

Switchable Chlorine Atom Transfer Radical Reactions

Corresponding Author: Professor Jin Xie

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Editorial note: Reviewer 2 mentions "previous reviewer comments are addressed very well" though the manuscript had not been previously peer reviewed. These comments from the authors were in response to editorial feedback only.

Version 1:

Reviewer comments:

Referee #1

(Remarks to the Author)

Alkyl chlorides rank among the most commercially abundant and widely employed building blocks in organic synthesis. Their activation via single-electron transfer remains challenging, owing to higher C–Cl bond dissociation energies relative to C–Br and C–I bonds and the greater electronegativity of chlorine. Although precedents exist, the reported strategies have largely centred on copper-catalysed SET activation of activated organochlorides, particularly α -chloro carbonyl compounds (Nature 2023, 618, 294; Nature 2021, 596, 250). Against this backdrop, the present work represents a significant breakthrough in the SET activation of unactivated alkyl chlorides. The methodology provides a general and robust platform capable of engaging diverse alkyl chlorides under mild conditions.

Among radical reactions, both ATRA and ARTP have been extensively studied. Notably, both transformations are applicable for activated organochlorides. There are two key challenges for the unactivated alkyl chlorides: a) How to achieve sufficient reactivity to cleave the strong C–Cl bonds in substrates whose bond dissociation energies exceed those of products b) How to preserve the weaker C–Cl bonds present in the products. In this work, Xie and co-workers elegantly addressed the synthetic challenges outlined above. They have creatively designed a relay catalysis process in which a dinuclear copper catalyst (cat.A1) cooperates with a mononuclear copper catalyst (cat.B): the former activates the C–Cl bond in the substrate, while the latter reconstructs the C–Cl bond in the product, with chlorine shuttling between the two catalytic species. To gain mechanistic insight, the authors performed control experiments, including EPR spectroscopy to detect radical intermediates and Cu(II) species, and ^{31}P NMR tracing to monitor the relay process between the dinuclear and mononuclear copper complexes. In addition, DFT studies are clear and convincing.

A diverse range of alkyl chlorides bearing various functional groups is well tolerated, enabling the late-stage modification of complex molecules. The authors judiciously used terminal electron-withdrawing alkenes to match radical polarity in the addition step. The authors also demonstrated the feasibility of aryl chlorides and the results are promising.

As shown in Fig. 5, the ratio of cat.A1 to cat.B enables selective activation of either $\text{C}(\text{sp}^3)\text{--Cl}$ or $\text{C}(\text{sp}^2)\text{--Cl}$ bonds for the ATRA process. The authors have showed gram-scale experiments which underscores the practical utility of the method.

Not only ATRA, but a switchable chlorine-atom transfer platform has been developed. In the absence of cat.B, the reaction delivers ATRP products. To the best of my knowledge, this represents the first example of copper-catalysed ATRP using unactivated alkyl chlorides - a point rationalized and well supported by the control experiments. More excitingly, poly(vinyl chloride) (PVC), the world's third most widely consumed plastic, can be employed as a substrate for chemical post-modification under these conditions. This strategy therefore offers a promising synthetic approach to PVC waste recycling

Clearly, this work is of significant scientific merit and aligns well with the high standards of novelty and impact consistently sought by Nature. In view of the above observations, I recommend acceptance of the manuscript, subject to satisfactory revision addressing the following points:

1. The authors highlight a counterintuitive selectivity in the abstract and introduction: although the substrate (an unactivated alkyl chloride) has a strong C–Cl bond and the product (the ATRA adduct) has a weaker one, the catalyst selectively cleaves the substrate's C–Cl bond while leaving the product's C–Cl bond intact. Can a competition experiment be designed to directly demonstrate this selectivity. For instance, the authors could subject substrate 1 and product 3 together to the standard reaction conditions and determine which is consumed preferentially.

2. In Che's work (Ref. 20), they employed a large excess of unactivated R-Cl (92 equiv.) to get a moderate yield of ~40% by using NHC-type dinuclear copper catalyst. The Cl-bridged dinuclear copper catalyst (cat.A1) reported in Xie's work is much more efficient, ~3 equiv for ATRA reaction and very good yield (up to 87%) was obtained. This reviewer suggests that the authors comment on this point as doing so would further strengthen the novelty and significance of their work.

3. On page 12, 'this' in the sentence is twice: 'Encouraged by the broad substrate generality with alkyl chlorides, we further applied this this tiered copper catalysis strategy to performing ATRA reactions of aryl chlorides.'

4. Chemical grafting modification of PVC is an effective strategy to improve its properties. Although the authors have presented TGA and other characterization data for the modified PVC in Supplementary Information, this reviewer would suggest the authors give appropriate discussion for these data.

5. In the reference section, the authors should use the same style for all references. Please check them carefully.

6. Some references are suggested for consideration: Nature 2025, 640, 107 (activated R-Cl activation and radical ligand transfer process); Science 2019, 364, eaav9713 (photoexcited copper catalysis); Chem. Soc. Rev. 2022, 51, 5287; Ref. 3 is suggested to replace by this early one in ATRA, such as Kharasch, M. S., Jensen, E. V. & Urry, W. H. Addition of derivatives of chlorinated acetic acids to olefins. J. Am. Chem. Soc. 1945, 67, 1626.

Referee #2

(Remarks to the Author)

A study (previous reviewer comments are addressed very well) on ATRA and ATRP reactions is presented, using an intriguing catalyst platform based on copper. Many exciting discoveries have been made that allow the switchable addition of unactivated alkylchlorides to alkenes, initiating ATRP reactions or giving ATRA products. I am impressed by the binuclear activity of the copper catalyst responsible for the SET to generate radicals from simple alkylchlorides. Good scope and meaningful applications are reported; insightful mechanistic studies backed up by DFT calculations complement the synthetic aspects of the study.

Minor comments:

1. The type of dual catalytic activity, i.e. that of electron-rich copper(I) complexes being responsible for SET, and Cu(II)-N,N-complexes decisive for ligand transfer, has been discovered by Fu et al. Although this study is cited (reference 25), this achievement should be stated more clearly (rather than citing this work as one of several examples of relay catalysis), since the current study would not have been possible without applying this concept.

2. Some language polishing (wrong use of articles) would further improve this study.

Overall, this is an excellent study, greatly advancing the field of copper photocatalysis and ATRA chemistry. I enthusiastically support publication of this study in Nature.

Oliver Reiser

Version 2:

Reviewer comments:

Referee #1

(Remarks to the Author)

The authors have pertinently addressed all the concerns/comments raised earlier in my response. The manuscript is recommended for publication in its present form.

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Point-by-point response to reviewers

Response to reviewers:

Reviewer: 1

Comments: Alkyl chlorides rank among the most commercially abundant and widely employed building blocks in organic synthesis. Their activation via single-electron transfer remains challenging, owing to higher C–Cl bond dissociation energies relative to C–Br and C–I bonds and the greater electronegativity of chlorine. Although precedents exist, the reported strategies have largely centred on copper-catalysed SET activation of activated organochlorides, particularly α -chloro carbonyl compounds (Nature 2023, 618, 294; Nature 2021, 596, 250). Against this backdrop, the present work represents a significant breakthrough in the SET activation of unactivated alkyl chlorides. The methodology provides a general and robust platform capable of engaging diverse alkyl chlorides under mild conditions.

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Clearly, this work is of significant scientific merit and aligns well with the high standards of

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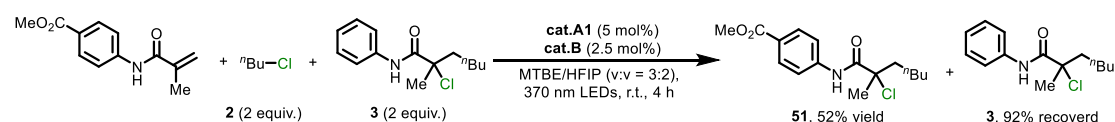
Thank you very much for your positive comments and valuable suggestions.

According to your suggestions, we conducted additional mechanistic experiments. We hope that these revisions address your concern and show that our intention was to provide a comprehensive and scientifically valuable study. We believe the revised manuscript now achieves a better balance between demonstrating the generality of the findings and highlighting the most significant results. The following is a point-to-point response to your suggestions.

A few specific points:

1. The authors highlight a counterintuitive selectivity in the abstract and introduction: although the substrate (an unactivated alkyl chloride) has a strong C–Cl bond and the product (the ATRA adduct) has a weaker one, the catalyst selectively cleaves the substrate's C–Cl bond while leaving the product's C–Cl bond intact. Can a competition experiment be designed to directly demonstrate this selectivity. For instance, the authors could subject substrate **2** and product **3** together to the standard reaction conditions and determine which is consumed preferentially.

Our answer: Thank you very much for your valuable suggestions. Accordingly, we designed and conducted the following selectivity experiment: equimolar amounts of **2** and **3** were subjected to the standard ATRA reaction conditions. Under these conditions, compound **2** afforded its ATRA product **51** in 52% isolated yield, while compound **3** was recovered in 92% isolated yield (93% recovery by GC). These results support preferential activation of the substrate C–Cl bond over that of the product.



We have added the following sentence to the revised manuscript: “In addition, the competition experiment between equimolar amounts of **2** and **3** indicated preferential C–Cl bond activation of the substrate over the product (see details in the Supplementary Information, Section 8.12)”.

Further experimental details are provided in Section 8.12 of the Supplementary Information.

2. In Che's work (Ref. 20), they employed a large excess of unactivated R–Cl (92 equiv.) to get a moderate yield of ~40% by using NHC-type dinuclear copper catalyst. The Cl-bridged dinuclear copper catalyst (cat.A1) reported in Xie's work is much more efficient, ~3 equiv for ATRA reaction and very good yield (up to 87%) was obtained. This reviewer suggests that the authors comment on this point as doing so would further strengthen the novelty and significance of their work.

Our answer: Thank you very much for your helpful suggestion. We have added a

comparison with this study to the manuscript, as following in the revised manuscript: “In 2024, Che reported an elegant NHC–dicopper complex²¹ for arylalkylation of N-arylacrylamides using only two unactivated alkyl chlorides, however, a large excess of alkyl chlorides (30–92 equiv.) were required to deliver modest yields of 24–46%. To probe the role of the intermetallic distance, we prepared a series of dinuclear copper complexes with systematically varied Cu–Cu distances by modulating anions (Extended Data Table 1, entries 2–4). Among these, **cat.A1**, which features the shortest Cu–Cu distance, delivered the highest yield, which might imply that shorter Cu–Cu distance would enhance cuprophilic interactions^{33,34} to promote C–Cl cleavage”.

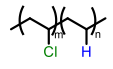
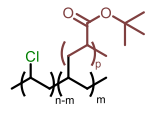
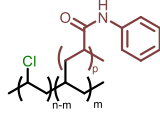
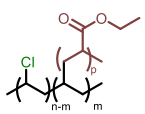
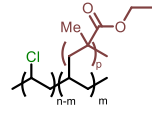
3. On page 12, 'this' in the sentence is twice: 'Encouraged by the broad substrate generality with alkyl chlorides, we further applied this this tiered copper catalysis strategy to performing ATRA reactions of aryl chlorides.'

Our answer: Thank you very much for your kind reminder. We have already removed the redundant 'this' in the sentence. The revised sentence reads: “Encouraged by the broad substrate scope with alkyl chlorides, we further applied this tiered copper catalysis strategy to aryl chlorides^{40,41}”.

4. Chemical grafting modification of PVC is an effective strategy to improve its property es. Although the authors have presented TGA and other characterization data for the modified PVC in Supplementary Information, this reviewer would suggest the authors give appropriate discussion for these data.

Our answer: Thank you very much for your valuable suggestions. We have added the following description to the main text: “Thus, the thermal properties of PVC would be tailored via hydrodechlorination or graft modification (see details in the Supplementary Information, Section 7.2), thereby broadening its potential application”.

In Section 7.2 of the Supplementary Information, we have provided a more detailed discussion of the thermal properties of the modified PVC: “Regarding the thermal properties, we found that hydrogenation of PVC significantly lowers its T_g, which may facilitate processing. In contrast, the effect of graft modification depends on the nature of the grafted monomer: acrylate-based grafting also reduces the T_g of PVC, whereas acrylamide-based modification increases it. Furthermore, the polymer dispersities remained similar to that of pristine PVC, indicating that no significant chain-scission side reactions occurred during the modification process”.

Structure	Polymer	Dehalogenation ratio	Grafting ratio	M_n	D	T_g	T_{ds}
	PVC	-	-	106.1 kDa	1.63	84.7 °C	288.2 °C
	105 (1 h)	4.8%	-	104.0 kDa	1.65	72.6 °C	288.4 °C
	105 (3 h)	8.7%	-	101.0 kDa	1.62	63.0 °C	289.8 °C
	105 (12 h)	10.7%	-	99.3 kDa	1.63	48.2 °C	295.0 °C
	106	-	13.0%	116.2 kDa	1.74	80.5 °C	242.9 °C
	107	-	8.0%	116.1 kDa	1.51	92.2 °C	274.2 °C
	108 (0.5 h)	-	4.8%	109.0 kDa	1.63	76.9 °C	284.7 °C
	108 (1 h)	-	9.9%	113.7 kDa	1.71	64.0 °C	288.0 °C
	108 (1.5 h)	-	13.4%	118.0 kDa	1.63	59.3 °C	289.7 °C
	108 (2 h)	-	16.2%	120.2 kDa	1.66	55.7 °C	291.8 °C
	108 (2.5 h)	-	18.6%	127.7 kDa	1.60	52.0 °C	294.4 °C
	108 (3 h)	-	21.8%	136.0 kDa	1.70	49.9 °C	296.1 °C
	109	-	16.5%	130.3 kDa	1.78	84.6 °C	279.4 °C

Supplementary Table 20. Data of modified PVC

5. In the reference section, the authors should use the same style for all references. Please check them carefully.

Our answer: Thank you very much for your kind reminder. We have reviewed the reference list and standardized the formatting.

6. Some references are suggested for consideration: Nature 2025, 640, 107 (activated R-Cl activation and radical ligand transfer process); Science 2019, 364, eaav9713 (photoexcited copper catalysis); Chem. Soc. Rev. 2022, 51, 5287; Ref. 3 is suggested to replace by this early one in ATRA, such as Kharasch, M. S., Jensen, E. V. & Urry, W. H. Addition of derivatives of chlorinated acetic acids to olefins. J. Am. Chem. Soc. 1945, 67, 1626.

Our answer: Thank you very much for your valuable suggestions. We have added the three suggested references and replaced the previous Ref. 3 with J. Am. Chem. Soc. 1945, 67, 1626.

3. Kharasch, M. S., Urry, W. H. & Jensen, E. V. Addition of derivatives of chlorinated acetic acids to olefins. *J. Am. Chem. Soc.* **67**, 1626 (1945).

24. Hossain, A., Bhattacharyya, A. & Reiser, O. Copper's rapid ascent in visible-light photoredox catalysis. *Science* **364**, eaav9713 (2019).

25. Engl, S. & Reiser, O. Copper-photocatalyzed ATRA reactions: Concepts, applications, and opportunities. *Chem. Soc. Rev.* **51**, 5287–5299 (2022).

26. Zhong, F., Li, R., Mai, B. K., Liu, P. & Fu, G. C. Photoinduced copper-catalysed deracemization of alkyl halides. *Nature* **640**, 107–113 (2025).

Reviewer: 2

Comments: A study (previous reviewer comments are addressed very well) on ATRA and ATRP reactions is presented, using an intriguing catalyst platform based on copper. Many exciting discoveries have been made that allow the switchable addition of unactivated alkylchlorides to alkenes, initiating ATRP reactions or giving ATRA products. I am impressed by the binuclear activity of the copper catalyst responsible for the SET to generate radicals from simple alkylchlorides. Good scope and meaningful applications are reported; insightful mechanistic studies backed up by DFT calculations complement the synthetic aspects of the study.

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Our answer: We thank the reviewer for the kind reminder. We have revised the sentence as follows: "Recently, Fu and coworkers disclosed an elegant dual-copper relay system, in which a Cu/bisphosphine complex served as the photocatalyst while a copper/diamine complex mediated C-N coupling.²⁷".

2. Some language polishing (wrong use of articles) would further improve this study.

Our answer: Thank you for this helpful suggestion. We have carefully reviewed the manuscript and corrected article usage and other grammatical errors. We have also revised several sentences to improve clarity and readability.

Overall, this is an excellent study, greatly advancing the field of copper photocatalysis and ATRA chemistry. I enthusiastically support publication of this study in Nature.

We sincerely thank this reviewer for the encouraging comments and generous assessment of our work.