Catalytic Photoredox Carbobromination of Unactivated Alkenes with α-Bromocarbonyls via Mechanistically Distinct Radical-Addition Radical-Pairing Pathway

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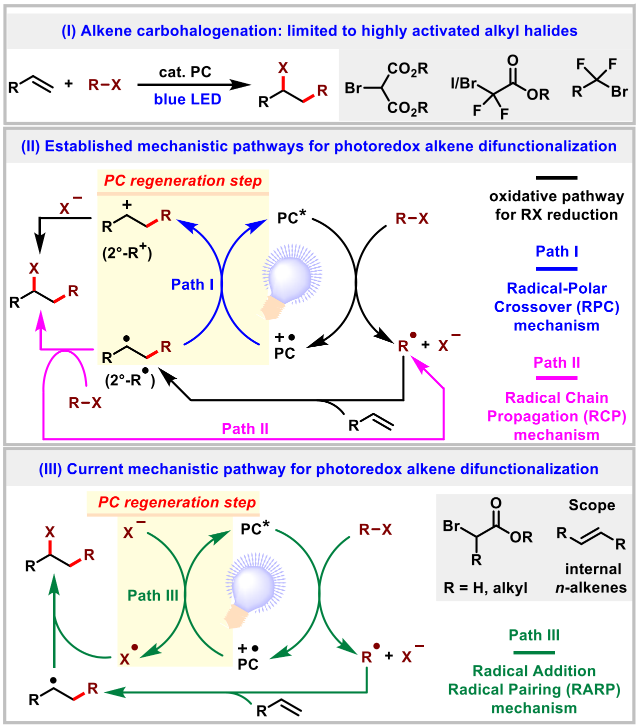
Supporting Information Placeholder

ABSTRACT: We disclose a catalytic photoredox carbobromination of unactivated alkenes with α-bromocarbonyl compounds under a blue LED light. The reaction proceeds with α-bromoesters, α-bromonitriles and α-bromo-γ-lactones along with terminal and 1,2-disubstituted internal alkenes. Reactions with indenes and 1,1-disubstituted alkenes generate alkylated alkenes. Mechanistic studies by product selectivity and three-way competitive crossover experiments suggest that the reaction operates by a unique radical-addition radical-pairing (RARP) mechanism. The catalytic turnover is achieved by a single electron reduction of $PC^{\bullet+}$ by Br^{-}, rather than by alkyl radical (R•), and the product is generated by the pairing of Br• and R•, instead of the combination of Br^{-} and a carbocation (R^{+}).

Catalytic difunctionalization of unactivated alkenes is emerging as a powerful tool to synthesize complex carbon skeleton rapidly from readily available starting materials. Among several approaches, introduction of a halogen atom concomitant to the formation of a $C(sp^3)$-$C(sp^3)$ bond across vicinal $C(sp^2)$ carbons on alkenes creates $C(sp^3)$-halogenated carbon homologs (Scheme 1.I). In particular, addition of an α-carbonyl fragment and a halogen would generate γ-halogenated carbonyl compounds enabling further functional group incorporation at the γ-position distal to carbonyls that is otherwise difficult to attain without a multistep endeavor. To date, a number of methods have been developed for carbohalogenation of unactivated alkenes under both the metal[1] and photoredox-catalyzed[2] reaction conditions.[3,4] However, these methods are largely limited to either intramolecular processes or the use of activated reagents, such as Br_2FCH, $[Ph_3PCF_2H]^{+}[Br]^{-}$, $BrCH(CO_2R)_2$, $Br_2C(CO_2R)_2$, ICF_2CO_2R, F_2BrCR and F_2CBrCO_2R, as the source of carbon and halogen.[5]

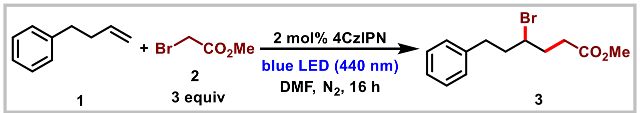
Mechanistically, the carbohalogenation of an alkene is proposed to occur by an atom transfer radical addition (ATRA) process. This reaction is initiated by a stepwise or concerted homolysis of the carbon-halogen bond in haloalkanes followed by the addition of a carbon-centered radical to an alkene to generate a second carbon radical. In transition metal-catalyzed ATRAs,[3] the second carbon radical abstracts a halogen atom from the oxidized metal catalyst thereby forming the product and regenerating the catalyst. Under photoredox catalysis,[4] variation exists as to how the second carbon radical is halogenated and the PC is regenerated.[6] A most commonly accepted mechanism is the radical-polar crossover (RPC) pathway (Scheme 1.II, Path I) in which the carbon radical regenerates PC by a single electron transfer to $PC^{\bullet+}$, and the resultant carbocation combines with a halide anion (X^{-}) to form carbohalogenated products.[2f,2g,2i,7] Alternatively, a PC could simply function as a radical initiator, and the reaction proceeds by a radical chain propagation (RCP) mechanism (Scheme 1.II, Path II) via the abstraction of a halogen atom from haloalkanes directly by the carbon radical.[8] Herein, we report a mechanistically distinct radical-addition/radical pairing (RARP) pathway for the catalytic photoredox carbobromination of unactivated alkenes with simple α-bromocarbonyl compounds (Path III) (Scheme 1.III). The catalytic turnover is achieved by a single electron reduction of $PC^{\bullet+}$ by Br^- and the product is generated by the pairing of Br• and 2°-R•.



Scheme 1. (I) Status of alkene carbohalogenation reaction. (II) Established catalytic pathway. (III) New catalytic pathway.

In our quest to difunctionalize unactivated alkenes under photoredox catalysis, we examined the reaction of 4-phenylbutene (**1**) with α-bromoacetate **2** using different photocatalysts (PCs) in blue LED light under inert atmosphere (Table 1, entries 1-5). The reaction with 4CzIPN furnished carbobromination (**3**) in best yield (91%) (entry 1). While $Ru(bpy)_3(PF_6)_2$ and $Ru(bpz)_3(PF_6)_2$ were ineffective, other Ru- and Ir-catalysts, eosin Y sodium salt and fluorescein, furnished the product **3** in good yields (entries 2-5). The reactions conducted without the blue LED, 4-CzIPN or in dark afforded no carbobromination product (entries 6-7), suggesting the roles of both the blue LED and 4CzIPN for catalysis. The reaction remained optimal at 3 equiv of α-bromoacetate and 2 mol% 4CzIPN since lowering their loadings generated lower amounts of the carbobrominated product **3** (entries 8-11). Except MeCN and DMA, which generated the product **3** in 30% and 70% respectively, other common solvents, such as DCE, THF, DMSO, NMP, toluene and dioxane remained ineffective (entries 12-14).

Table 1. Optimization of reaction parameters[a]



1 + 2 (3 equiv) → 3

entry	modified conditions	yield of 3 (%)[b]
1	none	95 (91)
2	eosin Y-Na or fluorescein instead of 4CzIPN	50, 57
3	$Ru(bpy)_3(PF_6)_2$ or $Ru(bpz)_3(PF_6)_2$ instead of 4CzIPN	trace
4	$Ru(bpy)_3(PF_6)_2$ or $Ru(bpz)_3(PF_6)_2$ instead of 4CzIPN	50, 57
5	$Ir(dtbbpy)(ppy)_2PF_6$ or $Ir(dFCF_3ppy)(bpy)_2PF_6$ instead of 4CzIPN	78, 68
6	no blue LED or 4CzIPN	0
7	ambient light or dark instead of blue LED	0
8	1 equiv $BrCH_2CO_2Me$	50
9	4 equiv $BrCH_2CO_2Me$	92
10	0.10 mol % 4CzIPN	60
11	1.0 mol % 4CzIPN	85
12	MeCN instead of DMF	30
13	DMA instead of DMF	70
14	DCE, THF, DMSO, NMP, toluene or dioxane instead of DMF	0

[a]Reactions were conducted at 0.10 mmol scale in 0.5 ml solvent. [b]^{1}H NMR yields using tetrachloroethane as a standard. Isolated yield from a 0.50 mmol scale reaction in parenthesis.

Upon reaction optimization, we examined the scope of the reaction with regard to both alkenes and α-bromoesters (Table 2). The carbobromination reaction worked well with different α-bromoesters containing *n*-alkyl, *t*-alkyl, aryl and benzyl groups (**3**-**7**). The reaction was compatible with both acyclic and cyclic secondary esters, such as α-bromopropionate, α-bromofluoroacetate, α-dibromoacetate and α-bromo-γ-butyrolactone (**8**-**13**). Pleasingly, the carbobromination condition is applicable for the direct use of α-bromoacetic acid without protection, a reaction that generated a mixture of γ-bromocarboxylic acid (**12**) and γ-lactone (**13**) in a 2:1 mixture in 86% overall yield.

The reaction also demonstrated a broad scope with alkenes (**14**-**34**). Simple unfunctionalized linear alkenes and those bearing functional groups, such as bromide, alkoxy, esters, carbonates, nitriles, aryl ethers and alkyl ethers, could be conveniently carbobrominated with α-bromoacetic ester, α-bromoacetonitrile and α-bromo-γ-butyrolactone (**14**-**28**). The reaction condition is also applicable for the carbobromination of 1,2-disubstituted internal alkenes in acyclic, cyclic and bicyclic structures (**29**-**34**). The identical diastereoselectivity (1.2:1) observed for the carbobromination of *cis*-3-hexene (**32**) and *trans*-4-octene (**33**) suggests the involvement of radical intermediates. In addition, we also applied the reaction condition for carbobromination of alkenes tethered to pharmaceuticals and complex natural products for complexity tolerance. As demonstrated in products **35**-**40**, alkenes tethered to the complex natural products, such as vitamin E, estrone and dihydrocholesterol, and the pharmaceuticals, like loxoprofen and indomethacin, generated carbobrominated products in good yields. Reactions of 1,1-disubstituted alkenes and indenes proceeded to generate alkylated alkenes (**41**-**48**), rather than carbobromination products, under the current reaction conditions. These alkene alkylations could be conducted with α-bromocarboxylates, α-bromonitriles and α-bromo-γ-butyrolactones. The carbobromination products could be readily derivatized with different nucleophiles. For example, Br could be displaced by Cl, I, OAr, NR_2 and SAr (**49**-**53**). The products could also be elaborated with exogenous and indigenous carbon nucleophiles furnishing products with new carbon-carbon bonds and cyclopropyl rings (**54**-**55**).

Next, we conducted a series of experiments in order to deduce the working underpinnings for the alkene carbobromination reaction. We determined that the α-C radicals are electrophilic in nature since a competition reaction between primary and secondary α-bromocarboxylates generated the corresponding products in 4:1 ratio, respectively, favoring the primary α-bromoacetate (Scheme 2.I). We also observed that the reaction changed color from light yellow to orange indicative of Br_2 generation (Scheme 2.IIa,b). The formation of Br_2 was further confirmed by UV-Vis spectral analysis of the reaction mixture

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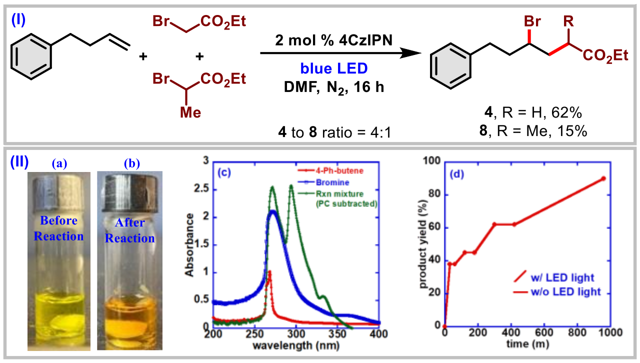
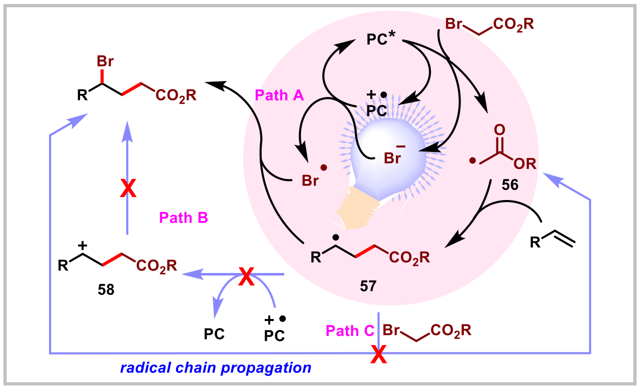
(Scheme 2.IIc). Experiments under LED light and dark (Scheme 2.IId), and quantum yield calculation (Φ = 0.0145) indicate that the reaction doesn't proceed by radical chain propagation, and support a closed photoredox catalytic cycle.[8a] In addition, the Stern-Volmer analysis showed fluorescence quenching by α-bromoester, while no quenching by alkene, indicating that α-bromoester interacts with the excited state photocatalyst in the catalytic reaction (See SI for details). On the basis of these studies, we propose a catalytic cycle (Scheme 3) in which a α-C• (**56**) undergoes electrophilic addition to an alkene generating a 2°-C• (**57**) via oxidative reduction of α-bromocarboxylate by PC*. The bromide anion (Br^-) then reduces $PC^{\bullet+}$ to PC and generates a $Br^\bullet$,[9] which combines with the 2°-C• (**57**) to form carbobrominated product (Path A).

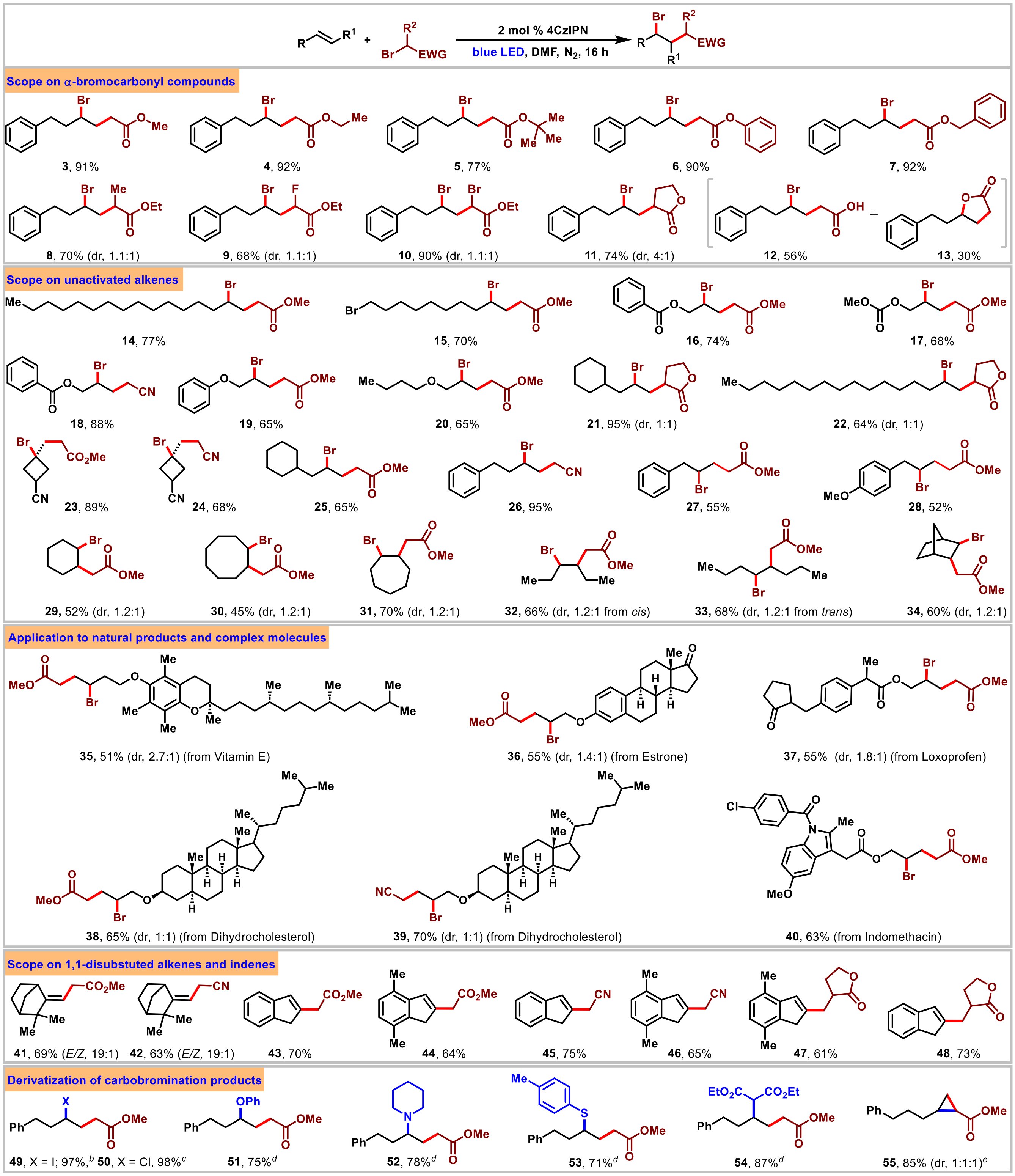


Scheme 2. (I) Competition study. (II). (a), (b) Colors before and after reactions. (c) UV-Vis analysis. (d) Light-dark reaction.



Scheme 3. Proposed catalytic cycle.

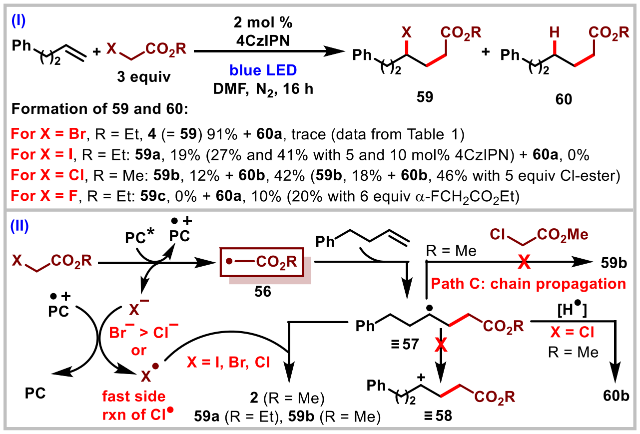
Table 2. Scope of carbobromination reaction with alkenes and α-bromocarbonyls[a]



[a]Reactions were run at 0.50 mmol scale in 2.5 mL DMF unless stated otherwise. The percentage numbers are the yields of isolated products. [b]NaI, acetone, 50 °C. [c]LiCl, DMF, 90 °C. [d]OPh, piperidine, SC$_6$H$_4$Me or CH$_2$(CO$_2$Et)$_2$, K$_2$CO$_3$, DMF, 50 °C. [e]NaH, DMF, 90 °C.

One of the key mechanistic aspects we interrogated was the identity of the reductant that supplied an electron to PC$^{\bullet+}$ to regenerate PC since this knowledge holds key to understanding product generation via radical-addition/radical pairing (RARP, Path A), radical-polar crossover (RPC, Path B) or radical chain propagation (RCP, Path C) pathway (Scheme 3). Attempts to intercept possible carbocations (**58**), the intermediate of RPC pathway, with various nucleophiles (KCl, KI, NaN_3, TMSCN, KOAc and CsF) remained unsuccessful, suggesting that such carbocations (**58**) are less likely to be present (see SI for details). In addition, reactivity profile study of α-I, α-Br, α-Cl and α-F-acetic acid esters indicated a Br > I > Cl trend with Cl generating the product in lower yield (12%), F entirely unreactive and Br as the optimal halide for alkene carbohalogenation (Scheme 4.I). Both the α-F and α-Cl esters generated hydroalkylated products **60a** and **60b** in significant amounts. The lower yield of hydroalkylation with α-F ester than with α-Cl ester is consistent with the relative strengths of the C-F and C-Cl bonds but the mechanisms for C-Cl and C-F bond activation are different (*vide infra*).

For Cl, the formation of both the carbochlorination (**59b**) and the hydroalkylation (**60b**) products in 12% and 42% yields, respectively, is an evidence for the catalytic turnover of PC upon single electron reduction of $PC^{\bullet+}$ by Cl^- and the 2°-alkyl radicals (**57**) undergo H-atom abstraction faster than reacting with Cl• potentially due to its low concentration as a result of slow reduction of $PC^{\bullet+}$ by Cl^- or faster consumption of very reactive Cl• by side reactions (Scheme 4.II). Moreover, the lower yield of carbohalogenation with α-Cl (**59b**, 12%) than with α-Br (**2**, 91%) and the generation of a significant amount of hydroalkylation (**60b**, 42%) with α-Cl is consistent with similar efficacy for the generation of α-C• from both the α-Cl and α-Br esters, and either the slower rate for the reduction of $PC^{\bullet+}$ by Cl^- than by Br^- or the consumption of more reactive Cl• by side reactions faster than pairing with 2°-alkyl radicals. However, for α-I, since hydroalkylation (**60a**) was not observed at low carboiodination (**59a**), the result indicates that the interception of 2°-alkyl radicals (**57**) by I• is sufficiently fast and the low efficiency for carboiodination is likely a function of slow generation of α-C• by α-I (during its reduction by PC*).[10]



Formation of 59 and 60:

For X = Br, R = Et, **4** (= **59**) 91% + **60a**, trace (data from Table 1)

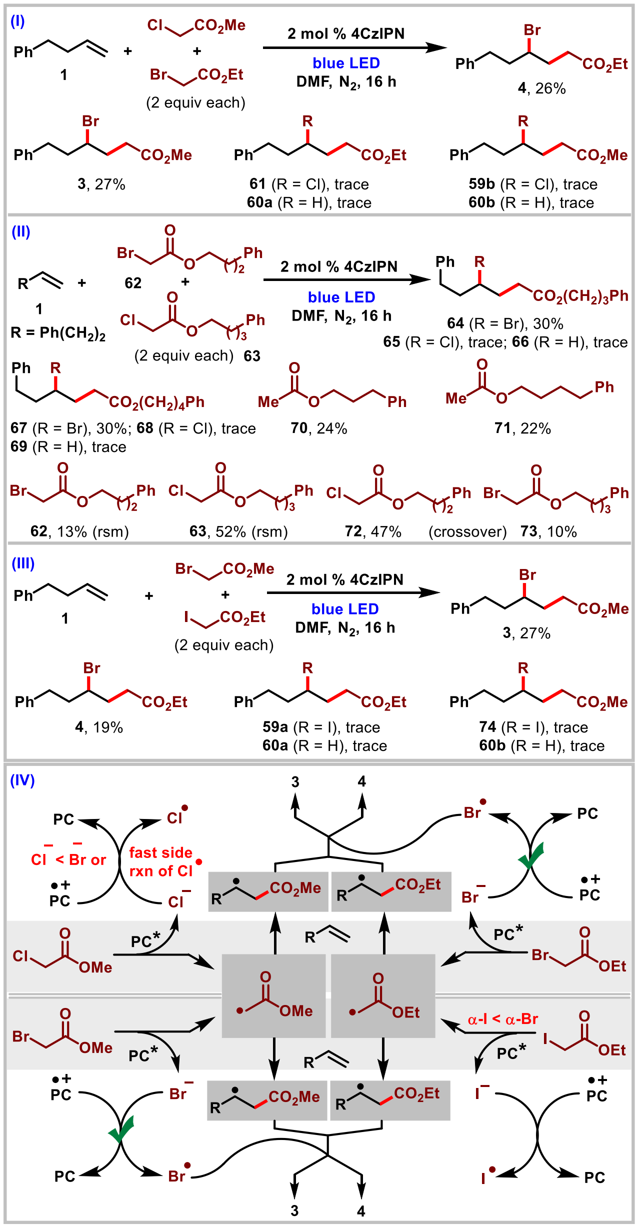
For X = I, R = Et: **59a**, 19% (27% and 41% with 5 and 10 mol% 4CzIPN) + **60a**, 0%

For X = Cl, R = Me: **59b**, 12% + **60b**, 42% (**59b**, 18% + **60b**, 46% with 5 equiv Cl-ester)

For X = F, R = Et: **59c**, 0% + **60a**, 10% (20% with 6 equiv α-FCH_2CO_2Et)

Scheme 4. (I) Reactivity profile for α-I, α-Br, α-Cl and α-F acetic acid esters. (II) Mechanistic analysis of the reactivity profile.

Moreover, we conducted a three-way competitive crossover experiments with α-I, α-Br and α-Cl acetic acid esters in an effort to discern further mechanistic details (Scheme 5). A competitive crossover between ethyl α-Br and methyl α-Cl-esters generated the direct and crossover carbobrominated products **4** and **3** with Br• in 26% and 27% yields whereas the corresponding analogs with Cl• (**61**, **59b**) and hydroalkylation products (**60a**, **60b**) were formed only in traces (Scheme 5.I). The high product selectivity with a 1:1 ratio for the direct and crossover carbobromination suggests that both the α-Br and α-Cl-esters generate α-C radicals with a similar rate. However, only the direct and crossover carbobrominated products **4** and **3** predominate because either the generation of, and interception of 2°-alkyl radicals by, Br• proceeds faster than Cl• or the higher reactivity of Cl• causes it to undergo side reactions faster than pairing with 2°-alkyl radicals (Scheme 5.IV). In addition, the high level of crossover selectively with only α-bromoester and the formation of only trace amounts of hydroalkylation products suggest that the addition of α-C• to an alkene is likely rate-limiting. An additional competition experiment of alkene **1** with phenylpropyl α-bromoester **62** and phenylbutyl α-chloroester **63** produced the reduced esters **70** and **71** in 1:1 ratio (46% yield) along with the direct and crossover carbobrominated products (**64**, **67**) (1:1, 60% yield) with only traces of carbochlorination (**65**, **68**) and hydroalkylation (**66**, **69**) (Scheme 5.II), further providing strong evidence for the rate-limiting addition of α-C• to an alkene. This analysis is further supported by an almost quantitative conversion of the remaining phenylpropyl α-bromoester **62** to its corresponding phenylpropyl α-chloroester **70** by Cl⁻ or Cl• likely through an S_N2 or a radical reaction.



Scheme 5. Three-way competitive crossover experiments. (I) and (II) Between α-Br and α-Cl esters. (III) Between α-Br and α-I esters. (IV) Mechanistic analysis.

We also performed a competitive crossover experiment between methyl α-Br and ethyl α-I-esters, which generated the direct and crossover carbobrominated products **3** and **4** with Br• in 32% and 22% yields along with only traces of analogs with I• (**59a**, **62**) and hydroalkylation (**60a**, **60b**) (Scheme 5.III). This outcome indicates that α-C• is generated faster with α-Br than with α-I due to the higher dissociative reduction potential of α-iodoesters than that of α-bromoesters[10] and that Br• reacts with 2°-alkyl radicals much faster than I• (Scheme 5.IV). An overall trend for the generation of α-C• is Cl ~ Br > I, which is in contrast to that of the metal-catalyzed ATRA carbohalogenation of an alkene (I > Br).[1a,1b,3a] Analogous comparative crossover studies of α-F ester separately with α-Cl, α-Br and α-I esters indicate that hydroalkylation by α-F ester doesn't proceed by the generation of α-C• (see SI for details). Overall, these mechanistic studies also reveal and explain one of the most enigmatic observations under photoredox conditions that only largely bromoalkanes, and sometimes iodoalkanes, participate in alkene carbohalogenation.[2]

In summary, we developed a catalytic visible light photoredox carbobromination of unactivated alkenes with α-bromocarbonyl compounds. The reaction is applicable for the carbobromination of terminal and 1,2-disubstituted internal alkenes with α-bromoesters, α-bromonitriles and α-bromo-γ-lactones. Reactions of 1,1-disubstited alkenes and indenes generated alkylated alkenes. Mechanistic studies by product selectivity, radical probes and three-way competitive crossover experiments indicated that the current carbobromination is achieved by an unprecedented radical addition-radical pairing (RARP) pathway. The catalytic turnover is enabled by a one-electron reduction of $PC^{\bullet +}$ by Br^-, and the subsequent pairing of Br• with R• generates the product.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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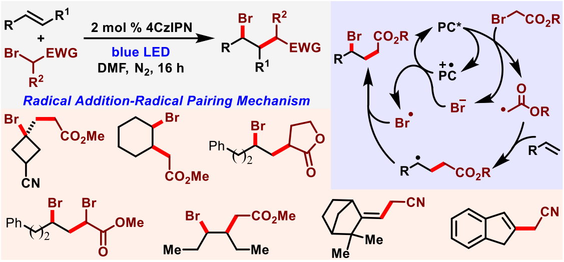
2 mol % 4CzIPN
blue LED
DMF, N$_2$, 16 h
Radical Addition-Radical Pairing Mechanism
R
R^1
Br
EWG
R^2
PC*
PC$^{+\bullet}$
Br$^-$
Br$^\bullet$
Br CO$_2$R
OR
CO$_2$R
CO$_2$Me
CN
Ph
OMe
Me