Our Responses to the Comments of the Referees

Referee 1

Comments: The manuscript “A Theoretical Study on Pd–catalyzed Friedel–Crafts Intermolecular Acylation: Does Generated In Situ Aroyl Triflate Act as A Reactive Electrophile to Functionalize C–H Bond of Arenes?” by Guo, Li et al. deals with the computational investigation of the feasibility of Friedel–Crafts Acylation process for the formation of aromatic ketones catalyzed by Pd complexes. In particular, the authors make some predictions on the feasibility of the process catalyzed by the Pd(CO)$_3$ complex and three different possible reaction pathways have been investigated. According to the present reviewer, although the authors have been carried out carefully the calculations, the manuscript lacks of the analysis of the electronic underpinnings, which rule the obtainment of the main reaction intermediates and a comparison with the same process catalyzed by the Pd(PR$_3$)$_3$. Without these aspects, the manuscript is only a series of numbers and energetics without any solid chemical meaning. In addition, according to the present reviewer, some hints should be provided about the energy barriers associated to the formation of the AgI starting from AgAr with the exchange of the ligands with the palladium complex. The authors can perform a relaxed scan for the approaching of the AgAr and the final formation of the Ag-I bonding. For the aforementioned reasons, according to the present reviewer at this level the manuscript has to be largely improved before reconsideration for the publication on Catalysts.

Our response: Many thanks referee for your time and recommending publication after some alterations.

Comment 1: “In particular, the authors make some predictions on the feasibility of the process catalyzed by the Pd(CO)$_3$ complex and three different possible reaction pathways have been investigated. According to the present reviewer, although the authors have been carried out carefully the calculations, the manuscript lacks of the analysis of the electronic underpinnings, which rule the obtainment of the main reaction intermediates and a comparison with the same process catalyzed by the Pd(PR$_3$)$_3$.”

Our response: Following the referee’s suggestions, additional calculations were conducted on the Friedel–Crafts intermolecular acylation catalyzed by Pd(Bu)$_3$. The computed reaction
energy profile was depicted in Figure 1 and was also included in Figure S4 of Supporting Information. DFT calculation reveals that the reaction mechanism catalyzed by Pd(PtBu)₂ is similar to that mediated by Pd(CO)₃, which is composed of sequential steps of C‒I bond oxidative addition, CO insertion, reductive elimination and C‒H bond functionalization. As seen from Figure 1, transformation of phosphine coordinated–palladium–aroyl intermediate INT5 to the aroyl triflate requires an accessible reaction barrier of 27.2 kcal mol⁻¹, but this process is exergonic by 1.5 kcal mol⁻¹, indicative of formation of the aroyl triflate as a strong electrophilic intermediate to functionalize C‒H bond of arenes from the palladium–aroyl intermediate with phosphine ligand is thermodynamically unfavorable. On the other hand, compared to Pd(CO)₃, Pd(PtBu)₂ proceeds C‒I bond oxidative addition relatively favorable. However, the steps of C‒H bond functionalization starting from several resultant potential electrophiles (INT4, INT5 and INT6) require reaction heights ranging from 36.5 to 44.3 kcal mol⁻¹ with respect to the most stable species (INT5), which are much higher than that (32.1 kcal mol⁻¹) in the case of Pd(CO)₃. Taken together, a phosphine–bound palladium–aroyl intermediate INT5 is generated as the most thermodynamically favorable species in the whole reactions for Pd(PtBu)₂ catalyst. Most importantly, the C‒H bond functionalization from this species is prohibited by an extremely high reaction barrier of 44.3 kcal mol⁻¹. The added sentence of “see the detailed computational results of reaction mechanism mediated by Pd(PtBu)₂” is marked in yellow between line 229 and 230 of the revised manuscript.

In addition, NBO analysis for the key species was conducted and the corresponding electronic density on Pd atom of each species was shown in Table 1. In parallel, the sentence of “see electronic densities of Pd atom for phosphine or CO coordinated–palladium–aroyl intermediates in Table S2 of Supporting Information” was added in the revised manuscript and marked in yellow.
Figure 1. Computed reaction energy profile of Friedel–Crafts intermolecular acylation catalyzed by the Pd(PtBu)₃ at M06/6-311++G(d,p) //B3LYP/6-31G(d):sdd level of theory.

Table 1. Mulliken charge values for key species

<table>
<thead>
<tr>
<th>Species</th>
<th>Mulliken charge on Pd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(CO)₃</td>
<td>-0.227799</td>
</tr>
<tr>
<td>Pd(PtBu)₃</td>
<td>-0.987729</td>
</tr>
<tr>
<td>(CO)Pd(PtBu)</td>
<td>-0.547567</td>
</tr>
<tr>
<td>(CO)₂Pd–COAr(OTf)</td>
<td>-0.124507</td>
</tr>
<tr>
<td>(PtBu)₃Pd(CO)–COAr(OTf)</td>
<td>-0.544271</td>
</tr>
</tbody>
</table>
Comment 2: “In addition, according to the present reviewer, some hints should be provided about the energy barriers associated to the formation of the AgI starting from AgAr with the exchange of the ligands with the palladium complex. The authors can perform a relaxed scan for the approaching of the AgAr and the final formation of the Ag-I bonding.”

Our response: We exactly agree with the referee’s comment that some hints should be provided about the energy barriers associated to the formation of the AgI. We performed a relaxed scan for the approaching of the Ag–I bond from 2.96Å to 2.66Å on basis of reactant complex nascent from species B’ and the aromatic silver, which is shown as Figure 2. The calculations indicate that as the bond length of Ag-I changes from 2.96Å to 2.66Å, the corresponding energy continuously decreases. This indicates that the anion exchange process might be a barrierless process.

Figure 2. A relaxed scan for the approaching of the Ag–I bond from 2.96Å to 2.66Å on basis of reactant complex nascent from species B’ and the aromatic silver.
Referee 2

Comments: “The authors are reporting a careful computational study on the Pd-catalyzed Friedel-Crafts acylation reaction of arenes to ketones. The computational study is very complete and details provided are sufficient to allow others to reproduce the work. I am suggesting below some minor changes that in my view will improve the quality of the manuscript.

i) The color code for spheres in the ball & stick representation in Figures 1-4, 6 and 7 must be added to the figure captions.

ii) Correct inconsistencies in which plural nouns are followed by singular verbs and vice-versa.

iii) Several calculated systems present aromatic rings and the quality of the calculation may suffer from deficiencies in the handling of dispersion interactions by the standard density functional theory approaches used in their work. Maybe the authors are interested in inserting the reference RSC Adv., 2013, 3, 13085-13100 (DOI: 10.1039/C3RA40713F), where it is reviewed that the “M06 functionals are able to approximate model dispersion effects at short-range”, that “M06 functionals … were suggested … for systems containing transition metal elements” and also that “M06 family of functionals seems to be a good choice for handling molecular systems where weak intermolecular interactions exist.”, for supporting the quality calculation reported in the manuscript.”.

Our response: Many thanks referee for highly positive comments and recommending publication with a little additional consideration.

Comment 1: “The color code for spheres in the ball & stick representation in Figures 1-4, 6 and 7 must be added to the figure captions.”

Our response: We thank the referee for bring our attention to the missing of “The color code for spheres in the ball & stick representation in Figures”. As suggested by referee, color balls in the optimized structures were labelled and included in the related Figures.

Comment 2: “Correct inconsistencies in which plural nouns are followed by singular verbs and vice-versa.”

Our response: We deeply apologize for these errors in the original manuscript, which were corrected in the revised manuscript.
Comment 3: “Several calculated systems present aromatic rings and the quality of the calculation may suffer from deficiencies in the handling of dispersion interactions by the standard density functional theory approaches used in their work. Maybe the authors are interested in inserting the reference RSC Adv., 2013, 3, 13085-13100 (DOI: 10.1039/C3RA40713F), where it is reviewed that the “M06 functionals are able to approximate model dispersion effects at short-range”, that “M06 functionals ... were suggested ... for systems containing transition metal elements” and also that “M06 family of functionals seems to be a good choice for handing molecular systems where weak intermolecular interactions exist.”, for supporting the quality calculation reported in the manuscript.”

Our response: Thank you for this suggestion. The suggested reference was added in the revised manuscript (see ref. [11a] in revised manuscript) and a brief description of reliability of M06 was also given in Computational details), which were marked in yellow.