nature portfolio

Peer Review File

Nickel-Catalyzed Regiodivergent Hydrosilylation of α-(Fluoroalkyl)styrenes without Defluorination

Editorial Note: Parts of this Peer Review File have been redacted as indicated to remove third-party material where no permission to publish could be obtained.

REVIEWER COMMENTS

Reviewer #1 (Remarks to the Author):

The ability to produce regio-divergent products depending on ligand structure is an important accomplishment. The scope of CF3-styrenes that participate in both processes is sufficiently broad, and the products are demonstrated to be easily converted into valuable synthetic intermediates.

However, the origin of regio-divergence is not well rationalized and the mechanistic work is insufficient to support the author's conclusions. In particular, the KIE studies are flawed. In the text the authors refer to the reactions as a competition experiments, implying the reagents are competing for either hydrogen or deuterium silanes within the same reaction flask. Conversely, the Figure 6 label associated with these experiments refers to these as parallel KID studies (which appears to be accurate based on the content within the Supporting Information). The experiments themselves, as they are written in the Supporting Information, are not of sufficient rigor to yield useful mechanistic data. First, the experiments describe taking 0.55mL samples from a reaction that contains 2.0mL of solvent. Six data points are shown, suggesting that a total volume of 3.3mL was removed, far more than is available given the stated stoichiometries and molarity. Second, all reactions display a significantly large non-zero y-intercept relative to their slopes, yet no explanation for this behavior is given. Lastly, the data spans, at most, only three percent of the overall conversion stated for a given reaction (in Figure 23 in the SI, a value of 0.003M represents just 3% conversion for a 0.1M reaction, in Figure 24 a value of 0.0002M represents less than 1% of the overall conversion). Either there are serious errors in reporting accurate numbers, or the reactions have not converted sufficiently to create meaningful data.

The rationale for a regio-switch in the proposed mechanism is not well reasoned (also labeled as Figure 6, but should be Figure 7). The authors claim that the orientation of Ni-H insertion from A to B is the result of the sigma-withdrawing effects of the CF3 group. However, the electronics of species going from C to D is identical, making it unreasonable to expect a high level of the opposite regioisomer via an analogous insertion.

Reviewer #2 (Remarks to the Author):

The authors report a noteworthy example of a nickel-catalyzed hydrosilylation reaction on 1,1-disubstituted styrene derivatives containing alpha-trifluoromethyl groups. Importantly, the authors demonstrate two sets of reaction conditions using different ligands (triphenylphosphine and BINAP) that result in different regioisomers of silicon-containing products, allowing for high levels of regioselectivity in the synthesis of both benzylic and homobenzylic silane products. This is significant due to the importance of trifluoromethyl groups in biological applications. The authors also report that using both catalyst systems, they were able to avoid the previously reported beta-fluoride elimination. While this manuscript is a valuable contribution, it will need significant revisions, corrections and additions before it is suitable for publication. Below are: a) general comments and questions, b) supporting information errors and questions and c) some constructive writing suggestions.

General comments and questions:

The substrate scope compatible with both sets of conditions contains good diversity with respect to carbocyclic-styrene derivatives used. However, it would be good to know if the methods were compatible with a broader diversity of potentially reducible functional groups. For example, aldehydes, ketones, imines, amides, nitriles? I see that methyl esters are not tolerated – are more bulky esters tolerated? Similarly, only benzofuran and thiophene/benzothiophene are demonstrated with respect to heterocycles. If this reaction could be extended to others it would be synthetically more valuable.
Chloride substitutents are tolerated but what about other halides and pseudohalides?
Did the authors observe hydrosilylation of the cyclooctadiene from the nickel catalyst, if this happened was there any issues with purification?
Did the authors observe the products from silane redistribution. For example, decomposition of diphenylsilane into phenysilane ($PhSiH_3$) and triphenylsilane (Ph_3SiH)? – $PhSiH_3$ can go further to SiH_4 (hazardous). This has been noted to occur in other catalysts. On this point I would suggest the authors include a general safety note within their procedure for the use of silane reagents to highlight the possibility for the formation of volatile and potentially pyrophoric silanes. See: Tetrahedron, 2019, 3330-3335.
Examples of further derivatisation reactions is nice; however, I would suspect that the scope of benzylic silane diversifications to be broader. For example, formation of benzylic radical species from benzylic silanes has been established, see: Eur. J. Org. Chem., 2020. M 1459-1465. Melchiorre, P. Nature Chem 9, 868–873 (2017). Additionally, for example benzylic silanes can act as benzylic anion equivalents and be involved in addition reactions, see: O'Shea, D. F. Tetrahedron, 2013, 6448-6460. If these methods were applicable to the benzylic silicon products produced here, this might be a synthetically valuable way to install CF¬3 groups to many different types of molecules.
There are some important (regiodivergent) hydrosilylation references missing: Angew. Chem. Int. Ed. 2020, 59, 19115. Asian J. Org. Chem. 2021, 10, 2379. Chem. Sci., 2019, 10, 5079-5084. Organometallics 2020, 39, 18, 3441–3451. Org. Lett. 2021, 23, 4, 1434–1439.

Supporting information:

Page 7 – L:B ratio from SI doesn't match main manuscript >20:1 (SI), 7:1 manuscript.
Page 7 – Yield 3h SI doesn't match manuscript 99% vs. 80%. There are several examples throughout where the L:B ratios and yields from the SI do not match the main manuscript. Please carefully check all of these.
Page 9 – 3l yield reported within SI doesn't match manuscript.
Page 10 – 3o, 90.2 mg exceeds 100% yield. 3p 94.5 mg = 0.212 mmol = 106% yield. There are many examples of miscalculations throughout the supporting info. Please revise.
Page 12 – mass of 3v (Chemical Formula: $C_{26}H_{21}F_5Si$, Exact Mass: 456.1333) does not match structure drawn.
Page 14 - Molecular Weight: 412.5712, 74.5 mg = 0.18 mmol = 90%
Page 27 – I appreciate that there are significant C-F couplings but the 13C NMR of compound 6 is of poor quality – peaks look barely above the noise.
Page 43 – For the KIE experiments, large aliquots (0.55 mL from a 2 mL mixture?) were taken at seemingly random time intervals over a short period of time 30 minutes into the reaction using PPh_3 and 70 minutes into the reaction using BINAP without any explanation

for these choices. It would be good to see a reaction progress monitoring for each reaction with aliquots taken at defined time points (not random) for each set to a yield greater than 50%. From the data provided it is not clear if the limited time period examined in each case is still within an induction period or if this is the true initial rate of reaction. Could the authors additionally ensure that the 19F NMR method used for quantitation is ‘quantitiative’ (i.e long d1) – I could not see this noted anywhere.
Most of the spectra presented look good and of good purity, however they are presented only to a low height of less than half the page. Typically, these should be inserted with peaks higher/taller on the page. I appreciate that the authors have included magnified sections where appropriate.

Manuscript clarity:

While the text is generally clear and understandable there are parts where the level of English could be improved. Below are some highlighted examples of unclear text and where some references are required.
Line 24 - “Organofluorine compounds have been widely used in the area of pharmaceuticals, agrochemicals and materials science.” – requires a reference
Line 30 - “One attractive strategy for the synthesis of alkyl-CF3 compounds would be the direct transformation of α-CF3 transition-metal intermediates, but much more challenge due to the thermodynamically favored β-F elimination.” – requires a reference
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Line 95 – “loaded lower yield of desired product” – loaded? Gave lower yield of the desired product.
Line 114 – alkene 3i
Line 132 – The text states that TBAT was used however the scheme states TBAF.
Line 133 – ‘oxidated’ – oxidised.
Figure 1. i) “vary limited” – spelling very, ii) “more challenge” – more challenging, iii) I agree many examples of the outlined transformations exist, the authors should explicitly add references within the scheme (eg. Add ref. x,y,z below the structures).
Figure 4. yield is misspelt a few times within this scheme.
Figure 5. yield is misspelt.

To the comments of Reviewer 1:

Comments : The ability to produce regio-divergent products depending on ligand structure is an important accomplishment. The scope of CF3-styrenes that participate in both processes is sufficiently broad, and the products are demonstrated to be easily converted into valuable synthetic intermediates.

Reply: We sincerely thank the reviewer's positive comments.

Comments 1: However, the origin of regio-divergence is not well rationalized and the mechanistic work is insufficient to support the author's conclusions. In particular, the KIE studies are flawed. In the text the authors refer to the reactions as a competition experiments, implying the reagents are competing for either hydrogen or deuterium silanes within the same reaction flask. Conversely, the Figure 6 label associated with these experiments refers to these as parallel KID studies (which appears to be accurate based on the content within the Supporting Information). The experiments themselves, as they are written in the Supporting Information, are not of sufficient rigor to yield useful mechanistic data. First, the experiments describe taking 0.55mL samples from a reaction that contains 2.0 mL of solvent. Six data points are shown, suggesting that a total volume of 3.3 mL was removed, far more than is available given the stated stoichiometries and molarity. Second, all reactions display a significantly large non-zero y-intercept relative to their slopes, yet no explanation for this behavior is given. Lastly, the data spans, at most, only three percent of the overall conversion stated for a given reaction (in Figure 23 in the SI, a value of 0.003M represents just 3% conversion for a 0.1M reaction, in Figure 24 a value of 0.0002M represents less than 1% of the overall conversion). Either there are serious errors in reporting accurate numbers, or the reactions have not converted sufficiently to create meaningful data.

Reply: Thank you very much for the valuable comment. We have corrected the KIE studies in the revised manuscript and Supplementary Information.

First, we previous performed the parallel KIE studies and determined the yield of products by ^{19}F NMR with (trifluoromethyl)benzene as an internal standard. The six data points were taken in one NMR tube and monitored by ^{19}F NMR.

Second, for the non-zero y-intercept of Ni/BINAP system, we proposed the reaction need an induction period for the generation of activated Nickel catalyst. During this induction period, only starting materials observed by ^{1}H NMR and ^{19}F NMR.

Lastly, we performed the new parallel KIE studies with several bench reactions method but not NMR tube method. These new KIE studies were monitored to ~15% conversion, and rate constants were calculated for each reaction using the initial rates method. According to these new KIE studies, the KIE value for Ni/PPh_3 was changed from 0.6 to 0.4, and the KIE value for Ni/BINAP was changed from 1.0 to 1.1. The new KIE results are consisted with our previous conclusion.

In the revised manuscript, we have corrected the "competition experiments" to "parallel KIE studies" in paragraph 8. We also corrected the KIE data from 0.6 to 0.4 for Ni/PPh_3, and 1.0 to 1.1 for Ni/BINAP in Figure 6D.

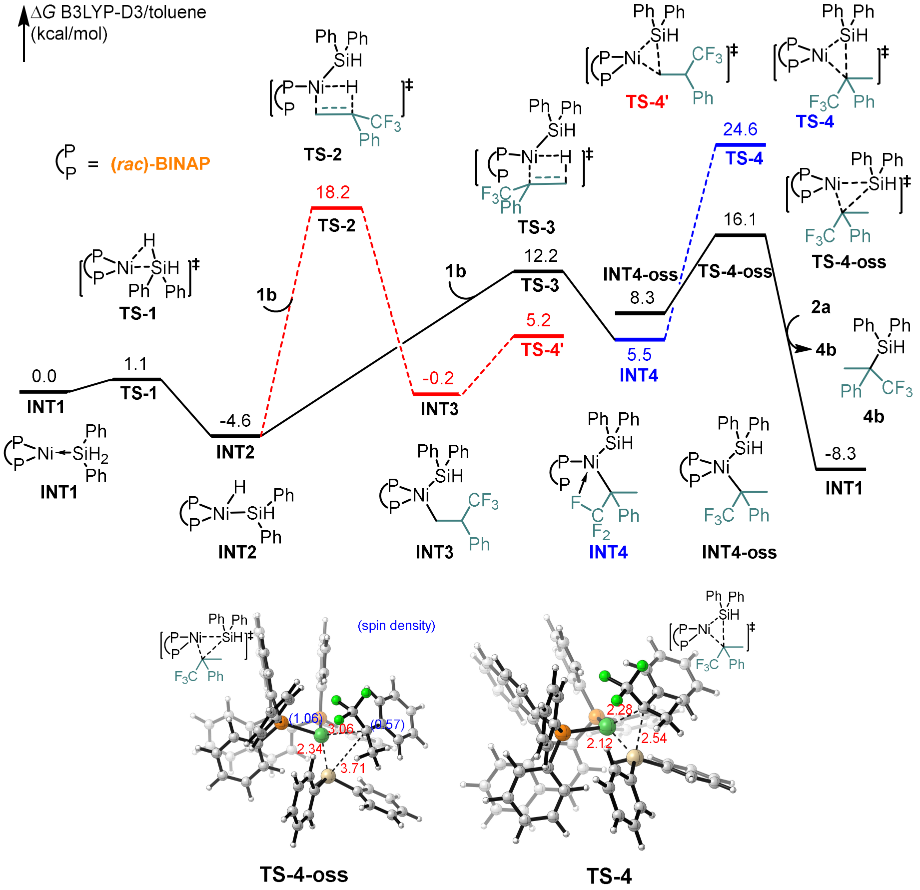
In the Supporting information, we have added the new KIE procedures in the Supplementary Fig. 33 and Supplementary Fig. 34, and explained the non-zero reason as an induction period for the generation of activated Nickel catalyst.

Comments 2: The rationale for a regio-switch in the proposed mechanism is not well reasoned (also labeled as Figure 6, but should be Figure 7). The authors claim that the orientation of Ni-H insertion from A to B is the result of the sigma-withdrawing effects of the CF3 group. However, the electronics of species going from C to D is identical, making it unreasonable to expect a high level of the opposite regioisomer via an analogous insertion.

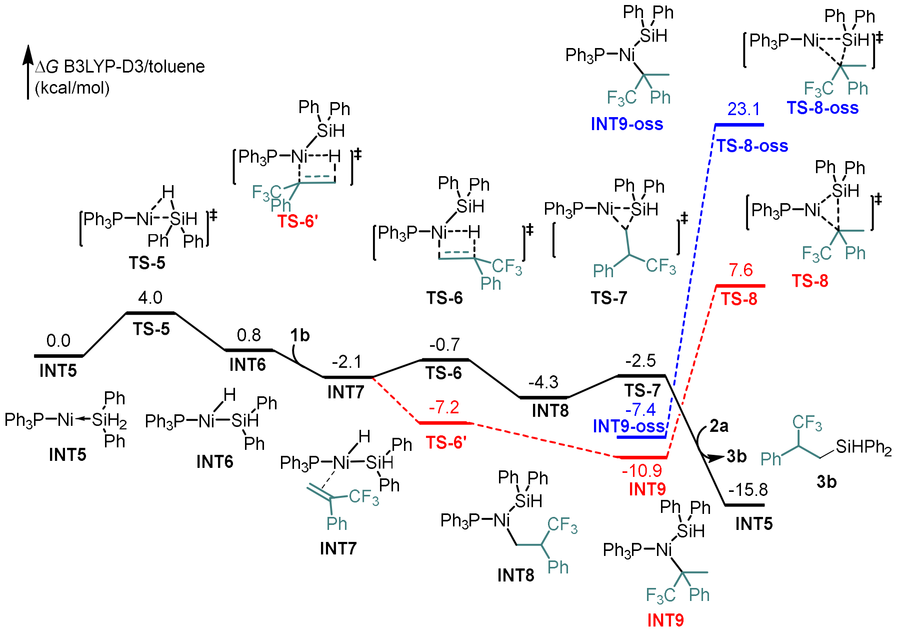
Reply: Thank you very much for the valuable comment. To explain regio-switch of the reaction, we performed several experiments and detailed DFT studies.

Based on our mechanism studies (Figure 6) and literature report, we proposed the Chalk-Harrod pathway in our reaction systems. The EPR result also support the Chalk-Harrod pathway in our system. Products **13** and **14** from the cyclopropyl-containing alkene, indicating the Ni-H insertion pathway but not Ni-Si insertion pathway for Ni/PPh_3 and Ni/BINAP catalyst systems (Figure 6B). The formation of products **11** and **12** also indicated the steric hindrance of substituent in alkene could control the regioselectivity of Ni-H insertion (Figure 6B). Recently, Cook's mechanism studies on the hydrosilylation regioselectiviy also support our proposed reaction pathway (*ACS Catal.* **2022**, *12*, 11002−11014.).

We also performed detailed density functional theory (DFT) calculations to explain the reason of regioselectivity. As shown in Scheme R1, the detailed mechanism of Ni/BINAP systems was performed. The open-shell singlet transition state **TS4-oss** was crucial for the construction of *tetra*-substituted C(sp^3)–Si bond. This unique open-shell singlet reaction mechanism is attributed to the d-d orbital transformation in the nickel center (*ACS Catal.* **2021**, *11*, 10681−10693.) and steric repulsion between BINAP with the trifluoromethyl group. As shown in Scheme R2, the reaction mechanism of Ni/PPh3 system was performed. The high selectivity of the generation of *anti*-Markovnikov product can be attributed to the elevated energy barrier for C(sp^3)–Si reductive elimination energy barrier.



Scheme R1. DFT calculation for the Ni/BINAP systems to give product **4**.



Scheme R2. DFT calculations for the Ni/PPh_3 systems to give product **3**.

In the revised manuscript, we have added detailed density functional theory (DFT) calculations in Figure 7 and Figure 8. We also added the detailed mechanism and the reasons in paragraph 9 and paragraph 10. We also cited the reference (*ACS Catal.* **2022**, *12*, 11002−11014.) as Ref 68 and (*ACS Catal.* **2021**, *11*, 10681−10693.) as Ref 69.

In the Supplementary information, we have added these EPR experiments in Supplementary Figures 19-22.

To the comments of Reviewer 2:

Comments : The authors report a noteworthy example of a nickel-catalyzed hydrosilylation reaction on 1,1-disubstituted styrene derivatives containing alpha-trifluoromethyl groups. Importantly, the authors demonstrate two sets of reaction conditions using different ligands (triphenylphosphine and BINAP) that result in different regioisomers of silicon-containing products, allowing for high levels of regioselectivity in the synthesis of both benzylic and homobenzylic silane products. This is significant due to the importance of trifluoromethyl groups in biological applications. The authors also report that using both catalyst systems, they were able to avoid the previously reported beta-fluoride elimination. While this manuscript is a valuable contribution, it will need significant revisions, corrections and additions before it is suitable for publication. Below are: a) general comments and questions, b) supporting information errors and questions and c) some constructive writing suggestions.

Reply: We sincerely thank the reviewer's positive and valuable comments.

General comments and questions:

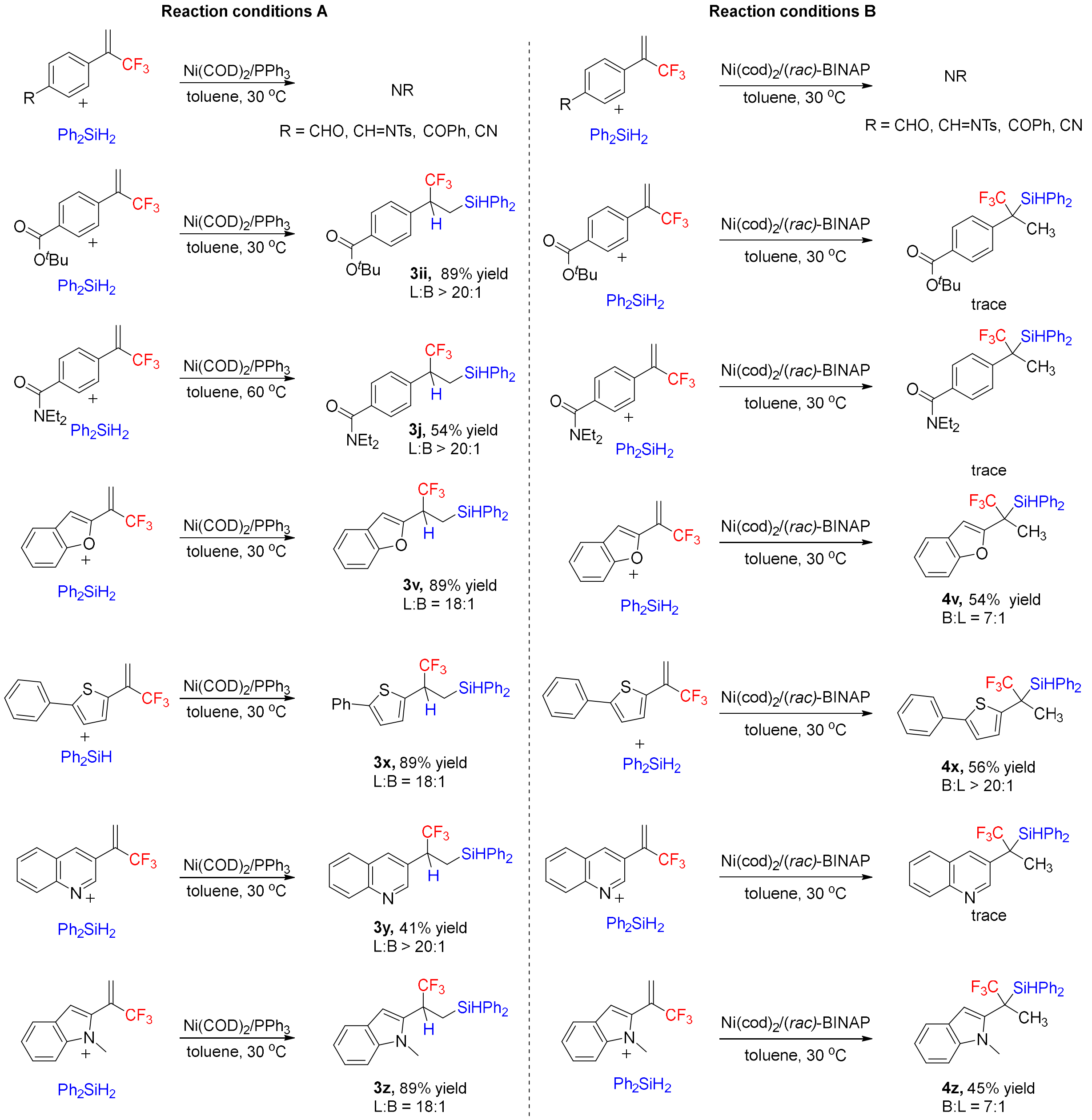
Comments 1: The substrate scope compatible with both sets of conditions contains good diversity with respect to carbocyclic-styrene derivatives used. However, it would be good to know if the methods were compatible with a broader diversity of potentially reducible functional groups. For example, aldehydes, ketones, imines, amides, nitriles? I see that methyl esters are not tolerated – are more bulky esters tolerated? Similarly, only benzofuran and thiophene/benzothiophene are demonstrated with respect to heterocycles. If this reaction could be extended to others it would be synthetically more valuable.

Reply: Thank you very much for the valuable comment.

The amide and *tert*-butyl substituted esters were tolerated under the reaction conditions A (Ni/PPh_3 system), giving the corresponding linear products **3ii** and **3j**. No desired branched products **4ii** and

4j were observed for the amide and *tert*-butyl substituted esters under the reaction conditions B (Ni/BINAP system). When the alkenes with other reducible functional groups including aldehyde, kentone and imine and nitrile groups were investigated, no desired products **3** or **4** were observed. For example, the aldehyde-containing alkene only lead to the alcohol containing alkene without hydrosilylation product **3** or **4**, even with 8.0 eq of Ph_2SiH_2.

Other heterocycles including quinolone and indole were successfully to give the desired products **3y** and **3z** under the reaction conditions A. The benzofuran, thiophene, and indole also could be delivered to the branched products **4v**, **4x** and **4z** (Scheme R3).



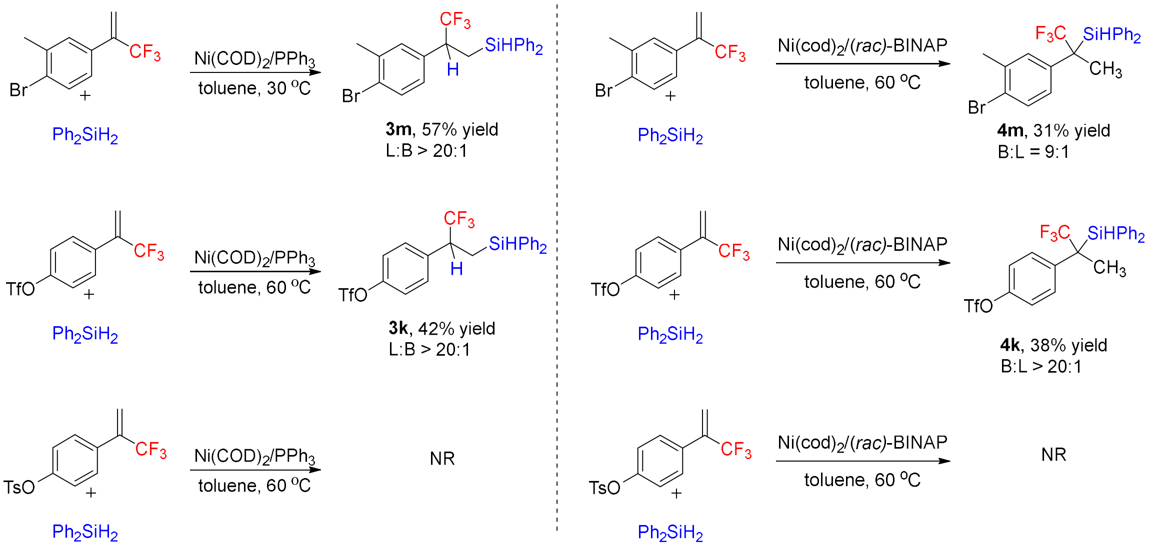
Scheme R3. Substrates scope of alkenes with other functional groups and heterocycles.

In the revised manuscript, we have added these results in Figure **3** and Figure **4**, respectively. We also added the sentence “The reaction can also tolerate reactive groups such as esters (**3i**, 85% yield and **3ii**, 89% yield), amine (**3j**, 54% yield) and triflate (**3k**, 42% yield). Other reduction-sensitive functional groups such as aldehydes, ketones, imines were not compatible for this hydrosilylation.” and “Pleasingly, the N-heterocycles containing alkenes including quinolone and indole also reacted smoothly to provide corresponding products (**3y**, 41% yield, L:B > 20:1 and **3z**, 89% yield, L:B = 18:1).” in paragraph 5. We have added the sentence “The reduction-sensitive functional groups including aldehydes, ketones, imines and amines were not compatible.” and “Other (hetero)aryl-substituted alkenes such as furan, thiophene and indole were also compatible (**4v**, 54% yield, **4x**, 56% yield and **4z**, 45% yield).”in paragraph 6.

We also updated the labeled numbers of products **3** and **4** in the manuscript and supplementary information.

Comments 2: Chloride substitutents are tolerated but what about other halides and pseudohalides?

Reply: We thank the reviewer for the valuable comment. The Br- substituted alkene was successful delivered to the corresponding product **3m** and **4m**. While, no desired product observed for the I-containing substrate. We also tested the pseudohalide groups such as –OTs and –OTf. The –OTf containing substrate was successfully to give the desired products **3k** or **4k**. While, –OTs resulted in starting materials recovered (Scheme R4).



Scheme R4. Substrates scope of alkenes with other halides and pseudohalides.

In the revised manuscript, we have added these results in Figure **3** and Figure **4**. We also added the sentence “The reaction can also tolerate reactive groups such as esters (**3i**, 85% yield and **3ii**, 89%

yield), amine (**3j**, 54% yield) and triflate (**3k**, 42% yield).” in paragraph 5. We also added the sentence “For the triflate substituted alkenes, the desired hydrosilylation product **4k** was obtained in 38% yield.” in paragraph 6.

Comments 3: Did the authors observe hydrosilylation of the cyclooctadiene from the nickel catalyst, if this happened was there any issues with purification?

Reply: We thank the reviewer for the comment. By HPLC and ^{1}H NMR, we observed the hydrosilylation of the cyclooctadiene from the nickel catalyst. This cyclooctadiene hydrosilylation product did not influence the purification of our desired products.

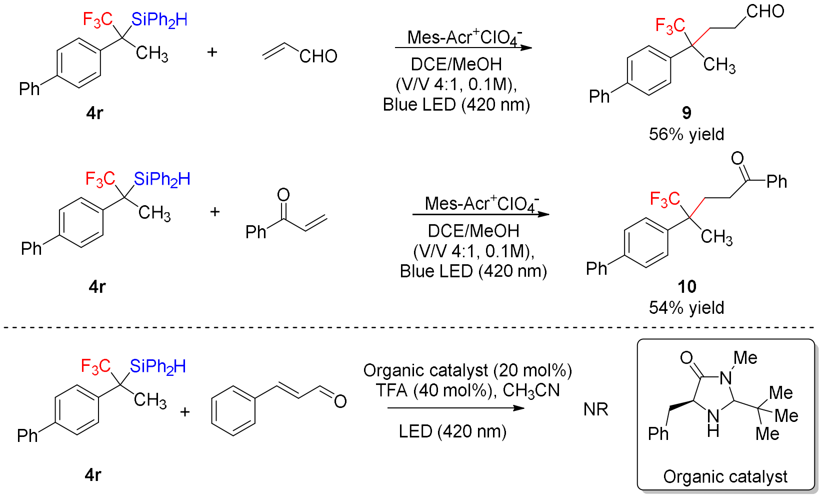
Comments 4: Did the authors observe the products from silane redistribution. For example, decomposition of diphenylsilane into phenysilane (PhSiH3) and triphenylsilane (Ph3SiH)? – PhSiH3 can go further to SiH4 (hazardous). This has been noted to occur in other catalysts. On this point I would suggest the authors include a general safety note within their procedure for the use of silane reagents to highlight the possibility for the formation of volatile and potentially pyrophoric silanes. See: Tetrahedron, 2019, 3330-3335.

Reply: We thank the reviewer for the comment. By HPLC and ^{1}H NMR of the crude reaction mixtures, we didn’t observe the silane redistribution products phenysilane ($PhSiH_3$) and triphenylsilane (Ph_3SiH). While, as there are some literature reports for observe the silane redistribution, we added the Safety note in the supporting information.

In the Supporting information, we have added the “Safety note: Given the hazardous nature of the gaseous products might be formed in the hydrosilylation reacitons, precautions should be taken when using any hydrosilane reagent, particularly if conducted on a large scale.” in the general synthetic procedures.

Comments 5: Examples of further derivatisation reactions is nice; however, I would suspect that the scope of benzylic silane diversifications to be broader. For example, formation of benzylic radical species from benzylic silanes has been established, see: Eur. J. Org. Chem., 2020. M 1459-1465. Melchiorre, P. Nature Chem 9, 868–873 (2017). Additionally, for example benzylic silanes can act as benzylic anion equivalents and be involved in addition reactions, see: O’Shea, D. F. Tetrahedron, 2013, 6448-6460. If these methods were applicable to the benzylic silicon products produced here, this might be a synthetically valuable way to install CF¬3 groups to many different types of molecules.

Reply: We thank the reviewer for these suggestions. According to the literature report (*Eur. J. Org. Chem.,* **2020**. 1459-1465.), we realized the radical conjugated addition of benzylic silane **4r** to activated alkenes by visible-light photocatalysis, affording the high value CF$_3$-containing products with quaternary carbon center (**9**, 56% yield and **10**, 54% yield). We have added these results in the revised manuscript in Figure 5. We also performed the visible-light induced benzylic radical addition to α, β-unsaturated aldehyde with amine catalyst through C–Si bond cleavage (*Nature Chem.* **2017**, *9*, 868–873.), while, no desired product was observed (Scheme R5).



Scheme R5. Transformation of **4r** via benzylic radical species.

Additionally, we tried the benzylic anion conditions reactions. Several bases and coupling partners were investigated, but no desired addition product obtained and only β-F elimination product **5** was observed (*J. Org. Chem.* **2021**, *86*, 13160−13168) (Scheme R6).

[Redacted]

Scheme R6. Transformation of **4r** via benzylic anion species.

In the revised manuscript, we have added the generation of **9** and **10** in Figure 5. We also added the sentence “The visible-light-mediated C–Si bond cleavage for the conjugate addition of **4r** with activated alkenes was realized, and gave the valuable CF_3-containing products with quaternary carbon center (**9**, 56% yield and **10**, 54% yield)" in paragraph 7.

In the supporting information, we have added the procedure for the generation of **9** and **10**. We also added the ^1H NMR, ^{13}C NMR and HRMS of **9** and **10**.

Comments 6: There are some important (regiodivergent) hydrosilylation references missing: Angew. Chem. Int. Ed. 2020, 59, 19115. Asian J. Org. Chem. 2021, 10, 2379. Chem. Sci., 2019, 10, 5079-5084. Organometallics 2020, 39, 18, 3441–3451. Org. Lett. 2021, 23, 4, 1434–1439.

Reply: Thank you very much for these suggestions. As there are already 70 references in the manuscript, we deleted several not so important previous references Ref 23, 25, 29, 65, 69 and 70. We have cited these (regiodivergent) hydrosilylation references as new Ref 56, 57, 58, 59, 60. We also updated the references in the manuscript.

In the revised manuscript, we have added these references in the manuscript and updated other references in the manuscript.

Supporting information:

Comments 7:

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Reply: We sincerely thank you very much for these corrections.

1. We did these experiments again for the generation of **3h** and other products including **3b**, **3c**, **3e**, **3f**, **3g**, **3h**, **3i**, **3j**, **3k**, **3m**, **3n**, **3q**, **3aa**, **4b**, **4l**, **4o** and **4s**. We corrected the yield and B:L ratio according to the new results in the revised manuscript and Supporting information.

2. We did the experiment again to get the yield and B:L ratio of **3l**. We updated these results in the manuscript and Supporting information.

3. We did the experiment again to get the yield and B:L ratio of **3o**. We updated these results in the manuscript and Supporting information.

4. We have corrected it according to our HRMS data.

5. We have corrected it.

6. We have got new ^{13}C NMR spectra of compound **6**, and changed the ^{13}C NMR of the product **6** and **5**.

7. We did the parallel KIE studies again with several bench reactions. The new the KIE studies were monitored to ~15% conversion, and rate constants were calculated for each reaction using the initial rates method. These new KIE studies are consisted with our previous conclusion. We have added these new KIE procedures in the Supplementary Fig. 33 and Supplementary Fig. 34.

We also changed the spectra present to one page for all Supplementary Figures.

Manuscript clarity:

Comments 8:

While the text is generally clear and understandable there are parts where the level of English could be improved. Below are some highlighted examples of unclear text and where some references are required.

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(15) Line 133 – ‘oxidated’ – oxidised.

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(17) Figure 4. yield is misspelt a few times within this scheme.

(18) Figure 5. yield is misspelt.

Reply: We sincerely thank you very much for these corrections and suggestions.

1. We have added the Ref 1-4 after this sentence.
2. We have added the Ref 18-20 after this sentence.
3. We have corrected it.

4. We have corrected it.
5. We have changed the sentence “The regiodivergent hydrosilylation would be a practical tool for the rapid construction of organosilanes complexity.” to “The regiodivergent hydrosilylation would be a practical tool for the rapid construction of value-added organosilanes.”
6. We have changed the “pincer liganded” to “pincer ligated”.
7. We have changed the “This 1:1 ratio might be benefit for the coordination of 1a to nickel center and performed high reactivity” to “This 1:1 ratio might be benefit for generation of high reactivity nickel catalyst”
8. We have corrected it.
9. We have corrected it
10. We have corrected it.
11. We have changed the sentence of “probably due to this Ni:BINAP ratio be benefit for the generation of high active Nickel catalysis.” to “indicating the importance of the nickel:BINAP ratio in the formation of an optimally active nickel catalyst.”
12. We have changed the sentence “loaded lower yield of desired product” to “ gave lower yield of the desired product.”
13. This reviewer might refer to the Line 114 – alkene **1ii**. We have added the alkene **1ii** in line 114.
14. We have corrected it.
15. We have corrected it.
16. We have corrected it.
17. We have corrected it.
18. We have corrected it.

Other changes:

Other typos were corrected in the revised manuscript and Supporting Information.

Attached please find our revised manuscript and Supporting information. We are pleased to answer any further questions.

Sincerely yours,

Dachang Bai

REVIEWER COMMENTS

Reviewer #2 (Remarks to the Author):

The authors have substantially revised their manuscript, and this has now become a much more comprehensive study for this nice set of two reactions. The previous version of this manuscript contained lots of typographical errors and the supporting information was full of discrepancies, and it was difficult to read and understand. However, this revised version is much better, and I thank the authors for their additional work and careful consideration of the points raised on the previous version.

As part of the revision, the authors have expanded the applicable substrate scope to try all of the suggested substrates. This has been much more successful than I had imagined that it would be. A few more examples of further derivatization have also been added, including a nice photoredox 1,4-radical addition reaction.

For the mechanism, the authors have gone to considerable lengths to bolster their prior assertions. The manuscript now includes some further experiments, including EPR (lack of signal…) and also now has DFT studies on both reactions. Both of the DFT analyses add value to the manuscript.

I would therefore be supportive of the publication of this manuscript.

Some minor points for consideration:
Compound 3y is a quinoline and not quinolone.
In Figure 5 – add the catalyst loadings used for compounds 7, 9, 10.
SI:
“All the reactions were carried out under argon atmosphere in a nitrogen-filled glove box.” – Ar atmosphere in N2 glovebox – Can the authors double check that this is correct.

Reviewer #3 (Remarks to the Author):

In this manuscript, the authors report an elegant study of regiodivergent hydrosilylation of α-(fluoroalkyl)styrenes using nickel(0) catalysis. As a computational chemist, my expertise lies in the theoretical aspects rather than experimental procedures. I think that the theoretical study needs further analysis. Therefore, my recommendation is to accept the paper once the following revisions are carried out:

The underlying reasons behind ligand-controlled regioselectivity should be thoroughly analyzed.
For the insertion step, in BINAP system, the [2,1]-insertion is highly unfavorable, making it as the selectivity-determining transition state, while in PPh3 system, the [2,1]-insertion requires much lower in energy.
For the reductive elimination, the open-shell transition state is much lower in energy than the closed-shell one, while the opposite trend is observed for the PPh3 system.
It would be insightful to conduct calculations using two PPh3 ligands to assess whether similar conclusions can be drawn. In the BINAP system, the dissociation of one phosphine ligand prior to insertion makes the step energetically demanding. A similar scenario may be anticipated with two PPh3 ligands, potentially leading to opposite regioselectivity compared

to using one PPh3 ligand. Experimentally verifying these predictions would be beneficial.

To the comments of Reviewer 2:

Comments : As part of the revision, the authors have expanded the applicable substrate scope to try all of the suggested substrates. This has been much more successful than I had imagined that it would be. A few more examples of further derivatization have also been added, including a nice photoredox 1,4-radical addition reaction.

For the mechanism, the authors have gone to considerable lengths to bolster their prior assertions. The manuscript now includes some further experiments, including EPR (lack of signal…) and also now has DFT studies on both reactions. Both of the DFT analyses add value to the manuscript.

I would therefore be supportive of the publication of this manuscript.

Reply: We sincerely thank the reviewer's positive comments.

Comments 1: Some minor points for consideration:

Compound 3y is a quinoline and not quinolone.

In Figure 5 – add the catalyst loadings used for compounds 7, 9, 10.

Reply: Thank you very much for these suggestions. We have changed "quinolone" to "quinolone". We also added the catalyst loadings used for compounds 7, 9, 10.

Comments 2: SI:

"All the reactions were carried out under argon atmosphere in a nitrogen-filled glove box." – Ar atmosphere in N2 glovebox – Can the authors double check that this is correct.

Reply: Thank you very much for the correction. We have corrected them.

To the comments of Reviewer 3:

Comments: In this manuscript, the authors report an elegant study of regiodivergent hydrosilylation of α-(fluoroalkyl)styrenes using nickel(0) catalysis. As a computational chemist, my expertise lies in the theoretical aspects rather than experimental procedures. I think that the theoretical study needs further analysis. Therefore, my recommendation is to accept the paper once the following revisions are carried out:

The underlying reasons behind ligand-controlled regioselectivity should be thoroughly analyzed.

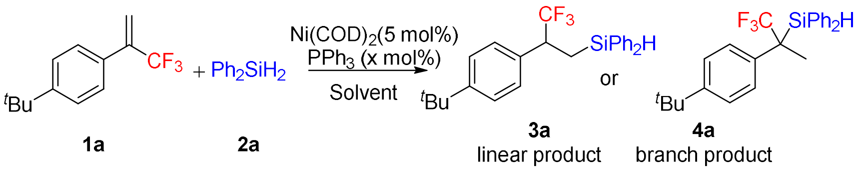
Reply: We sincerely thank the reviewer's positive comments.

Comments 1: For the insertion step, in BINAP system, the [2,1]-insertion is highly unfavorable, making it as the selectivity-determining transition state, while in PPh_3 system, the [2,1]-insertion requires much lower in energy. For the reductive elimination, the open-shell transition state is much lower in energy than the closed-shell one, while the opposite trend is observed for the PPh3 system.

It would be insightful to conduct calculations using two PPh3 ligands to assess whether similar conclusions can be drawn. In the BINAP system, the dissociation of one phosphine ligand prior to insertion makes the step energetically demanding. A similar scenario may be anticipated with two PPh3 ligands, potentially leading to opposite regioselectivity compared to using one PPh3 ligand. Experimentally verifying these predictions would be beneficial.

Reply: Thank you very much for the valuable comment.

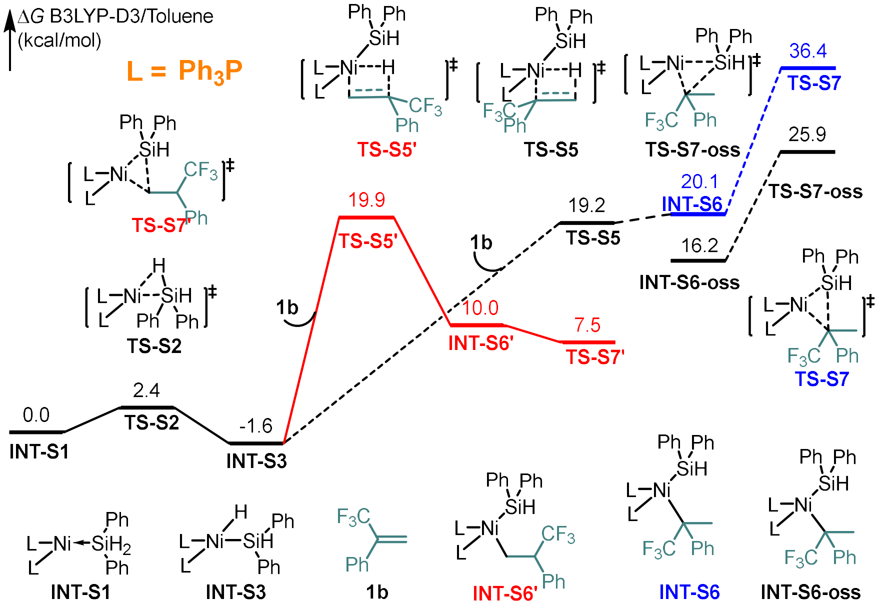
For experimental results. As shown in Scheme R1, only linear product **3a** was observed with different PPh_3 loading and higher reactivity was observed when using one PPh_3 to Nickel.



Entry	PPh_3 (x mol%)	Solvent	T/(°C)	Yield	**L:B (3a:4a)**
1	5 mol%	toluene	30	96	>20:1
2	10 mol%	toluene	30	17	>20:1
3	15 mol%	toluene	30	15	>20:1
4	20 mol%	toluene	30	10	>20:1

Scheme R1. The regioselcetivity with different Ni/PPh_3 ratio.

For DFT calculation. The free energy profile of two PPh_3 to Nickel center has also been calculated. As shown in Scheme R2, the activation barrier with two PPh_3 is much higher than one PPh_3 in Fig. 8 to generate linear product, these results are consistent with our experimental results of in Scheme R1 (entries 2 and 3 in Fig. 2). We also considered the open-shell singlet species with two PPh_3, the energy barrier via **TS-S7-oss** for the C(sp^3)-Si bond formation with an activation barrier of 25.9 kcal/mol, which indicated that the formation of branch product is also unfavourable.



Scheme R2. DFT calculation for energy profiles with two PPh_3 coordinated to nickel center

In the revised manuscript, we have added the sentence “We also exclude the reaction pathway with two PPh_3 ligand bound-Ni(0) species (for more details in Supplementary Figure 39, and entry 2 *vs* 3 in **Fig. 2**).”

In the Supporting information, we have added the DFT calculation with two PPh_3 coordinated to nickel center in the Supplementary Fig. 39.

Other changes:

Other typos were corrected in the revised manuscript and Supporting Information.

Attached please find our revised manuscript and Supporting information. We are pleased to answer any further questions.

Sincerely yours,

Dachang Bai

REVIEWERS' COMMENTS

Reviewer #3 (Remarks to the Author):

The concerns have been addressed satisfactorily. I, therefore, recommend the publication of this work.