nature portfolio

Peer Review File

Catalytic Acceptorless Complete Dehydrogenation of Cycloalkanes

Corresponding Author: Professor Motomu Kanai

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)
In the present work, Kanai and coworkers report a dual hydrogen atom transfer (HAT)-enabled multicatalyst system that enables the complete dehydrogenation of unactivated cycloalkanes at room temperature under visible light irradiation. Authors optimized the reaction conditions through a large screening of reaction parameters and probed substrate scope with generally moderate yields of resultant aromatics. Because of the significance of effective hydrogen liberation technology from liquid organic hydrogen carriers, this work has significant potential in applications for clean energy supply through controllable hydrogen store and transport. To this end, however, authors failed to evaluate the production of hydrogen but only focus on the dearomatization to afford aromatics. Also, mechanistic studies are severely inadequate so that it is completely elusive regarding the working process of catalytic system. With more experiments on systematic hydrogen evaluation and mechanistic studies, this work may be reconsidered by Nat. Commun.

Reviewer #2

(Remarks to the Author)
Liquid organic hydrogen carrier (LOHC) technology, particularly cycloalkanes such as cyclohexane and methylcyclohexane, provides a safe and efficient means of storing and transporting hydrogen. However, homogeneous catalytic acceptorless dehydrogenation (CAD) of cycloalkanes characterized by elevated aromatization selectivity under mild conditions remains unrealized. Herein, the authors disclose a successful CAD of cycloalkanes with comprehensive aromatization via a dual HAT-enabled multicatalyst system. I expect this work will have a high impact, meriting publication in Nat. Commun. once the authors consider the following minor points.

1. The condition in Fig. 4 (‘after filtration through a short pad of silica gel, this process was repeated’) is difference from the condition f in figure 3 (‘after 16 h, another set of the catalysts was added’). Why did the authors adopt different experimental procedures in condition optimization and substrate scope investigation?
2. In table S2.2, benzene and p-xylene have similar properties when used as solvents, but there was an obvious difference in the yield of toluene. Please provide a explanation.
3. In SI, if the dehydrogenation results of the substrates are only detected by GC, the original GC data should be provided.
Some minor issues:
1. Page 3, a metal complex (Mn), n should be superscripted.
2. In the text, the compound name should be bolded, for example: PC1, Co-1, Co-2.
3. Please check the reference format carefully including those in SI, such as: capitalization of titles.
4. In SI, there is a significant error about the 1H NMR of compound 1d, the number of hydrogen atoms is incorrect.
5. There are obvious impurities in the 1H NMR and 13C NMR of compound 2e.

Reviewer #3

(Remarks to the Author)
In this contribution, Kanai and coworkers describe the development of a homogeneous system effective for achieving catalytic acceptorless dehydrogenation of cyclohexanes, which are expected to be useful LOHCs. Under the influence of a pertinent photoredox catalyst, a catalytic cycle comprising carbon radical generation via hydrogen atom transfer (HAT) with

saturated hydrocarbons, cobalt-catalyzed desaturation and hydrogen evolution is operative and complete dehydrogenation of the target alkanes proceeds with good efficiency over a wide range of substrates. In addition to the choice of the photoredox catalyst and chlorine radical source, the presence of a second HAT catalyst and pyridine base was found to be very important in promoting the reaction. This catalytic system is distinct in that it enables endothermic complete dehydrogenation by preventing the reaction from being terminated at the alkene stage (single dehydrogenation), despite the mild conditions compared to the conventional methods. The use of the flow reactor leads to an increase in the efficiency of the dehydrogenation, which also represents an attractive feature of the present system from future perspective. All of these aspects create general enthusiasm for this well-executed study and bolster the case for its publication in Nature Communications. My support is almost unconditional, yet the manuscript would be strengthened if the following issues were properly addressed by the authors.

My only concern is the ambiguity of the discussion on why TPA is necessary as an HAT catalyst. Mechanistic experiments (Fig. 6b) revealed that the role of the second HAT catalyst has a significant effect on the dehydrogenation process after the second reaction, but it remains unclear why chlorine radical-mediated HAT alone reduces the efficiency of the second and third reactions. Since chlorine radicals inherently have the potential for undergoing radical addition with alkenes, such side reactions might be involved. For instance, checking how the efficiency changes when the reaction of methylcyclohexene (4a) with TPA is carried out in the absence of TBACl would offer some insights into whether the chlorine radical may be inhibited by the product formed in the first reaction.
I also suggest that tracing the attenuation of the chlorine radical/benzene π complex in the transient absorption spectrum in the presence of not only methylcyclohexane (Fig. S7) but also 4a would allow for the estimation of the rate of hydrogen abstraction by the chlorine radical at the allylic position, which provides useful information.

Version 1:

Reviewer comments:

Reviewer #2

(Remarks to the Author)
The authors have addressed all my concerns, the manuscript could be accepted in the current version.

Reviewer #3

(Remarks to the Author)
[Note from the Editor: Reviewer #3 assessed also the response given to reviewer #1]

After careful reading of this revised version, I appreciate that the authors tried to provide in-depth elucidation of the reaction mechanism, particularly why two types of HAT catalysts are necessary, using time-resolved ESR and transient absorption spectroscopy. However, the description and discussion based on the outcome of these analyses are somewhat subjective to be deliberately consistent with the conclusion. While I support publication in Nature Communications, I would strongly suggest the authors to make appropriate modifications in order for the manuscript to be suitable for publication in consideration of the following points, where more detailed discussion and explanation are needed. (I understand that complete mechanistic elucidation is difficult and beyond the scope of this manuscript.)

1) The transient absorption spectra to the point of complete attenuation should always be included at least in SI. Without the full spectrum, it is difficult to understand the lifetime of each transient species and also the simultaneous observation of two transient species.
2) Why the Ir(II) species observed until 2 μs in the time-resolved ESR spectrum was not attributed in the transient absorption spectrum? In addition, while the Ir(II) species was only observed after 0.2 μs in the ESR measurement, the complex of the chloro radical with benzene was observed immediately after irradiation of the pulsed laser in the transient absorption spectroscopy measurement. This time lag should be clarified as these two species should be observed essentially at the same time if the chloride ion was oxidized by the excited-state Ir(III) complex.
3) I am afraid if the assignment of the chloro radical-benzene complex observed in the transient absorption spectrum (but not in the time-resolved ESR) is correct.
4) Regarding the discussion in line 7-11 in page 9, I assume that the lifetime of the transient species would be in the range of ns, judging from Figure 7d. Yet it is difficult to assess precisely because there are no spectra including the fitting curves, from which these lifetimes were calculated. Furthermore, although the increase in the lifetime of TPA radical was ascribed to the increase in its concentration, this interpretation is incorrect because the increase in the concentration of the active species does not change the lifetime, but only increases the intensity of the spectrum. There must be another reason why the lifetime of the TPA radical increased in the presence of TBACl.
5) The discussion about the transient absorption spectrum in Page 8 sounds qualitative. It would be better to discuss about the lifetime quantitatively using specific values.
6) It is unclear why pyridine was added in the measurement of the transient absorption spectrum shown in Figure 7a. According to the presumed mechanism, pyridine is not involved in the generation of chloro radical, and hence a similar spectrum should be obtained in the absence of pyridine.
7) In the transient absorption spectrum in Figure 7a, a change in lifetime was observed upon addition of alkane 1a. It would be worthwhile to plot the inverse of the lifetime after the change against the change in the concentration of 1a. If a linear proportional relationship was revealed, it indicates that the reaction of chloro radical with 1a has the first-order dependence,

and the rate constant can be calculated from the slope of the plot. Similarly, in Figure 4d-(3), it would be possible to evaluate if a linear relationship appears when plotting the inverse of the lifetime against the concentration of alkene 4a added. Comparison of the obtained rate constants would allow quantitative discussion on the reaction rates of the chloro radical with 1a and the TPA radical with 4a.
8) Considering the BDE of the benzyl C-H bond of the product, toluene (2a), which is smaller than that of the reaction substrate, discussion on the possible intervention of the product inhibition would provide useful information for the journal readership. (In the transient absorption measurement shown in Figure 7a, I wonder whether the lifetime of the transient species would be changed by the addition of 2a.)
9) It is ambiguous why the ps-scale transient absorption spectra were measured (Figure S10). If the authors claimed that they observed the same transient species as that detected in the ns-scale transient absorption spectra, it is important to make quantitative discussion based on the comparison of the lifetime of the transient species calculated from each spectrum.
10) It has not been experimentally proven that Co-1 is not involved in the generation of HAT agent. It would be relevant to confirm if the addition of Co-1 would lead to alter the spectrum shown in Figure 7d-(3), which was measured under the conditions close to those for the catalytic reaction.
11) As a minor point, since the spectrum of TPA radical shown left side in Figure 7e is saturated, it should be rescaled as rendering the peak top visible.

Version 2:

Reviewer comments:

Reviewer #3

(Remarks to the Author)
I have carefully read through this second revised version, together with the response letter, and found that all the concerns raised in the previous round of review, particularly those about the reaction mechanism, have been properly addressed. I think that this modified manuscript is now acceptable for publication in Nature Communications without any further alterations.

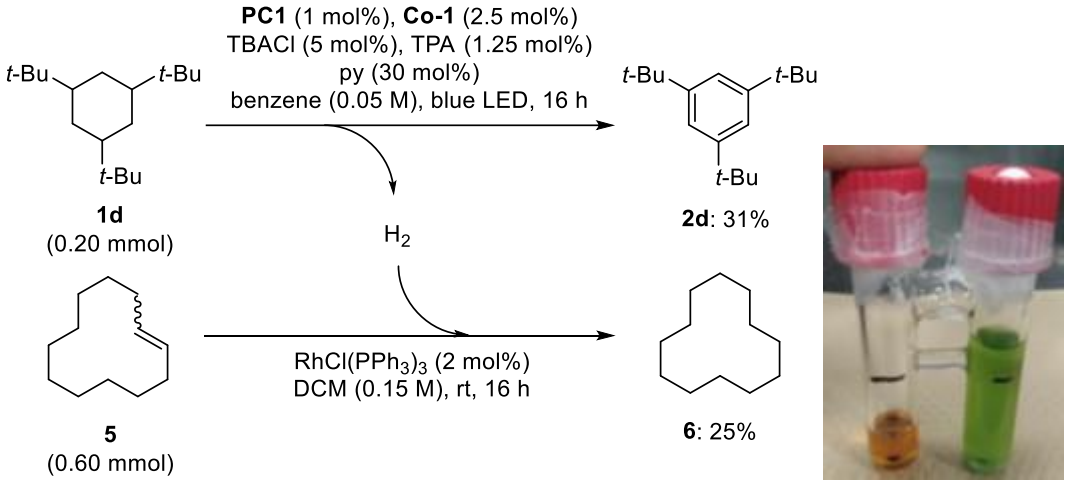
Responses to Reviewer 1:

In the present work, Kanai and coworkers report a dual hydrogen atom transfer (HAT)-enabled multicatalyst system that enables the complete dehydrogenation of unactivated cycloalkanes at room temperature under visible light irradiation. Authors optimized the reaction conditions through a large screening of reaction parameters and probed substrate scope with generally moderate yields of resultant aromatics. Because of the significance of effective hydrogen liberation technology from liquid organic hydrogen carriers, this work has significant potential in applications for clean energy supply through controllable hydrogen store and transport.

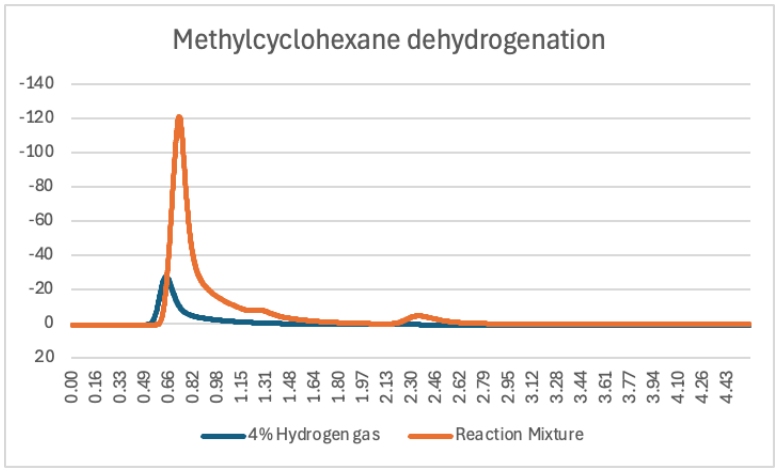
(1-1) **Reviewer's comment:** To this end, however, authors failed to evaluate the production of hydrogen but only focus on the dearomatization to afford aromatics.

Authors Response: We appreciate the reviewer's positive feedback and valuable suggestions. We have carefully addressed the concerns raised by the reviewer, and incorporated the following experiments/results, which verify hydrogen gas production, into the revised manuscript:

1) **CO-ware experiment:** To evaluate the production of hydrogen gas, a two-pot transfer hydrogenation was conducted. The result shown below supported that desaturation was, at least mainly, due to the evolution of hydrogen gas. This result has already been documented in Fig. 6c of the previous main text (Fig. 6 in the revision).



2) **Hydrogen gas evaluation by GC:** To directly detect hydrogen gas evolution, the dehydrogenation reaction of methylcyclohexane **1a** was performed under the standard conditions and 0.5 mL gas in the reaction vessel was analyzed by gas chromatography (GC). As shown in the below GC chart, we successfully observed hydrogen gas evolution. This result has been incorporated to the revised main text (page 7) and section 8 of SI.



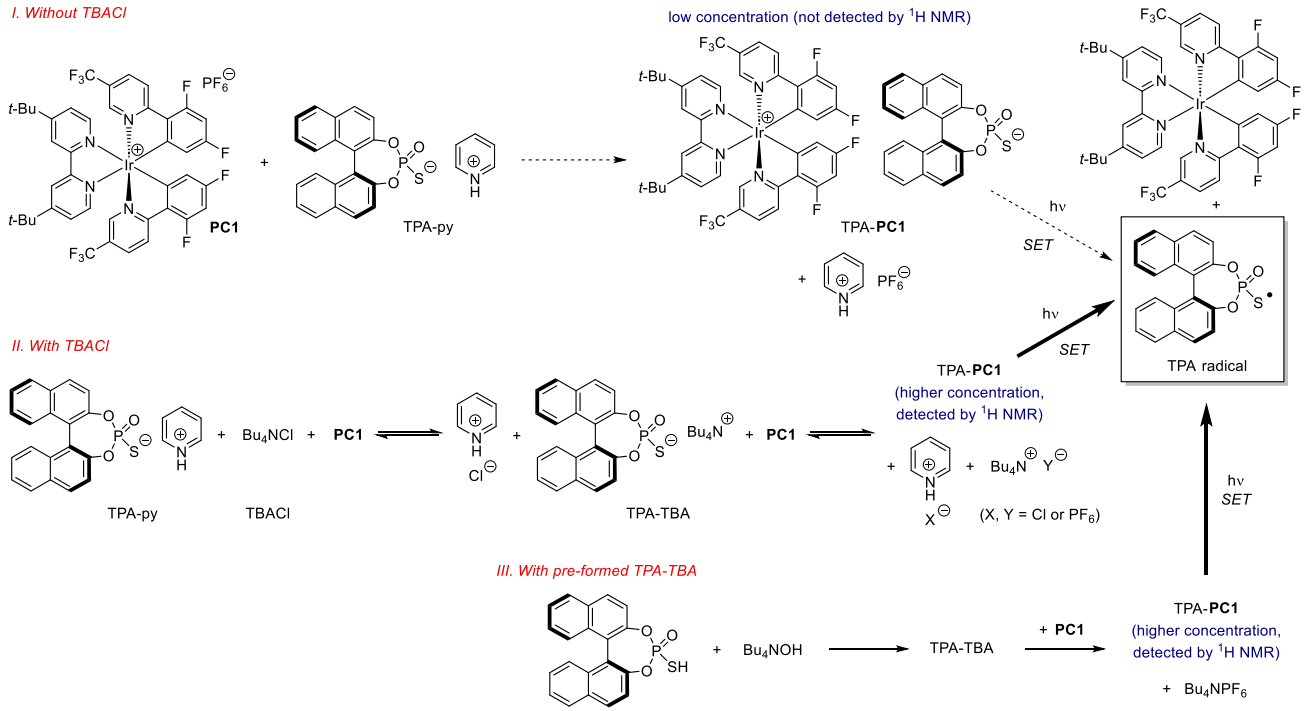
(1-2) **Reviewer's comment:** Also, mechanistic studies are severely inadequate so that it is completely elusive regarding the working process of catalytic system. With more experiments on systematic hydrogen evaluation and mechanistic studies, this work may be reconsidered by Nat. Commun.

We appreciate the reviewer for clarifying the point to improve our work. As noted by the reviewer, our achievement represents the first catalytic complete dehydrogenation of unactivated cycloalkanes at room temperature. This is the primary novelty of our study. The key to enabling this reaction is the dual HAT catalysis mediated by chlorine and TPA radicals. However, how these two radicals synergize to achieve this novel reactivity was not clear in the initial submission. In response to the reviewer's feedback, we have conducted systematic mechanistic investigations which includes, transient absorption measurements and additional experiments to clarify the dual HAT mechanism. The following four points are critical and have been addressed in the revision.

1) **Chlorine radical is effective for the initial HAT of alkanes, but not for the subsequent HAT of alkene intermediates:** To characterize the HAT reactivity of the chlorine radical, we conducted transient absorption (TA) experiments in the presence of **PC1**, TBACl, and pyridine in benzene solvent, under conditions without substrates, with alkane **1a**, or with alkene **4a** (Fig. 7a). The concentration of the chlorine radical-benzene π-complex, which was assessed by the absorption intensity at 400 nm in TA, decreased more rapidly in the presence of **1a** than its absence. This is because the chlorine radical was consumed by HAT of **1a**. In the presence of alkene **4a**, however, the decay speed of chlorine radical was slower than without substrates. This result suggests that a stable chlorine radical-alkene π-complex was formed when alkenes were present, reducing the HAT reactivity of chlorine radical. A relevant observation of taming the chlorine radical reactivity through π-complex formation was reported by Russell (newly cited as ref 49). This observation is consistent with the reaction profile; the dehydrogenation reaction mainly terminated at the alkene stage if TPA was absent (i.e., single HAT conditions by chlorine radical derived from TBACl: Fig. 3, entry 4). Furthermore, chlorine radical alone promoted dehydrogenation of alkene **4a** only in 25% yield (Fig. 7c). These results have been included in the revised main text (Fig. 7a, 7c).
2) **TPA-TBA is the effective precursor of the active HAT catalyst for alkene intermediates:** Because TPA alone did not promote dehydrogenation of alkane **1a** (Fig. 7b) but still facilitated the complete dehydrogenation reaction under dual HAT conditions (Fig. 3), the TPA radical catalyst must be something to do with the dehydrogenation step from alkene intermediates. Thus, we investigated dehydrogenation of alkene **4a** in detail by examining the presence or absence of TBACl and/or TPA. The individual use of TBACl alone or TPA alone resulted in low yields of toluene (25% in both cases: Fig. 7c). However, the coexistence of TBACl and TPA markedly enhanced the yield (66%: Fig. 7c). We hypothesized that the tetrabutylammonium salt of TPA (TPA-TBA) is generated in the reaction mixture through counter-ion exchange between TPA and TBACl, and TPA-TBA is the active catalyst precursor for dehydrogenation of alkene intermediates (please see the scheme below). Consequently, we prepared TPA-TBA under chloride-free conditions and subjected this salt to the dehydrogenation reaction of **4a**. As a result, toluene was produced in an improved 70% yield (Fig. 1c). These results are consistent with our hypothesis. These results have been included in the revised main text (Fig. 7c).
3) **Under the dual HAT conditions, the concentration of TPA radical increased:** The increased ionic characteristics of TPA-TBA, compared to TPA alone (forming pyridinium salt, TPA-py, under the reaction conditions), would enhance the generation of TPA radical than using TPA alone. Through TA experiments, we indeed confirmed that the concentration of TPA radical significantly increased by the presence of TBACl or using TPA-TBA, compared to TPA alone (Fig. 7d). Global analysis of TA data showed that the decay time constant of TPA radical was much longer ($\tau_1 > 10^3$ ps) with TBACl than that without TBACl (τ_1 = 529 ps). These results indicate that the generation of TPA-TBA in the reaction mixture under the optimized reaction conditions, enhances the generation of TPA radical, thereby accelerating the dehydrogenation reaction of alkenes. These results have been added to the revised main text (Fig. 7d and 7e).
4) **TPA-TBA forms a complex with PC1 (TPA-PC1), promoting the TPA radical formation through single electron transfer:** In order to rationalize the higher efficiency of TPA-TBA than TPA alone in the TPA radical generation, we analyzed interactions between TPA-TBA or TPA alone with **PC1** using ^{1}H NMR experiments.

Titration of **PC1** with TPA-TBA showed a concentration-dependent downfield shift of the protons at 3,3'-positions of the bipyridine ligand of **PC1**. A similar downfield shift of **PC1** was also observed in the presence of TPA and TBACl. These results suggest that TPA-TBA forms a complex with **PC1**, facilitating an efficient electron transfer and thereby enhancing the TPA radical generation. In contrast, when TPA alone was mixed with **PC1**, no such downfield shift was observed. Therefore, the significant differences in the TPA radical concentration depending on the presence or absence of TBACl are likely due to the difference in the complexation ability of TPA-py or TPA-TBA with **PC1**. These results have been added to the revised main text and supplementary information (Fig. S10-14).

Therefore, while the chlorine radical generated from **PC1** and TBACl is essential for the initial dehydrogenation of alkanes, a key to the dual HAT conditions is the TBA-mediated enhancement of TPA radical by increasing the concentration of its precursor, TPA-**PC1**, thus facilitating the dehydrogenation of alkene intermediates. On the basis of observations 1)–4), the overall scheme underlying the mechanism to increase the TPA radical concentration, is summarized in the below scheme.



Accordingly, we have included our working hypothesis for the mechanism for the increased reactivity under the dual HAT conditions, in Fig. 7f of the revised manuscript. In addition, Fig. 2 has been revised to better reflect the clarified mechanism of the dual HAT catalysis.

Responses to Reviewer 2:

Liquid organic hydrogen carrier (LOHC) technology, particularly cycloalkanes such as cyclohexane and methylcyclohexane, provides a safe and efficient means of storing and transporting hydrogen. However, homogeneous catalytic acceptorless dehydrogenation (CAD) of cycloalkanes characterized by elevated aromatization selectivity under mild conditions remains unrealized. Herein, the authors disclose a successful CAD of cycloalkanes with comprehensive aromatization via a dual HAT-enabled multicatalyst system. I expect this work will have a high impact, meriting publication in Nat. Commun. once the authors consider the following minor points.

Author Response: We thank the reviewer for the positive and insightful comments. In the revised manuscript, we have addressed the raised concerns and provided the point-by-point response, as itemized below.

(2-1) **Reviewer's comment:** The condition in Fig. 4 ('after filtration through a short pad of silica gel, this process was repeated') is difference from the condition f in Figure 3 ('after 16 h, another set of the catalysts was added'). Why did the authors adopt different experimental procedures in condition optimization and substrate scope investigation?

Author Response: We thank the reviewer for pointing out our misleading description. Indeed, both conditions were identical. We have revised our description in footnote f of Fig. 3.

(2-2) **Reviewer's comment:** In table S2.2, benzene and p-xylene have similar properties when used as solvents, but there was an obvious difference in the yield of toluene. Please provide a explanation.

Author Response: We thank the reviewer for this question. The use of *p*-xylene provided lower yield than benzene, likely due to the presence of two benzylic methyl groups. The benzylic C–H bonds existing in a high concentration as a solvent, competed with the substrate in the HAT step. We have included this rationalization in Table S2.2.

(2-3) **Reviewer's comment:** In SI, if the dehydrogenation results of the substrates are only detected by GC, the original GC data should be provided.

Author reply: We thank the reviewer for the valuable suggestion. According to the suggestion, we have included the GC data in section 6 in the revised SI.

(2-4) **Reviewer's comment:** Some minor issues:

1. Page 3, a metal complex (Mn), n should be superscripted.

Author reply: We have corrected the concerns.

(2-5) **Reviewer's comment:** 2. In the text, the compound name should be bolded, for example: PC1, Co-1, Co-2.

Author reply: We have corrected the concerns.

(2-6) **Reviewer's comment:** 3. Please check the reference format carefully including those in SI, such as: capitalization of titles.

Author reply: We have checked and corrected in reference section.

(2-7) **Reviewer's comment:** 4. In SI, there is a significant error about the 1H NMR of compound 1d, the number of hydrogen atoms is incorrect.

Author reply: We thank the reviewer for pointing out the errors in NMR. In the revised version we have updated the NMR.

(2-8) **Reviewer's comment:** 5. There are obvious impurities in the 1H NMR and 13C NMR of compound 2e.

Author reply: The separation of the starting material **1e** and product **2e** was difficult using silica gel chromatography. Therefore, we provided the NMR yield and incorporated the crude NMR plot. There are no obvious impurity peaks other than **1e** and **2e**. ^{1}H NMR integrations matched with theoretical values.

Responses to Reviewer 3:

In this contribution, Kanai and coworkers describe the development of a homogeneous system effective for achieving catalytic acceptorless dehydrogenation of cyclohexanes, which are expected to be useful LOHCs. Under the influence of a pertinent photoredox catalyst, a catalytic cycle comprising carbon radical generation via hydrogen atom transfer (HAT) with saturated hydrocarbons, cobalt-catalyzed desaturation and hydrogen evolution is operative and complete dehydrogenation of the target alkanes proceeds with good efficiency over a wide range of substrates. In addition to the choice of the photoredox catalyst and chlorine radical source, the presence of a second HAT catalyst and pyridine base was found to be very important in promoting the reaction. This catalytic system is distinct in that it enables endothermic complete dehydrogenation by preventing the reaction from being terminated at the alkene stage (single dehydrogenation), despite the mild conditions compared to the conventional methods. The use of the flow reactor leads to an increase in the efficiency of the dehydrogenation, which also represents an attractive feature of the present system from future perspective. All of these aspects create general enthusiasm for this well-executed study and bolster the case for its publication in Nature Communications. My support is almost unconditional, yet the manuscript would be strengthened if the following issues were properly addressed by the authors.

(3-1) **Reviewer's comment:** My only concern is the ambiguity of the discussion on why TPA is necessary as an HAT catalyst. Mechanistic experiments (Fig. 6b) revealed that the role of the second HAT catalyst has a significant effect on the dehydrogenation process after the second reaction, but it remains unclear why chlorine radical-mediated HAT alone reduces the efficiency of the second and third reactions. Since chlorine radicals inherently have the potential for undergoing radical addition with alkenes, such side reactions might be involved. For instance, checking how the efficiency changes when the reaction of methylcyclohexene (4a) with TPA is carried out in the absence of TBACl would offer some insights into whether the chlorine radical may be inhibited by the product formed in the first reaction.

Author reply: We sincerely appreciate the reviewer's truly insightful comment. Thanks to the reviewer's very important suggestions, we are now confident that the concern has been addressed (please also refer to (3-2) below).

In the reaction mixture of alkene **4a** and TBACl shown in previous Fig. 6b (now Fig. 7c in the revised version), no chlorinated products of alkene **4a** or toluene (**2a**) were detected. Furthermore, the newly performed TA experiments revealed that the decay rate of chlorine radical was indeed slower in the presence of **4a** than its absence (Fig. 7a, please also see (3-2)). Therefore, the interception of the chlorine radical through covalent bond formation with the alkene intermediate is not occurring in this case. These experimental results have been included in the main text.

The experiment suggested by the reviewer (dehydrogenation of **4a** using the TPA catalyst in the absence of TBACl) resulted in only 25% yield of toluene (**2a**). When we prepared tetrabutylammonium salt of TPA (TPA-TBA) under chloride-free conditions and used as a HAT catalyst, however, **2a** was obtained in a significantly improved 70% yield. Those results indicate that the active HAT catalyst responsible for dehydrogenation of alkene intermediates, is the TPA radical derived from TPA-TBA, not the chlorine radical. Those results have been included in the revised main text (Fig. 7c).

(3-2) **Reviewer's comment:** I also suggest that tracing the attenuation of the chlorine radical/benzene π complex in the transient absorption spectrum in the presence of not only methylcyclohexane (Fig. S7) but also 4a would allow for the estimation of the rate of hydrogen abstraction by the chlorine radical at the allylic position, which provides useful information.

Author reply: Here again, we appreciate the reviewer's highly valuable suggestion. Accordingly, we measured the transient absorption of chlorine radical in the presence of alkene **4a** to find that the decay rate of the chlorine radical decreased in the presence of **4a**, compared to its absence (Fig. 7a). This result suggests that the chlorine radical forms a stable π-complex with **4a**, retarding the HAT process. A relevant observation of taming the chlorine radical reactivity through π-complex formation was reported by Russell (newly cited as ref 49). This observation is consistent with the fact that, despite the intrinsically potent HAT activity of the chlorine radical, the dehydrogenation reaction was mainly terminated at the alkene stage in the absence of TPA (Fig. 3, entry 4). These results and discussion have been included in Fig. 7a and the revised main text.

Thanks to the valuable comments from all the reviewers, especially Reviewer 3, our additional studies have identified the following five main issues as the mechanism underlying the enhanced reactivity of the dual HAT catalysis. We have included these new findings in the revised main text and Supplementary information.

1) Chlorine radical promotes the initial HAT of alkanes for the first dehydrogenation step, but is not effective for the subsequent HAT of alkene intermediates (Fig. 7a, 7c).
2) TPA radical does not promote the initial HAT of alkanes, but promotes the subsequent HAT of alkene intermediates for complete dehydrogenation (Fig. 7b, 7c).
3) Under the dual HAT conditions, a tetrabutylammonium salt of TPA (TPA-TBA) is generated through ion exchange. TPA-TBA is the effective precursor of the active HAT catalyst for alkene intermediates (Fig. 7c).
4) Under the dual HAT conditions, the concentration of TPA radical increases, allowing for the efficient dehydrogenation of alkene intermediates (Fig. 7d, 7e).
5) TPA-TBA forms a complex with **PC1** (Fig. S10–S14), facilitating the TPA radical formation through single electron transfer (Fig. 7d, 7e).

Responses to Reviewer 3:

After careful reading of this revised version, I appreciate that the authors tried to provide in-depth elucidation of the reaction mechanism, particularly why two types of HAT catalysts are necessary, using time-resolved ESR and transient absorption spectroscopy. However, the description and discussion based on the outcome of these analyses are somewhat subjective to be deliberately consistent with the conclusion. While I support publication in Nature Communications, I would strongly suggest the authors to make appropriate modifications in order for the manuscript to be suitable for publication in consideration of the following points, where more detailed discussion and explanation are needed. (I understand that complete mechanistic elucidation is difficult and beyond the scope of this manuscript.)

Author reply:

We again sincerely appreciate the reviewer for valuable comments on our manuscript, which are very helpful in further improving the quality and preciseness of our manuscript. We worked hard to address the points this reviewer raised.

(3-1) **Reviewer's comment:** The transient absorption spectra to the point of complete attenuation should always be included at least in SI. Without the full spectrum, it is difficult to understand the lifetime of each transient species and also the simultaneous observation of two transient species.

Author reply:

Thank you very much for your valuable suggestion. We agree that observing transient absorption until complete decay would, in principle, be insightful. However, in systems like ours, where chemical reactions progress and lead to the formation of long-lived species, it is challenging to capture a full decay using current technology, and it is generally uncommon in the field. Standard femtosecond laser setups typically measure up to only a few nanoseconds, but our advanced setup extended this to 2000 nanoseconds, allowing a far longer observation window. By using such advanced setup, we have succeeded in observing profiles of chlorine (Fig. 7a) and TPA radicals (Fig. 7d). For these reasons, we are confident that our presentations of TA spectra are valid.

(3-2) **Reviewer's comment:** [1)] Why the Ir(II) species observed until 2 μs in the time-resolved ESR spectrum was not attributed in the transient absorption spectrum? In addition, while the Ir(II) species was only observed after 0.2 μs in the ESR measurement, the complex of the chloro radical with benzene was observed immediately after irradiation of the pulsed laser in the transient absorption spectroscopy measurement. [2)]This time lag should be clarified as these two species should be observed essentially at the same time if the chloride ion was oxidized by the excited-state Ir(III) complex.

Author reply:

1) As the reviewer pointed out, Ir species derived from **PC1** are indeed involved in the TA spectra observed at 400 nm. The TA spectra at 400 nm contain absorptions of the excited Ir catalyst (**PC1**), the one-electron reduced **PC1**, chlorine radical, and TPA radical. However, we discuss differences in TA spectra depending on the conditions. Contributions of Ir species to TA spectra are consistent under all the conditions we studied. Therefore, we do not have to consider contributions of Ir species in discussing differences between the TA spectra.

   For example, in Fig. 7a, we compared TA spectra under three conditions after normalization: **PC1** + TBACl + pyridine (py), **PC1** + TBACl + py + methylcyclohexane (**1a**), and **PC1** + TBACl + py + methylcyclohexene (**4a**). Because PET proceeds solely between chloride of TBACl and **PC1**, generating chlorine radical and reduced **PC1**, but not between **1a** or **4a** and **PC1**, we can evaluate the effects of **1a** or **4a** on the chlorine radical concentration by comparing the TA spectra under the three conditions.
2) The initially generated singlet radical pairs after PET are EPR-silent. After the dissociation of the radical pairs and relaxation to the triplet state, radicals were observed by EPR. This is the origin of the time lag. We have already explained this in Fig. S3 in Supplementary Information (SI) of the previous submission.

(3-3) **Reviewer's comment:** I am afraid if the assignment of the chloro radical-benzene complex observed in the transient absorption spectrum (but not in the time-resolved ESR) is correct.

Author reply:

The assignment is based on several previous reports of the chlorine radical-benzene complex (*J. Am. Chem. Soc.* **1985**, *107*, 5464; *J. Am. Chem. Soc.* **2021**, *143*, 6060). To clarify that there are previous reports for the absorption of the chlorine radical-benzene complex, we have cited these papers as refs 49 and 50.

(3-4) **Reviewer's comment:** Regarding the discussion in line 7-11 in page 9, I assume that the lifetime of the transient species would be in the range of ns, judging from Figure 7d. [1)] Yet it is difficult to assess precisely because there are no spectra including the fitting curves, from which these lifetimes were calculated. [2)] Furthermore, although the increase in the lifetime of TPA radical was ascribed to the increase in its concentration, this interpretation is incorrect because the increase in the concentration of the active species does not change the lifetime, but only increases the intensity of the spectrum. There must be another reason why the lifetime of the TPA radical increased in the presence of TBACl.

Author reply:

1) We described time constants, not lifetimes, in the part pointed out by the reviewer in the previous submission. There, to avoid complications from secondary or later radicals derived from primary chlorine and TPA radicals, we used TA spectra in the ultrafast (picosecond) range to calculate the time constants using global analysis. Thus, the time constants are based on the picosecond-range TA data (Fig. S9).
   According to this reviewer's comment, we have shown TA results with curve fitting in Figs S7, S8, and S9. Furthermore, according to the reviewer's subsequent comment (please see below 2), we have deleted the discussion based on time constants from the main text and tabulated the time constants in SI Figs S7, S8, and S9.
2) We thank the reviewer for this important comment. The reviewer is correct. The coexistence of TBACl and TPA generated a higher concentration of TPA radical than TPA alone without TBACl (Fig. 7e; please compare red lines under conditions 1 and 3). This is the origin of the observed synergistic effects between TBACl and TPA. According to the reviewer's comment, we have modified the main text to focus our discussion on "amplitude", which corresponds to the radical concentration (intensity), not the time constants, as follows: *Under condition (1), the amplitude of TPA radical at 400 nm was 9.5 x 10^{-4}, while under condition (2), the amplitude of the chlorine radical-benzene π-complex at 400 nm was 10.5 x 10^{-4}. Under condition (3), however, the amplitude of TPA radical at 400 nm was 2.7 times higher (25.5 x 10^{-4}) than TPA only under condition (1). These results suggest that the coexistence of TPA and TBACl generates TPA-TBA in the reaction mixture, enhancing TPA radical production and accelerating the dehydrogenation reaction of alkene intermediates.*

(3-5) **Reviewer's comment:** The discussion about the transient absorption spectrum in Page 8 sounds qualitative. It would be better to discuss about the lifetime quantitatively using specific values.

Author reply:

According to the reviewer's suggestion, we obtained time constants from kinetic fitting analysis and have included them in the main text. Time constants for all the TA data used in this study have been tabulated in Figs S7, S8, and S9.

(3-6) **Reviewer's comment:** It is unclear why pyridine was added in the measurement of the transient absorption spectrum shown in Figure 7a. According to the presumed mechanism, pyridine is not involved in the generation of chloro radical, and hence a similar spectrum should be obtained in the absence of pyridine.

Author reply:

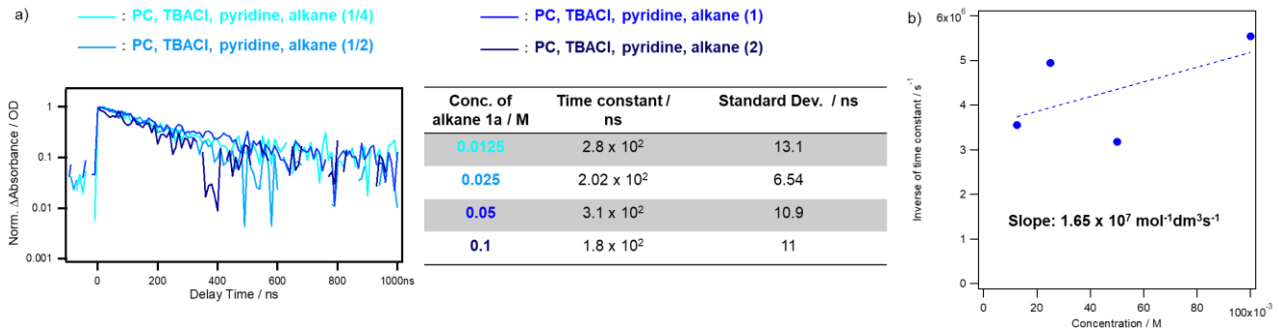
During the optimization of the reaction conditions summarized in Fig. 3, we found that adding pyridine improved the yield of product toluene. Therefore, we measured TA in Fig. 7a under the optimized reaction

conditions in the presence of pyridine. We hypothesize that pyridine works as a Brønsted base to deprotonate TPA, generating TPA-py and facilitating ion exchange to generate TPA-TBA, the active precursor for the TPA radical (see Fig. 7f). Consistent with this hypothesis and as pointed out by the reviewer, the TA experiment using **PC1** and TBACl showed that adding pyridine did not affect the concentration of chlorine radical. Accordingly, this result has been added in Fig. S11.

(3-7) **Reviewer's comment:** In the transient absorption spectrum in Figure 7a, a change in lifetime was observed upon addition of alkane 1a. It would be worthwhile to plot the inverse of the lifetime after the change against the change in the concentration of 1a. If a linear proportional relationship was revealed, it indicates that the reaction of chloro radical with 1a has the first-order dependence, and the rate constant can be calculated from the slope of the plot. Similarly, in Figure 4d-(3), it would be possible to evaluate if a linear relationship appears when plotting the inverse of the lifetime against the concentration of alkene 4a added. Comparison of the obtained rate constants would allow quantitative discussion on the reaction rates of the chloro radical with 1a and the TPA radical with 4a.

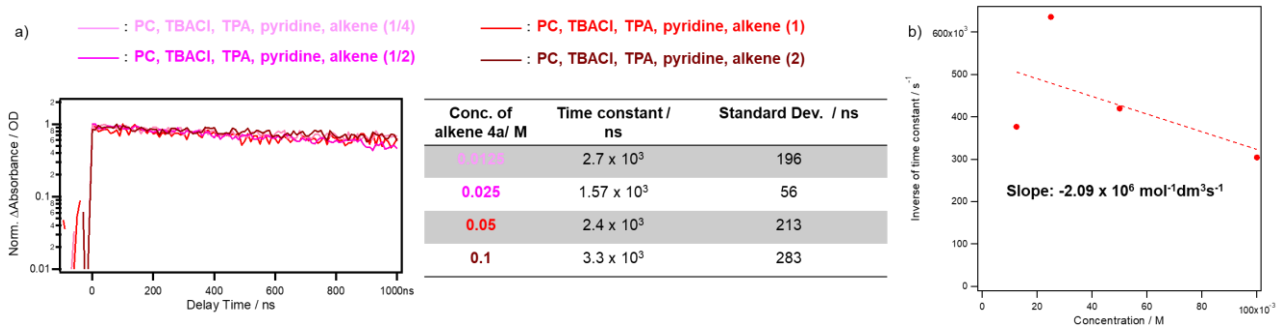
Author reply:

According to the suggestion, we measured TA spectra under varied concentrations of **1a** in the presence of **PC1**, TBACl, and pyridine (Fig. R1a). We plotted the relationship between the inverse of time constant and the concentration of **1a** (Fig. R1b). However, deviations were large, and it was difficult to obtain a reliable conclusion. The same was true for the TA analysis under varied concentrations of **4a** in the presence of **PC1**, TBACl, TPA, and pyridine (Fig. R2). Therefore, it was not possible to evaluate the quantitative kinetics for the two HAT processes from **1a** and **4a** by TA. We hope the reviewer understands the difficulties in this challenging measurement.



Conc. of alkane 1a / M	Time constant / ns	Standard Dev. / ns
0.0125	2.8 x 10^2	13.1
0.025	2.02 x 10^2	6.54
0.05	3.1 x 10^2	10.9
0.1	1.8 x 10^2	11

Fig. R1. Relationship between the obtained time constant of alkane **1a** and time constant of chlorine radical. Time profiles of transient absorption of a mixture of **PC1** (0.0005 M), TBACl (0.000625 M), and pyridine (0.015 M) in benzene with MCH (**1a**, 0.0125 M, 0.025M, 0.05 M and 0.1 M) at 400 nm. The sample was excited by a 2 μJ, 355 nm laser pulse with 800 ps duration at 500 Hz.



Conc. of alkene 4a/ M	Time constant / ns	Standard Dev. / ns
0.0125	2.7 x 10^3	196
0.025	1.57 x 10^3	56
0.05	2.4 x 10^3	213
0.1	3.3 x 10^3	283

Fig. R2. Relationship between the obtained time constant of alkene **4a** and time constant of radical species. Time profiles of transient absorption of a mixture of **PC1** (0.0005 M), TBACl (0.000625 M), TPA (0.000156 M) and pyridine (0.015 M) in benzene with methylcyclohexene (**4a**, 0.0125 M, 0.025M, 0.05 M and 0.1 M) at

400 nm. The sample was excited by a 2 μJ, 355 nm laser pulse with 800 ps duration at 500 Hz.

(3-8) **Reviewer's comment:** Considering the BDE of the benzyl C-H bond of the product, toluene (2a), which is smaller than that of the reaction substrate, discussion on the possible intervention of the product inhibition would provide useful information for the journal readership. (In the transient absorption measurement shown in Figure 7a, I wonder whether the lifetime of the transient species would be changed by the addition of 2a.)

Author reply:

We thank the reviewer for this constructive suggestion. Accordingly, we measured the TA of a mixture of **PC1**, TBACl, pyridine, and methylcyclohexane (**1a**) in the presence of toluene (**2a**) and compared the spectrum with that in the absence of **2a**. As a result, the TA intensity, which corresponds to the chlorine radical concentration, decreased in the presence of **2a**. This result suggests that the generated chlorine radical is consumed through HAT of **2a**.

Furthermore, we confirmed the product inhibition by performing the dehydrogenation reactions of **1a** by adding various amounts of a product analog, *p*-xylene. As a result, the yield of toluene (**2a**) diminished upon increasing the amount of *p*-xylene.

These TA and product inhibition reaction results have been included in Fig. S12 and section 11 in SI, respectively. We have also added the following sentence in the main text (p. 5) to state the existence of product inhibition: This moderate yield is partly attributable to the inhibitory effect of the competing hydrogen atom abstraction at the benzylic position of **2a** (section 11 and Fig. S12 in Supplementary information).

(3-9) **Reviewer's comment:** It is ambiguous why the ps-scale transient absorption spectra were measured (Figure S10). If the authors claimed that they observed the same transient species as that detected in the ns-scale transient absorption spectra, it is important to make quantitative discussion based on the comparison of the lifetime of the transient species calculated from each spectrum.

Author reply:

While the nanosecond-scale TA (Figs 7a (= S7), 7d (= S8), and S12) was used for analyzing HAT processes involving relatively slow (compared to electron transfer) C–H bond cleavage by chlorine or TPA radicals, the picosecond-scale TA (Fig. S9) was used for analyzing the ultrafast electron transfer processes between **PC1** and TBACl or TPA. To avoid complications from secondary or later radicals generated through chemical reactions of chlorine or TPA radical, we needed to evaluate the concentration of the each radical generated in the faster time region. Therefore, we employed picosecond-scale TA spectra for global analysis to obtain decay associated spectra (DAS) corresponding to the resulting time constants. As a result, we selectively extracted each of the two radicals (i.e., chlorine and TPA radicals) by global analysis. This allowed us to obtain DAS of chlorine radical and TPA radical as shown in Fig. 7e.

To clarify the meanings of measuring picosecond-scale TA, we have modified the main text as follows: *Furthermore, to avoid complications by the generation of secondary or later radicals, the ultrafast picosecond-scale TA data (Fig. S9) were analyzed by global fitting with a fitting function consisting of the sum of exponential decay components.*

We have also cited a reference for global analysis as Ref S13 in Fig. S10 legend.

(3-10) **Reviewer's comment:** It has not been experimentally proven that Co-1 is not involved in the generation of HAT agent. It would be relevant to confirm if the addition of Co-1 would lead to alter the spectrum shown in Figure 7d-(3), which was measured under the conditions close to those for the catalytic reaction.

Author reply:

In response to this reviewer's comment, we measured a temporal profile of transient absorption of a mixture of **PC1**, TPA, TBACl, pyridine, and **Co-1** (Fig. R3). The TA intensity, which corresponds to the concentrations of chlorine and TPA radicals, decreased but was still significantly observed especially in the early delay times. The decrease in the radical concentration is likely due to the radical trap by Co(II) species derived from **Co-1** under

the conditions of TA measurement in the presence of **PC1** (Fig. R4).

To confirm the decrease in chlorine radical concentration caused by the presence of **Co-1**, we performed the Giese reaction between **1a** and benzalmalononitrile (Fig. R5). The HAT process from **1a** by chlorine radical is a key step of the reaction; thereby, the yield of the product depends on the efficiency of the HAT process. Yield decreased in the presence of **Co-1**; however, the product was still formed (49% *vs.* 25%). This result is consistent with the TA result.

There are differences between TA conditions and real reaction conditions. For example, while TA conditions use intermittent pulse irradiation, the real reaction conditions continuously irradiate light. The Co(III) species generated by the radical trap could be reduced back to chlorine or TPA radical and Co(II) under the reaction conditions. While we understand that TA conditions do not completely reflect the real reaction conditions, especially considering the high complexity of the present mulicatalytic system, the TA results without **Co-1** are consistent with the reaction results. We conducted our study from both the reaction and spectroscopic sides, always complementary and backing up each other. We also mentioned in the main text that the mechanism shown in Fig. 7f is a working hypothesis postulated from the sum of the results obtained by multiangle studies. The reviewer thoughtfully understands that comprehensive mechanistic elucidation is difficult and beyond the scope of this work.

Accordingly, we have added the TA result in the presence of **Co-1** (Fig. R3) and the Giese reaction results (Fig. R5) with the following sentence in SI as Fig. S13: *The absorbance change, corresponding to the concentrations of chlorine and TPA radicals, decreased but was still significantly observed especially in the early delay times. Furthermore, the following results support that* ***Co-1*** *decreased the concentration of chlorine radical, but still a significant concentration of chlorine radical existed for HAT to proceed.*

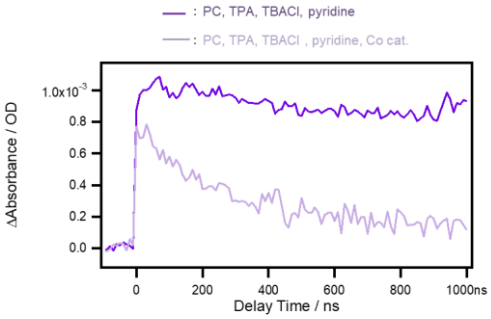


Fig. R3. Effect of **Co-1** on the concentration of chlorine and TPA radicals. Time profiles of transient absorption of a mixture of **PC1** (0.0005 M), TBACl (0.000625 M), TPA (0.000156 M), and pyridine (0.015 M) in benzene with and without **Co-1** (0.0003125 M) at 400 nm. The sample was excited by a 2 μJ, 355 nm laser pulse with 800 ps duration at 500 Hz.

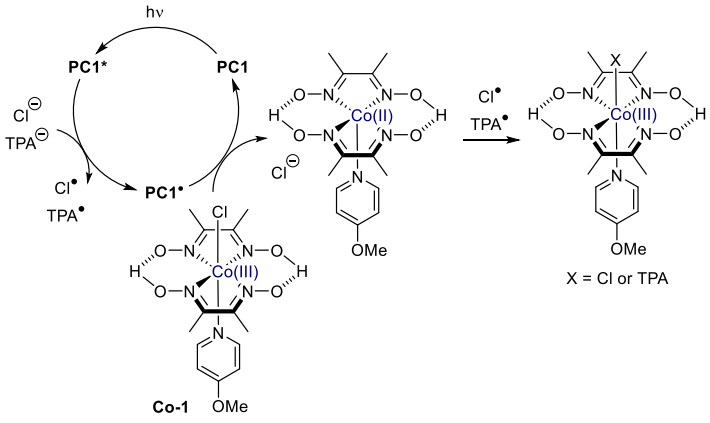


Fig. R4. Possible quenching mechanism of radical species by **Co-1** under TA conditions.

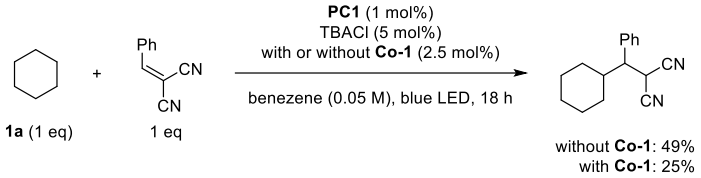


Fig. R5. Effect of **Co-1** on the reaction between cyclohexane (**1a**) and benzalmalononitrile.

(3-11) **Reviewer's comment:** As a minor point, since the spectrum of TPA radical shown left side in Figure 7e is saturated, it should be rescaled as rendering the peak top visible.

Author reply:

According to the reviewer's comment, we double-checked any possibility of saturation of TPA radical-related signal for the chart in Fig. 7e. However, there was no significant peak, whose emission was longer than 450 nm, related to TPA radical. Thus, we have posted a revised chart with the maximum vertical axis value in Figs 7e and S10.

Responses to Reviewer 3:

I have carefully read through this second revised version, together with the response letter, and found that all the concerns raised in the previous round of review, particularly those about the reaction mechanism, have been properly addressed. I think that this modified manuscript is now acceptable for publication in Nature Communications without any further alterations.

Author reply: We thank reviewer 3 for the constructive comments throughout the revisions. We are delighted to hear that all the concerns have been satisfactorily addressed.