³ XEC products, the preliminary observations are promising. We will continue to study this system using a combination of mechanistic and synthetic experiments.



Scheme C4: Electroreductive C(sp²)-C(sp³) coupling.

5. “*Minor “Matteson” is misspelled in the main text.*”

Response: This typo has been corrected.