

Peer Review File

Manuscript Title: Reductive Alkyl-Alkyl Coupling from Isolable Nickel-Alkyl Complexes

Reviewer Comments & Author Rebuttals

Reviewer Reports on the Initial Version:

Referee #1 (Remarks to the Author):

In this report Sevov et al. disclose a versatile platform for alkyl-alkyl cross coupling. The methodology as disclosed is powerful and a large step forward. I anticipate that it will be widely used to generate molecules and building blocks that would require significant synthetic campaigns. The power of the methodology presented and the scholarship of the mechanistic studies warrant publication in Nature.

The first breakthrough came through the identification of stable Nickel alkyl species. The authors identified a ligand scaffold with unique stability toward generation of these Ni-alkyl species. They identified multiple different routes to the same species which demonstrate the robustness of the species towards different formation and isolation conditions. Relatively few isolable Ni-alkyl species are known in the literature, and I am not aware of any comparable general framework for creating bench-stable but still reactive species. The authors understate the uniqueness of this platform, as the reagents that they have created have much wider applicability beyond the XEC reaction the authors highlight (although those are likely the most unique and highest value). It would be easy to envision future protocols stemming from this work utilizing these reagents in all different alkyl-type cross couplings.

The second major advance is the reactivity identified with these stabilized Ni-alkyl species. The authors demonstrate excellent yields for a variety of coupling partners under a general but seemingly optimizable set of conditions. In the examples shown, the authors operate under a single current density for their system, and I would expect from my experience that each of the individual reactions would be highly sensitive to current density which in turn leads me to believe that each of the examples shown with reasonable yield could likely be higher with limited optimization. The authors correctly highlight that many of the “comparable” protocols often result in a statistical mixture of products arising from non-biased radical formation. Often these product distributions are biased through the use of multiple equivalencies of a “cheaper” components. The reaction described in this work appears more likely to work on more complex couplings where two “high-value” sp³ partners could be coupled.

The authors then proceed to give some mechanistic justification for the observed generality and limited failures of the methodology.

In total, the work is a magnificent step forward towards a fully general means to make Csp³-Csp³ bonds. I expect the uptake of such a reaction will be immediate and impactful in medicinal chemistry. The key critique is that the reaction requires stoichiometric amounts of nickel. I don't find that particularly challenging considering the value proposition this reaction put forward. It is easy to imagine implementing this chemistry to shorten sequences of 3-4 steps or in some cases much more. In the pharmaceutical industry, time is far more valuable than almost any reaction component so imagining sequences that might require 1-3 weeks to execute being shortened down to a few days far exceeds the value of the nickel metal and effort to remove it.

Referee #2 (Remarks to the Author):

This is great fundamental science and faultless scholarship, as we have come to expect from Sevov and co-workers. Here the group, joined by a scientist at Merck, find that alkyl-Ni(II)BPI complexes are isolable and stable at ambient temperature. These isolable organometallics will cross-couple with a variety of carbon-centered radical precursors like organozincs, organohalides, Katrizky salts or NHPI esters (I would prefer to see the seminal JACS 2016 5016 by Weix cited somewhere). Aside from the benefits to HTE/ diversification, there are nice mechanistic insights such as the exclusion of a Sanford-like SH2 C–C bond formation in preference for reductive elimination from a dialkylnickel, and an explanation for lower yields from Zn compared to cathodic reduction (although I'm not sure I understand why e-chem performs well here in light of the authors' previous JACS 2020 paper on electron shuttles).

The Ni-alkyl complexes are not expensive to prepare and can be isolated or directly coupled with alkyl electrophiles. The authors should comment somewhere on toxicity, both at the cellular and organism level. These reactions would be powerful for direct-to-biology scaffold diversification, and readers should be reassured that residual nickel complexes would not decrease cell viability (I don't think they would). I do worry about the toxicity of these reagents for the user, however. Some comment based on toxicology literature is essential.

The main drawback to this paper is its reliance on the glovebox to synthesize the isolable organometallics AND carry out the cross-couplings. This makes sense in a sophisticated industrial setting where HTE facilities regularly employ glove boxes. However, this is not widespread across the majority of synthetically-oriented labs in industry and academia. If the authors can demonstrate these reactions using standard or even sloppy technique (undried solvents, flasks under balloon or even open to the air) outside the glovebox, there is a greater possibility that the community would adapt this strategy.

Having said that, I think the main criteria for publication in Nature (or any high-tier journal that provides a highly visible platform) is whether it significantly impacts what the community knows or how it carries out research/ solves problems (although that is for the editor to decide ultimately). Not all Nature papers live up to these rigorous criteria, but that should not lower the standards. This is a nice study, but not the first to report stable alkyl-Ni complexes, nor use them in cross-couplings. It is a good solution to the problem of 1:1 cross-coupling and I agree with the authors that previous reports of heteroselectivity have fallen far short of ideal. I also agree that 30 mol% Ni is not appreciably different than 100 mol%. However, I don't think this work will have a MAJOR impact on what the community knows/believes, or goes about solving problems in synthesis.

A few other comments:

1. It would be helpful to see how functional groups like alcohols, amines, ketones, and nitriles affect these reactions.
2. Look for small typos: for example, in p. 3, "Most importantly... generate the cross-coupled product 3 in 86% yield (Fig. 1B, right)." should be changed to "... (Fig. 1C, right)". In p. 9, reference 18 and reference 29 are the same.
3. In the Supplementary Information the ^1H NMR and ^{13}C NMR spectra of some compounds are on the same page, while others are on the different pages. The inconsistency is not reader-friendly.
4. Why didn't the authors explore any examples of photochemical cross-electrophile coupling? Are the organonickel complexes photosensitive? If so, at what wavelengths?

Referee #3 (Remarks to the Author):

The manuscript by Sevov, Kalyani, and coworkers describes a general strategy to construct C(sp³)–C(sp³) bonds from various coupling partners, including nucleophiles, electrophiles, and radical precursors. Mechanistic studies support the capture of radicals at the nickel(II) complexes to form nickel(III) intermediates, which mediates slow carbon–carbon bond forming reductive elimination. The authors present a general and useful method that addresses the long-standing challenge of cross-coupling two C(sp³) moieties with high yield and high selectivity. The scope is particularly relevant and interesting, as the authors demonstrated the coupling of drug-like moieties and unnatural amino acids. Overall, the manuscript provides a unique advancement in the methodology of C(sp³)–C(sp³) bond formation, which is of significant interest in drug discovery. The manuscript's significance is broad and high, making it suitable for the readers of Nature.

I recommend publication after the following comments and suggestions are addressed:

1. The substrate scope demonstrated in the paper is impressive and highlights the power of this method. It would be impactful to show the synthesis of noncanonical amino acids with biotin or halotags. Would the method be compatible with a chlorotag?
2. It would be more significant if the derivatization of carbohydrate substrates could occur at the anomeric position, while the current data show derivatization at the C5 and C6 positions of ribose and galactose. It would be interesting to analyze the d.r. of these reactions.
3. In investigating the mechanism, the authors provide strong evidence that the reaction proceeds through an inner-sphere mechanism rather than SN₂. Their stereochemical probe is especially well-planned and well-executed.
4. Regarding the EPR experiment, it is usually difficult to distinguish nickel(I) from nickel(III) signals. The g-values of the proposed nickel(III) are different from those cited in the study by Mirica and Sanford (DOI: 10.1021/jacs.9b02411). The coordination geometry is most closely related complex reported by the Vicic group (DOI: 10.1021/ja4030462), which is also observed at different g-values. It would be useful to gather EPR data of the corresponding nickel(I) to confirm that the EPR signal assigned to nickel(III) is not nickel(I) formed after reductive elimination. Additionally, it seems unlikely that stable nickel(III) would form in the presence of a 10-fold excess of Zn(0).
5. The authors should provide the EPR spectrum with the magnetic field as the x-axis, as well as g-values.
6. In Fig. 1, the authors conclude that τ correlates with yield, suggesting that deviation from square planar geometry explains the drop in yield. While complex 2-Cy had the lowest yield and highest τ value, this does not seem sufficient to conclude that there is a direct trend. For example, 2-Me has an increase of 0.04 in τ value from 2-CyPr, but only a 4% decrease in yield. In contrast, 2-Cy has an increase of 0.06 in τ value from 2-Me, but sees a 79% decrease in yield.

7. The authors mention in the text that they computationally evaluated the barrier to reductive elimination. They should show the structures of the transition states and energy diagrams either in the supplementary information (SI) or the manuscript.

8. The supplementary information lacks page numbers.

9. In the main text, the authors mention that they conducted control experiments to ensure that the nickel-alkyl bond does not reversibly homolyze in solution and that complex 24 is stable. It is unclear how this experiment was conducted and on what time scale. Including this data in the SI would support this claim. Additionally, from the experiment with 2-hex-1-ene radical clock alone, it is possible that the rapid in-cage rebinding of the radical outcompetes the 5-endo and 6-exo cyclizations, which would be much slower than the diffusion-controlled radical recombination of the alkyl radical and nickel(I).

10. A point mentioned multiple times is the scalability and stability of the Ni(II)-alkyl complexes as isolable cross-coupling partners. However, their stability was only briefly mentioned in the text. An analysis similar to that performed by Engle and colleagues (Acc. Chem. Res. 2024, 57, 3, 312–326) would add to the impact of this work.

Reviewer 1 – Recommended Publication

There were no comments to address from Reviewer 1. We thank the Reviewer for the supportive comments of the work.

Reviewer 2 – Requested Revisions

1. These isolable organometallics will cross-couple with a variety of carbon-centered radical precursors like organozincs, organohalides, Katritzky salts or NHPI esters (I would prefer to see the seminal JACS 2016 5016 by Weix cited somewhere).

[Response]: We have now included this seminal contribution on coupling reactions of NHPI esters as reference 21 in the manuscript.

2. The authors should comment somewhere on toxicity, both at the cellular and organism level.

[Response]: We have added references that discuss the toxicity of metals, including Ni toxicity (see references 1 and 2 in the SI). We would like to note that this work is not targeted towards process chemistry where thorough purification would be required to remove metal contaminants. Rather, this stoichiometric chemistry is targeted towards medicinal chemistry where molecules are often purified by HPLC. HPLC purification would remove any Ni contaminants from organic products that are to be used for assays. Moreover, the stoichiometric Ni byproduct has not been a problem in our isolations using conventional chromatography. The complex is readily precipitated out of solution or decomposed upon workup with acidic water.

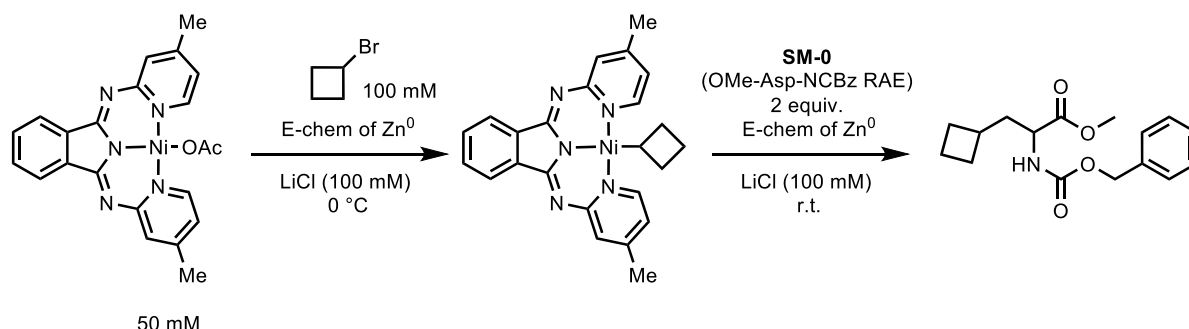
3. I do worry about the toxicity of these reagents for the user, however. Some comment based on toxicology literature is essential.

[Response]: Unfortunately, we do not have toxicological data on these exact complexes beyond the references we added in the revised SI (see previous comment). However, we would like to note that Ni complexes of this ligand have been used as storage chemistries in flow batteries (doi.org/10.1021/jacs.6b07638) as well as synthesis (doi.org/10.1021/jacs.0c01475 and doi.org/10.1038/s41557-024-01528-7). Notably, these references do not include the many examples of BPI-metal complexes used in other applications. The first systematic study of these complexes stems from work done at the Ford motor company developing BPI-ligated metal complexes, including Ni (doi.org/10.1021/jo00431a011 and doi.org/10.1021/ic50224a024). Collectively, this metal-complex architecture has been studied for decades. Nonetheless, we have included a note in the SI stating that, “[The toxicology of the organonickel complexes has not been studied. Handling of organonickel complexes should be done with care.](#)”

4. The main drawback to this paper is its reliance on the glovebox to synthesize the isolable organometallics AND carry out the cross-couplings. This makes sense in a sophisticated industrial setting where HTE facilities regularly employ glove boxes. However, this is not widespread across the majority of synthetically-oriented labs in industry and academia. If the authors can demonstrate these reactions using standard or even sloppy technique (undried solvents, flasks

under balloon or even open to the air) outside the glovebox, there is a greater possibility that the community would adapt this strategy.

[Response]: This is an excellent suggestion to bolster the practicality of the methodology. We have now performed the reaction under a variety of conditions as well as in an IKA ElectraSyn. The table below includes specific alterations to the rigorous conditions used in the preliminary work and is included in the SI as **Figure S7**. These data show that reactions are compatible with moisture from undried solvents, and reactions can be set up outside of the glovebox and degassed by simply pump-cycling to exchange the atmosphere for nitrogen prior to electrolysis/reductive activation. As expected, reactions open to air fail completely. The data is included in the SI and is reproduced below. Additionally, we have included a discussion in the manuscript on the practicality of the method, which reads, “Finally, tolerance studies revealed that reactions do not require rigorously dry conditions (see the SI, Fig. S7). Reaction mixtures can be prepared under ambient conditions with undried solvents and simply degassed prior to reductive activation. Such reactions generated products in only slightly lower yields (**7d**, 66% yield) than those conducted with rigorously inert and dry conditions in a glovebox (83% yield). Additionally, reactions doped with additives containing various functional groups (nitriles, amines, alcohols, etc. see the SI, Fig. S8) generated coupled products in similar yields to those without additives. Collectively, these results highlight the practicality of the method and the mild conditions for coupling.” The data included in the SI are reproduced below.



Atmosphere Prep- aration Cond.	Solvent	Reductant for the en- tire reaction	Yield (GC)
Glovebox	Dry (1:1) THF:DMF	E-chem	71%
Glovebox	Dry (1:1) THF:DMF	E-chem (IKA)	62%
atmosphere, N ₂ pump cycle	Wet (1:1) THF:DMF	E-chem	42%
atmosphere, N ₂ pump cycle	Wet (1:1) THF:DMF	E-chem (IKA)	41%
Open to air	Wet (1:1) THF:DMF	E-chem	0%
Glovebox	Dry (9:1) THF: DMF	Zn	83%
atmosphere, N ₂ pump cycle	Wet (9:1) THF: DMF	Zn	66%
Open to air	Wet (9:1) THF: DMF	Zn	0%

5. This is a nice study, but not the first to report stable alkyl-Ni complexes, nor use them in cross-couplings. It is a good solution to the problem of 1:1 cross-coupling and I agree with the authors that previous reports of heteroselectivity have fallen far short of ideal. I also agree that 30 mol% Ni is not appreciably different than 100 mol%. However, I don't think this work will have a MAJOR impact on what the community knows/believes, or goes about solving problems in synthesis.

[Response]: As noted by in the manuscript and supported by the comments of other Reviewers, there are no other examples of Ni-Alkyl complexes that exhibit this combination of persistence and synthetic utility/reactivity. Usually, reactivity is hampered for the sake of promoting persistence (or vice-versa). Moreover, we generate these complexes akin to how Grignard reagents are generated: directly from the alkyl electrophile. Regarding the utility, the analogous Ni-Aryl chemistry is already used in at least 4 pharmaceutical companies (that we are aware of) as well as 2 academic labs. We believe this already exceeds the impact of many other reports in the area. In addition to this robust scope, this work also provides insights into the foundations of organonickel and metalloalkyl chemistry that have been elusive to attain.

6. It would be helpful to see how functional groups like alcohols, amines, ketones, and nitriles affect these reactions.

[Response]: We agree with the Reviewer that evaluating functional group compatibility is critical to the utility of the methodology. We would like to note that many of the substrates in the manuscript contain the noted functional groups. As examples, free alcohols (**20**), BOC or Cbz carbamates (see amino acids) esters (many), and ketals (**17**, **22**, many others) are all tolerated. We have now performed a functional group tolerance study popularized by Glorius to measure the yield of cross-coupling products from reactions that contained additives with the noted functional groups. As shown in the data below, product yields were all above 80%, including the control reaction. Additionally, the additives were all recovered in high yields. We have included these data in the SI as Fig. S8 and have added a comment about these results in the manuscript, which reads, “Additionally, reactions doped with additives containing various functional groups (nitriles, amines, alcohols, etc. see the SI, Fig. S8) generated coupled products in similar yields to those without additives.”

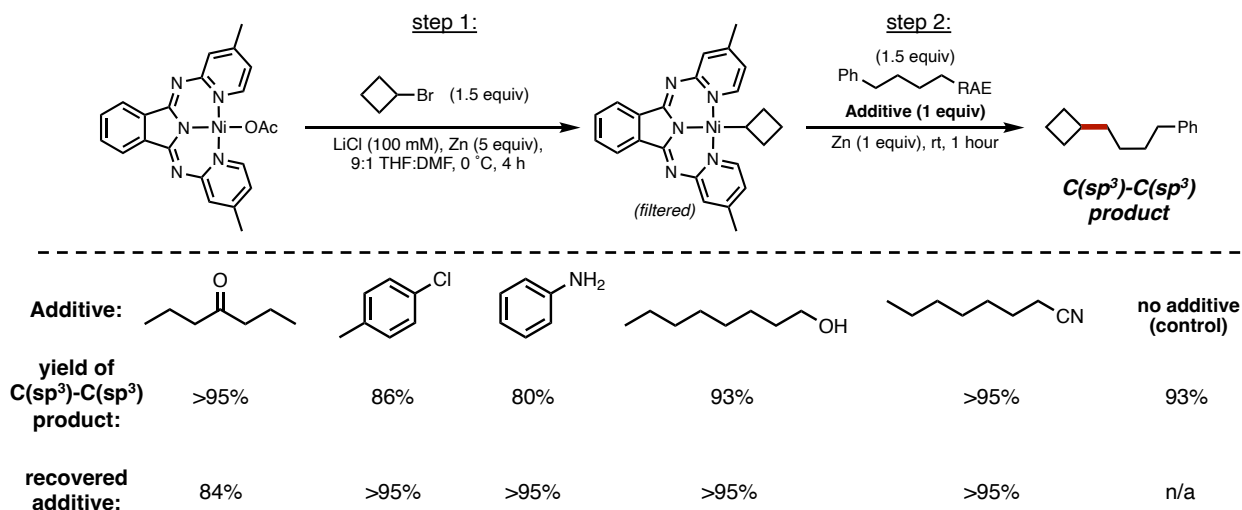


Figure S8. Yield of the C(sp³)-C(sp³) cross-coupled product with functional group additives added in step 2 of the reaction scheme.

7. *Look for small typos: for example, in p. 3, “Most importantly... generate the cross-coupled product 3 in 86% yield (Fig. 1B, right).” should be changed to “... (Fig. 1C, right)”. In p. 9, reference 18 and reference 29 are the same.*

[Response]: We have corrected the noted typos and references.

8. *In the Supplementary Information the ¹H NMR and ¹³C NMR spectra of some compounds are on the same page, while others are on the different pages. The inconsistency is not reader-friendly.*

[Response]: It is indeed nice to have the spectra on a single page, which is why we formatted the pages in this manner. This is the case for the majority of the spectra, but in some cases extra spectra like COSY or NOESY plots disrupt the nice pairings of ¹H/¹³C as the reviewer noted. We elect to keep the format as is.

9. *Why didn't the authors explore any examples of photochemical cross-electrophile coupling? Are the organonickel complexes photosensitive? If so, at what wavelengths?*

[Response]: We do not believe the complexes are photosensitive because they have been stored without protection from light. Reactions are also performed without protection from ambient light. We have not attempted photochemical reactions because this falls well outside the scope of the chemistry reported here. This extensive report already covers mechanism, synthetic scope, and fundamental Ni-alkyl chemistry. This would be an excellent future endeavor! However, this likely will not be trivial because we would have to select a photocatalyst and reductant that are compatible with the organonickel complex. The Ni complex, rather than reductant, may simply quench the excited state of the photocatalyst. In contrast, the use of electrochemistry is ideal for these net-reductive reactions. It is for this reason that we first employed electrochemistry for these reactions.

Reviewer 3 – Recommended Publication Following Revisions

1. The substrate scope demonstrated in the paper is impressive and highlights the power of this method. It would be impactful to show the synthesis of noncanonical amino acids with biotin or halotags. Would the method be compatible with a chlorotag?

[Response]: We thank the Reviewer for the positive comment and have performed a few additional experiments based on the suggestion. Specifically, we have performed a functional group compatibility study (popularized by Glorius) of the coupling reaction with added chloroarene as a chlorotag. The C–C coupled product was formed in a lower yield compared to the reaction without a bromobenzene additive. Bromoarene additive was completely consumed when introduced either during step 1 or step 2 of the reaction.

We have now performed a functional group tolerance study popularized by Glorius to measure the yield of cross-coupling products from reactions that contained additives with the noted functional groups. As shown in the data below, product yields were all above 80%, including the control reaction. Additionally, the additives – including a chloroarene as suggested by the Reviewer – were all recovered in high yields. Bromoarenes undergo competitive activation by Ni under reductive conditions and are not compatible with the chemistry. We have included these data in the SI as Fig. S8 and have added a comment about these results in the manuscript, which reads, “Additionally, reactions doped with additives containing various functional groups (nitriles, amines, alcohols, etc. see the SI, Fig. S8) generated coupled products in similar yields to those without additives.” Finally, we anticipate the biotin coupling would be successful given the established functional group compatibility.

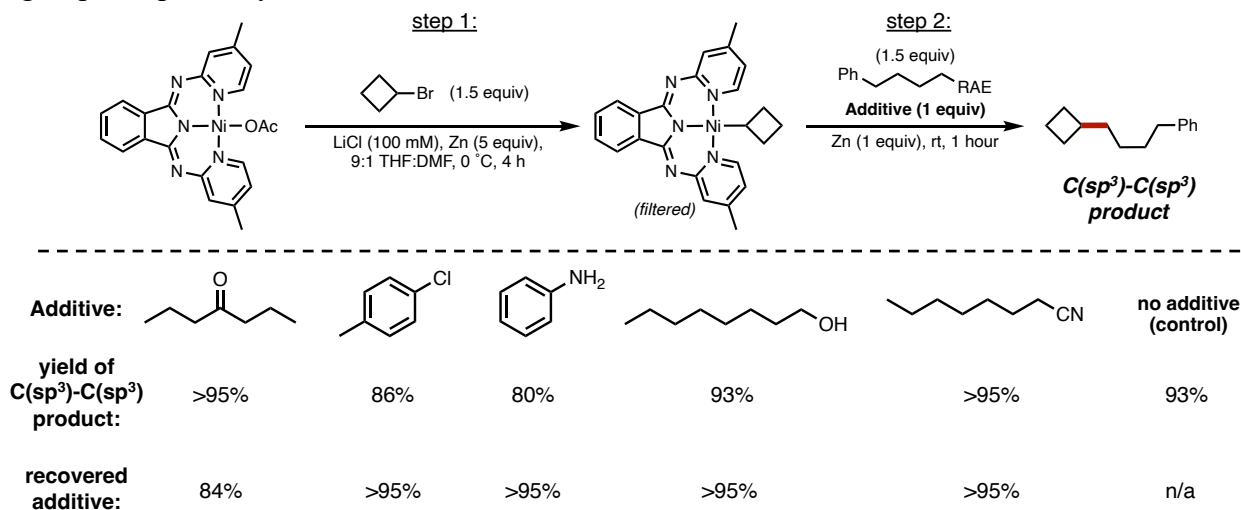
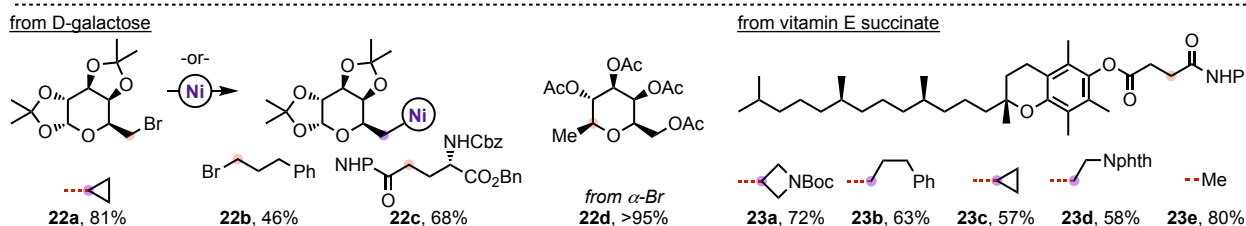


Figure S8. Yield of the C(sp³)-C(sp³) cross-coupled product with functional group additives added in step 2 of the reaction scheme.

2. It would be more significant if the derivatization of carbohydrate substrates could occur at the anomeric position, while the current data show derivatization at the C5 and C6 positions of ribose and galactose. It would be interesting to analyze the d.r. of these reactions.

[Response]: We thank the Reviewer for the excellent suggestion. Alkylation of the anomeric position of brominated sugars can be easily done with this methodology. We have now included a reaction of commercial α -bromo-D-galactose tetraacetate (CAS: 3068-32-4) and **2-Me** (generated *in situ* and telescoped). The product was isolated as a single stereoisomer in near-quantitative yield. Full characterization of the product is included in the SI, and the product is also included in the manuscript as **22d**. We have provided a discussion of this result in the manuscript, which reads, “Alkylation of the anomeric position of galactose occurs in high yield from the corresponding bromide to generate methylated galactose **22d** as a single stereoisomer.” The modified section of Fig. 3 containing **22d** is reproduced below:



3. In investigating the mechanism, the authors provide strong evidence that the reaction proceeds through an inner-sphere mechanism rather than S_N2 . Their stereochemical probe is especially well-planned and well-executed.

[Response]: We thank the Reviewer for this kind note.

4. Regarding the EPR experiment, it is usually difficult to distinguish nickel(I) from nickel(III) signals. The *g*-values of the proposed nickel(III) are different from those cited in the study by Mirica and Sanford (DOI: 10.1021/jacs.9b02411). The coordination geometry is most closely related complex reported by the Vicic group (DOI: 10.1021/ja4030462), which is also observed at different *g*-values. It would be useful to gather EPR data of the corresponding nickel(I) to confirm that the EPR signal assigned to nickel(III) is not nickel(I) formed after reductive elimination. Additionally, it seems unlikely that stable nickel(III) would form in the presence of a 10-fold excess of Zn(0)

[Response]: We agree with both points the Reviewer has made. Indeed, Ni(III) is unlikely to persist for long periods in an excess of Zn. We propose this competitive reduction as a cause of low yields from some coupling reactions mediated Zn (see Figure 4C, bottom path to generate a dialkyl Ni^{II} complex that doesn't undergo RE). However, in this experiment we note that an aliquot of the solution (excluding the Zn) is collected and frozen for EPR analysis. This traps any Ni(III) intermediates that hadn't undergone heterogeneous Zn reduction. Additionally, the alkyl bromide is still present in the sampled solution. As a result, it is unlikely that Ni(I) would be stable under conditions with so much homogeneous electrophile.

Nonetheless, we sought to obtain additional support for this claim. We reduced the BPI-Ni(III)-OAc complex in the absence of electrophile to generate the putative BPI-Ni(I) intermediate. EPR spectroscopic analysis of this intermediate reveals distinct resonances from those claimed to be from Ni(III) (see plot B below). These spectra are reproduced below and are included in the SI:

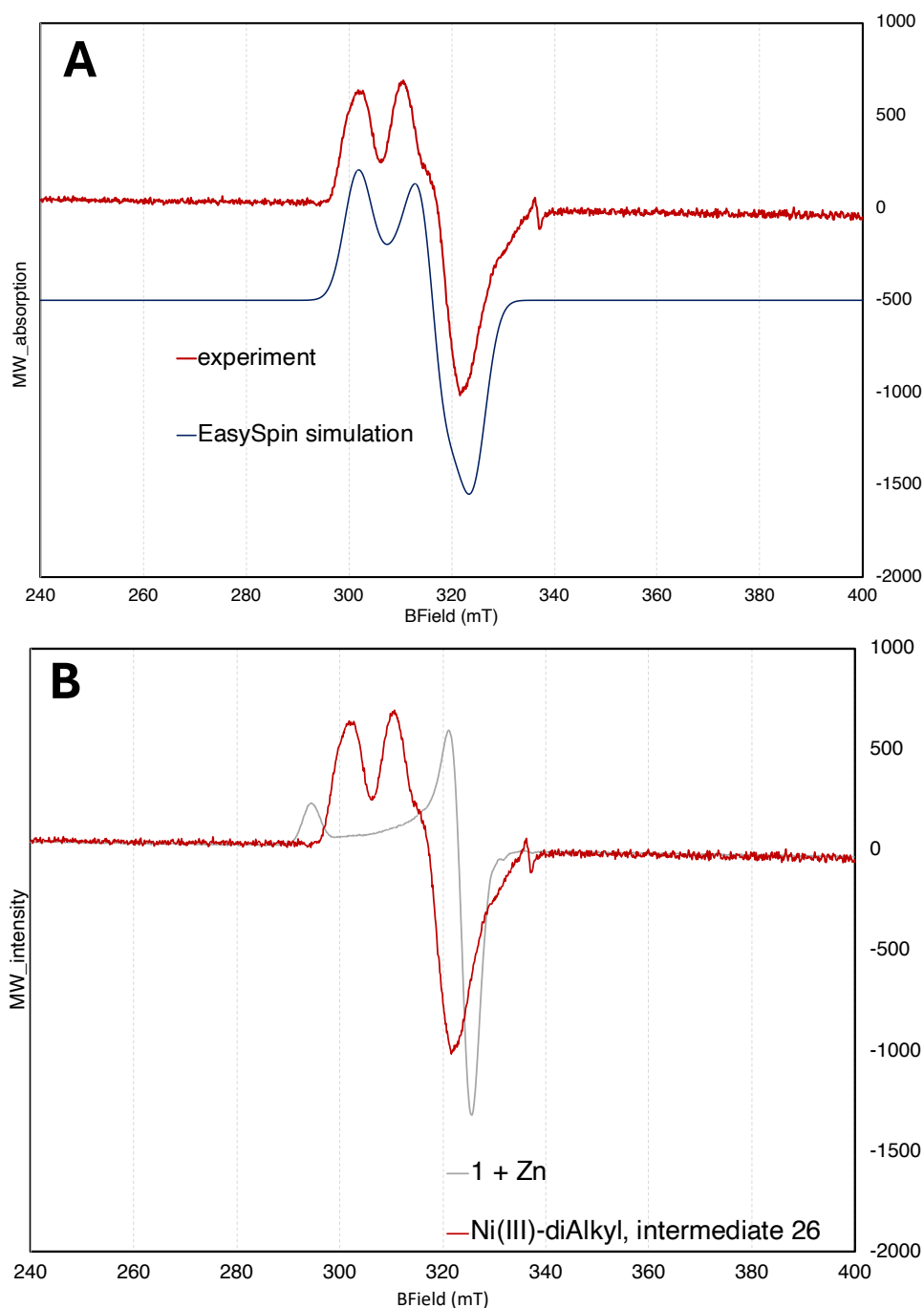


Figure S5. (A) EPR spectrum of the Ni(III)(dialkyl) intermediate **26** with the overlaid EasySpin simulation. (B) EPR spectrum of a mixture of **1** and Zn overlaid with the spectrum of intermediate **26**.

5. The authors should provide the EPR spectrum with the magnetic field as the x-axis, as well as *g*-values.

[Response]: We have updated the plot according to the suggestion to show both axes.

6. In Fig. 1, the authors conclude that τ correlates with yield, suggesting that deviation from square planar geometry explains the drop in yield. While complex 2-Cy had the lowest yield and highest τ value, this does not seem sufficient to conclude that there is a direct trend. For example, 2-Me has an increase of 0.04 in τ value from 2-CyPr, but only a 4% decrease in yield. In contrast, 2-Cy has an increase of 0.06 in τ value from 2-Me, but sees a 79% decrease in yield.

[Response]: We agree with the reviewer and have tempered the claim. Rather, we suggest that the effect of distortion is a threshold effect. This is more consistent with studies by Sigman, Hansen, and Weix on XEC reactions from complexes that are tetrahedral vs. square planar (*JACS* **2024**, 146, 3043). Reactions catalyzed by distorted complexes in that report similarly demonstrate binary results of either high yields or no yield at all. The revised discussion now reads, “Geometric distortion beyond a certain threshold, rather than steric encumbrance around the Ni center (calculated by %V_{bur}), may contribute to the low yields of C(sp³)-C(sp³) coupled products from stoichiometric reactions (Fig. 1D, bottom). Reactions of complexes with $\tau_4 \leq 0.3$ resulted in highest yields of cross-coupled products. In contrast, reactions with the cyclohexyl analog 2-Cy ($\tau_4 = 0.36$) generated coupled products in just 12% yield before further reaction development (*vide infra*).”

7. The authors mention in the text that they computationally evaluated the barrier to reductive elimination. They should show the structures of the transition states and energy diagrams either in the supplementary information (SI) or the manuscript.

[Response]: We have now included images of the computed structures as well as an energy diagram. These extensive data are included in pages S125-S135 of the SI.

8. The supplementary information lacks page numbers.

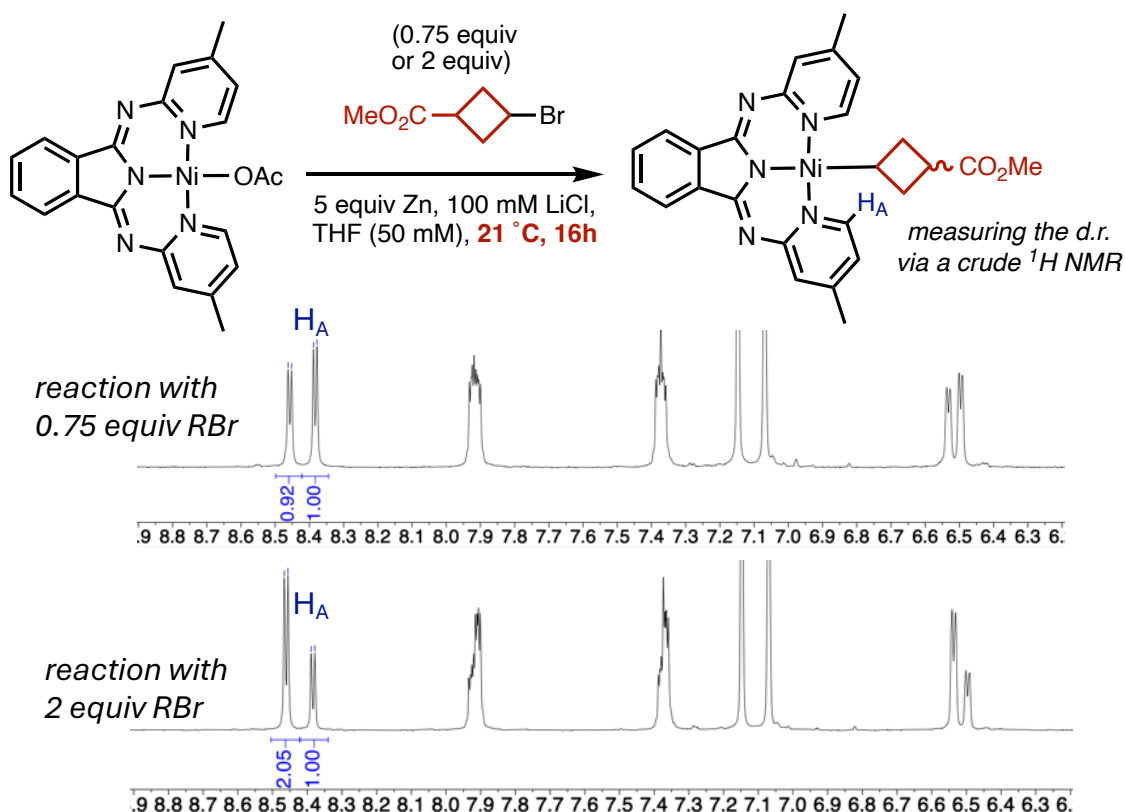
[Response]: We thank the reviewer for the note and have corrected the omission.

9. In the main text, the authors mention that they conducted control experiments to ensure that the nickel-alkyl bond does not reversibly homolyze in solution and that complex 24 is stable. It is unclear how this experiment was conducted and on what time scale. Including this data in the SI would support this claim. Additionally, from the experiment with 2-hex-1-ene radical clock alone, it is possible that the rapid in-cage rebinding of the radical outcompetes the 5-endo and 6-exo cyclizations, which would be much slower than the diffusion-controlled radical recombination of the alkyl radical and nickel(I).

[Response]: The coupling reaction with the Ni-hexenyl substrate served to demonstrate that the Ni-alkyl bond does not homolyze, which could scramble the stereochemistry of **24** under the reaction conditions. This experiment is critical to the validity of the stereochemical probe. Drawing a conclusion from the stereochemistry of the product mixture would be flawed if the stereochemistry of the Ni-alkyl complex scrambles during the reaction. As discussed in the manuscript, we only observed products of the uncyclized alkyl fragment. This would suggest that (i) the alkyl group does not homolyze or that (ii) the radical intermediate is caged and so short-lived that it is recaptured prior by Ni prior to 5-endo cyclization (faster than 10⁵ s⁻¹). If this latter scenario is the case (a possibility suggested by the Reviewer), it is then also unlikely that this caged radical would have the lifetime to flip around in order to scramble the

stereochemistry of the Ni-alkyl complex **24**. As noted, it is this scrambling that we were most concerned with for our stereochemical analysis.

To further support our claim regarding the stereochemical stability of complex **24**, we were able to prepare **24** as a ~0.9:1 mixture of syn and anti stereoisomers. Like the 2:1 mixture of stereoisomers discussed in the manuscript, this 0.9:1 mixture did not undergo any scrambling over time. These data further underscore the stereochemical stability of the Ni-alkyl complex such that we can make meaningful conclusions on the mechanism based on a stereochemical analysis of the product. ¹H NMR spectra of the 0.9:1 and 2:1 stereochemical mixtures are reported below.



10. A point mentioned multiple times is the scalability and stability of the Ni(II)-alkyl complexes as isolable cross-coupling partners. However, their stability was only briefly mentioned in the text. An analysis similar to that performed by Engle and colleagues (*Acc. Chem. Res.* 2024, 57, 3, 312–326) would add to the impact of this work.

[Response]: The organonickel complexes are sensitive towards oxygen but are stable to moisture and protic functional groups (e.g., free alcohols, see product **20**). Although complexes can be stored in bottles for extended periods, we do not feel the comparison to the Engle work is relevant. In particular, the work by Engle establishes alternative Ni(0) precursors that are more stable than Ni(COD)₂. The stability study in that work is important because Ni(COD)₂ is frustratingly unstable when stored outside the freezer or in ambient conditions. Here, there is no comparison of other storable Ni-alkyl complexes. Moreover, these organonickel intermediates

are typically generated in situ and coupled with a second electrophile: much like a Grignard reagent. Rather than a study analogous to Engle's, we have now added studies on reactions that were set up outside of a glovebox and with "wet" solvents (see our response to comment #4 from Reviewer 2). In brief, the reactions can be performed using a much less rigorous setup with only a minor reduction in yield. We believe these studies are ultimately more impactful for the method and more helpful to the end-user.

Reviewer Reports on the First Revision:

Referee #2 (Remarks to the Author):

The revised manuscript from Sevov and co-workers mostly addresses our criticism. The main problem that I thought diminished the work was the requirement for glovebox preparation and use of the organonickel complexes. The authors find that the reaction can be performed with undried solvents that have been degassed with simple protocols. A couple points to address in the revised manuscript:

1. Why does the IKA ElectraSyn provide poorer yields? How old are the electrodes and how many times can they be used to provide these yields? A few groups across the community have observed similar problems. A proposed advantage of electrochemistry is the avoidance of stoichiometric reductants. But short lifetimes of the electrodes remove any advantage while retaining the major downsides of electrochemistry like cost, scalability, safety hazards etc. (at least, for non specialists).
2. One claim the authors make about this work is the low cost of the alkylnickel complex ("inexpensive" is used 5 times). However, I could not find a breakdown of the cost of materials and supplies. The authors should provide this support or remove the claim. (this is only a minor point)

A few thoughts for the authors and editor alike. If these organonickel complexes represent a major breakthrough for cross-coupling and if we agree that use of stoichiometric nickel is not particularly important, then follow-up papers (by this group or others) that render the nickel substoichiometric even at low mol% must be seen as incremental advances (assuming the ligand set and conditions are similar). I can't see both results as major breakthroughs; now is the time to decide.

Referee #3 (Remarks to the Author):

The authors have addressed my comments satisfactorily. This manuscript is suitable for publication in Nature and will be highly impactful.

Reviewer 2

1. Why does the IKA ElectraSyn provide poorer yields? How old are the electrodes and how many times can they be used to provide these yields? A few groups across the community have observed similar problems. A proposed advantage of electrochemistry is the avoidance of stoichiometric reductants. But short lifetimes of the electrodes remove any advantage while retaining the major downsides of electrochemistry like cost, scalability, safety hazards etc. (at least, for non specialists).

[Response]: The issue with the IKA system is not with the electrodes. In fact, we routinely reuse the electrodes in our home-built cells. The issue with IKA is properly sealing the cells to eliminate air leaks during the course of the reaction. This is a common issue with IKA. The system works well when placed inside of a glovebox.

2. One claim the authors make about this work is the low cost of the alkylnickel complex (“inexpensive” is used 5 times). However, I could not find a breakdown of the cost of materials and supplies. The authors should provide this support or remove the claim. (this is only a minor point).

[Response]: We previously detailed the cost per gram to prepare the BPI-Ni-OAc complex (Nature Chemistry, 2024). A cost estimation is performed in that report, and we have included reference 23 alongside the discussion of cost. Finally, we have improved the writing by removing some of the repetitive descriptors regarding the cost of the complex.

3. A few thoughts for the authors and editor alike. If these organonickel complexes represent a major breakthrough for cross-coupling and if we agree that use of stoichiometric nickel is not particularly important, then follow-up papers (by this group or others) that render the nickel substoichiometric even at low mol% must be seen as incremental advances (assuming the ligand set and conditions are similar). I can’t see both results as major breakthroughs; now is the time to decide.

[Response]: This is indeed an interesting argument! However, I strongly believe both catalytic and stoichiometric reactions would be impactful in their own right. There are a lot of fundamental challenges that need to be addressed in order to design a catalytic system that can selectively cross-couple two distinct alkyl fragments. Such a reaction would represent an entirely new strategy and major advance in catalytic C–C bond-forming reactions. As an example, we have seen the power of size-selective radical sorting recently popularized by MacMillan, Shenvi, Lin, and others. A new paradigm for catalyst-controlled substrate selectivity could significantly advance the field of cross-coupling.

Reviewer 3

1. The authors have addressed my comments satisfactorily. This manuscript is suitable for publication in Nature and will be highly impactful.

[Response]: We thank the Reviewer for their time in reviewing this manuscript and their support of this work.