nature portfolio

Peer Review File

Mechanistic development of a mild palladium-catalyzed C-S/C-H cross-coupling of thioesters with azoles

Corresponding Author: Dr Jesse Dallenes

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)
The present manuscript by de Vos and Dallenes reports on a mild palladium-catalyzed C-S/C-H cross coupling of thioesters with azoles. The work is located on the interface of organic synthetic chemistry and detailed spectroscopic methods to uncover the reaction mechanism. Therefore, the authors needed to address different cohorts of chemists, which worked out well.
The reaction seems to be quite sensitive towards temperature and Cu(I)-salt and amount of ligand used. The depiction of a sensitivity screening (developed by F. Glorius) could help to narrow down important parameters and help when reproducing the results.
The substrate scope is decent in variability, especially as different heterocycles are explored. It should be pointed out positively, that two drug related compounds are included in decent yield. However, it seems like none of the products was isolated and product yield was only determined via GC/MS or 1H NMR. It would be highly desirable to isolate at least some of the products to demonstrate applicability for the synthesize of these compounds for a broader chemical community.
The demonstration of the orthogonal cross-coupling is very nice and gives good hints that an orthogonal reaction can be feasible. The authors are encouraged to really demonstrate such a 2 step procedure.
For the H/D exchange experiment it would be important to perform a reactions where the rations of K2CO3, CuBr and triethyl phosphite match the optimized reaction conditions (experiment with 39% deuteration). Especially as triethyl phosphite plays an important role in the catalytic cycle based on the kinetic results.
Figure 5a is not strait forward to understand – what are the boxes representing – and a more detailed description would be highly beneficial for the understanding of this work. Figure 5b represents a very plausible reaction mechanism and is strait forward.
Overall, the manuscript can be considered for publication after major revisions.

Reviewer #2

(Remarks to the Author)
This manuscript reports a palladium-catalyzed, copper-mediated C–H acylation of azoles using thioesters under comparatively mild conditions. The work combines synthetic methodology with mechanistic investigations (kinetics, H/D exchange, and operando XAS) to propose a non-canonical Pd–Cu cooperative mechanism. The study addresses an important challenge in C–H acylation chemistry by expanding substrate scope to include imidazoles, fused N-heterocycles, and aliphatic thioesters while employing a weak base and low Pd loading. The manuscript is well written, and certainly will bring new information to readers. Therefore, I strongly suggest accepting this article, however, few corrections are needed before the final acceptance:

1. The manuscript concludes that Cu-phosphite-mediated C–H deprotonation is rate limiting. This interpretation is reasonable but not fully demonstrated. No kinetic isotope effect (KIE) measurements are reported, please perform intermolecular or parallel KIE experiments and report reaction orders quantitatively.

2. The XAS data indicate Pd–Cu interactions and are consistent with a bimetallic species. However, the manuscript presents the Pd–S–Cu intermediate almost as an established fact.
State that the Pd–S–Cu complex is a "proposed" or "most consistent" structure rather than a definitively identified

intermediate.

3. The manuscript proposes a "nucleophilic displacement oxidative addition" mechanism.
Use more cautious language and acknowledge alternative mechanistic possibilities.

4. The authors propose dual functions for Cu(I): Thioester activation and Azole deprotonation. Evidence for each role individually is indirect.
Can you discuss alternative interpretations of the copper effect?

Reviewer #3

(Remarks to the Author)
The authors report the acylation of azoles with thioesters under Pd/Cu cocatalysis in the presence of a base. Closely related reactions have previously been reported using thioesters (Ref. 26), acyl fluorides (Ref. 25), and carboxylic acids (Ref. 27). Although the authors have somewhat expanded the substrate scope and further optimized the reaction conditions, the principal novelty of the manuscript lies in the mechanistic studies. In particular, the in operando X-ray studies provide notable insight into the reaction. However, the proposed mechanism appears to involve relatively conventional Pd/Cu cocatalysis, and the mechanistic findings seem to have contributed only marginally to the expansion of the reaction scope, while the reported yields are generally moderate to low.

Further questions and concerns:
1) The authors should address why 3 equivalents of benzothiazole were used in the experiments presented in Table 1 and Figure 3, but not in the experiments presented in Figure 2.
2) “DPPF” in Table 1 should be fully defined.
3) The authors should include the specific values and equation they used to calculate the activation energy.
4) Why was 2.5 mol % of Pd(COD)DQ and 20 mol % of triethyl phosphate used as standards in the mechanistic studies when the reaction development and scope used 1 mol % and 40 mol %?
5) What the colored banners on the left-hand side of Figure 5 represent is unclear.
6) Which figure corresponds to what proposed chemical species is unclear in Figure 5. In general, Figure 5 is not clear to a non-specialist. Figure 5 should be edited to more clearly explain the authors’ claims.
7) In Figure 3, the applicability towards orthogonal cross-coupling is implied; however, did the authors investigate how the presence of Pd(COD)DQ, triisopropyl phosphite and CuBr would affect a one-pot sequential coupling sequence?
8) Providing in the supporting information the actual values of the data presented in Figure 4’s graphs in tables would be useful.
9) The entry number “18” for Figure 2 should be included in the text.
10) Qualifiers like “great” and “decent” should be removed, and actual yields should be added in the text

Reviewer #4

(Remarks to the Author)
I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Communications Chemistry initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
The authors have addresses all my comments and the manuscript can be accepted for publication without any further changes.

Reviewer #2

(Remarks to the Author)
I am happy with their corrections and I recommend for accepting this article

Reviewer #3

(Remarks to the Author)
The authors revised the manuscript and addressed my concerns, and the other reviewers' questions and comments. I believe the revised manuscript can be considered for publication.

Reviewer #4

(Remarks to the Author)
I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Communications Chemistry initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

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Reviewer 1

The present manuscript by de Vos and Dallenes reports on a mild palladium-catalyzed C-S/C-H cross coupling of thioesters with azoles. The work is located on the interface of organic synthetic chemistry and detailed spectroscopic methods to uncover the reaction mechanism. Therefore, the authors needed to address different cohorts of chemists, which worked out well.

1) The reaction seems to be quite sensitive towards temperature and Cu(I)-salt and amount of ligand used. The depiction of a sensitivity screening (developed by F. Glorius) could help to narrow down important parameters and help when reproducing the results.

We thank the reviewer for their suggestion and have performed the sensitivity assessment; the results are discussed in the updated main text. The figure and raw data have been added in the supplementary information. In general, the reaction had low sensitivity to variations in reaction conditions. The largest decrease in yield was observed with increased temperature (90 °C instead of 80 °C), lower CuBr loading (1.5 eq. instead of 2 eq.) or adding 5 µl water to the mixture before reaction.

An increased temperature likely results in accelerated catalyst deactivation, leading to a lower overall yield despite increased kinetics (see Figure 4c). The negative effect of a lower copper loading could be due to coordinative saturation of Cu by the phosphite ligand and azole after longer reaction times, when a significant amount of active CuBr has already been transformed into inactive Cu-thiolate. Finally, the negative influence of water could be the result of thioester hydrolysis and the formation of inactive copper hydroxide species.

2) The substrate scope is decent in variability, especially as different heterocycles are explored. It should be pointed out positively, that two drug related compounds are included in decent yield. However, it seems like none of the products was isolated and product yield was only determined via GC/MS or 1H NMR. It would be highly desirable to isolate at least some of the products to demonstrate applicability for the synthesize of these compounds for a broader chemical community.

We agree with the reviewer that, although the work focuses mainly on catalysis and mechanistic investigations, it is essential for synthetic applications to demonstrate that the compounds can be isolated. Consequently, we have chosen to isolate compounds nr. 12 and 18, since both are derived from pharmaceutically relevant substrates. The isolated yields and NMR spectra of the purified products are included in the updated manuscript and supplementary information.

3) The demonstration of the orthogonal cross-coupling is very nice and gives good hints that an orthogonal reaction can be feasible. The authors are encouraged to really demonstrate such a 2 step procedure.

Once again we agree that, although synthesis by itself is not the main focus of the work, it is valuable to demonstrate the possibility of a two-step procedure. We have included an initial proof-of-concept orthogonal cross-coupling sequence in the main manuscript (Figure 3b), utilizing heteroaromatic 5-bromo-1-methyl benzimidazole as a non-trivial example. The coupling of S-butyl thiobenzoate with 5-bromo-1-methyl benzimidazole gave the desired product in 48% yield. After removal of solids, the crude reaction mixture was used without further purification for a follow-up Suzuki-Miyaura coupling using 4-methylphenyl boronic acid, which gave a yield of 44%, leading to an overall yield of 21%. Although relatively low, we posit that further optimization should improve the yield of this two-step procedure (outside the scope of this work).

4) For the H/D exchange experiment it would be important to perform a reactions where the rations of K2CO3, CuBr and triethyl phosphite match the optimized reaction conditions (experiment with 39% deuteration). Especially as triethyl phosphite plays an important role in the catalytic cycle based on the kinetic results.

We have performed the H/D-exchange experiment utilizing 2 eq. of K_2CO_3, 2 eq. of CuBr and 40 mol% of triethylphosphite, which matches the ratios of the optimized conditions. 66% deuterium incorporation was observed, indicating that exchange is possible in the actual reaction conditions.

5) Figure 5a is not strait forward to understand – what are the boxes representing – and a more detailed description would be highly beneficial for the understanding of this work. Figure 5b represents a very plausible reaction mechanism and is strait forward.

We agree that Figure 5a can be ambiguous for people not familiar with X-ray absorption spectroscopy and the related data analysis. Firstly, we have edited the colors of the figure so that the link between the proposed structures and the acquired data is more clearly represented. Secondly, we have provided more explanation regarding the acquired data, the data analysis and the extracted chemical information in the main text. "Finally, the speciation of the Pd catalyst in the presence of various reaction components was investigated using *in operando* X-ray absorption spectroscopy (XAS) (Figure 5a, Supplementary Tables 8-9 and Supplementary Figures 13-15). Fitting of Extended X-ray Absorption Fine Structure (EXAFS) provided information about the coordination environment around the Pd atom, which was used to propose possible intermediate complexes in the catalytic cycle." We have also expanded the figure caption to clearly state that proposed structures are drawn on the left and EXAFS/XANES data is shown on the right. We hope that with these changes the content of the figure will be clearer.

Overall, the manuscript can be considered for publication after major revisions.

Reviewer 2

This manuscript reports a palladium-catalyzed, copper-mediated C–H acylation of azoles using thioesters under comparatively mild conditions. The work combines synthetic methodology with mechanistic investigations (kinetics, H/D exchange, and operando XAS) to propose a non-canonical Pd–Cu cooperative mechanism. The study addresses an important challenge in C–H acylation chemistry by expanding substrate scope to include imidazoles, fused N-heterocycles, and aliphatic thioesters while employing a weak base and low Pd loading. The manuscript is well written, and certainly will bring new information to readers. Therefore, I strongly suggest accepting this article, however, few corrections are needed before the final acceptance:

1) The manuscript concludes that Cu-phosphite-mediated C–H deprotonation is rate limiting. This interpretation is reasonable but not fully demonstrated. No kinetic isotope effect (KIE) measurements are reported, please perform intermolecular or parallel KIE experiments and report reaction orders quantitatively.

We agree with the reviewer and have performed parallel kinetic isotope effect experiments and included these in Figure 4. A parallel KIE of 1.95 was observed, indicating that C-H bond cleavage of the azole is involved in the rate limiting step.

2) The XAS data indicate Pd–Cu interactions and are consistent with a bimetallic species. However, the manuscript presents the Pd–S–Cu intermediate almost as an established fact. State that the Pd–S–Cu complex is a "proposed" or "most consistent" structure rather than a definitively identified intermediate.

We have changed our language regarding this complex in the manuscript to more accurately reflect that it is the result of fitted data, instead of a directly identified intermediate.

3) The manuscript proposes a "nucleophilic displacement oxidative addition" mechanism. Use more cautious language and acknowledge alternative mechanistic possibilities.

Since both complex (1) and (2) already contain both the thioester and azole in an activated form, and complex (1) being the catalytic resting state, we believe that a concerted step involving nucleophilic attack of the azolyl moiety on the Pd-center, accompanied by a shift of electron density from Pd to the carbonyl group, and abstraction of the thiolate group by Cu(I) is the most likely. However, we agree that there is no direct evidence that excludes a traditional oxidative addition-transmetalation sequence and have mentioned this in the main text.

4) The authors propose dual functions for Cu(I): Thioester activation and Azole deprotonation. Evidence for each role individually is indirect. Can you discuss alternative interpretations of the copper effect?

Aside from thioester activation and azole deprotonation, we believe it is also possible that copper plays a role in preventing catalyst poisoning from highly coordinating functional groups (like thiolates or coordinating heterocycles). This can also explain why imidazole compounds perform better than in similar systems. We have added this hypothesis to the discussion of the substrate scope in the main text.

Reviewer 3

The authors report the acylation of azoles with thioesters under Pd/Cu cocatalysis in the presence of a base. Closely related reactions have previously been reported using thioesters (Ref. 26), acyl fluorides (Ref. 25), and carboxylic acids (Ref. 27). Although the authors have somewhat expanded the substrate scope and further optimized the reaction conditions, the principal novelty of the manuscript lies in the mechanistic studies. In particular, the in operando X-ray studies provide notable insight into the reaction. However, the proposed mechanism appears to involve relatively conventional Pd/Cu cocatalysis, and the mechanistic findings seem to have contributed only marginally to the expansion of the reaction scope, while the reported yields are generally moderate to low.

Further questions and concerns:

1) The authors should address why 3 equivalents of benzothiazole were used in the experiments presented in Table 1 and Figure 3, but not in the experiments presented in Figure 2.

The reaction optimization started using 3 eq. of benzothiazole, since this led to higher yields in the early stages of reaction development. However, from a synthetic point of view a large excess of a reaction component should be avoided. This is why, in the substrate scope, we sought to use only 1.1 eq. of arene wherever possible. In order to more clearly portray this change in conditions we have added another entry to the optimization table, which uses 1.1 eq. of benzothiazole and a reaction time of 24 hours, and explain why we prefer these conditions in the main text.

2) “DPPF” in Table 1 should be fully defined.

We thank the reviewer for noticing this detail and have mentioned the full name in the table.

3) The authors should include the specific values and equation they used to calculate the activation energy.

Quantitative data for the Arrhenius plot and activation energy calculations were added to the supplementary information.

4) Why was 2.5 mol % of Pd(COD)DQ and 20 mol % of triethyl phosphate used as standards in the mechanistic studies when the reaction development and scope used 1 mol % and 40 mol %?

Some mechanistic studies were performed before reaction optimization was fully finished, leading to slight disparities in reaction conditions. However, we believe that these differences do not influence the conclusions taken from the data in any way, especially seeing the 0^{th} order dependence on Pd catalyst loading revealed by the initial rate experiments.

5) What the colored banners on the left-hand side of Figure 5 represent is unclear.

Copied from the answer to comment 5 from reviewer 1: We agree that Figure 5a can be ambiguous for people not familiar with X-ray absorption spectroscopy and the related data analysis. Firstly, we have edited to colors of the figure so that the link between the proposed structures and the acquired data is more clearly represented. Secondly, we have provided more explanation regarding the acquired data, the data analysis and the extracted chemical information in the main text. “Finally, the speciation of the Pd catalyst in the presence of various reaction components was investigated using *in operando* X-ray absorption spectroscopy (XAS) (Figure 5a, Supplementary Tables 8-9 and Supplementary Figures 13-15). Fitting of Extended X-ray Absorption Fine Structure (EXAFS) provided information about the coordination environment around the Pd atom, which was used to propose possible intermediate complexes in the catalytic cycle.” We have also expanded the figure caption to clearly state that proposed structures are drawn on the left and EXAFS/XANES data is shown on the right. We hope that with these changes the content of the figure will be clearer.

6) Which figure corresponds to what proposed chemical species is unclear in Figure 5. In general, Figure 5 is not clear to a non-specialist. Figure 5 should be edited to more clearly explain the authors’ claims.

We direct the reviewer to our answer to comment 5.

7) In Figure 3, the applicability towards orthogonal cross-coupling is implied; however, did the authors investigate how the presence of Pd(COD)DQ, triisopropyl phosphite and CuBr would affect a one-pot sequential coupling sequence?

Once again we agree that, although synthesis by itself is not the main focus of the work, it is valuable to demonstrate the possibility of a two-step procedure. We have included an initial proof-of-concept orthogonal cross-coupling sequence in the main manuscript (Figure 3b), utilizing heteroaromatic 5-bromo-1-methyl benzimidazole as a non-trivial example. The coupling of S-butyl thiobenzoate with 5-bromo-1-methyl benzimidazole gave the desired product in 48% yield. After removal of solids, the crude reaction mixture was used without further purification for a follow-up Suzuki-Miyaura coupling using 4-methylphenyl boronic acid, which gave a yield of 44%, leading to an overall yield of 21%. Although relatively low, we posit that further optimization should improve the yield of this two-step procedure (outside the scope of this work).

The utilization of the crude reaction mixture shows that a follow-up cross-coupling is possible in the presence of triisopropyl phosphite and leftover reactants. However, follow-up reactions attempted without removal of solids gave significantly lower yields, indicating that insoluble salts could negatively impact the reaction.

8) Providing in the supporting information the actual values of the data presented in Figure 4's graphs in tables would be useful.

All quantitative data for figure 4 has been included in the supplementary information.

9) The entry number "18" for Figure 2 should be included in the text.

We thank the reviewer for noticing this oversight.

10) Qualifiers like "great" and "decent" should be removed, and actual yields should be added in the text

We agree with the reviewer that these terms are inherently vague, but have kept them in the text for the sake of readability. However, we have added all actual yields to the main text as well to ensure that there is no ambiguity.

Reviewer 4

I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Communications Chemistry initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.