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Peer Review File

Stereoretentive Decarbonylative C(sp^3)-C(sp^3) Cross-Coupling

Corresponding Author: Professor Daniel Weix

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This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Referee #1

(Remarks to the Author)
Wu, Weix, and coworkers report the stereoretentive C(sp3)-C(sp3) cross-electrophile coupling of amino acid-derived activated esters with alkyl iodides under nickel catalysis. Key for their achievement is the use of 2-pyridyl esters which enable stereoretentive 2-electron oxidative addition and decarbonylation.

The authors present a well-executed optimization campaign and interesting mechanistic insights regarding the oxidative addition step as well as the slow stereoablation process of the oxidative addition complex. The substrate scope of activated esters includes proline-derived structures and a series of acyclic natural amino acid-derived structures. Due to the broad range of suitable amino acids, this method is useful to access chiral amines via net-decarboxylative alkylation. Other substrates than amino acid-derived activated esters, however, are not shown. Primary and secondary alkyl iodides are compatible coupling partners, and the overall functional group tolerance is good. The method was applied to the synthesis of several synthetic intermediates of known bioactive compounds, highlighting its synthetic utility.

On the other hand, conceptually, the work is a follow-up of the author's previous work (ref. 26), in which a C(sp3)-C(sp3) cross-electrophile coupling between alkyl 2-pyridinyl esters and alkyl iodides was developed, based on a decarbonylative 2-electron oxidative addition. The general concept and synthetic strategy are therefore known. Even more important: stereoretentive deuteration of amino acid-derived alkyl 2-pyridinyl esters has been shown in ref. 26 as well, making the concept of stereoretentive functionalization of amino acid-derived alkyl 2-pyridinyl esters known as well. Furthermore, substrate 1 of the present work was already used in ref. 26 in a stereoretentive C(sp3)-C(sp3) cross-electrophile coupling with an alkyl iodide (in the SI of ref. 26: 7% yield with 75% ee or 12% yield with 65% ee). This finding was reoptimized in the present work.

Overall, the method is a follow-up to the group's previous work (ref. 26). While I believe that the method holds some synthetic value for the preparation of chiral amines from easily accessible amino acids, I understand the work as the reoptimization of a previously disclosed finding (ref. 26). Therefore, actual conceptual novelty is absent, as pointed out above, making this work unfit for publication in Nature.

Regardless of this work's publication status, I recommend addressing the following concerns that could improve the quality of this manuscript:

1. The supporting information is lacking a section about failed substrates.
2. Do substrates other than amino acid derivatives work? In the original method (ref. 26), activated esters derived from other acids were suitable substrates as well. However, when it comes to stereoretentive functionalizations (in the present work and in ref. 26), amino acid-derived structures are used exclusively. I assume that other substrates cannot be coupled stereoretentively. Why is that the case?
3. Along these lines: What influence on the speed of racemization does the nitrogen protecting group have? I can imagine that coordination of the carbamate moiety to the nickel can keep the metal at the same face of the formed enamine in case β-hydride elimination takes place, thereby slowing down racemization. I would be interested in a systematic racemization rate

study (as done for compound S28 – see SI chapter 3.4) for different protecting groups but also for different substrates that are not derived from amino acids.
4. How about other alkyl radical precursors instead of alkyl iodides, such as alkyl bromides, Katritzky salts or NHPI esters?

Referee #2

(Remarks to the Author)
In this manuscript, Wu, Weix, and co-workers report a stereoretentive C(sp3)–C(sp3) cross-electrophile coupling reaction through the decarbonylation of 2-pyridyl esters. Recently, there has been high interest in developing effective C(sp3)–C(sp3) cross-coupling reactions, particularly those that can use native functional groups commonly found in organic molecules. While there has been significant progress in this area using various catalytic systems, achieving stereoselectivity remains a challenge. One approach that has seen significant success is using a chiral catalyst in a stereoablative enantioselective coupling. An alternative approach that has seen less progress is developing stereospecific reactions that use chiral, enantioenriched starting materials.

In one approach, Baran demonstrated that chiral alcohols can be converted into sulfonyl hydrazines that undergo nickel-catalyzed stereoretentive cross-coupling reactions through a proposed diazene intermediate and rapid in-cage radical capture. This strategy was used for C(sp3)–C(sp2) cross-coupling reactions (ref. 17, Nature, 2025, 85) and was recently extended to the C(sp3)–C(sp3) variant in a preprint published on ChemRxiv (10.26434/chemrxiv.10001512/v1).

Weix is pursuing an alternative approach that focuses on the use of carboxylic acids as starting materials and a mechanistically distinct two-electron oxidative addition mechanism in order to achieve stereoretention. In 2024, they reported that nickel catalysts can undergo oxidative addition into 2-pyridyl esters and decarbonylation to form an alkyl nickel species, which can then be captured by primary alkyl halides (Science, 2024, 1331). In that prior work, they demonstrated through deuterium labeling that the oxidative addition and decarbonylation is likely stereoretentive. However, they were unable to achieve the stereoretentive cross-coupling due to competing beta-hydride elimination.

In the present work, they overcome this problem by identifying an alternative bidentate ligand system that achieves high-yielding alkyl-alkyl coupling with nearly perfect enantiospecificity. The reaction converts abundant chiral amino acid starting materials into useful cross-coupled products, and they have several nice demonstrations of the synthetic utility in accessing both natural products and new chiral building blocks. I can see immediate interest in using this reaction for library synthesis in the pharmaceutical industry. Mechanistically, this paper also identifies an interesting mechanism by which CO is sequestered through a rapid coupling with alkyl radicals. This side process allows them to overcome a potential challenge associated with CO buildup in the reaction vessel and the formation of LNi(CO)x species. Notably, the authors were also able to isolate the key nickel-alkyl species in order to observe its racemization and verify its stoichiometric reactivity toward the desired coupling. On the basis of both the synthetic utility of this reaction and the new mechanistic insights, I think this is a notable advance over their prior work and can recommend publication in Nature. I have only a few minor suggestions for revisions described below:

1) In the characterization of complex 8, the authors employed TMSCl to exchange the X-type ligand for crystallization. It is unclear whether this modification influences the rate of racemization and, consequently, the enantiospecificity or efficiency of the subsequent C–C coupling. It would therefore be informative for the authors to perform the same set of stoichiometric reactions in the absence of TMSCl (without isolation of the Ni alkyl complex) and evaluate the enantiospecificity of the coupling leading to 9.

2) In the manuscript text, it is not made clear how long it takes for complex 8 to be generated and how long it is sitting in solution before the stoichiometric reaction with 2 and Mn are carried out. It would be valuable for the authors to provide these details and perhaps to also examine different aging times of 8 in order to track the decrease in enantiospecificity as it is allowed to racemize in solution.

3) This is a somewhat minor point, however, I found the description of the X-ray data in the manuscript text to be a bit cumbersome. I think most of the details can be moved to the supporting information. In my mind, the key point is that the authors obtained complex 8 as a racemate, which then led them to examine the racemization process. Details regarding the crystal polymorphs and even the structural information are somewhat unnecessary to the main points of the paper.

4) The examination of substrate scope for both cyclic and acyclic amino acids is very thorough. However, unless I missed it, the authors do not comment on other classes of chiral carboxylic acids that lack an alpha-amino group. I do not view the absence of these substrates as detracting from the overall publishability of the work. That said, it would be interesting to understand how the method performs with alpha-oxygenated chiral carboxylic acids. More broadly, there are several other commercially available or readily synthesized alpha-stereogenic carboxylic acids that could be readily evaluated and help define the generality and limitations of the reaction.

5) The authors propose that the racemization process may be occurring through a reversible beta-hydride elimination mechanism. This proposal seems plausible. However, I wonder if there are experiments that could be used to probe this question in more detail. For example, is it possible to incorporate a deuterium label that would allow the beta-hydride elimination to be detected? Alternatively, is there a radical clock substrate that can be designed to probe for a potential reversible nickel-carbon homolysis to form a carbon-centered radical?

Version 1:

Reviewer comments:

Referee #1

(Remarks to the Author)
Wu, Weix, and coworkers present a revised manuscript which includes major additional experimental work to address the raised concerns. The added α-hydroxy acid-derived substrates alongside initial results on different alkyl radical precursors significantly broaden the method's applicability. Furthermore, detailed mechanistic experiments were added to investigate decomposition and racemization pathways, which are very informative.

Overall, I am satisfied by the efforts undertaken to answer my technical concerns, and I think the manuscript has significantly benefitted from the additional experiments. However, I would like to reiterate my main concern regarding the conceptual novelty: The concept of stereoretentive decarbonylative functionalization of 2-pyridyl esters was demonstrated as part of a previous publication by the same author (ref. 26), including an unoptimized version of the exact reaction disclosed in the present work (SI of ref. 26). The lack of ground-breaking conceptual novelty, which is an absolute requirement for publication in Nature, therefore still disqualifies this work from publication in Nature.

Nevertheless, having developed this concept into a synthetically useful method is a valuable achievement, and the additional mechanistic insights are interesting. Consequently, I think this work would be suitable for publication in a Nature family journal like Nature Chemistry or Nature Catalysis.

Referee #2

(Remarks to the Author)
In my initial review of this work, I thought that the work was sufficiently innovative and broadly impactful to warrant publication in Nature. I recommended minor revisions be made to examine some of the mechanistic proposals in more detail and to expand the scope of carboxylic acids, if possible. The authors have thoroughly addressed both of these points in their revisions. The additional mechanistic experiments are quite illuminating, and the demonstration of alpha-oxygenated carboxylic acids enhances the synthetic utility of the reaction. I have no further recommendations and can recommend acceptance of this current manuscript as is.

Response to Reviews

Our responses to the reviewer comments and questions are detailed below. We have substantially changed and improved the manuscript as well as added a number of new experimental results.

The **reviewer comments are in bold-faced black** and our responses are in blue text.

Referee #1

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The authors present a well-executed optimization campaign and interesting mechanistic insights regarding the oxidative addition step as well as the slow stereoablation process of the oxidative addition complex. The substrate scope of activated esters includes proline-derived structures and a series of acyclic natural amino acid-derived structures. Due to the broad range of suitable amino acids, this method is useful to access chiral amines via net-decarboxylative alkylation. Other substrates than amino acid-derived activated esters, however, are not shown. Primary and secondary alkyl iodides are compatible coupling partners, and the overall functional group tolerance is good. The method was applied to the synthesis of several synthetic intermediates of known bioactive compounds, highlighting its synthetic utility.

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We thank the reviewer for detailed reading of the manuscript and our related work. However, we respectfully disagree with the conclusion that our work lacks conceptual novelty. The key concept here, one which we think could have broad implications in cross-coupling, is the realization of decarbonylative, stereospecific coupling. While we demonstrate the feasibility with α-amino acids and α-hydroxy acids with alkyl iodides, there appears to be no fundamental barrier to extending this concept to all chiral carboxylic acids and every kind of coupling partner in the future. It is true that our previous study set the stage for this current study, but this is the first to realize the concept in any kind of general fashion. In some ways this idea has been obvious for decades (Whitesides showed (de)carbonylation, a 1,1-migration, was

stereospecific in *J. Am. Chem. Soc.* **1969,** *91*, 4313 and Rovis showed stereospecific decarbonylation with nickel in *J. Am. Chem. Soc.* **2003**, *125*, 10498). That it has taken until now to realize it, in our view, makes it all the more exciting!

At a more granular level, this paper uses a different catalyst (bidentate vs tridentate, a crucial change that was not anticipated by our previous work), a different approach to the removal of CO (parallel carbonylative coupling, a new way to avoid CO poisoning), and operates at a lower temperature (70 °C down to rt, important due to lower stability of alkylnickel intermediates). All of these were essential to realizing useful yields and e.s.

In response to this criticism and other questions, we have added significant studies on the major decomposition pathways for the alkylnickel intermediates and show why the rate of radical generation is crucial to not only e.s., but also yield. In addition, we have broadened the scope to include α-hydroxy acids, demonstrating that this approach should eventually be generalizable.

Regardless of this work's publication status, I recommend addressing the following concerns that could improve the quality of this manuscript:

We thank the reviewer for insightful suggestions and critiques. These questions have led to new experiments that significantly extend the scope of stereoretentive decarbonylative cross-coupling, and shed light on the effect of β-H elimination on racemization. Our detailed responses appear below.

1. The supporting information is lacking a section about failed substrates.

We agree that this would be useful information. A section entitled "Examples of unsuccessful substrates" was added to the content in Supplementary Information, details are shown in the following figure (Fig. R1).

Among alkyl iodides tested, the alkyl iodides bearing a free alcohol resulted in no product formation due to transesterification to 2-pyridyl esters. *Tert*-Butyl iodide and Bicyclo[1.1.1]pentyl iodide are not suitable for decarbonylative cross-coupling under these conditions. Ethyl 2,2-difluoro-2-iodoacetate was also tested, however, only trace amount of cross-coupling product was detected, both substrates decomposed in the reaction.

Among 2-pyridyl esters tested, a 2-pyrrolidone carboxylic acid ester was not tolerated. A α-tertiary

acid (α-methyl proline) was found to be challenging because of slow oxidative addition and/or decarbonylation. A 2-pyridyl ester bearing an N-Boc indoline moiety provided low yield of cross-coupling product. β-hydride elimination was observed as the major side reaction (and we used this in our studies on decomposition pathways). A 2-pyridyl ester derived from Naproxen also resulted in a low yield of cross-coupling product due to fast β-hydride elimination and/or slow decarbonylation, giving the corresponding ketone and alkene compounds as the major side products.

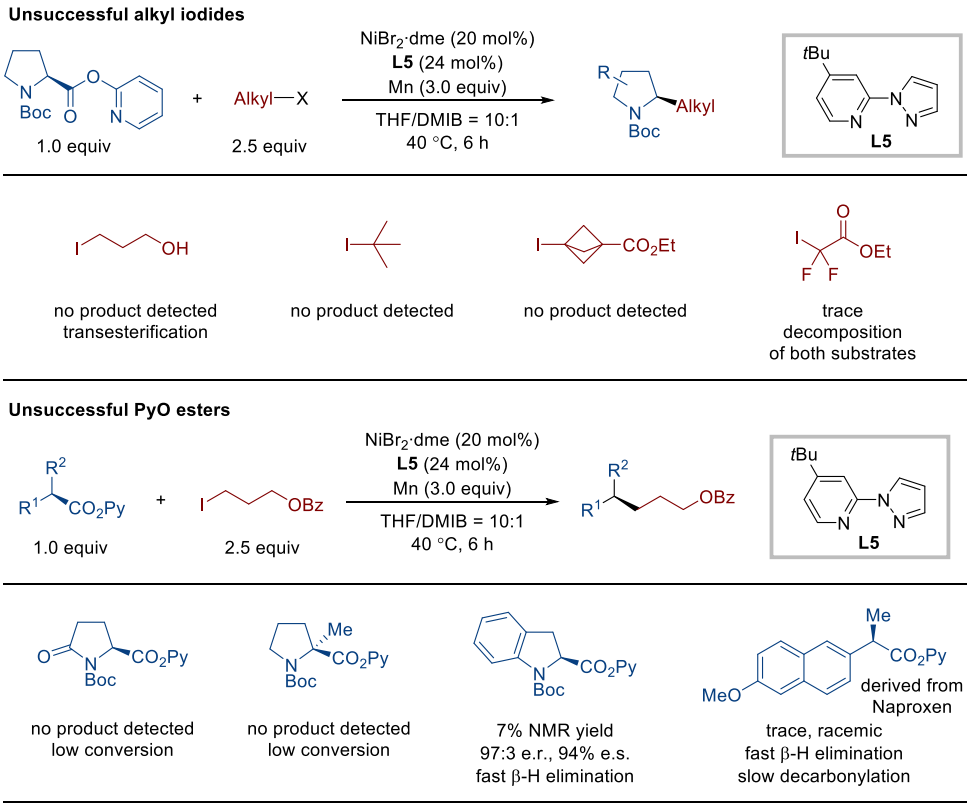


Fig. R1. Summary of unsuccessful substrates. This data appears in revised Table S12-S13.

2. Do substrates other than amino acid derivatives work? In the original method (ref. 26), activated esters derived from other acids were suitable substrates as well. However, when it comes to stereoretentive functionalizations (in the present work and in ref. 26), amino acid-derived structures are used exclusively. I assume that other substrates cannot be coupled stereoretentively. Why is that the case?

It is correct that these current conditions appear to require some kind of functional group, perhaps to stabilize the organonickel intermediate or assist in decarbonylation. A good example is the attempted coupling of Naproxen (see Fig. R1 above), where we observed cross-ketone product along with the alkene derived from decarbonylation and β-hydride elimination. We view this as encouraging for future studies and catalyst design – decarbonylation still occurs, we just don't have the right balance of stability

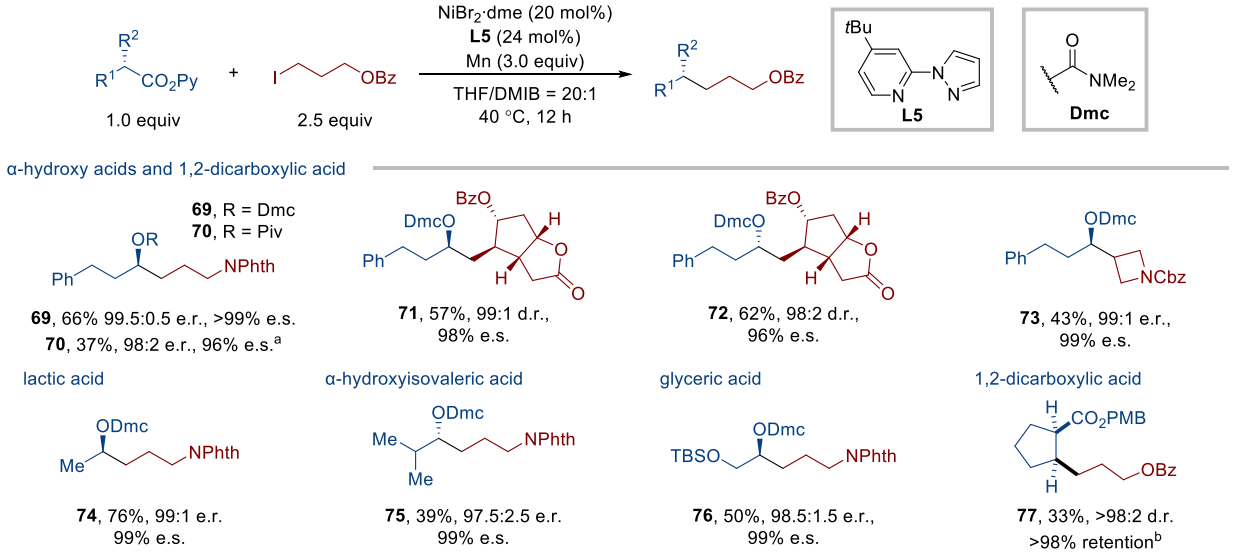
and reactivity with our current system. This certainly may require considerable advances, but it proves it is possible.

In response to this question, we examined other carboxylic acids with potentially-coordinating functional groups and found excellent results with α-hydroxy acids (another common component of the chiral pool) and mixed esters of a 1,2-dicarboxylic acid.

New paragraph highlighting these new substrates:

> Our conditions also work for the stereoretentive decarbonylative cross-coupling of α-hydroxy acid derivatives to afford protected chiral alcohols with uniformly high e.s. (**69**-**76**) (Fig. R2). While a variety of esters provided high e.s., Dmc (dimethylcarbamyl) provided both high e.s. and higher yield (see Table R2). Both 1° and 2° alkyl iodides are suitable for cross-coupling (**69**-**73**). This approach allows for easy synthesis of diastereomers with remote stereocenters (**71** and **72**). Coupling of esters derived from lactic acid (**74**), α-hydroxyisovaleric acid (**75**), and glyceric acid (**76**) all provided chiral alcohols in 99% e.s., despite the potential for β-H elimination. Additionally, we found a promising result with a *syn*-1,2- dicarboxylate substrate to give **77** in 33% yield with >98% stereoretention.

Overall, these additional examples highlight the generality of these conditions for different α-coordinating groups. These results have been added to the manuscript and Supplementary Information, details are shown in the following table.



Isolated yields are shown. Condition: 2-pyridyl ester (0.2 mmol), alkyl iodide (0.5 mmol), Mn (0.6 mmol) solvent (THF:DMIB = 20:1, 1 mL), 40 °C, 12 h. [a]THF (1 mL) as solvent, 24 h .[b]THF (1 mL) as solvent, 60 °C.

Fig. R2. Extended data on α-hydroxy acid and 1,2-dicarboxylic acid derivatives. This data appears in revised Figure 4.

3. Along these lines: What influence on the speed of racemization does the nitrogen protecting group have? I can imagine that coordination of the carbamate moiety to the nickel can keep the metal at the same face of the formed enamine in case β-hydride elimination takes place, thereby slowing down racemization. I would be interested in a systematic racemization rate study (as done for compound S28 – see SI chapter 3.4) for different protecting groups but also for different substrates that are not derived from amino acids.

This is a great question and led us to a better understanding of racemization and decomposition. The reviewer was correct: the nitrogen protecting group does have an effect. In the course of these additional studies, it became clear that our original deuteration experiments with D^+ were not the best approach because they did not probe the multiple steps of the racemization process and were disconnected from the reaction conditions (no radicals present). Indeed, our new studies allow us to categorize substrates into one of three categories based upon the relative rates of β-elimination, alkene exchange, and Ni-H re-insertion vs the rate of the radical capture step. Thereby shedding light on stereospecificity control in catalytic reactions, the key conceptual advance in this paper.

As noted above, the deuteration experiments with D^+ were very different than the catalytic cross-coupling reactions and suffered from challenges related to very slow protonation of acylnickel(II) species (that may be present), low stability of the alkylnickel intermediate towards other decomposition pathways, and the need for a second stereocenter (for reporting) (Fig. R3). While the data provided the same qualitative answer as our new studies, it was unclear if it was catalytically relevant. We elected to remove this data in favor of the new studies.

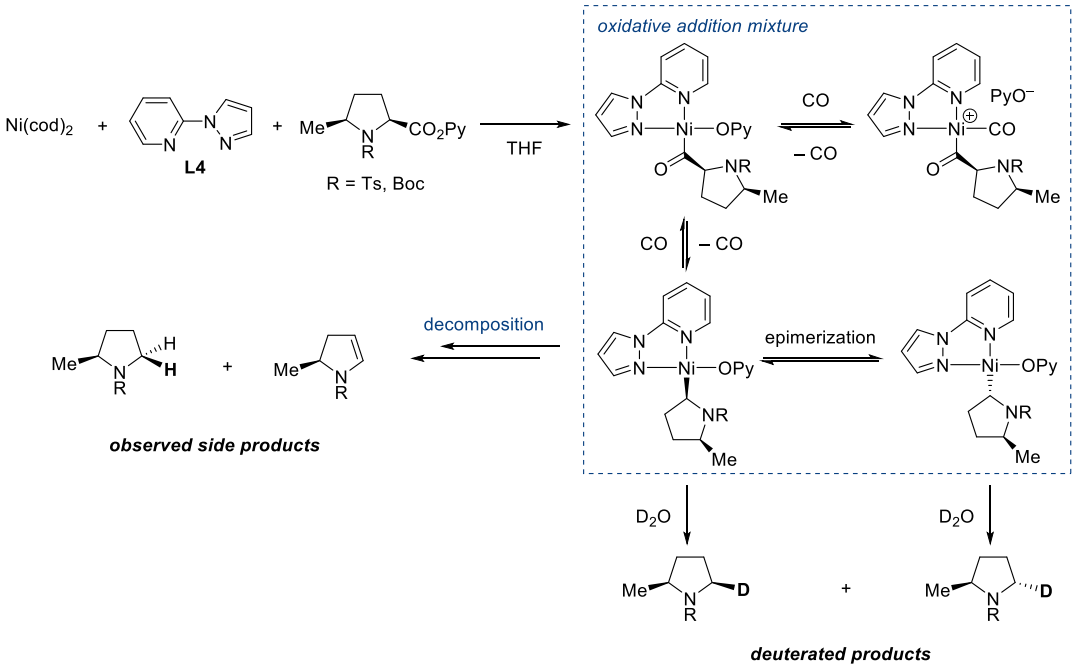


Fig. R3. Challenges with the original deuteration experiments. Slow protonation of acylnickel, low stability of alkylnickel species, and large mechanistic differences from the catlaytic reaction (electrophilic protonation vs radical capture) all led us to examine other approaches to understanding racemization.

As a different tactic, additional experiments were conducted to directly address how different protecting groups and substrates impact the racemization rate and yield in cross-coupling reactions. We conducted the stoichiometric cross-coupling of different types of 2-pyridyl esters with alkyl iodides (Table R1). The proline 2-pyridyl esters with Boc and Ts protecting groups (**1**, **7**), acyclic amino acid 2-pyridyl ester (**87**), and α-oxygenated acid 2-pyridyl ester (**91**) were selected as model substrates. In all cases, oxidative addition and radical capture process formed the cross-coupling products, meanwhile, alkenes were observed as one of the side products. This is consistent with the fact that our Ni-Alkyl intermediates could undergo β-hydride elimination.

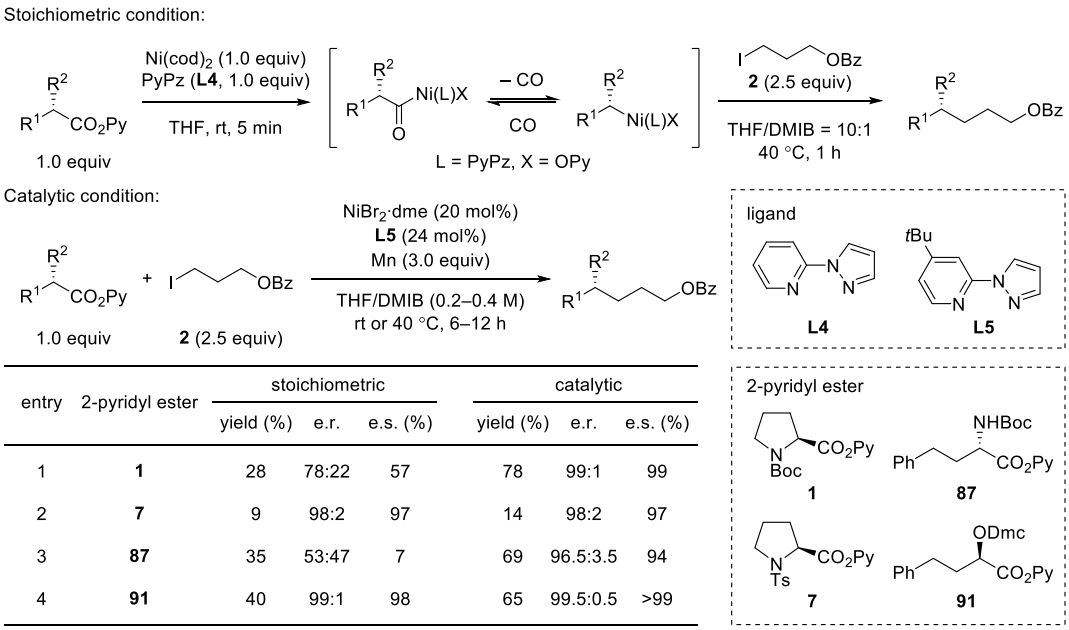
As suggested by the reviewer, coordination of the carbamate (N-Boc) to the nickel can keep the metal at the substrate (**1**), thereby slowing down the dissociation (k_D) and decomposition. However, re-insertion of Ni-H to alkene would result in the formation of the other enantiomer of Ni-Alkyl, thereby decreasing the e.s. (57%) of cross-coupling product (Table R1, entry 1).

In the reaction of Ts-Pro (**7**), the weaker coordination results in fast dissociation of alkene and decomposition of nickel species, the re-insertion of Ni-H to alkene is not favorable, thus resulting in low yield with high e.s. of cross-coupling product (9% yield, 97% e.s., Table R1, entry 2).

In the cross-coupling of acyclic amino acid 2-pyridyl ester (**87**), nearly full racemization of coupling product was observed in the stoichiometric reaction (Table R1, entry 3). This data is consistent with a scenario where alkene exchange and Ni-H re-insertion is faster than radical capture. Alternatively, it might be that the Boc-coordinated enacarbamate can isomerize to coordinate with Ni-H on the opposite face without release. Regardless, this results in lower enantiospecificity.

In contrast to amino acid derivatives, α-hydroxy acid 2-pyridyl esters show higher enantioselectivity along with better yield under stoichiometric conditions (Table R1, entry 4). This could be attributed to slower hydride elimination and/or Ni-H re-insertion.

Table. R1. Comparison experiments of stoichiometric and catalytic cross-coupling This data appears in revised Extended Data Fig. 2 and Table. S10.



entry	2-pyridyl ester	stoichiometric			catalytic		
		yield (%)	e.r.	e.s. (%)	yield (%)	e.r.	e.s. (%)
1	**1**	28	78:22	57	78	99:1	99
2	**7**	9	98:2	97	14	98:2	97
3	**87**	35	53:47	7	69	96.5:3.5	94
4	**91**	40	99:1	98	65	99.5:0.5	>99

Additional experimental data was observed in the cross-coupling reaction of the 2-pyridyl ester bearing N-Boc indoline moiety. Despite rapid β-hydride elimination, the cross-coupling product was formed in 7% yield with 95% enantiospecificity. This data is consistent with fast β-hydride elimination and slow Ni-H re-insertion and results in low yield but high enantiospecificity in catalytic reactions.

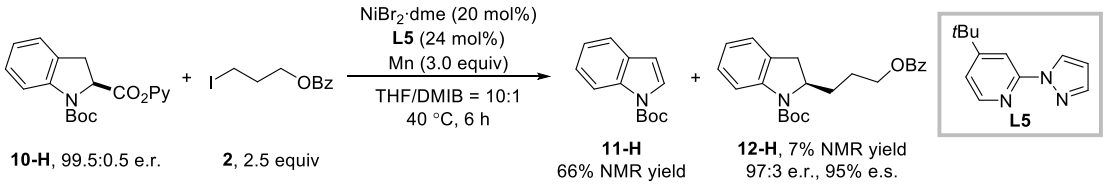


Fig. R4. Decarbonylative cross-coupling of N-Boc indoline 2-pyridyl ester. This data appears in revised Extended Data Fig. 2 and supplementary information Chapter 3.8.2.

We also performed a series of competition experiments (Fig. R5) to shed light on the stereoablation and understand alkene exchange and Ni-H re-insertion for several different substrates. Our initial studies established that an unhindered vinylcarbamate (**92**) could intercept Ni-H species, albeit with varying efficiency depending upon the carboxylic acid ester (**87** vs **91**). We also showed that the enecarbamate of proline decarbonylation (**95**) is much slower to reinsert than **92**. Finally, we established that this appears to be a Ni-H process – without the pyridyl ester, the coupling products are not observed.

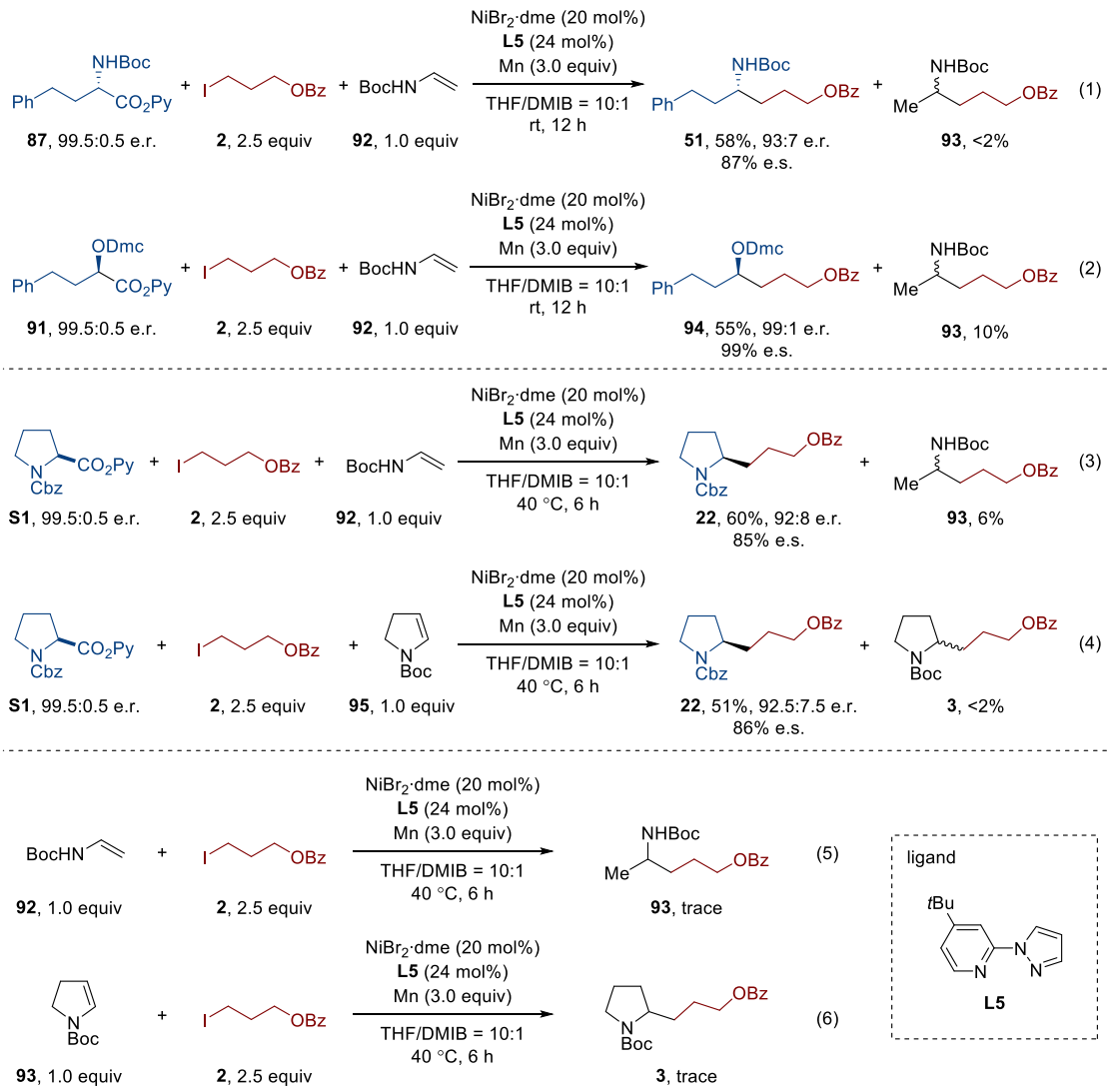
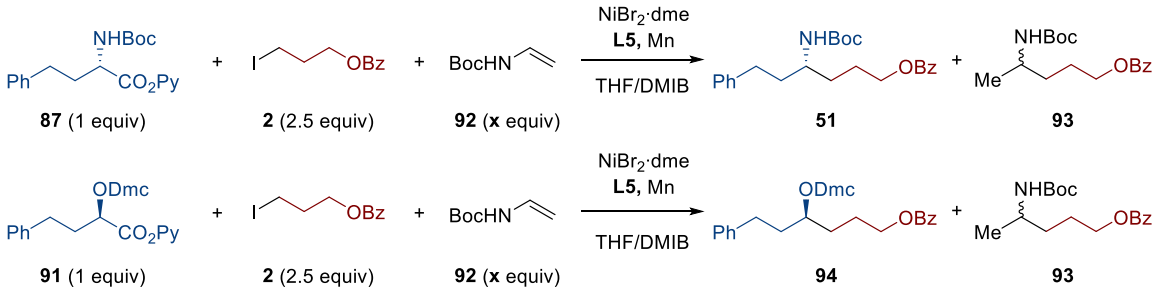


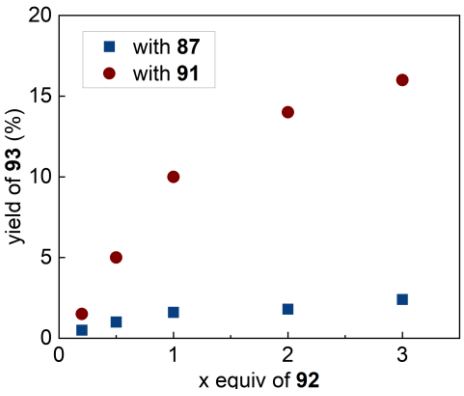
Fig. R5. Summary of competition and control experiments for Ni-H re-insertion. This data appears in Extended Data Fig. 2 and supplementary information Chapter 3.8.3.

Next, a series of competition experiments using different concentrations of *tert*-butyl vinylcarbamate **92** were conducted (Fig. R6). Corrected SFC yields with 1,3,5-TMB as internal standard are shown. Yield of the Ni-H re-insertion product **93** increased as the concentrations of enacarbamate increased, but this was more evident for the **91** than for **87**. These results indicate that β-hydride elimination is possible for both amino acid and α-hydroxy acid 2-pyridyl esters. But the β-hydride eliminated product of the former lead to slower dissociation and/or faster Ni-H re-insertion than the latter with alkenyl ether moieties.



entry	x	reaction with **87**				reaction with **91**			
		yield (%) of **93**	yield (%) of **51**	e.r.	e.s. (%)	yield (%) of **93**	yield (%) of **94**	e.r.	e.s. (%)
1	0.2	0.5	57	93.5:6.5	88	1.5	56	99.5:0.5	99
2	0.5	1	58	93:7	87	5	53	99.5:0.5	99
3	1	1.6	58	93:7	87	10	55	99.5:0.5	99
4	2	1.8	56	93:7	87	14	54	99.5:0.5	99
5	3	2.4	54	92.5:7.5	86	16	52	99.5:0.5	99

Condition: 2-pyridyl ester (0.2 mmol, 1.0 equiv), alkyl iodide (2.5 equiv) $NiBr_2$·dme (20 mol%), **L5** (24 mol%), Mn (3.0 equiv), THF/DMIB (10:1, 0.2 M), rt, 12 h. SFC yield using 1,3,5-trimethoxybenzene as internal standard are shown.



Proposed mechanism:

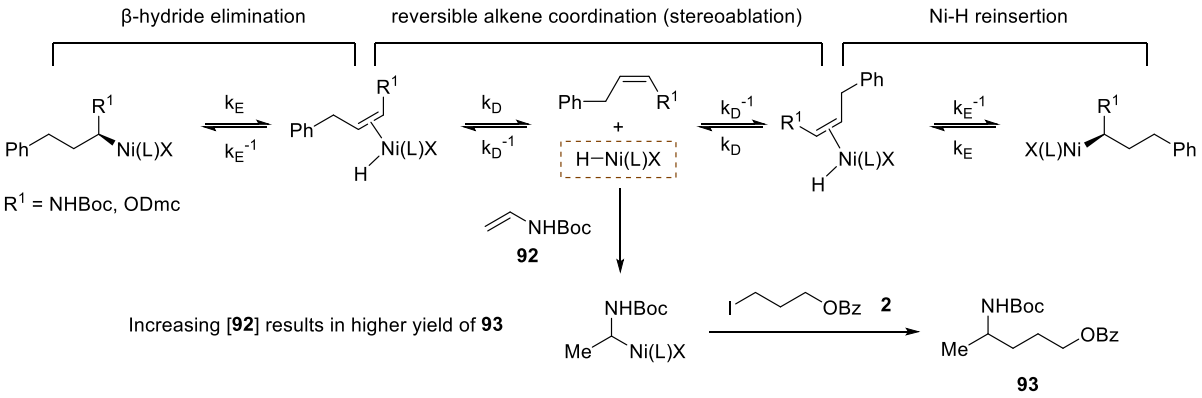
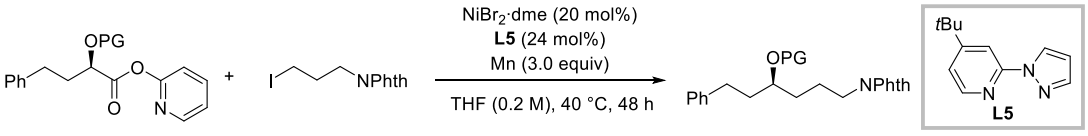


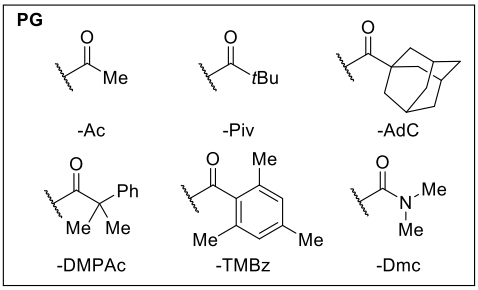
Fig. R6. Competition experiment of Ni-H re-insertion with different concentrations of enacarbamate. This data appears in Extended Data Fig. 2 and Fig. S19.

A series of α-oxygenated acid 2-pyridyl esters bearing different protecting groups were further examined (Table R2), and they all produced decarbonylative cross-coupling products with high enantiospecificity. Carbamyl group was the optimal protecting group that gave higher yield with high e.s. (Table R2, entry 6).

Table. R2. Protecting group effect of α-oxygenated acid derivatives. This data appears in revised Extended Data Fig. 2 and Table. S11.



entry	PG	yield (%)	e.r.
1	Ac	33	99:1
2	Piv	35	98:2
3	AdC	42	99.5:0.5
4	DMPAc	35	>99.5:0.5
5	TMBz	30	99:1
6	Dmc	58	>99.5:0.5



This data is consistent with a racemization process that involves β-hydride elimination, alkene exchange, and Ni-H re-insertion (Fig. R7). The ease of alkene exchange and Ni-H re-insertion influences the yield and stereospecificity, with the structure and protecting group both influencing the relative rates. For substrates with fast re-incorporation, such as acyclic N-Boc amino acids, slower radical capture results in lower e.s. For substrates with slow re-incorporation, such as α-hydroxy acids, slow re-incorporation means e.s. is maintained at the expense of yield (due to loss/decomposition of alkene). This data explains why, under catalytic conditions, matching the rate of radical generation is key to obtaining both high yields and high e.s.

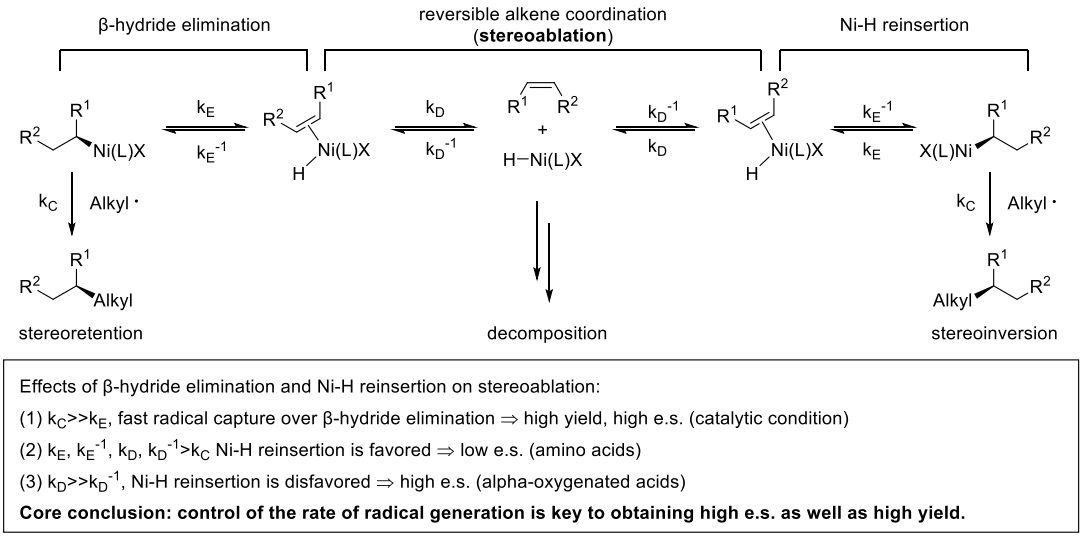
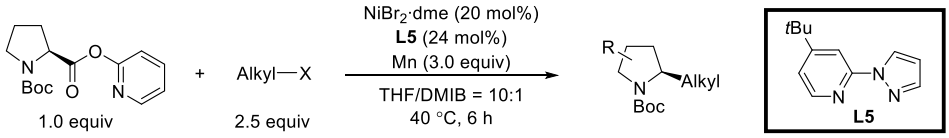
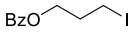
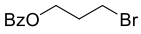
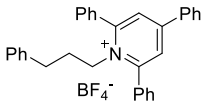
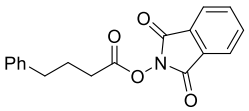


Fig. R7. proposed mechanism of stereoablation. This data appears in revised Extended Data Fig. 2 and Fig. S16.

4. How about other alkyl radical precursors instead of alkyl iodides, such as alkyl bromides, Katritzky salts or NHPI esters?

We tested out the other radical precursors as the reviewer suggested (Fig. R8). All these radical precursors can react with 2-pyridyl esters to form decarbonylated products with promising e.s. Reaction with an alkyl bromide gave low yield but high enantiospecificity under our standard conditions. In-situ generation of the alkyl iodide by using NaI as additive boosted the yield at the expense of enantiospecificity. Reactions of a 2-pyridyl ester with a Katritzky salt provided the decarbonylative product in 23-39% yield with 90-97% e.s. Finally, the NHP ester is more challenging and resulted in a 15% yield and 51% e.s. when DMIB was used as solvent to accelerate radical generation. Overall, the alkyl iodide is the best radical precursor under these conditions. We plan to explore these reactions further and will report our results in due course.



radical precursor				
standard condition	78%, 99:1 e.r. 99% e.s.	12%, 96:4 e.r. 93% e.s.	39%, 94.5:5.5 e.r. 90% e.s.	trace
optimized condition (deviation from above)	as above	58%, 92:8 e.r. 85% e.s. (with 1.0 equiv of NaI)	23%, 98:2 e.r.[a] 97% e.s. (with DMIB as solvent)	15%, 75:25 e.r.[a] 51% e.s. (with DMIB as solvent)

[a]NMR yield using TMB as internal standard

Fig. R8. Comparison of different radical precursors. This data appears in revised Table. S9.

Referee #2

In this manuscript, Wu, Weix, and co-workers report a stereoretentive C(sp3)–C(sp3) cross-electrophile coupling reaction through the decarbonylation of 2-pyridyl esters. Recently, there has been high interest in developing effective C(sp3)–C(sp3) cross-coupling reactions, particularly those that can use native functional groups commonly found in organic molecules. While there has been significant progress in this area using various catalytic systems, achieving stereoselectivity remains a challenge. One approach that has seen significant success is using a chiral catalyst in a stereoablative enantioselective coupling. An alternative approach that has seen less progress is developing stereospecific reactions that use chiral, enantioenriched starting materials.

In one approach, Baran demonstrated that chiral alcohols can be converted into sulfonyl hydrazines that undergo nickel-catalyzed stereoretentive cross-coupling reactions through a proposed diazene intermediate and rapid in-cage radical capture. This strategy was used for C(sp3)–C(sp2) cross-coupling reactions (ref. 17, Nature, 2025, 85) and was recently extended to the C(sp3)–C(sp3) variant in a preprint published on ChemRxiv (10.26434/chemrxiv.10001512/v1).

Weix is pursuing an alternative approach that focuses on the use of carboxylic acids as starting materials and a mechanistically distinct two-electron oxidative addition mechanism in order to achieve stereoretention. In 2024, they reported that nickel catalysts can undergo oxidative addition into 2-pyridyl esters and decarbonylation to form an alkyl nickel species, which can then be captured by primary alkyl halides (Science, 2024, 1331). In that prior work, they demonstrated through deuterium labeling that the oxidative addition and decarbonylation is likely stereoretentive. However, they were unable to achieve the stereoretentive cross-coupling due to competing beta-hydride elimination.

In the present work, they overcome this problem by identifying an alternative bidentate ligand system that achieves high-yielding alkyl-alkyl coupling with nearly perfect enantiospecificity. The reaction converts abundant chiral amino acid starting materials into useful cross-coupled products, and they have several nice demonstrations of the synthetic utility in accessing both natural products and new chiral building blocks. I can see immediate interest in using this reaction for library synthesis in the pharmaceutical industry. Mechanistically, this paper also identifies an interesting mechanism by which CO is sequestered through a rapid coupling with alkyl radicals. This side process allows them to overcome a potential challenge associated with CO buildup in the reaction vessel and the formation of LNi(CO)x species. Notably, the authors were also able to isolate the key nickel-alkyl species in order to observe its racemization and verify its stoichiometric reactivity toward the desired coupling. On the basis of both the synthetic utility of this reaction and the new mechanistic insights, I think this is a notable advance over their prior work and can recommend publication in Nature. I have only a few minor suggestions for revisions described below:

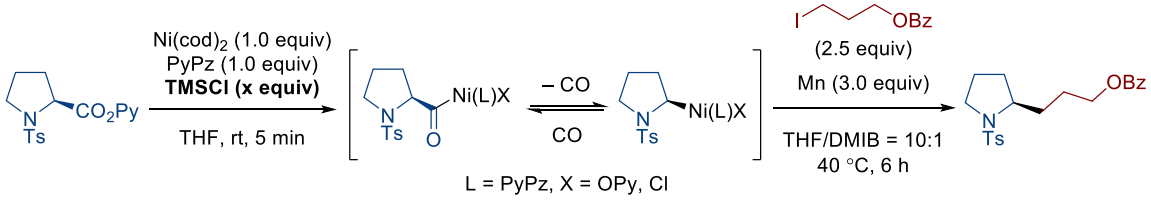
We thank the reviewer for their detailed reading of the manuscript as well as their suggestions and comments. The questions raised led us to gather more mechanistic data on anion effect and aging time

of Ni-Alkyl complex. We also gathered more data on the scope and successfully coupled α-hydroxy chiral carboxylic acid derivatives as the reviewer suggested. Finally, we gathered evidence that supports the proposed mechanism, in which the racemization process occurred through a reversible β-hydride elimination mechanism over homolysis. Our detailed responses appear below.

1) In the characterization of complex 8, the authors employed TMSCl to exchange the X-type ligand for crystallization. It is unclear whether this modification influences the rate of racemization and, consequently, the enantiospecificity or efficiency of the subsequent C–C coupling. It would therefore be informative for the authors to perform the same set of stoichiometric reactions in the absence of TMSCl (without isolation of the Ni alkyl complex) and evaluate the enantiospecificity of the coupling leading to 9.

We have collected additional data and observed an influence of the X-type ligand on the e.s. of stoichiometric reactions, as suspected by the Reviewer. In the stoichiometric reaction applying 1.0 equiv of TMSCl as additive, the decarbonylative cross-coupling product was observed in 60% e.s., indicating that Cl could influence the enantiospecificity of the subsequent C–C coupling.

Table. R3. X-type ligand effect of stoichiometric cross coupling of N-Ts proline 2-pyridyl ester. This data appears in revised supplementary information Chapter 3.3.3.



Entry	x equiv of TMSCl	yield (%)	e.r.	e.s.
1	0	13	97.5:2.5	96
2	1.0	10	79.5:20.5	60

2) In the manuscript text, it is not made clear how long it takes for complex 8 to be generated and how long it is sitting in solution before the stoichiometric reaction with 2 and Mn are carried out. It would be valuable for the authors to provide these details and perhaps to also examine different aging times of 8 in order to track the decrease in enantiospecificity as it is allowed to racemize in solution.

We agree that this detail is essential. We apologize that it was not clear in our first submission. The reaction time for synthesis of complex **8** is 5 min before precipitation by addition of pentane. Complex **8** was kept as solid before adding solvent in studies on its reactivity. These details have been added to the

main text and supplementary information. New sentences in the revised main text appear as below:

"…By mixing an equimolar amount of **6**, **L4** and **7** **in THF for 5 min**, the resulting alkylnickel(II) complex **8** could be isolated after an anion swap from pyridonate to chloride…"

"…**Complex 8 was kept as solid before adding solvent in studies on its reactivity**…"

Additionally, we spent some effort to examine the aging time of complex **8** as the reviewer suggested. However, these experiments revealed that complex **8** is relatively unstable in THF solution at rt. Full decomposition of **8** was observed after stirring in THF for 5 min at rt, alkene and alkane were characterized as the major decomposition products. In the stoichiometric reactions, the complex is added as a solid along with the other reagents, explaining why product could still be observed. The crystallization was performed in ether/pentane, where it appears to have better stability. The NMR data was obtained in benzene-d_6, where it is considerably more stable.

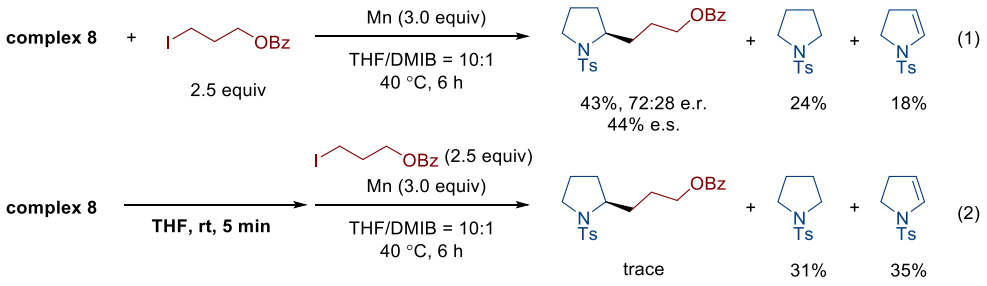


Fig. R9. Stoichiometric reaction and decomposition of complex 8 . This data appears in revised supplementary information Chapter 3.3.1 and 3.3.2.

3) This is a somewhat minor point, however, I found the description of the X-ray data in the manuscript text to be a bit cumbersome. I think most of the details can be moved to the supporting information. In my mind, the key point is that the authors obtained complex 8 as a racemate, which then led them to examine the racemization process. Details regarding the crystal polymorphs and even the structural information are somewhat unnecessary to the main points of the paper.

We have adjusted the description of the X-ray data, but elected to keep some of the overall description – the distortion from square planar is a parameter that Sevov and Kalyani found to be important in their stoichiometric studies (*Nature* **2024**, *634*, 585; *Dalton Trans.* **2007**, 955). New sentences in the revised manuscript appear below:

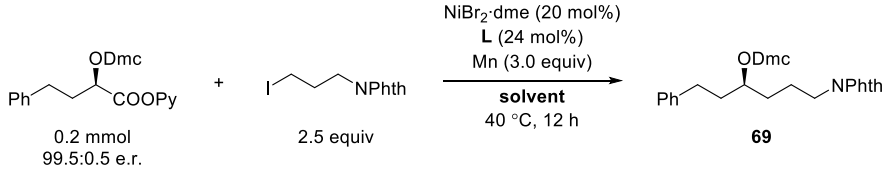
In both forms, the complex exhibits a distorted square planar geometry ($\tau4$ = 0.0784(8) / 0.0686(12)) and the metrics are comparable to those in related alkylnickel(II) complexes (see Supplementary Information for additional details).

4) The examination of substrate scope for both cyclic and acyclic amino acids is very thorough. However, unless I missed it, the authors do not comment on other classes of chiral carboxylic acids that lack an alpha-amino group. I do not view the absence of these substrates as detracting from the overall publishability of the work. That said, it would be interesting to understand how the method performs with alpha-oxygenated chiral carboxylic acids. More broadly, there are several other commercially available or readily synthesized alpha-stereogenic carboxylic acids that could be readily evaluated and help define the generality and limitations of the reaction.

We agree that this would add to the impact of the work; α-hydroxy chiral carboxylic acids are among the most abundant chiral carboxylic acids that are commercially available, and we're also interested in their reactivity.

We spent some effort optimizing the condition for α-oxygenated acid 2-pyridyl esters. By examining the influence of protecting group, ligand, and solvent (Table R2 and R4), resulting in a slight change of our standard conditions, we successfully coupled the dimethylcarbamyl protected α-hydroxy acid 2-pyridyl esters with alkyl iodides in 66% isolated yield with nearly perfect enantiospecificity (Table R4, entry 2).

Table. R4. Optimization of α-hydroxy acid derivatives. This data appears in revised Table S9.



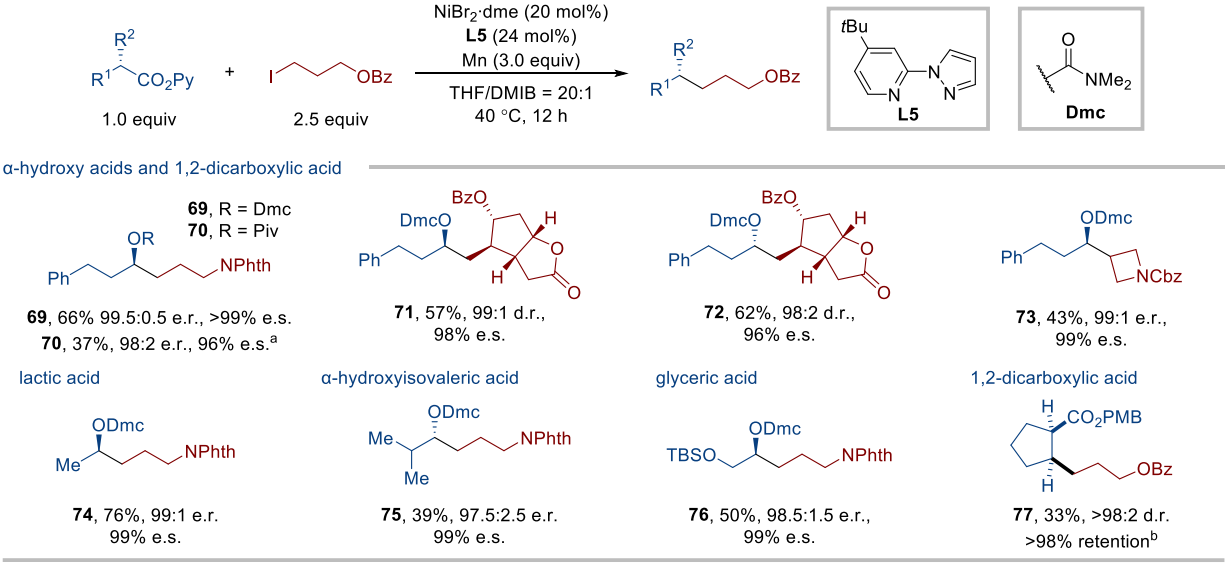
entry	L	solvent	isolated yield (%)	e.r.
1	**L4**	THF:DMIB (20:1)	65	99.5:0.5
2	**L5**	**THF:DMIB (20:1)**	**66**	**99.5:0.5**
3	**L7**	THF:DMIB (20:1)	58	99.5:0.5
4	**L8**	THF:DMIB (20:1)	63	99.5:0.5
5[a]	**L5**	THF	58	99.5:0.5
6	**L5**	THF:DMIB (10:1)	55	99.5:0.5

Dmc, dimethylcarbamyl. [a]Reaction time was 24 h.

Our conditions also work for the stereoretentive decarbonylative cross-coupling of α-hydroxy acid derivatives to afford protected chiral alcohols with uniformly high e.s. (**69**-**76**) (Fig. R10). While a variety of esters provided high e.s., Dmc (dimethylcarbamyl) provided both high e.s. and higher yield (see Table

R2). Both 1° and 2° alkyl iodides are suitable for cross-coupling (**69**-**73**). This approach allows for easy synthesis of diastereomers with remote stereocenters (**71** and **72**). Coupling of esters derived from lactic acid (**74**), α-hydroxyisovaleric acid (**75**), and glyceric acid (**76**) all provided chiral alcohols in 99% e.s., despite the potential for β-H elimination. Additionally, we found a promising result with a *syn*-1,2-dicarboxylate substrate to give **77** in 33% yield with >98% stereoretention.

These results have been added to the manuscript and Supplementary Information.



Isolated yields are shown. Condition: 2-pyridyl ester (0.2 mmol), alkyl iodide (0.5 mmol), Mn (0.6 mmol) solvent (THF:DMIB = 20:1, 1 mL), 40 °C, 12 h. [a]THF (1 mL) as solvent, 24 h .[b]THF (1 mL) as solvent, 60 °C.

Fig. R10. Extended data on α-hydroxy acids and 1,2-dicarboxylic acid derivatives. This data appears in revised Figure 4.

5) The authors propose that the racemization process may be occurring through a reversible beta-hydride elimination mechanism. This proposal seems plausible. However, I wonder if there are experiments that could be used to probe this question in more detail. For example, is it possible to incorporate a deuterium label that would allow the beta-hydride elimination to be detected? Alternatively, is there a radical clock substrate that can be designed to probe for a potential reversible nickel-carbon homolysis to form a carbon-centered radical?

This is a great question. This inspired us to further investigate our mechanism.

For the first question "…is it possible to incorporate a deuterium label that would allow the beta-hydride elimination to be detected?", we designed and synthesized deuterium labeled N-Boc indoline 2-pyridyl ester, where the deuterium atoms are *trans* to H and ester group (**10**). As β-hydride elimination is a *cis*-elimination, the alkene (indole) product would exhibit high deuterium incorporated at both the 2- and 3-positions. If this occurred by a radical process, a lower level of D-incorporation would be expected at the 3-postion. Our results are consistent with β-hydride elimination (≥95% D at both positions) (Fig. R11, eq 1). Moreover, in a catalytic reaction (Fig. R11, eq 2), the yield of cross-coupling product (**12**) was low due to fast β-hydride elimination, but the decarbonylated and beta-hydride eliminated product (**11**) deuterated N-Boc indole was formed in high yield with 95% and 96% deuterium incorporation on 2- and 3- position, respectively. This data strongly suggests that the nickel alkyl intermediates are prone to β-hydride elimination (Fig. R11).

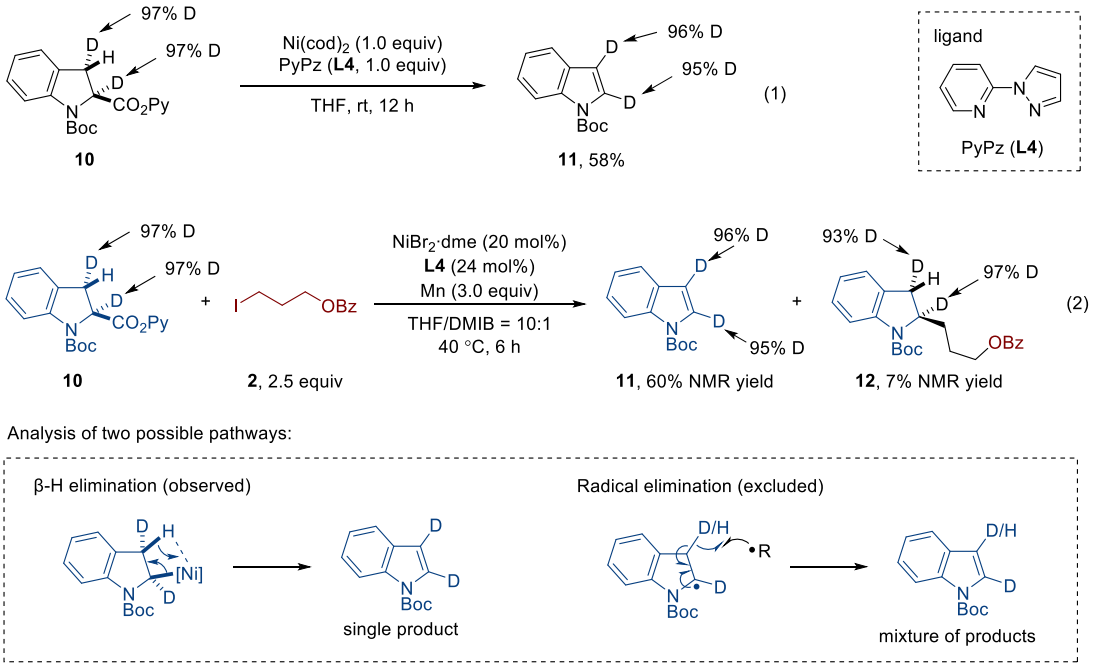


Fig. R11. Extended data on α-hydroxy acids and β-ester acid derivatives. This data appears in revised Figure 2c and supplementary information Chapter 3.4.

For the second question "…is there a radical clock substrate that can be designed to probe for a potential reversible nickel-carbon homolysis to form a carbon-centered radical?", we synthesized the 2-pyridyl ester (**13**) bearing a terminal alkene that is suitable for radical cyclization (Fig. R12). The catalytic reaction of this substrate with an alkyl iodide under decarbonylative conditions resulted in an 83% yield of the cross-coupling product with 78% e.s. (Fig. R12, eq 1); the ring-closing product was not detected. In contrast, the NHP ester analogue (**16**), which will react by a radical pathway, formed both unrearranged and rearranged products as racemates in 14% and 28% NMR yield (*cis*:*trans* = ~5:1), respectively (Fig.

R12, eq 2).

Furthermore, the stoichiometric reaction of the 2-pyridyl ester (**13**) with (**L4**)Ni(cod)$_2$ formed the corresponding Ni-Alkyl species, which could further undergo direct protonation/deuteration or migratory insertion to the terminal alkene to form the ring-closing product. Notably, only *trans*- cyclization product (***trans*-S35**) was detected, which is consistent with the stereochemical principles of the migratory insertion mechanism (Fig. R12, eq 3). In comparison, the reaction of the radical precursor NHP ester (**16**) under the same condition formed the radical cyclization-dimerization products in 10% isolated yield with *cis*-1,2-disubstituted cyclopentyl dimers (**S36**) as the major isomers (*cis*:*trans* = ~5:1) (Fig. R12, eq 4).

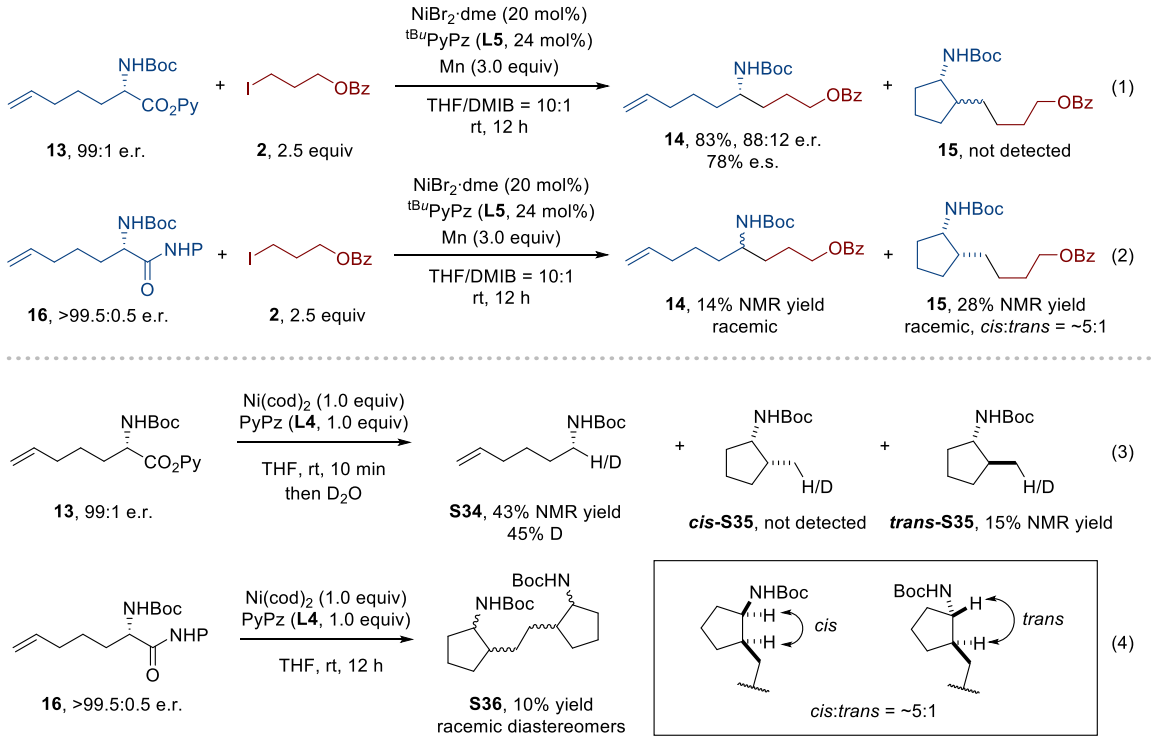


Fig. R12. Radical clock experiments. This data appears in revised Figure 2d and supplementary information Chapter 3.5.

Overall, under both stoichiometric and catalytic conditions, reactions with the NHP ester formed the *cis*-cyclopentane products as the major diastereomer. This is consistent with the literature on other reactions of 1-substituted hex-5-enyl radicals (*J. Am. Chem. Soc.* **1989**, *111*, 1759; *J. Am. Chem. Soc.* **2005**, *127*, 5518). In contrast, the reactions with 2-pyridyl esters resulted in no *cis*-cyclization product. Instead, the cyclization under the stoichiometric condition formed the *trans*-diastereomer selectively. This data supports a classic organometallic migratory insertion mechanism: the oxidative addition and decarbonylation sequence forms the key nickel alkyl species, which could coordinate with the terminal alkene, the subsequent insertion of Ni-C to alkene affords the *trans*-disubstituted product

stereoselectively (*Chem* **2017**, *3*, 268; *J. Am. Chem. Soc.* **2001**, *123*, 11133; *J. Am. Chem. Soc.* **2004**, *126*, 6332). These results are inconsistent with reversible nickel-carbon homolysis to form a carbon-centered radical.

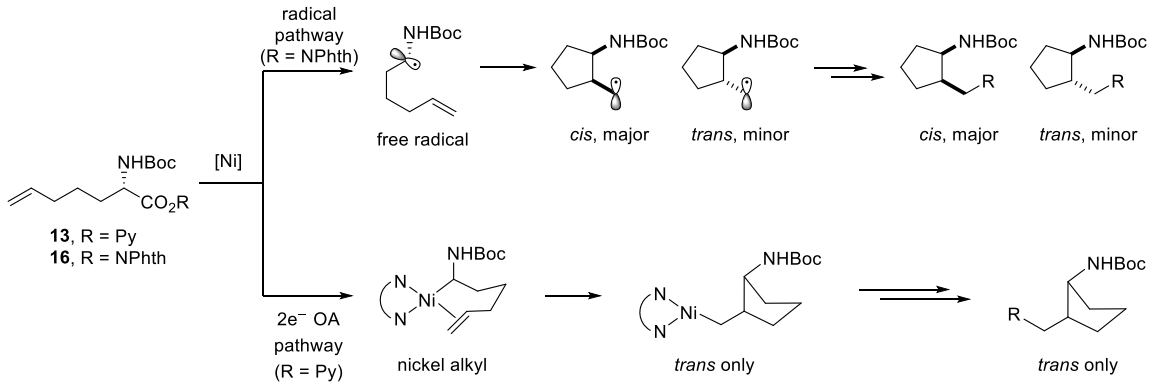


Fig. R13. Proposed mechanism in radical clock experiments. Counting anions and oxidation states are omitted for clarity. This data appears in revised Figure 2d and supplementary information Chapter 3.5.

Overall, these experiments support the proposed mechanism of reversible beta-hydride elimination and exclude the possibility of a potential reversible nickel-carbon homolysis. These results have been added to the manuscript (Fig. 2) and supplementary information (Charpter 3.5).