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π -Allylpalladium Complexes in Synthesis: An Update

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Editor-in-Chief of
Synthesis

Torino, January 30, 2019

Dear prof. Knochel,

First of all, we apologize for the inaccuracies and mistakes contained in the first version of the review manuscript " **π -Allyl Palladium Complexes in Synthesis: An Update**", by Stefano Parisotto and Annamaria Deagostino that you can find here in revised form. We thank the reviewers for their comments. We agree with them and the text has been modified according to the forwarded suggestions. In the following, please find our answers to the criticisms of the reviewers (in bold). In particular, we added many schemes which are later specified, but this caused an increase in the review length that is now seventeen pages. We hope that you would consider this new version appropriate for the publication in *Synthesis*.

As far as the suggestions of referee 1 are concerned:

1) In the text, many examples have been summarized without figures. In my opinion, figures should be provided for all cases in a review to provide the readers with as much information as possible.

We agree with the referee and we added figure 1 and the following schemes whose captions are highlighted in green: 3, 4, 7, 9, 10, 11, 14, 20, 22, 23, 25, 28, 30, 33, 34, 36, 40, 43, 44, 46, 47, 48, 51, 53, 54, 55, 57.

2) The authors wish to show a comprehensive insight into the use of π -allyl palladium complexes in the reactions. However, they have missed many typical papers which should be cited in the manuscript. For example, they mentioned Pd-catalyzed allylic alkylation using 1,3-dithianes as umpolung nucleophiles (Ref 16). However, the reaction has been previously reported by the Zhang group (cited as Ref 12 in Ref 16) and the authors have not cited the paper at all. I suspect the authors only selected the publications which provided a reaction pathway and so have missed many useful papers. As for allylic substitution reactions with inactivated allylic substrates, please see: Chem. Soc. Rev., 2015, 44, 7929-7967. The authors should pay attention to the works of many established research groups, such as Booker-Milburn, Liu-Zhu Gong, M. S. Sigman, Yian Shi, Backvall, Wanbin Zhang, Shu-Li You, Chun-Jiang Wang and etc.

We agree with the referee and we added the Zhang research group paper and the Chem. Soc. Rev. review, see references 20 and 33 highlighted in yellow. We also implemented the review with the research reported by the

groups of Shu-Li You (page 3, ref. 10, 11, 12 and 13) and Chun-Jiang Wang (pag. 6, ref. 31 and 32). The text is highlighted green, references in yellow. As far as the other cited groups they were already cited in the first version (references 50, 51, 53, 67, 38, 39, 40 of the first version of the review). Finally, we consider the work of prof. Booker-Milburn on Pd(II) couplings beyond the scope of our review.

3) Many minor mistakes, including but not limited to: 1) Page 2, compound 10 is wrong; 2) Something is wrong with the sentence below Scheme 7; 3) Page 6, right column, the sentence “optically active protected furyl alcohol 56”; 4) What does the “z” above the arrow in Scheme 22 mean; 5) The structure of compound 59; 6) Scheme 28 is difficult understood; 7) The structure of compound 102 in Scheme 30 is wrong; 8) The mistakes for journal name were found in referees 62 and 76.

We agree with the referee and we corrected the mistakes 1, 2, 3, 4 where z was substituted by **69**, 5, 6 where letters **a**, **b** and **c** were added in the scheme 28 (now number 50) and in the text (highlighted in yellow) and 8 (now ref. 71 and 85, highlighted in yellow), whereas the structure **102** was checked and corrected.

As far as the suggestions of referee 2 are concerned:

1) In many instances, whole paragraphs—sometimes two consecutively—describe complex structures and/or reaction sequences that are difficult to follow without a picture. In this regard, this is not helpful as a review other than it directs the reader to the original resource. One such example is on page 2, in the paragraph beginning “Poli and co-workers recently reported....” Another is on page 3: “Allyl carbonates have been exploited....” The preceding paragraph also has no accompanying scheme, and there are numerous others. Perhaps the most egregious is under Scheme 17 on page 6: I have absolutely no idea what the product of the reaction even is.

We agree with the referee and we refer to the answer 1) of the referee 1. We added the schemes for all the indicated paragraphs and the sentence under scheme 17 (now scheme 29) was modified and highlighted in yellow.

2) In contrast, the authors take two entire pages to describe the desaturation work by the Newhouse laboratory (pages 10–12) and in schemes depict several papers that research group has published (Schemes 32–36). The reaction concept in each of these schemes is the same; only the identity of the electron-withdrawing group differs (in one case, a total synthesis application is shown). This seems excessive, especially compared to the treatment of others’ work.

We agree with the referee and we eliminated schemes 33 and 34 and reduced the discussion on the Newhouse work.

3) Another point of confusion throughout the review is the idea of a Pd-pi-allyl species as 1) an intermediate, 2) a catalyst, 3) a pre-catalyst, or 4) a reagent. First, in both the abstract and conclusion, the authors discuss a Pd-pi-allyl complex as a “reagent”, but I see no evidence of that presented in the review since a reagent is a species that is consumed in a chemical reaction and not regenerated, necessitating that it be used stoichiometrically. I think that in every single case, a Pd-pi-allyl species is regenerated at the end of the reaction. It seems undisputed that Pd-pi-allyls are intermediates in all the reactions presented. What is unclear is the authors’ definitions of catalyst and pre-catalyst even though they entitle one section “Allyl-palladium based

pre-catalysts". Since a catalyst must be regenerated in each reaction, several of the complexes the authors refer to as "catalysts" (e.g., 145 in Scheme 41 or 150 in Scheme 42) should actually be called pre-catalysts.

We are aware of the fact that sometimes could be misleading to indicate the π -allyl Pd species as reagent or (pre)-catalyst, so we decided to distinguish when the allyl unit is incorporated in the final product (reagent) or not (catalyst). Obviously, in many cases the π -allyl Pd complex acts both as reagent and catalyst. We reasoned each time which was the most important aspect (see for example scheme 7). To better elucidate this concept, the first paragraph of the section titled "Allyl-palladium based pre-catalysts" and that under scheme 64 were modified and highlighted in yellow.

Moreover, we changed the title of the last section in "Allyl-palladium complexes exploited as reactants and pre-catalysts" and in that section the word catalysts was substituted by pre-catalysts (see page 15, pre-catalyst 228).

3) They should also consider that in several instances before this "pre-catalyst" section, Pd- π -allyl "pre-catalysts" are also used in reactions (e.g., Schemes 21 and 22).

In both these cases, as evidenced before, we preferred to emphasize the presence of the allyl unit in the products, both this examples describe the synthesis of allylic amines starting from conjugated dienes.

4) In the "Conclusions" paragraph, the last sentence reads, "The last part of the review has been dedicated to those transformations catalyzed by Pd π -allyl complexes, whose relative stability allowed these species to be isolated and studied." This is a gross overstatement. The last section of the review did not really differ much from the previous sections; the stability of the Pd- π -allyl complexes did not feature prominently in the chemistry presented nor was the use of Pd- π -allyl complexes as precatalysts unique to this section.

The sentence has been changed to "The last part of the review has been dedicated to those transformations involving Pd π -allyl species as pre-catalyst or reactant. In such reactions the allylic moiety is not incorporated in the final product" and highlighted in yellow.

Errors in Schemes, Scheme Titles, and Textual Descriptions of Schemes

1) The title scheme is overcrowded and I am unsure what the authors are attempting to depict. Very few of the molecules shown under each heading appear to correspond to the heading.

We agree with the referee and we simplified the graphical abstract.

2) Scheme 1 is confusing. It does not seem possible that intermediate 'B' could afford either of the two products connected to it by the reaction arrows. For intermediate 'C', it seems more appropriate to have the 'R' substituent be 'R(Ar)' given the two products shown.

We are sorry that the scheme 1 was not clear. In order to demonstrate the richness of the chemistry of Pd π -allyl intermediates, we wanted to indicate that structures A, B or C, which are obtained in different ways, could undergo manifold transformations and not to specify a certain reactive path for intermediates A or B or C. For these reason we framed all these three species indicating a general reactivity regardless the starting complex.

3) The title of Scheme 2 is "Directing group assisted allylation of indoles" but the reaction is not directed. The indole 3-position is blocked for allylation but that does not mean the reaction is directed to the 2-position. A directing group is one within a substrate that interacts with a catalyst or reagent to control positional selectivity. In this respect, the authors' page 3 description of allylation of pentafluorobenzene as a "directed oxidative addition of the allylic pivalate to palladium" is also incorrect.

We agree with the referee and we changed the caption of scheme 2 in “Catalytic allylation and benzylation of indoles”, highlighted in yellow. As far as the “directed oxidative addition of the allylic pivalate to palladium” it was taken from the original paper, nevertheless we changed in “through an oxidative addition of palladium to the allylic pivalate” and highlighted in yellow.

4) In Scheme 4, the authors have omitted the lactam’s carbonyl in the product. In the title of the scheme, they have used the British spelling of “cyclisation” but in most instances use American spellings. Later on page 13 they write “centred” instead of “centered”.

We agree with the referee and we correct the mistakes and highlighted in yellow.

5) In Scheme 6, the authors have written 84-99% yield but in the text they write “yields superior to 84% and enantiomeric excesses between 84 and 99% (scheme 6).”

We agree with the referee and we correct the mistakes and highlighted in yellow, now scheme 12.

6) When describing product 19 in Scheme 7, the authors refer to the scaffold as a “pyrrolo-indole fused ring system” but that is not an accurate description of the functionality within this compound.

We agree with the referee and we changed in “fused tricyclic system containing a *N*-arylated pyrrolidin-2-one” (now scheme 13).

7) In Scheme 8, the authors write ‘Mes’ as an abbreviation for mesyl within compound 24, but the abbreviation for mesyl is ‘Ms’. The abbreviation ‘Mes’ stands for mesityl, which is quite different. The title of Scheme 8 describes couplings of allyl halides with *N*-mesylhydrazones but the scheme shows more than that, also depicting allyl halide couplings with diazoreagents.

We agree with the referee and we corrected the abbreviation and modified the caption of the scheme (now number 15), highlighted in yellow.

8) The title of Scheme 9 includes “...allylation of allylic chlorides” but the authors mean “allylation with allylic chlorides”.

We agree with the referee and we modified the caption of the scheme (now number 16).

9) In Scheme 10, compound 29 should contain an *N*-sulfonylimine but it is currently drawn in a more saturated state.

We checked the structure described in the original paper and it corresponded to that reported in the review by us (now structure 54, scheme 17).

10) When describing compound 35 in Scheme 11, the authors write “1,2,3,4-tetrahydro-quinoxaline (*sic*) derivatives 35” but that is not an accurate description of this molecule.

We agree with the referee and we modified the name in the text to 4-amino-5-hydroxyacrylates, highlighted in yellow, (now scheme 18, compound 61).

11) When showing their own work in Scheme 12, the authors show a diazo reagent as the precursor to the Pd carbene but in reality (and as they have written in the text) an *N*-tosylhydrazone was used. This is a carry-over error from a scheme in their original publication. Also, the alkyl Pd intermediate in this scheme as ‘Ph’ written as one of the substituents but this group is written generically as ‘Ar’ in compounds earlier in the catalytic cycle.

In the text we described our work as a palladium(0) catalyzed reaction of vinyl oxiranes **62** with *N*-tosylhydrazones, because these latter are the precursor of diazo compounds which are the active species and are *in situ* produced by the deprotonation of tosylhydrazone. Diazo compound is the real species which is involved in

the catalytic cycle, while tosylhydrazones are the reagents. To better elucidate this concept, we added the following sentence in the text “as the precursor of the diazo compound which is the effective coupling partner”, highlighted in yellow and modified the scheme (now 19) adding the phrase “from N-tosylhydrazone” under the diazo compound structure. We also substituted Ph with Ar in the alkyl Pd intermediate in the cycle.

12) In Scheme 13, the subscript ‘n’ is inadvertently within the parentheses instead of outside them.

We agree with the referee and we modified the scheme (now number 21).

13) In Scheme 14, showing R1 and R2 generically is misleading as it makes it seem like the R2 substituent has shifted a carbon in product 41a. In reality, the R2 substituent in the starting material is always a methyl group, which results in a regioisomeric mixture depending on the direction of beta-hydride elimination. This scheme should be amended to reflect this more accurately. In the description of the scheme, “cinnamyl” is spelled incorrectly.

We agree with the referee and we modified the scheme (now 24) separating the reactions where the reagents are cinnamyl (product **76a**) and aliphatic allylic alcohols, (**76b** and **c**) respectively. We also corrected the word cinnamyl, highlighted in yellow.

14) In the title of Scheme 16, the authors have written the Italian word for “and”.

We agree with the referee and we modified the caption of the scheme (now number 27), highlighted in yellow.

15) In Scheme 19, the ketone functional group within starting material 56 should actually be an alcohol with (R) configuration, which is obtained by enantioselective reduction of the ketone with the CBS catalyst. The alcohol then cyclizes intramolecularly onto the Pd- π -allyl. Instead of “chiral phosphine” over the reaction arrow, the authors should write which phosphine was used. It was Segphos.

We agree with the referee and we modified the scheme (now number 32).

16) In Scheme 20, the authors are missing an arrow from the cycle to the products 61 and 62. In the text, 61 and 62 are given two different names, but in the scheme only one structure is drawn. In fact, the entire cycle is only drawn such that one product would be obtained, so why would there be two products, 61 and 62? Also, in the title of Scheme 20, the authors have written “deamination” but they mean “diamination”.

We agree with the referee and we apologize for the misleading. This scheme refers to a Pd(II) diamination reaction firstly reported for 1,2 diamines and then extended, in another article, to 1,4- derivatives with the same mechanism that we tried to incorporate in the same scheme. We have modified the scheme (now number 35) reporting only the 1,2 diamination product. We also changed the text before the scheme adding the sentence “Depending on the substrates and the annulation involved, [4 + 2] or [4 + 4], tetrahydroquinoxaline **115** or 1,6-benzodiacinederivatives were respectively obtained. In the mechanism proposal, here described for the 1,2-diamination of dienes **113**” were the modifications are highlighted in yellow.

17) For the text describing Scheme 21, the authors have written “A more electron deficient significantly increases the catalyst reactivity...” A more electron deficient what? There is inadvertently no space between 5 and mol % over the reaction arrow of the scheme; the ‘5 mol %’ should be in parentheses. For product 68, the R2 should actually be R5. Within compound 68, there are actually two stereogenic centers and the way the authors have drawn the wedge linking the two of them makes the stereochemistry ambiguous. I think the title of the scheme should read “Enantioselective intermolecular coupling of dienes and C- or N-nucleophiles”.

We agree with the referee and we modified the text to “A more electron-deficient phosphine within the ligand”, highlighted in yellow, the scheme (now number 37) and the caption.

18) In describing Scheme 22, the authors write “Pd(coc)Cl₂” but mean “Pd(cod)Cl₂”. Earlier they had completely capitalized COD. They should choose one format. For the bottom equation of Scheme 22, over the reaction arrow they have written “Z (5%)” but they mean “69 (5 mol %)”.

We agree with the referee and we corrected to Pd(cod)Cl₂, highlighted in yellow, we also modified the capitalized COD in the paragraph between scheme 8 and 9. The scheme (now number 38) has been modified following the referee 2 suggestions.

19) In Scheme 23, the authors show a phosphoramidite as ligand 76, but in the text they have indicated that this should be a SOX ligand. Looking at the original publication, this should in fact a SOX ligand although phosphoramidites were explored, owing to this research group’s successful use of phosphoramidites in previously published chemistry.

We agree with the referee and modified the ligand structure in the scheme (now number 39).

20) In Scheme 43, complex 154 should have the ‘6’ of ‘PF₆’ subscripted. In the reaction equation, the authors should write “154 (10 mol %)” instead of “10 mol % cat” for both accuracy and consistency. In the bottom half of the scheme, the authors should include the ‘Ar’ substituent on each intermediate and include the relative stereochemistry. The authors do not describe the mechanism in the text but show intermediates 155 and 156 en route to 153 anyway in the scheme.

We agree with the referee, the scheme (now number 68) has been modified following the referee 2 suggestions. On the contrary, the bottom half of the scheme has not been modified because there it is described a general mechanism. To better elucidate the concept, the following sentence has been added: “As described in the bottom half of the scheme 68, if a nitrogen containing ligand is used in the Pd-catalyzed reaction, the nucleophile will attack the central carbon affording the palladacycle **241** and the final cyclopropane **242**”, in the paragraph below the scheme, highlighted in yellow.

Titles of Sections

1) The title of Section 2 is “pi-Allyl palladium complexes mediated allylation reactions” but should at least be “pi-Allyl palladium complex-mediated allylation reactions”. However, this same title could apply to Section 3. It is just that the Pd-pi-allyl is generated differently in Section 3 (from dienes or allenes) than it is in Section 2 (from allyl electrophiles). Perhaps a better title for Section 2 would be “pi-Allyl palladium complex-mediated allylation reactions with allyl electrophiles”.

We agree with the referee and we changed the title of section 2 to “π-Allyl Palladium complexes generated from allyl electrophiles”, highlighted in yellow.

2) Related to this, the title of Section 3 is “pi-Allyl palladium complexes obtained from Pd(II) complexes addition to dienes”. This should at least be altered to “pi-Allyl palladium complexes obtained from dienes and Pd(II) complexes”. But this section of the review is not as much about making Pd-pi-allyl complexes from dienes as it is about applications involving these intermediates generated from dienes. Perhaps a better title for this section would be “Allylation reactions with pi-allyl palladium complexes generated from dienes”.

We agree with the referee and we changed the title of section 3 to “ π -Allyl palladium complexes generated from dienes”, highlighted in yellow.

3) I have already described the issues I see with the title of Section 4 and subsection 4.4 (inadvertently not bolded in the abstract).

We agree with the referee and we changed the title of section 4 to “ π -Allylpalladium complexes exploited as reactants and pre-catalysts”. As far the sub-section 4.4 is concerned, in order to better elucidate the concept and answer to the referee we modified the text of the two first paragraphs of this section. The modifications are highlighted in yellow.

4) Finally, in the title of subsection 2.3, the authors use the word “Inactivated” but really mean “Unactivated” as inactive carries quite a different meaning. They also use the term “non-activated” in the text; while probably fine, there is really no need for a new term when “unactivated” will do.

We agree with the referee and we changed the term “inactivated” with “unactivated” within all the text.

Other

1) There are a few places where a section begins with a paragraph that is a single sentence. There is no reason to do that as this sentence can simply be the first sentence of the next paragraph. This occurs on page 1 under “Activated allylic compounds”, page 6 under “Conjugated dienes” (technically two sentences but the same principle applies), page 9 under “Allenenes”, and page 12 under “Allyl-palladium catalyzed synthesis of alkenylboronic acids”.

We agree with the referee and we changed the formatting of the paragraphs in the sections indicated by her/him.

2) Much of the review is written in the past tense, but on page 5, the paragraph beginning “All the transformations which afford nitrogen derivatives...” is for some reason written in the present tense. This should be changed.

We agree with the referee and we modified the text as indicated by the referee, modifications are highlighted in yellow.

3) In many instances, the authors have written “Corresponding author ‘and co.’” (e.g., “Zhang and co.” on page 5. Please change this to “Zhang and co-workers”, “Zhang *et al.*” or “the Zhang laboratory”.

We agree with the referee and we modified the text as indicated by the referee, modifications are highlighted in yellow.

4) In several cases, the authors have written a while sentence, then put a comma followed by “scheme x” or “see figure 1”. These statements should not follow a comma but instead should be in parentheses at the end of the sentences. For example, on page 7, the sentence should end “...affording the product with S configuration (see figure 1).”

In our opinion, to indicate schemes or figures after a comma is generally used, nevertheless we followed the referee indications in almost all the review.

5) On page 6, when describing Scheme 17, the authors write “Further studies on expanding the scope of nucleophiles are currently in progress.” How do the authors know that and even if they do, why should that be written in a review?

We agree with the referee and we eliminated the indicated sentence.

6) On page 6 under the “conjugated dienes” section, the authors write “Many research groups have dedicated intense efforts to three component reactions involving Pd catalyzed couplings.” But most of the reactions they show in this section are not three component couplings, they are two component couplings.

We agree with the referee and we modified the sentence to “One important strategy to obtain π -allyl Pd species exploits the addition of Pd(II) species to dienes in a Heck manner. Many research groups have contributed to this chemistry”, highlighted in yellow.

7) “Chiral induction” (page 7) is an incorrect term. It should be “enantioinduction”.

We agree with the referee and we substituted “Chiral induction” with “enantioinduction”, highlighted in yellow.

8) On page 10, the authors call a process “beta-hydride abstraction” when they mean “beta-hydride elimination” – beta-hydride abstraction is a different but related phenomenon that proceeds via a different mechanism.

We agree with the referee and we substituted “beta-hydride abstraction” with “beta-hydride elimination”, highlighted in yellow.

Yours sincerely,

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