nature portfolio

Peer Review File

Palladium-Catalyzed Remote Internal C(sp3)-H Bond Chlorination of Alkenes

Corresponding Author: Professor Xiao-Hui Yang

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

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
Yang and co-workers detail a remote hydrochlorination of alkenes enabled by a C-Cl reductive elimination from a high oxidation-state PdIV-alkyl/benzyl intermediate. This reaction exhibits the opposite regioselectivity to the system reported by Gosheng Liu [Li, X.; Jin, J.; Chen, P. & Liu, G. Catalytic remote hydrohalogenation of internal alkenes. Nat. Chem. 14, 425–432 (2022)]. This type of termination event is highly intriguing in the context of chain walking, particularly given the potential to use a remote trisubstituted position as a termination site. This represents an exceptional synthetic achievement.
The strategy to achieve thermodynamic regioselectivity is ingenious, specifically utilizing the lower activity of copper dichloride to facilitate halogenation not only at the benzylic position [precedented reactivity] but also at non-benzylic tertiary positions. The yields obtained from the remote chlorination range from moderate to good, demonstrating that direct hydrochlorination of olefins is a feasible access route with satisfactory yields. The range of electronic profiles and functional group diversity on the aromatic ring present at the benzylic termination site is significantly varied, and the types of scaffolds attached as examples support the claim of a practical technique in the context of drug discovery late-stage functionalization workflows. The study concludes with well-designed experiments probing the reaction mechanism, and the conclusions drawn from their results are sound.

Major comments:
- P. 2, bottom paragraph: The authors claim that “Bisphosphine ligands are critical for the reaction.”, but the reaction is low-yielding with other bisphosphine ligands and no conditions are reported w/o bisphosphine ligands. It would be appreciated if the authors could elaborate on the reaction outcome with non-bisphosphine ligands in the SI. Generally, a subsection on observations during reaction optimization would be useful in the SI.
- P. 2, bottom paragraph / Table 1 entry1 2: The authors claim that no chlorination is observed with Pd(CH3CN)2Cl2 instead of Pd(PhCN)2Cl2. It is intriguing that such a subtle change in the nature of the Pd-source completely shuts down the reaction. Can the presence of 10 mol% acetonitrile steers the reaction pathway from remote hydrochlorination to hydrogenation? (“Other palladium catalysts like Pd(CH3CN)2Cl2, PdBr2 or Pd(TFA)2 were less efficient, primarily resulting in alkene hydrogenation (entries 2–4).”) Please comment on the tolerance of the reaction to non-chlorinated solvents (especially acetonitrile in sub-stoichiometric amounts) or provide a rationale for the difference in reactivity for the two bis(nitrile)palladium dichloride precatalysts.
- P. 3, top paragraph / Table 1 entry 12: Is it a solvent or a temperature effect that DCE at 60 °C outperforms DCM? The setup detailed in the SI would not be suitable to run the reaction at 60 °C in DCM, so the authors should specify if the reaction in DCM was run at a different temperature.
- P. 3, bottom paragraph: The reaction is labelled as insensitive to the alkyl chain length, yet the presented scope explores a very limited range of distances. A more granular scope would better support the claim. For example, the state of the art is presented by Mazet with [J. Am. Chem. Soc. 2016, 138, 10344–10350] where 10 positions are reliably isomerized using palladium. A series of examples with 4, 6, 8, and 10 carbon atoms in the aliphatic chain would be of interest, especially if it illustrates the range insensitivity, or allows for a more precise appreciation of where the synthetic limit lies.
- Pp. 3&4, Scope: Yields of 40-60% should be labelled as moderate, 60-80% as good, and above 80% as very good/excellent.
- P. 4, Table 2: Regarding scope/limitations of the benzylic chlorination: 1) Can heterocycles (other than amide-protected indole 2v) such as furane, thiophene, pyridine, non-/alkyl-protected indole, morpholine, (alkyl-)piperazine be tolerated in the reaction? 2) If yes, can heteroaromatics serve as termination site for the benzylic chlorination?
- P. 4, Table 2: Regarding scope/limitations of the tertiary chlorination: In the context of remote functionalization, the use of a

trisubstituted position as a reliable termination site is of extremely high interest. However, it is disappointing to see the methyl substituent as a constant throughout the scope of such examples. Is it possible for this termination to occur with a different termination motif? If this was not further investigated, a series evaluating the maximum steric bulk tolerated as well as polarization effects would be highly interesting. I suggest attempting the transformation of a variety of substrates similar to example 1o:
1) Methyl replaced by ethyl, isopropyl, cyclohexyl, and tertiary butyl, pushing steric effects to the limit with good granularity.
2) Methyl replaced by aryls with various substituents (para CF3, ester, alkyl, trialkyl silyl, and methoxy), examining the influence of electronics at a tertiary substituted benzylic position.
3) Methyl could be replaced by fluorine to investigate if a F-substituent in the aliphatic chain can be bypassed to yield the benzylic chlorination product, or if the chain-walk stops at the secondary fluoride. If the Pd does not pass the F-substitution, does chlorination occur to give a CR2FCl-group, or does the electron-withdrawing nature of the F-substituent impede selective oxidation of the alkyl-PdII species in this position?
P. 5, Table 3: all styrenes in the scope are electron-poor or electron-neutral. Are electron-rich styrenes competent substrates for the direct hydrochlorination, or is oligomerization observed in these cases?
- P. 5, bottom: During the mechanism investigation, deuteration was observed to be homogeneous along the chain. The authors suggest that this is an indication of the poor regioselectivity of the Pd-H migratory insertion. How can this hypothesis be preferred over a very high propensity for dissociation at each step taken?
- P. 6, Figure 2b: During the mechanistic investigation, it is curious to see that the styrenyl product is not major in Figure 2b. Is this due to the absence of a water additive and a lack of activation of the silane? Is another hypothesis favored?
- P. 6, Figure 2d: The authors claim to observe complete erosion of ee, but do not report by which method this was determined. Neither the manuscript nor the SI report on any determination of the ee (optical rotation, chiral HPLC etc.). The authors need to add the original data for ee determination of product 2s from (S)-1s to the SI.
- The evidence and experiments supporting the dissociative mechanism are sufficient, but perhaps citing Kochi's review on the matter would be advisable [T. Kochi et al. Tetrahedron Letters 60 (2019) 150938].
- P. 7: Subsection "Discussion" would better be described as "Conclusions"
- Abstract and Conclusions/Discussion: The claim for late-stage modification in a pharmaceutical context is difficult to accept for anything but screening, as metal-catalyzed transformations are typically avoided in late-stage synthesis of drugs.
- P. 7, Conclusions/Discussion: The work would be much more impactful if other electrophiles than only CuCl2 could be employed in the remote internal-selective functionalisation of tertiary C-H bonds. The authors claim to be working on this at the moment. A proof of concept for at least one (unoptimised) transformation other than hydrochlorination would proof a more general applicability of the concept presented herein, as should be demonstrated for publication in a non-chemistry specific journal.
- Supporting Information:
o NMR spectra should also be provided for unpublished starting materials (1p-s, 1v-y)
o Mass spectroscopic data are missing for the following new compounds: 2c, 2q, 2p, 4k
o 13C NMR data of compound 8 are missing

Minor comments:
- General: As BINAP is a chiral ligand, it would be appropriate to specify if racemic BINAP was used, and if not the effect of the enantiomer should be investigated. The enantiomer/racemic mixture used can be specified in the General Information part of the Supporting Information.
- P. 2, Fig. 1a: "clocortolone" misspelled.
- P. 2, Fig.1c: Reference of Lui (Nat. Chem.) should be cited as 2022 (see Ref. 40)
- P. 2, bottom paragraph: "benzylic chloride 2a" instead of "benzylic chlorides 2a"
- Pp. 3&4, section titles: "Scope of …" instead of "Scope for …"
- Supporting Information:
1) Compound naming/numbering: For derivatives of pharmaceutical compounds, the relevant compound is oftentimes named "derivatives" instead of "derivative".
2) The reported NMR data of some compounds do not match the molecular structure. Please double-check the spectra of the following compounds and correct the reported data accordingly.
2f 1H NMR: resonance at 7.36 ppm cannot be a quartet and should be reported as a multiplet
2g 1H NMR: resonance at 4.84-4.76 ppm should integrate for only 1 proton (not 2H)
2n 13C NMR: one C too many
2p 13C NMR: number of aromatic Cs does not match with the structure
2w 13C NMR: several C resonances seem to be missing. Pleas check if they really all overlap
2y 1H NMR: 4 protons are missing!
4i 1H NMR: the sum of reported integrals exceeds the number of protons of 4i (2 Hs too many)
4j 13C NMR: one C missing
4l 13C NMR: one C too many
7 13C NMR: one C too many
9 Where does a JXH= 23.2 Hz (resonance at 5.20 ppm) come from? The assignment of this multiplet is suspicious.

3) The NMR spectra of compounds 2q and 2s show significant amounts of impurities. These need to either be removed by further purification or accounted for in the yield if the nature of the impurities is known (in that case, a corrected yield and purity can be given in the SI for the respective compounds).

Reviewer #2

(Remarks to the Author)
The manuscript entitled with “Palladium-Catalyzed Remote Internal C(sp3)–H Bond Chlorination of Alkenes” describes hydrochlorination to alkene derivatives. Irrespective of the position of the alkene bond, the protocol eventually delivers C(sp3)–H Bond chlorination to internal C(sp3)–H Bond via the well-known metal-walk pathway using palladium catalyst. CuCl2.H2O was used as the chlorinating reagent. Various alkene (both internal as well as external) substrates were utilized to demonstrate the substrate scope of the protocol and the desired products were obtained with a decent range of yields (43-63%). Mechanistic interrogative experiments were performed and the results were in support of the chain-walk process.

The chemistry reported here is a complementary approach of the Li et al report (reference 40). While Li et el utilized the more stable but less electron rich linear chain alkyl-Palladium species for the oxidative addition, the current work demonstrated the use of relatively less stable branched chain alkyl-Palladium species for the oxidation and subsequent functionalization.

Although the authors have mentioned the use of relatively less electrophilic chlorinating agent is crucial, a comparative analysis of various electrophilic chlorinating reagent starting from weaker to relatively stronger reagent and the output in terms of chlorination would be more convincing to prove hypothesis. Further, it would be nice for the readers if the reason for no reaction/no chlorination using NCS or PhICl2 (entries 8 and 9 table 1) as during the optimization process Li et at obtained both branched and linear alkyl chloride.
Regarding the substrate scope demonstration, I was wondering if it is possible to differentiate between benzylic carbon and tertiary carbon using a suitably designed substrate. and if it is possible, (as Li et al demonstrated the importance of ligand in delivering the selective chlorination) the, combination of an oxidant and suitably designed ligand can control the site of oxidative addition and provide either the sec-benzylic chloride or the tertiary alkyl chloride derivative.
Additionally, alicyclic substrate having alkene would have also been a nice addition in the table.

Reviewer #3

(Remarks to the Author)
In this manuscript, a Pd-catalyzed remote internal site-selective C(sp3)–H bond chlorination of alkenes via remote migratory hydrochlorination using a copper salt as the electrophilic chlorinating agent. A gram scale synthesis and the application of the approach to an isomeric mixture of alkenes and compounds of interest further showed the interest of the approach. Moreover, the results were supported by a mechanistic study.
A few points need to be addressed:
1) Previous works dealing with the chlorination of C(sp3) centers by Pd catalysis are missing and must be added to provide a comprehensive state-of-the-art.
2) Comments explaining the major difference of reactivity/selectivity observed in the work depicted by the group of Li (reference 40) and the authors' work need to be further highlighted and explained. Indeed, the authors remind that the “Precedent literatures have demonstrated that chlorination of Pd-benzyl complexes is kinetically more favorable than their Pd-alkyl counterparts58, 59” to justify the observed selectivity. However, they rationalized the work of Li by a “kinetically favored addition of a relatively large palladium center to the terminal carbon position”.
3) Despite a high regioselectivity, relatively modest yields between 40-60% are generally obtained for the remote functionalization, which reduce the synthetic utility of the methods. What are the other compounds obtained?
4) The direct hydrochlorination of styrenes and other alkenes (Table 3) is somehow far from the take-home message of the paper. In addition it is quite confusing for the reader why in the case of 4g, 4h for instance there is no walking chain.
5) A major concern is also the scale of the reaction (0.1 mmol) which is too small to be fully accurate (1.9 mg of catalyst).
6) In the supporting information, for each compound, the authors need to add several information:
a) Conditions used for the purification of the products, the quantity of the product they got (so far only yields are provided). In several cases further purification are necessary as for instance for the non-exhaustive list of the following compounds: 2e, 2g, 2s, 2t, 2u, 2v, 2x, 4k.
b) In addition in several cases the quality/resolution of the 13C is not good enough.
c) In addition, a signal in 1H NMR at 8 ppm has been observed in several cases. Did the authors get a by product? Which one?
d) In addition optimization of the reaction conditions (palladium catalysts, ligands, electrophilic chlorinating reagents, hydride sources, and solvents) would be interesting to be added in the SI.
Minor comment: a) The section entitled “Discussion” should be rather entitled “Conclusion”. b) “unprecedented” and not “unprecedent” remote internal site-selective
C(sp3)–H bond" and other typos need to be corrected

Taking into consideration the above comments and despite the interest of remote hydrochlorination reaction, this manuscript does not meet the criteria of significance of Nature Communications and I would recommend submitting it a more specialized journal.

Version 1:

Reviewer comments:

Reviewer #2

(Remarks to the Author)

[Note from the Editor: Reviewer #2 was asked to assess also the response given to reviewer #1.]

I have gone through the rebuttal letter.
The authors have performed experiments against the comments of the reviewers. Although many of the questions were not fully answered/justified (such as lack of product formation for heteroarene based substrates, or non-productivity of the electronically rich arenes or the table 3, as most of the examples are quite obvious), the manuscript could be considered for publication provided the pure spectra were attached. As mentioned by reviewer 3, the peak around 8 is still existing in the 1HNMR of spectra of many products.

I have gone through the point by point response of the authors against the comments of the Reviewer 1 and evaluated the response of the authors.

The authors have tried every possible way to answer all the comments of the reviewer 1. I must mention that in most of the cases the response is satisfactory and have meet the expectation. In some of the cases, the authors could not satisfy the expected results. Nonetheless, the reason for not obtaining the desired result has also been explained in every cases. The response has also been incorporated in the manuscript as well. Altogether, the quality and the clarity of the manuscript has been increased considerably.
Therefore, I feel, there is no reason for not accepting the manuscript for publication.

Reviewer #3

(Remarks to the Author)
In the revised version of the manuscript, the authors have addressed most of the points raised by the reviewer. Even though the quality of the manuscript have been improved, the novelty and significance of the work are still in my opinion not the one expected for a publication in Nature Communication.
Minor comments: in the introduction, the “amide derived from 8-aminoquinoline45,47” and not “aminoquinoline45,47” is the directing group and the authors should modify there manuscript accordingly.

Point-by-point response to reviewers' comments

Reviewer #1:

"*Yang and co-workers detail a remote hydrochlorination of alkenes enabled by a C–Cl reductive elimination from a high oxidation-state PdIV-alkyl/benzyl intermediate. This reaction exhibits the opposite regioselectivity to the system reported by Guosheng Liu [Li, X.; Jin, J.; Chen, P. & Liu, G. Catalytic remote hydrohalogenation of internal alkenes. Nat. Chem. 14, 425–432 (2022)]. This type of termination event is highly intriguing in the context of chain walking, particularly given the potential to use a remote trisubstituted position as a termination site. This represents an exceptional synthetic achievement.*

The strategy to achieve thermodynamic regioselectivity is ingenious, specifically utilizing the lower activity of copper dichloride to facilitate halogenation not only at the benzylic position [precedented reactivity] but also at non-benzylic tertiary positions. The yields obtained from the remote chlorination range from moderate to good, demonstrating that direct hydrochlorination of olefins is a feasible access route with satisfactory yields. The range of electronic profiles and functional group diversity on the aromatic ring present at the benzylic termination site is significantly varied, and the types of scaffolds attached as examples support the claim of a practical technique in the context of drug discovery late-stage functionalization workflows. The study concludes with well-designed experiments probing the reaction mechanism, and the conclusions drawn from their results are sound."

Response: Thank you very much for your high praise of our work. We really appreciate it.

Major comments:

> **1**. *"P. 2, bottom paragraph: The authors claim that "Bisphosphine ligands are critical for the reaction.", but the reaction is low-yielding with other bisphosphine ligands and no conditions are reported w/o bisphosphine ligands. It would be appreciated if the authors could elaborate on the reaction outcome with non-bisphosphine ligands in the SI. Generally, a subsection on observations during reaction optimization would be useful in the SI"*

Response: Thank you for your thoughtful review and valuable feedback. In response to your suggestion, we have added a detailed subsection on reaction optimization in

the SI on page S3-5, Table S1-6. This new section includes results with various ligands, such as nitrogen-based ligands and *N*-heterocyclic carbene (NHC) ligands. Our findings indicate that these ligands result in the formation of the alkene hydrogenation product rather than the desired hydrochlorination product. We believe that this additional information improves the completeness and clarity of our manuscript.

Additionally, we have revised the following sentence in the manuscript:

"Bisphosphine ligands are critical to the reaction, and nitrogen-based ligands and *N*-heterocyclic carbene (NHC) ligands give only a hydrogenation product (see SI for details)."

> **2**. *"P. 2, bottom paragraph / Table 1 entry1 2: The authors claim that no chlorination is observed with* $Pd(CH_3CN)_2Cl_2$ *instead of* $Pd(PhCN)_2Cl_2$*. It is intriguing that such a subtle change in the nature of the Pd-source completely shuts down the reaction. Can the presence of 10 mol% acetonitrile steers the reaction pathway from remote hydrochlorination to hydrogenation? ("Other palladium catalysts like* $Pd(CH_3CN)_2Cl_2$*,* $PdBr_2$ *or* $Pd(TFA)_2$ *were less efficient, primarily resulting in alkene hydrogenation (entries 2−4).") Please comment on the tolerance of the reaction to non-chlorinated solvents (especially acetonitrile in sub-stoichiometric amounts) or provide a rationale for the difference in reactivity for the two bis(nitrile)palladium dichloride precatalysts."*

Response: We appreciate the reviewer's insightful comments. In response, we performed the reaction in the presence of 20 mol% CH_3CN (the same amount as when $Pd(CH_3CN)_2Cl_2$ was used as catalyst) under standard conditions and found that the reaction was completely halted. We speculate that acetonitrile, with its stronger electronic donor properties and lower steric hindrance compared to benzonitrile, coordinates more readily to palladium. This competitive coordination may interfere with the binding of other ligands to palladium, potentially inhibiting the chlorination process.

To clarify the difference in reactivity between the two bis(nitrile)palladium dichloride precatalysts, we have included an explanation in the optimization discussion.

"Other palladium precatalysts, such as $Pd(CH_3CN)_2Cl_2$, $PdBr_2$ or $Pd(TFA)_2$, were less efficient, resulting primarily in isomerization and reduction of alkenes (entries 2–4). Chlorination was completely halted even in the presence of an additional 20 mol% CH_3CN under standard conditions. We speculate that CH_3CN, which coordinates more readily with palladium than PhCN, interferes with ligand binding and thus inhibits the chlorination process. Consequently, when $Pd(CH_3CN)_2Cl_2$ was used instead of

$Pd(PhCN)_2Cl_2$, the desired chloride **2a** was not obtained."

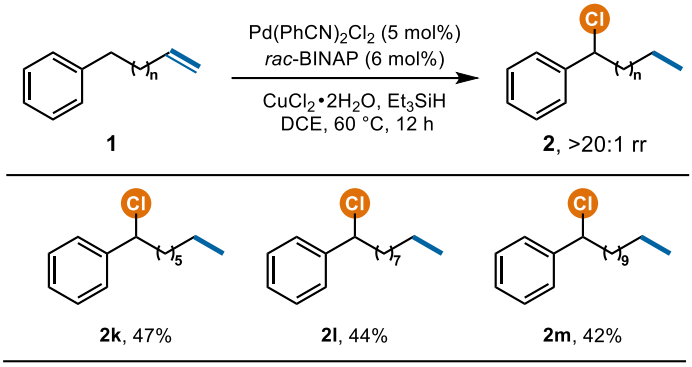
3. *"P. 3, top paragraph / Table 1 entry 12: Is it a solvent or a temperature effect that DCE at 60 °C outperforms DCM? The setup detailed in the SI would not be suitable to run the reaction at 60 °C in DCM, so the authors should specify if the reaction in DCM was run at a different temperature."*

Response: We appreciate the reviewer's great point. The reaction using DCM as the solvent was performed at its boiling point (40 °C). To clarify this, we have added a footnote in Table 1 to indicate the actual reaction temperature. Additionally, we performed a parallel reaction with DCE at 40 °C, which resulted in 45% yield, slightly higher than the 36% yield obtained with DCM. These results indicate that both the reaction temperature and the solvent affect the reaction outcomes. All relevant results are included in the SI in the optimization section.

4. *"P. 3, bottom paragraph: The reaction is labelled as insensitive to the alkyl chain length, yet the presented scope explores a very limited range of distances. A more granular scope would better support the claim. For example, the state of the art is presented by Mazet with (J. Am. Chem. Soc. 2016, 138, 10344–10350) where 10 positions are reliably isomerized using palladium. A series of examples with 4, 6, 8, and 10 carbon atoms in the aliphatic chain would be of interest, especially if it illustrates the range insensitivity, or allows for a more precise appreciation of where the synthetic limit lies."*

Response: Thank you for your constructive suggestions. We synthesized alkene substrates with longer aliphatic chains containing 6, 8, and 10 carbon atoms (**1k**–**1m**) and performed the chlorination under optimized conditions. The desired products (**2k**–**2m**) were obtained in similar isolated yields (42–47% yield). These substrates are now included in Table 2. Additionally, we have revised the relevant sentence to read as follows:

"The reaction is insensitive to the chain length between the C=C bond and the remote aryl group, ranging from 1 to 10 C-atoms (**2i**–**2m**, 42–62% yield)."



5. *"Pp. 3&4, Scope: Yields of 40-60% should be labelled as moderate, 60-80% as good, and above 80% as very good/excellent."*

Response: Thanks for your helpful suggestions. Based on your suggestions, we have revised the substrate scope discussion.

6. *"P. 4, Table 2: Regarding scope/limitations of the benzylic chlorination: 1) Can heterocycles (other than amide-protected indole **2v**) such as furane, thiophene, pyridine, non-/alkyl-protected indole, morpholine, (alkyl-)piperazine be tolerated in the reaction? 2) If yes, can heteroaromatics serve as termination site for the benzylic chlorination?"*

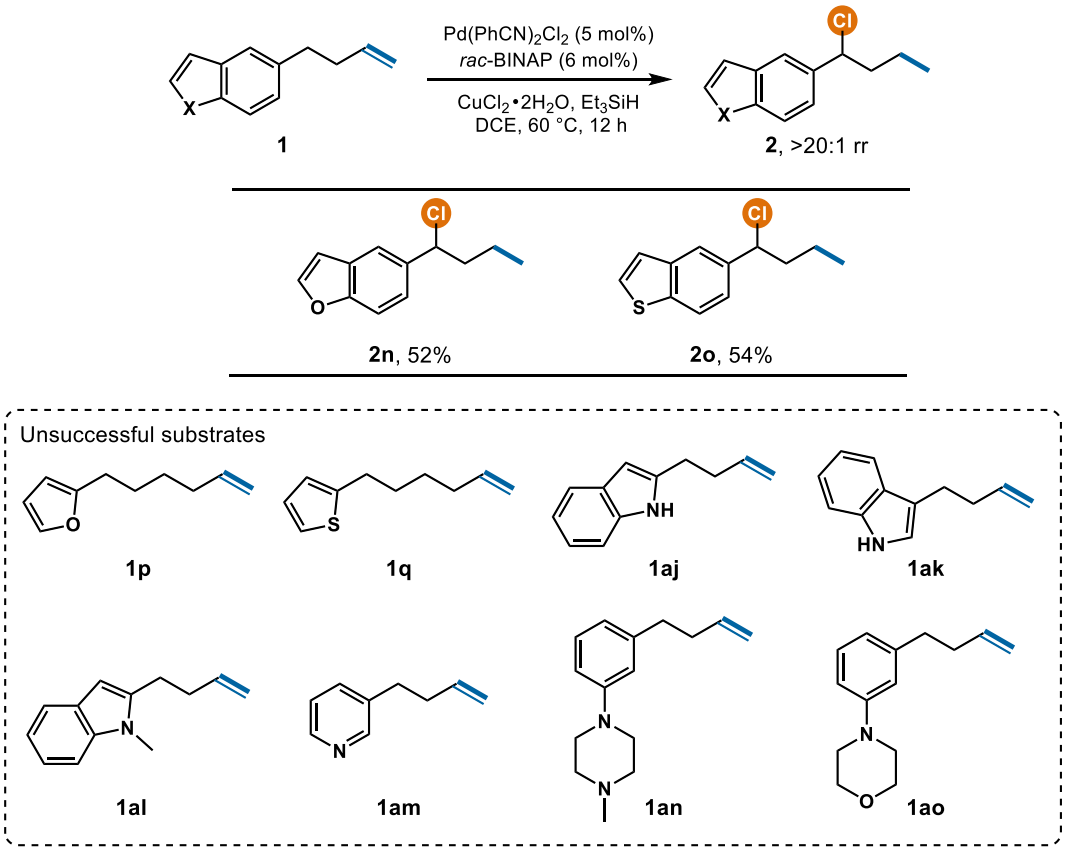
Response: We appreciate your valuable suggestions. Based on your recommendations, we have synthesized and examined several substrates under optimized conditions. Initially, we evaluated alkenes containing furan and thiophene (**1p** and **1q**). However, these reactions did not yield the desired products and instead resulted in oligomerization. Subsequently, we synthesized benzofuran and benzothiophene substrates (**1n** and **1o**). To our delight, we obtained the desired products (**2n** and **2o**) in 52% and 54% ^{1}H NMR yields, respectively. These compounds decompose easily on silica gel. To address this, we added thiophenol to the mixture after the reaction was complete, which facilitated the in-situ conversion of the chlorinated products into their corresponding thioether compounds, allowing their purification. These results indicate that while the reaction can tolerate furan and thiophene, these moieties are not suitable as termination sites for benzylic chlorination.

Additionally, alkenes containing non-/alkyl-protected indole, morpholine, and (alkyl-)piperazine (**1aj**-**1ao**) were evaluated. Under standard hydrochlorination conditions, these reactions were very messy and did not yield the desired products. We believe that the coordination of the nitrogen atom interferes with the reaction.

To better describe the scope of the reaction, we have included substrates **2n** and **2o**

in Table 2 and listed other non-reactive compounds in the SI on page S42 (Fig. S1). In addition, we have added a statement to the scope discussion.

"Heteroaromatic rings, such as furan and thiophene, demonstrate compatibility with the reaction (**2n** and **2o**); however, they cannot serve as termination sites for benzylic chlorination (**2p** and **2q**, see SI for other alkene substrates that show no reactivity)."



7. *"P. 4, Table 2: Regarding scope/limitations of the tertiary chlorination: In the context of remote functionalization, the use of a trisubstituted position as a reliable termination site is of extremely high interest. However, it is disappointing to see the methyl substituent as a constant throughout the scope of such examples. Is it possible for this termination to occur with a different termination motif? If this was not further investigated, a series evaluating the maximum steric bulk tolerated as well as polarization effects would be highly interesting. I suggest attempting the transformation of a variety of substrates similar to example 1o:*

1) Methyl replaced by ethyl, isopropyl, cyclohexyl, and tertiary butyl, pushing steric effects to the limit with good granularity.

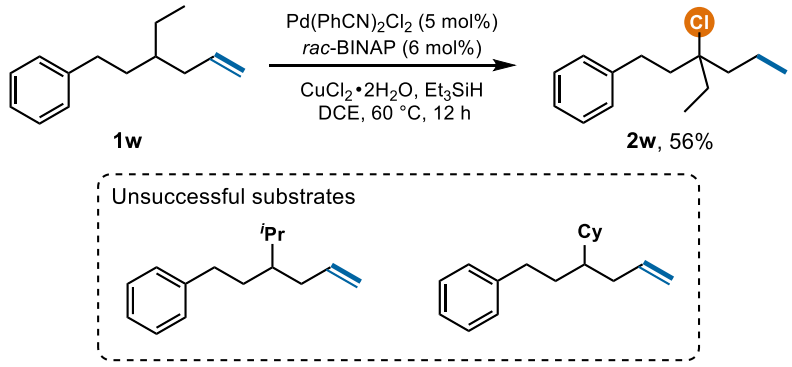
2) Methyl replaced by aryls with various substituents (para CF_3, ester, alkyl, trialkyl silyl, and methoxy), examining the influence of electronics

at a tertiary substituted benzylic position.

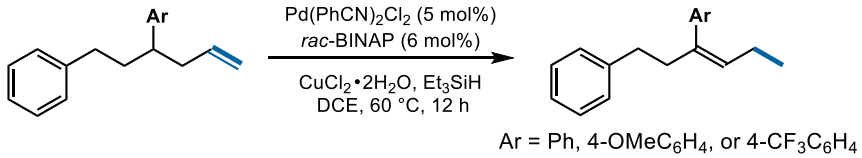
3) Methyl could be replaced by fluorine to investigate if a F-substituent in the aliphatic chain can be bypassed to yield the benzylic chlorination product, or if the chain-walk stops at the secondary fluoride. If the Pd does not pass the F-substitution, does chlorination occur to give a CR_2FCl-group, or does the electron-withdrawing nature of the F-substituent impede selective oxidation of the alkyl-PdII species in this position?"

Response: We appreciate your valuable suggestions. Based on your recommendations, we have designed and evaluated several substrates for chlorination under the optimized conditions. Specifically:

1) When the methyl group was replaced with an ethyl group, the tertiary chlorinated product **2w** was obtained in 56% yield. However, the reaction did not proceed with bulkier substituents such as isopropyl and cyclohexyl due to significant steric hindrance. We have included the results for **2w** in Table 2 of the manuscript, and the substrates that did not react are detailed in the SI on page S42 (Fig. S1).



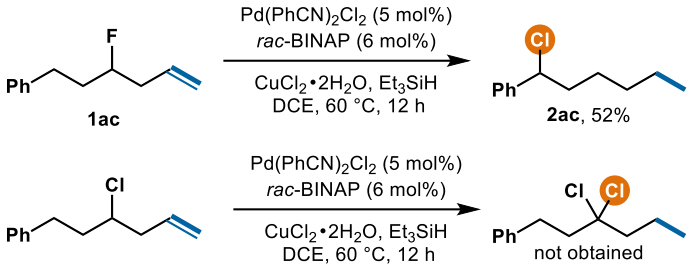
2) When the methyl group was replaced with aryl groups, only isomerized alkenes were obtained under the optimized conditions. These substrates, which did not yield the desired chlorinated products, are also documented in SI on page S42 (Fig. S1).



3) We synthesized an alkene (**1ac**) with an F-substituent in the aliphatic chain. Interestingly, we observed the formation of a defluorinated chlorination product **2ac** in 52% yield under standard conditions. This result suggests that β-F elimination likely occurred, leading to the formation of a Pd–F species. The presence of silane further facilitates the conversion of the Pd–F complex to Pd–H, allowing the chlorination reaction to continue. Inspired by your suggestion, we also investigated the chlorination of chlorine contained alkene, but only the hydrogenation product was obtained. The

data for the F-containing alkene **1ac** is presented in Table 2 of the manuscript, and the substrate that did not react is documented in SI on page S42 (Fig. S1). Additionally, we have added the following statement to the manuscript:

"Using an alkene **1ac** with a F-substituent in the aliphatic chain, a defluorinated chlorination product **2ac** was obtained in 52% yield. This result suggests that *β*-F elimination likely occurred, leading to the formation of a Pd–F species. The presence of silane further facilitates the conversion of the Pd–F complex to Pd–H, allowing the chlorination reaction to continue."



8. *"P. 5, Table 3: all styrenes in the scope are electron-poor or electron-neutral. Are electron-rich styrenes competent substrates for the direct hydrochlorination, or is oligomerization observed in these cases?"*

Response: Thank you for your question to the scope of styrenes. As you mentioned, electron-rich styrenes are highly susceptible to oligomerization, and no leading to the lack of observed chlorination products. To better illustrate the reaction scope, we have included a discussion of the reactivity of styrenes.

"Electron-rich styrenes are highly prone to oligomerization under these conditions, and no hydrochlorination products were obtained."

9. *"P. 5, bottom: During the mechanism investigation, deuteration was observed to be homogeneous along the chain. The authors suggest that this is an indication of the poor regioselectivity of the Pd-H migratory insertion. How can this hypothesis be preferred over a very high propensity for dissociation at each step taken?"*

Response: We greatly appreciate your helpful suggestions. We agree with the reviewer that it is difficult to determine the poor regioselectivity of the Pd–H migratory insertion from these results. In response, we have revised the discussion as follows:

"Additionally, an isotopic labelling experiment was performed using deuterated silane. Deuterium was observed at all methylenes, suggesting that migration of Pd–H species along the carbon chain of the alkenes indeed occurred (Fig. 2f, top). No

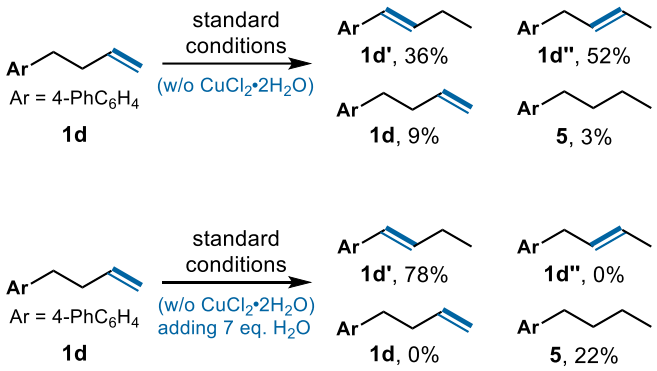
deuterium incorporation into the desired product was observed when D_2O was used, indicating that the silane is the sole hydrogen source (Fig. 2f, bottom).”

10. *“P. 6, Figure 2b: During the mechanistic investigation, it is curious to see that the styrenyl product is not major in Figure 2b. Is this due to the absence of a water additive and a lack of activation of the silane? Is another hypothesis favored?”*

Response: We appreciate your insightful suggestions. In response, we performed the reaction without $CuCl_2$ but with 7 eq. of H_2O, and observed that styrenyl derivatives **1d′** emerged as the major product. This result suggests that water activates the silane to promote the formation of Pd–H (*ChemCatChem* **6**, 1691–1697 (2014)), a phenomenon also observed in chain-walking reactions reported by Liu (*Nat. Chem.* **14**, 425–432 (2022)). To better elucidate the reaction mechanism, we have revised Fig. 2b to include this result. Additionally, we have updated the mechanism discussion as follows:

“When we subjected alkene **1d** to the standard reaction conditions in the absence of $CuCl_2{\cdot}2H_2O$, a mixture of alkenes resulting from alkene isomerization was observed (Fig. 2b, top). We also performed the chlorination reaction in the absence of $CuCl_2$ but with 7 eq. of H_2O, and observed that the styrenyl derivatives **1d′** emerged as the major product (Fig. 2b, bottom). These results suggest that alkene isomerization is independent of the presence of $CuCl_2{\cdot}2H_2O$ and indicate that water facilitates the isomerization process by activating the silane.[67]”

Fig. 2b:



11. *“P. 6, Figure 2d: The authors claim to observe complete erosion of ee, but do not report by which method this was determined. Neither the manuscript nor the SI report on any determination of the ee (optical rotation, chiral HPLC etc.). The authors need to add the original data for ee determination of product 2s from (S)-1s to the SI.”*

Response: Thank you for pointing this out. We have added the separation methods and the corresponding HPLC spectrum in the SI on page S45. Despite attempting various separation conditions, we found that no method offered a baseline separation. Nevertheless, it is evident that the product is racemic.

> **12**. *"The evidence and experiments supporting the dissociative mechanism are sufficient, but perhaps citing Kochi's review on the matter would be advisable [T. Kochi et al. Tetrahedron Letters 60 (2019) 150938]."*

Response: Thank you for bringing this paper to our attention. We have included this review as ref 76, and we believe that this review will help readers gain a more comprehensive understanding of chain-walking mechanisms.

> **13**. *"P. 7: Subsection "Discussion" would better be described as "Conclusions""*

Response: We apologize for this error. We have changed the "Discussion" to "Conclusion"

> **14**. *"Abstract and Conclusions/Discussion: The claim for late-stage modification in a pharmaceutical context is difficult to accept for anything but screening, as metal-catalyzed transformations are typically avoided in late-stage synthesis of drugs."*

Response: We appreciate the reviewer's valuable comments. We understand the challenges associated with late-stage modification in the pharmaceutical context and agree that metal-catalyzed transformations are typically avoided in late-stage drug synthesis. Late-stage functionalization is an important technique in drug discovery and synthesis. This approach allows for structural modifications while preserving the core active pharmaceutical scaffold, thereby altering the properties of the compound and enabling rapid screening of new drugs with enhanced activity. Our study aims to provide a method for such screening, as the introduction of a chlorine atom can impart beneficial properties to biologically active molecules, such as altering the electronic properties of nearby functional groups, enhancing their lipophilicity, and preventing metabolic oxidation at the chlorinated locus.

> **15**. *"The work would be much more impactful if other electrophiles than only $CuCl_2$ could be employed in the remote internal-selective*

functionalisation of tertiary C-H bonds. The authors claim to be working on this at the moment. A proof of concept for at least one (unoptimised) transformation other than hydrochlorination would proof a more general applicability of the concept presented herein, as should be demonstrated for publication in a non-chemistry specific journal."

Response: We appreciate the reviewer's valuable comments. We have explored various electrophiles, but none have yielded satisfactory results to date. Currently, we are only able to obtain a minimal amount of the migratory hydrobromination product, with a yield of less than 10%. We hope to achieve better results in the near future and will report them accordingly.

16. *"Supporting Information:*
*o NMR spectra should also be provided for unpublished starting materials (**1p-s**, **1v-y**)*
o Mass spectroscopic data are missing for the following new compounds: ***2c***, ***2q***, ***2p***, ***4k***
*o 13C NMR data of compound **8** are missing"*

Response: We are very grateful for your suggestion. The NMR spectra for the unknown compounds **1p-s** (now renumbered as **1x-1aa**) and **1v-y** (now renumbered as **1ae**, **1af**, **1ah**, **1ai**) have been included in the SI on pages S62-69. Additionally, the mass spectrometric data for compounds **2c**, **2q** (now renumbered as **2y**), **2p (**now renumbered as **2x)**, and **4k**, as well as the ^{13}C NMR data for compound **8**, are also included in the SI.

Minor comments:

17. *"(1) General: As BINAP is a chiral ligand, it would be appropriate to specify if racemic BINAP was used, and if not the effect of the enantiomer should be investigated. The enantiomer/racemic mixture used can be specified in the General Information part of the Supporting Information.*

Response: We are very grateful for your suggestion. We have clarified in the General Information section of the SI that racemic BINAP was used in our study. Additionally, we have revised the manuscript to replace "BINAP" with "*rac*-BINAP" throughout

(2)- P. 2, Fig. 1a: "clocortolone" misspelled.

- P. 2, Fig.1c: Reference of Lui (Nat. Chem.) should be cited as 2022 (see Ref. 40)
*- P. 2, bottom paragraph: "benzylic chloride **2a**" instead of "benzylic chlorides **2a**"*
- Pp. 3&4, section titles: "Scope of …" instead of "Scope for …"

Response: Thank you very much for catching these mistakes. We apologize for the errors and have made the corrections accordingly.

- Supporting Information:
1) Compound naming/numbering: For derivatives of pharmaceutical compounds, the relevant compound is oftentimes named "derivatives" instead of "derivative"

Response: Thank you very much for your valuable comments. We have revised the corresponding section accordingly.

2) The reported NMR data of some compounds do not match the molecular structure. Please double-check the spectra of the following compounds and correct the reported data accordingly.
2f *^{1}H NMR: resonance at 7.36 ppm cannot be a quartet and should be reported as a multiplet*

Response: Thank you very much for your helpful suggestions. We have made corrections accordingly.

2g *^{1}H NMR: resonance at 4.84-4.76 ppm should integrate for only 1 proton (not 2H)*

Response: Thank you very much for pointing this out. The overlap of the proton from the phenolic hydroxyl group with the benzylic hydrogen causes the integration to be observed as two protons in the 4.84–4.76 ppm range.

2n *13C NMR: one C too many*
2p *13C NMR: number of aromatic Cs does not match with the structure*
2w *13C NMR: several C resonances seem to be missing. Pleas check if they really all overlap*
2y *1H NMR: 4 protons are missing*
4j *13C NMR: one C missing*

4l *13C NMR: one C too many*
7 *13C NMR: one C too many*

Response: Thank you very much for catching these mistakes. We are sorry for these mistakes. We have made corrections accordingly.

9 *Where does a JXH= 23.2 Hz (resonance at 5.20 ppm) come from? The assignment of this multiplet is suspicious.*

Response: Thanks for pointing this out. We obtained product **9** with 1:1 dr. The resonance at 5.20 ppm should appear as a multiplet due to the overlap of the two isomers. We apologize for the previous errors and have made the corrections.

3) The NMR spectra of compounds ***2q*** *and* ***2s*** *show significant amounts of impurities. These need to either be removed by further purification or accounted for in the yield if the nature of the impurities is known (in that case, a corrected yield and purity can be given in the SI for the respective compounds).”*

Response: We are very grateful for your suggestion. We have repurified the compounds and updated the yields in the manuscript accordingly.

Reviewer #2:

“*The manuscript entitled with “Palladium-Catalyzed Remote Internal C(sp^3)–H Bond Chlorination of Alkenes” describes hydrochlorination to alkene derivatives. Irrespective of the position of the alkene bond, the protocol eventually delivers C(sp^3)–H Bond chlorination to internal C(sp^3)–H Bond via the well-known metal-walk pathway using palladium catalyst. $CuCl_2{\cdot}H_2O$ was used as the chlorinating reagent. Various alkene (both internal as well as external) substrates were utilized to demonstrate the substrate scope of the protocol and the desired products were obtained with a decent range of yields (43-63%). Mechanistic interrogative experiments were performed and the results were in support of the chain-walk process. The chemistry reported here is a complementary approach of the Li et al report (reference 40). While Li et el utilized the more stable but less electron rich linear chain alkyl-Palladium species for the oxidative addition, the current work demonstrated the use of relatively less stable branched chain alkyl-Palladium species for the oxidation and subsequent functionalization.*”

Response: Thank you very much for your nice and valuable comments.

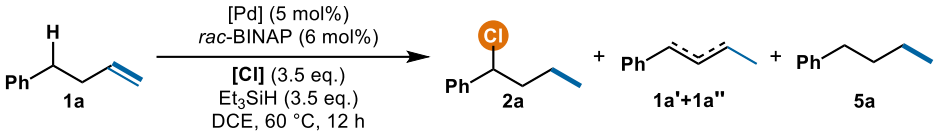
> **1**. *"Although the authors have mentioned the use of relatively less electrophilic chlorinating agent is crucial, a comparative analysis of various electrophilic chlorinating reagent starting from weaker to relatively stronger reagent and the output in terms of chlorination would be more convincing to prove hypothesis."*

Response: We greatly appreciate your insightful suggestions. In response, we investigated a range of chlorinating reagents, including *N*-chlorosuccinimide (NCS), *N*-chlorophthalimide (NCP), oxone/LiCl, ^{t}BuOCl, and $PhICl_2$. Using NCS, NCP, and oxone/LiCl, we observed only isomerization and reduction of alkenes as the major products, with no desired product formed. We also tested other ligands with these chlorinating reagents, but no chlorinated products were observed. No reaction was observed when ^{t}BuOCl was used as the chlorinating agent. Stronger chlorinating agents $PhICl_2$ did not yield any products when BINAP was used as the ligand. However, when DPEphos was employed as the ligand, a mixture of chlorinated products at various positions was detected. Based on these results, we have revised the optimization discussion accordingly.

"No desired chlorinated products were observed when using chlorinating reagents such as *N*-chlorophthalimide (NCP) and NCS; only isomerization and reduction of alkenes were obtained (entry 8). There are two possible explanations for this result. One is that NCP and NCS, due to their greater steric hindrance, are unable to oxidize the branched alkyl Pd^{II} species. The other possibility is that these oxidants may be converted into the corresponding imides in the presence of silane, which could subsequently coordinate with the catalyst and lead to its deactivation. When using the stronger oxidant $PhICl_2$, a mixture of chlorination products at different positions, along with a dichlorination product, was detected by GC-MS (entry 9). This result is likely due to the increased rate of oxidative chlorination facilitated by the stronger chlorinating reagent, which closely matches the rate of migration of the Pd–H species along the carbon chain, leading to the formation of a mixture of isomers."

Moreover, to illustrate the effects of different chlorinating reagents on the reaction, these results are included in the SI on page S3, Table S3.

Table S3. Screening of chlorinating reagents.



entry	[Cl]	**2a** (%)	**1a +1a'+ 1a''** (%)	**5a** (%)
1	**$CuCl_2 \cdot 2H_2O$**	**65**	**12**	**10**
2	NCS	/	74	25
3	NCP	/	41	55
4	Oxone+LiCl	/	92	7
5	^{t}BuOCl	/	/	/
6	$PhICl_2$	multiple isomers[a]	/	/

Determined by GC using 1,3,5-trimethoxybenzene as an internal standard.
[a]using DPEphos (Bis[(2-diphenylphosphino)phenyl]ether)

2. *"Further, it would be nice for the readers if the reason for no reaction/no chlorination using NCS or $PhICl_2$ (entries 8 and 9 table 1) as during the optimization process Li et at obtained both branched and linear alkyl chloride."*

Response: We are grateful for the constructive suggestions. Both the ligand and the chlorinating reagent are critical to the reaction. In Li's study, a pyridine-oxazoline ligand was used, whereas our system did not show any reaction with nitrogen-based ligands. Additionally, we found that substrates containing secondary amines or amides are incompatible with our reaction conditions. Based on these observations, we speculate that there are two possible reasons for the lack of reaction with NCS. One possibility is that NCS is unable to oxidize the branched alkyl Pd^{II} species due to its greater steric hindrance. The other possibility is that NCS may be converted into the corresponding imide in the presence of silane, which could then bind to the Pd center and thus prevent the formation of the desired product.

The use of the stronger chlorinating agent $PhICl_2$, in combination with the DPEphos ligand, resulted in a mixture of chlorinated products at various positions. This outcome is likely due to the increased oxidative chlorination rate promoted by the stronger chlorinating reagent. This increased rate of chlorination closely matches the migration rate of the Pd–H species along the carbon chain, leading to the formation of a mixture of isomers.

To clarify the effect of chlorinating reagents, we have revised the optimization discussion. We believe that this revision will help readers gain a more comprehensive understanding.

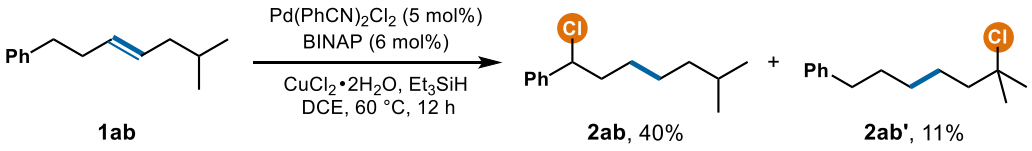
"No desired chlorinated products were observed when using chlorinating reagents such as *N*-chlorophthalimide (NCP) and NCS; only isomerization and reduction of alkenes

were obtained (entry 8). There are two possible explanations for this result. One is that NCP and NCS, due to their greater steric hindrance, are unable to oxidize the branched alkyl Pd^{II} species. The other possibility is that these oxidants may be converted into the corresponding imides in the presence of silane, which could subsequently coordinate with the catalyst and lead to its deactivation. When using the stronger oxidant $PhICl_2$, a mixture of chlorination products at different positions, along with a dichlorination product, was detected by GC-MS (entry 9). This result is likely due to the increased rate of oxidative chlorination facilitated by the stronger chlorinating reagent, which closely matches the rate of migration of the Pd–H species along the carbon chain, leading to the formation of a mixture of isomers."

3. *"Regarding the substrate scope demonstration, I was wondering if it is possible to differentiate between benzylic carbon and tertiary carbon using a suitably designed substrate. and if it is possible, (as Li et al demonstrated the importance of ligand in delivering the selective chlorination) the, combination of an oxidant and suitably designed ligand can control the site of oxidative addition and provide either the sec-benzylic chloride or the tertiary alkyl chloride derivative."*

Response: Thank you very much for your constructive suggestions. Based on your recommendation, we have designed and synthesized alkene **1ab**, where the benzylic C(sp^3)–H bond is positioned on one side of the alkene and the tertiary C(sp^3)–H bond is on the other side. When chlorination was performed under standard conditions, a mixture of benzylic chloride and tertiary chloride was obtained, with a ratio close to 4:1. We also explored various conditions with different ligands and oxidants, but no significant preference was observed. To improve the completeness of our research, we have included this result in Table 2. Additionally, we have added a statement to the substrate scope discussion, which reads as follows:

"A mixture of benzylic chloride (**2ab**) and tertiary chloride (**2ab′**) was obtained when chlorinating an alkene with a benzylic C(sp^3)–H bond on one side and a tertiary C(sp^3)–H bond on the other side."

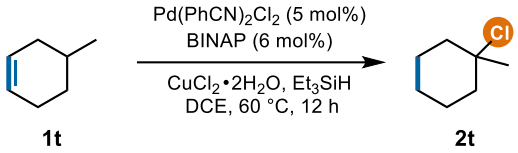


1ab **2ab**, 40% **2ab'**, 11%

4. *"Additionally, alicyclic substrate having alkene would have also been a nice addition in the table."*

Response: We appreciate the reviewer's valuable suggestion. In response, we have performed the chlorination of 4-methylcyclohexene and successfully obtained the desired migratory chlorination product **2t** in 56% yield. We have included this substrate in Table 2, and added a statement to the scope discussion.

"Chlorination of the alicyclic substrate **1t** delivered the desired product **2t** in 56% yield."



Reviewer #3:

"*In this manuscript, a Pd-catalyzed remote internal site-selective C(sp^3)–H bond chlorination of alkenes via remote migratory hydrochlorination using a copper salt as the electrophilic chlorinating agent. A gram scale synthesis and the application of the approach to an isomeric mixture of alkenes and compounds of interest further showed the interest of the approach. Moreover, the results were supported by a mechanistic study.*"

Response: Thank you very much for your favorable comments.

A few points need to be addressed:

> **1**. *"Previous works dealing with the chlorination of C(sp^3) centers by Pd catalysis are missing and must be added to provide a comprehensive state-of-the-art."*

Response: We thank the reviewer for the constructive suggestions. Pd-catalyzed chlorination of C(sp^3)–H bonds has been developed by various research groups, typically involving the use of nitrogen-containing functional groups as directing groups. Notable examples include sulfoximine (*Org. Lett.* **16**, 5258–5261 (2014)), aminoquinoline (*Chem. Sci.* **11**, 2455–2463 (2020); *Eur. J. Org. Chem.* **2016**, 3625–3630 (2016); *Chem. Commun.* **52**, 6423–6426 (2016)), and pyridine (*Chem. Sci.* **3**, 3192–3195 (2012); *Org. Lett.* **17**, 1200−1203 (2015)). Recently, Yu and coworkers developed a Pd(II)-catalyzed β-C(sp^3)–H chlorination of carboxylic acids, where the carboxyl group serves as the directing group (*J. Am. Chem. Soc.* **145**, 16297–16304 (2023)). In order to present the current progress in Pd-catalyzed chlorination of C(sp^3)–H bonds, we have incorporated the following sentences into the introduction. We

believe that this revision will help readers gain a comprehensive understanding of the state-of-the-art in this field.

"Most previous research on Pd-catalyzed chlorination of C(sp^3)–H bonds has predominantly used nitrogen-containing functional groups as directing groups, such as sulfoximine[44], aminoquinoline[45-47], and pyridine[48,49]. Recently, Yu and coworkers advanced this field by developing a Pd(II)-catalyzed β-C(sp^3)–H chlorination of carboxylic acids, where the carboxyl group serves as the directing group.[50]"

> **2**. *"Comments explaining the major difference of reactivity/selectivity observed in the work depicted by the group of Li (reference 40) and the authors' work need to be further highlighted and explained. Indeed, the authors remind that the "Precedent literatures have demonstrated that chlorination of Pd-benzyl complexes is kinetically more favorable than their Pd-alkyl counterparts[58, 59]" to justify the observed selectivity. However, they rationalized the work of Li by a "kinetically favored addition of a relatively large palladium center to the terminal carbon position""*

Response: Thank you very much for the insightful suggestions, and we apologize for the previous lack of clarity. A series of iterative migratory insertion and β-H elimination processes can generate either a linear alkyl Pd^{II} species or a branched alkyl Pd^{II} species. In general, the linear alkyl Pd^{II} species is more stable than the branched alkyl Pd^{II} species, as also noted in the reference (*Nat. Chem.* 14, 425–432 (2022)). In the research reported by the Liu group, exceptional chemo- and regio-selectivity is achieved using a well-designed pyridine-oxazoline ligand containing a hydroxyl group. This hydroxyl group forms a hydrogen bond with the oxygen of NCS, thereby accelerating the oxidation of the stable but less electron-rich linear linear alkyl Pd^{II} species by NCS to form the primary alkyl chloride. In contrast, our research uses $CuCl_2 \cdot H_2O$ to promote the kinetically favorable oxidation of the less stable but electron-rich branched alkyl Pd^{II} species, resulting in internal site-selective C(sp^3)–H bond chlorination. To clarify the key differences in reactivity and selectivity, we have revised our introduction as follows:

"Recently, Liu and coworkers achieved a remarkable breakthrough in remote migratory hydrochlorination of alkenes, enabling the selective chlorination of terminal C(sp^3)–H bonds (Fig. 1c).[40] The exceptional chemo- and site-selectivity is achieved through the use of a well-designed pyridine-oxazoline ligand containing a hydroxyl group. This hydroxyl group can form a hydrogen bond with the oxygen atom of *N*-

chlorosuccinimide (NCS), thereby accelerating the oxidation of stable linear alkyl Pd^{II} species by NCS to produce primary alkyl chlorides.

…

Iterative hydropalladation and β-H elimination of an alkene can generate either a linear alkyl Pd^{II} species **A** or a branched alkyl Pd^{II} species **B** (Fig. 1d). Generally, the linear alkyl Pd^{II} species **A** is more stable but less electron-rich compared to the branched alkyl Pd^{II} species **B**.[40] Precedent literatures have demonstrated that chlorination of the branched alkyl Pd^{II} species **B**, which has a more electron-rich palladium center, is kinetically more favorable than that of the linear alkyl Pd^{II} species **A** when exposed to relatively less reactive electrophilic chlorinating reagents, such as $CuCl_2$.[65, 66]"

> **3**. *"Despite a high regioselectivity, relatively modest yields between 40-60% are generally obtained for the remote functionalization, which reduce the synthetic utility of the methods. What are the other compounds obtained?"*

Response: Thank you very much for your questions. In addition to the desired chlorinated products, we also observed a small number of hydrogenated products and isomeric alkenes as by-products. To make it clearer, we have added a footnote 68 to the scope discussion.

"ref 68. Isomerization and reduction of alkenes are the primary by-products observed in substrates with low yields."

> **4**. *"The direct hydrochlorination of styrenes and other alkenes (Table 3) is somehow far from the take-home message of the paper. In addition, it is quite confusing for the reader why in the case of **4g**, **4h** for instance there is no walking chain."*

Response: We appreciate the reviewer's comments. We have included direct hydrochlorination in our study because efficient catalytic hydrochlorination of styrene derivatives remains challenging, despite the existence of various approaches for catalytic hydrochlorination of alkenes. We aim to present a general method that can be applied not only to chain-walking hydrochlorination but also to direct hydrochlorination of challenging alkene substrates.

For products **4g** and **4h**, tertiary chlorides were formed, which is why no chain walking was observed. These results are consistent with the chain-walking observations reported in Table 2. Chlorination occurred at the tertiary C(sp^3)–H bond

rather than the benzylic C(sp^3)–H bond when alkenes with a tertiary carbon in the chain (**2u**-**2aa**) were used.

> **5**. *"A major concern is also the scale of the reaction (0.1 mmol) which is too small to be fully accurate (1.9 mg of catalyst)."*

Response: We appreciate the reviewer's concern and fully understand. When we performed our reactions, we weighed larger amounts of catalyst (5.7 mg) and ligand (11.2 mg), prepared them as solutions in DCE (1.5 mL), and then added 0.5 mL of this solution to the reaction system to ensure the accuracy of the catalyst. Additionally, we routinely conducted the reaction in duplicate to verify the consistency of the yield. We apologize for the lack of clarity in the previous procedure description. We have revised the procedure to provide a clearer and more accurate description.

> **6**. *"In the supporting information, for each compound, the authors need to add several information:*
> *a) Conditions used for the purification of the products, the quantity of the product they got (so far only yields are provided). In several cases further purification are necessary as for instance for the non-exhaustive list of the following compounds:* ***2e***, ***2g***, ***2s***, ***2t***, ***2u***, ***2v***, ***2x***, ***4k***.

Response: Thank you very much for your great suggestions. In response, we have included the conditions used to purify the products and the quantities of products obtained. Additionally, we have updated the NMR spectra that were of poor quality, except for compound **2g**. Despite multiple attempts for the purification, we were unable to achieve perfect purity for compound **2g**. In response, we assessed the purity of **2g** by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard and have revised the yield accordingly. **2e** is on page S74; **2s** (now renumbered as **2aa**) is on page S88; **2t** (now renumbered as **2ad**) is on page S90; **2u** (now renumbered as **2ag**) is on page S93; **2v** (now renumbered as **2ae**) is on page S91; **2x** (now renumbered as **2ah**) is on page S94; **4k** is on page S97.

> *b) In addition, in several cases the quality/resolution of the ^{13}C is not good enough.*

Response: Thank you for your suggestions. We have updated the ^{13}C NMR spectra with poor quality.

c) In addition, a signal in ^1H NMR at 8 ppm has been observed in several cases. Did the authors get a byproduct? Which one?

Response: We are very grateful for your questions and thanks for pointing this out. We didn't observe this peak in the crude ^1H NMR of the reaction, indicating that it is not a byproduct. We determined that this signal originates from the solvent (ethyl acetate) used for purification and is absent when distilled ethyl acetate is used in the purification process.

d) In addition, optimization of the reaction conditions (palladium catalysts, ligands, electrophilic chlorinating reagents, hydride sources, and solvents) would be interesting to be added in the SI."

Response: Thank you very much for your valuable points and suggestions. In response, we have included the effects of each parameter–specifically palladium catalysts, ligands, chlorinating reagents, hydride sources, reaction temperature, and solvents–on reaction in the SI on page S3-5, Table S1-6. We believe that this additional information will improve the completeness and clarity of our manuscript.

7. *"Minor comment: a) The section entitled "Discussion" should be rather entitled "Conclusion". b) "unprecedented" and not "unprecedent" remote internal site-selective C(sp^3)–H bond" and other typos need to be corrected."*

Response: We appreciate the reviewer's valuable suggestions and sorry for these mistakes. We have made corrections accordingly.

"*Taking into consideration the above comments and despite the interest of remote hydrochlorination reaction, this manuscript does not meet the criteria of significance of Nature Communications and I would recommend submitting it a more specialized journal.*"

Response: We appreciate your recognition of the remote hydrochlorination as an interesting reaction. In the revised manuscript, we have performed an extensive series of experiments, and updated the manuscript based on these results as well as the constructive comments from the reviewers. We believe that these revisions have significantly strengthened the manuscript and addressed the concerns raised by the

reviewer. We hope that these improvements will encourage the reviewer to reconsider his/her initial decision.