Photocatalytic Denitrative Alkenylation of Nitroalkanes

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ABSTRACT: Reductive radical generation has become a cornerstone of modern photoredox chemistry. However, the synthesis of functionalized radical precursors remains a tedious multi-step process. In this study, we focus on the potential of the nitro group as a redox-active functional group and present denitrative alkenylation of nitroalkanes, facilitated by photoreductive generation of alkyl radicals from nitroalkanes. By taking advantage of the facile α-functionalization of nitroalkanes, we successfully generate various functionalized alkyl radicals, which are subsequently used in the alkenylation reactions.

Radical chemistry has undergone significant advancements facilitated by the emergence of photoredox chemistry, which has expanded the toolkit for chemists by enabling a diverse array of compounds to serve as radical precursors.[1–4] Among them, carboxylic acids are the most widely employed via a single electron oxidation of the carboxylate ions, owing to their relatively low redox potential and thermodynamic advantage via facile decarboxylation (Scheme 1A). In addition, their abundance in both natural and industrial feedstocks, and amenability to functionalize their carbon frameworks by classical carbonyl chemistry emphasizes the synthetic utility to access a wide range of organic compounds through decarboxylative C–C bond formations.[5–7] In contrast, redox-active esters such as *N*-hydroxyphthalimide ester serve as radical precursors capable of generating alkyl radicals via a single electron reduction, followed by eliminating CO_2 and redox-active groups (RAG), thereby offering a complementary approach for radical generation in synthetic chemistry (Scheme 1B).[8–10] However, redox-active esters are in common labile under the reaction conditions requisite for the pre-functionalization of their carbon frameworks. Consequently, alternative carboxylic acid derivatives, such as alkyl esters, are usually employed.[11] Additionally, a multi-step sequence including condensation of a carboxylic acid with a redox-active group is required to obtain the desired redox-active esters. Similarly, other radical precursors including alcohol and amine derivatives necessitate extra activation processes, which are not necessary for the strategic construction of carbon frameworks.

To improve the overall efficiency in synthetic schemes utilizing reductive radical generation, we focused on nitroalkanes, which have isoelectronic structures with carboxylic acids, regarding them as redox-active building blocks (Scheme 1C). Nitroalkanes can generate nitronate ions under mild reaction conditions due to the 10^{13}-times higher acidity of the α-protons in comparison to that of carboxylic acid derivatives.[12,13] Their amenability to facile C–C bond formation at the α-position through straightforward reactions with various electrophiles renders them valuable building blocks in organic synthesis. In addition to the classical reactions with carbonyl compounds,[14] imines,[15] and electron-deficient alkenes,[16] recent advancements have enabled arylations[17–20] and alkylations[21–24] facilitated by

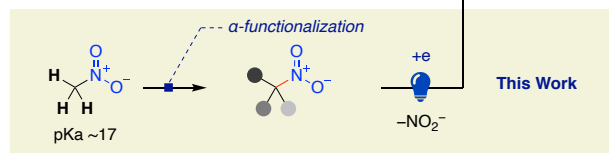## Scheme 1. Photoredox radical generation for C–C bond formations.

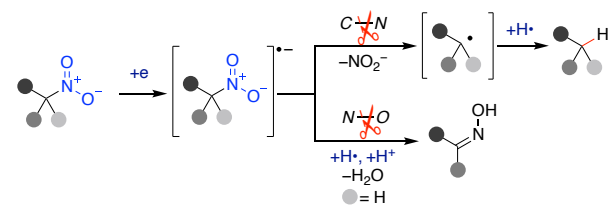A. Carboxylic acids as radical precursors
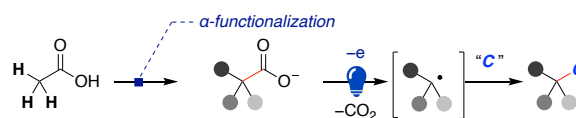
B. Redox-active esters as radical precursors
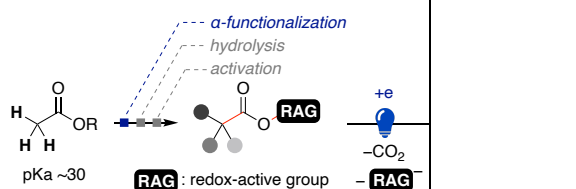
C. Nitroalkanes as radical precursors

D. Competitive over-reduction via radical anions of nitroalkanes

transition metal catalysis. The iterative application of these reactions has been routinely harnessed in multistep synthesis, notably in natural product synthesis, facilitating the construction of a myriad of diverse carbon frameworks.[25–27] In addition to the synthetic utility, the potent electron-withdrawing character of the nitro group enables it to accept one electron from electron donors to generate the radical anions, followed by the alkyl radicals through the C–N bond cleavage. However, in most cases,

the alkyl radicals capture a hydrogen atom, resulting in denitration products.[28]

Denitrative C–C bond formation via radical intermediates was first described over half a century ago. The pioneering works by Kornblum elucidated the denitrative substitution of tertiary nitroalkanes with carbon nucleophiles through the $S_{RN}1$ mechanism.[29,30] Additionally, Ono and co-workers have achieved the Giese addition reaction of alkyl radicals generated through the abstraction of the nitro groups by tin radicals.[31,32] In these instances, the utilization of a stoichiometric strong base or a toxic reducing agent was required. In our recent study, we reported the denitrative C–C bond-forming reactions employing 9-fluorenol as a single-electron reducing catalyst.[33] However, the application of basic conditions at high temperature hindered the utilization of nitroalkanes bearing base-sensitive functional groups, thereby limiting their synthetic potential.

In the precedent literature, photocatalytic reduction of nitroalkanes employing terminal reductants mainly yields oximes via the N–O bond cleavage although denitration occurs in the case of a highly reactive α-acylnitroalkane through the C–N bond cleavage.[34] These phenomena imply the over-reduction of radical anions generated through single-electron reduction competes with the mesolytic cleavage of the nitro groups (Scheme 1D). Therefore, we hypothesized that a redox-neutral system would lead to suppressing the side reactions. In this study, we present the first photocatalytic denitrative C–C bond-forming reaction of nitroalkanes.

Table 1. Optimization and Control Experiments[a]
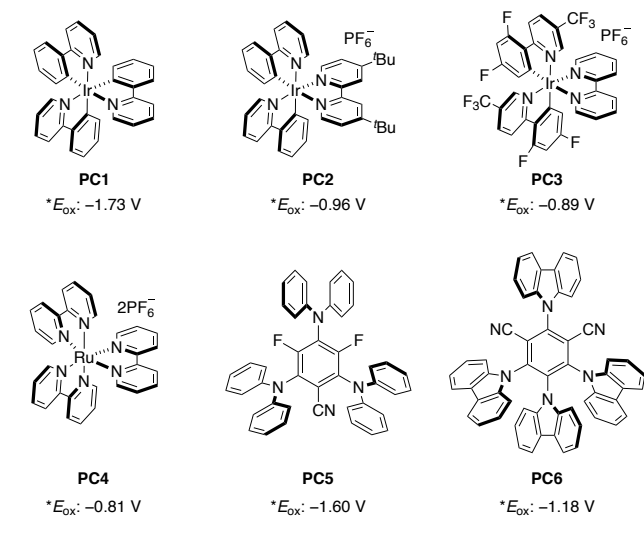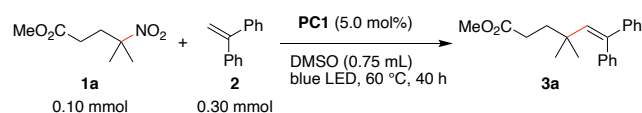
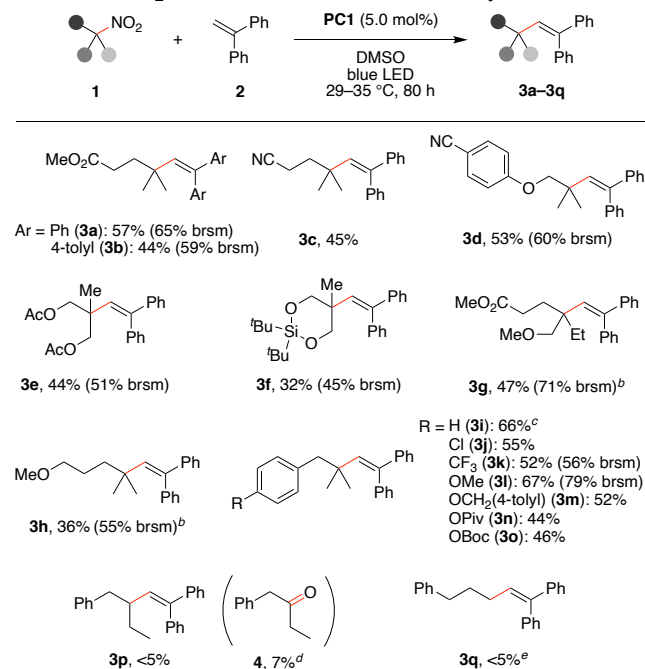| entry	deviation from the initial conditions	yield (%)[b]
1	none	49
2	**PC2** instead of **PC1**	13
3	**PC3** instead of **PC1**	<5
4	**PC4** instead of **PC1**	<5
5	**PC5** instead of **PC1**	47
6	**PC6** instead of **PC1**	<5
7	MeCN instead of DMSO	13
8	NMP instead of DMSO	11
9	No **PC1**	<5
10	No light	<5
11	32 °C, two blue LEDs	62[c]

[a]Reaction was carried out with **1a** (0.10 mmol), **2** (0.30 mmol), and **PC1** (5.0 mol%) in DMSO (0.75 mL) under blue LED irradiation at 60 °C for 40 h. [b]NMR yield using 1,4-pyrazine as the internal standard. [c]Reaction at 32 °C for 88 h on a 0.50 mmol scale using two Kessil blue LEDs.

To examine the denitrative alkenylation with 1,1-diphenylethylene (**2**), we selected nitroalkane **1a**, which was found to decompose under basic conditions used in our previous study,[35] possibly through the retro-Michael reaction. Our initial screening of the reaction conditions revealed that 5.0 mol% of Ir(ppy)₃, **PC1** as a photoredox catalyst in DMSO at 60 °C under blue-LED irradiation facilitated the conversion of **1a** to the expected product **3a** in 49% yield (entry 1, Table 1). Other iridium- and ruthenium-based photocatalysts with lower reducing ability in the excited state significantly decreased the reaction efficiency (entries 2–4).[36] Further investigation of organo-photocatalysts showed a similar trend, with stronger reductants in the excited state resulting in better efficiency (entries 5 and 6).[37] The choice of solvent was crucial in this reaction; other polar solvents exhibited lower conversion of **1a** (entries 7 and 8). Both the photocatalyst and light irradiation were necessary for the reaction (entries 9 and 10). After screening at 60 °C using one Kessil LED, we found that increasing the light intensity by using two Kessil LEDs improved the reaction efficiency and allowed us to lower the reaction temperature, affording **3a** in 62% yield, with 12% of **1a** remaining unreacted (entry 11).

Having established the optimal conditions, we investigated the scope of the denitrative alkenylation of various nitroalkanes (Table 2). The nitroalkanes possessing an electron-withdrawing group at the γ-position were readily synthesized by Michael reaction and were applicable to the denitrative alkenylation, affording the expected products **3a**, **3b**, and **3c** in moderate yields. The reaction of a Henry-type nitroalkane containing a β-oxygen-functional group, yielded β-aryloxy alkene **3d** in 53% yield. The doubly acyloxy- and siloxy-methylated nitroalkanes, which are accessed through the iterative Henry reaction with formaldehyde, also participated in the denitrative C–C bond formation, resulting in acyclic diester **3e** and cyclic silyl ether **3f**. Furthermore, the reaction of a nitroalkane with three different functional groups at the α-position proceeded, yielding alkene **3g** well-functionalized at the allylic position. A nitroalkane bearing a simple alkyl chain with the terminal methoxy group was also converted into alkene **3h**. A phenyl group at the β-position was tolerated to afford **3i** in 66% yield. Substituents at the *para*-position including chlorine (**3j**), an electron-withdrawing trifluoromethyl group (**3k**), or electron-donating alkoxy and acyloxy groups (**3l**–**3o**) led to the formation of the corresponding products. Although various tertiary nitroalkanes were successfully employed, the reactions of secondary and primary nitroalkanes did not proceed under the standard conditions (**3p** and **3q**).[38] Most of these substrates decomposed, and other by-products were not identified except for ketone **7** possibly derived from the Nef-type reaction. In the case of Henry-type 1,2-nitroalcohol **1t**, tandem cyclization occurred to form

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substituted tetrahydrofuran **5t** (Scheme 2A). The reaction of MOM-protected nitroalcohol **1r** resulted in a similar product. These findings suggest that the reactions proceed via carbocation intermediates, which cyclized, with releasing proton or the MOM group. In contrast, TIPS ether did not participate in the cyclization, but afforded the alkenylation product after the removal of the silyl group upon treatment with TBAF (**3s**). The alkylation of silyl enol ether **6** with α-nitroester **1u**, the nitro group serving as a leaving group, provided β-quaternary ketone **7u** with a yield of 31% (Scheme 2B). Thus, a wide range of nitroalkanes accessible via various α-functionalization are applicable to the denitrative C–C bond formation.

Table 2. Scope for the Denitrative Alkenylation[a]

Ar = Ph (**3a**): 57% (65% brsm)
4-tolyl (**3b**): 44% (59% brsm)

3c, 45%

3d, 53% (60% brsm)

3e, 44% (51% brsm)

3f, 32% (45% brsm)

3g, 47% (71% brsm)[b]

3h, 36% (55% brsm)[b]

R = H (**3i**): 66%[c]
Cl (**3j**): 55%
CF$_3$ (**3k**): 52% (56% brsm)
OMe (**3l**): 67% (79% brsm)
OCH$_2$(4-tolyl) (**3m**): 52%
OPiv (**3n**): 44%
OBoc (**3o**): 46%

**3p**, <5%

4, 7%[d]

3q, <5%[e]

[a]Reaction was carried out with nitroalkane **1** (0.50 mmol), **2** (1.5 mmol), and **PC1** (5.0 mol%) in DMSO (3.8 mL) in a range of 29–35 °C for 80 h using two Kessil LEDs with a fan cooling. Isolated yields are reported, with yields based on recovered starting material shown in parentheses when >5% of **1** was recovered. [b]120 h. [c]1.0 mmol scale at 60 °C for 40 h. [d]1H NMR yield using 1,4-pyrazine as the internal standard. [e]80 °C.

Scheme 2. Related transformations

A. Tandem cylization via intramolecular cation-trapping

5r, 24% (from **1r**)
5t, 54% (from **1t**)

3s, 42% (from **1s**)
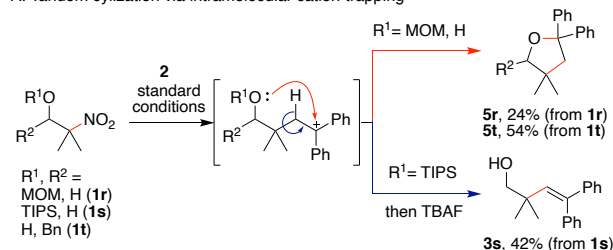
B. The alkylation of silyl enol ether with a nitroalkane

7u, 31%
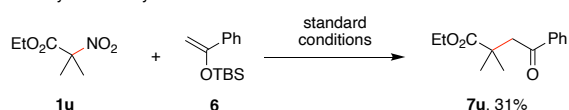
To gain insights into the reaction mechanism, we conducted several control experiments (Scheme 3). First, we performed the reaction of **1a** with **2** in the presence of commonly used single-electron transfer (SET) inhibitors, 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO, E_{red} = −0.36 V)[39] and 1,4-dinitrobenzene (E_{red} = −0.66 V),[40] which have less negative redox potential compared to nitroalkanes (E_{red} = ca. −1.7 V, Scheme 3A).[41,42] As a result, no conversion of **1a** was observed in either case. Stern–Volmer quenching studies were also conducted to probe SET from the excited state of **PC1** (Scheme 3B).[43,44] The linear plot clearly showed the quenching of excited **PC1** with **1a** predominantly occurred over that with **2**. In addition, we performed a light on/off experiment to determine if the reaction proceeded through a radical chain mechanism (Scheme 3C). The conversion of **1a** into **3a** was detected only under light irradiation, not under dark conditions, suggesting that a radical chain process was not involved in this reaction. To demonstrate the generation of alkyl radicals through the C–N bond cleavage, a radical-clock experiment using cyclopropane-containing substrate **1v** was examined.[45,46] The denitrative alkenylation product via ring-opening was obtained in 11% yield with a 58% recovery of **1v** (Scheme 3D). Furthermore, as shown in Scheme 2A, the reactions of **1r** and **1t** support the involvement of cationic intermediates, indicating a radical-polar crossover mechanism that involves the oxidation of alkyl radical intermediates.
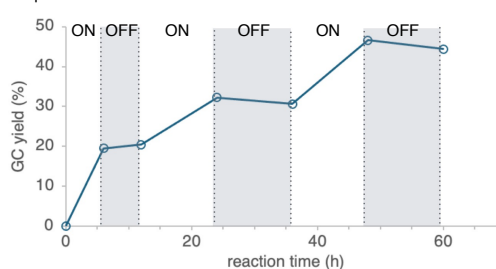
Scheme 3. Mechanistic investigations

A. SET inhibition experiments

1,4-dinitrobenzne: < 5%
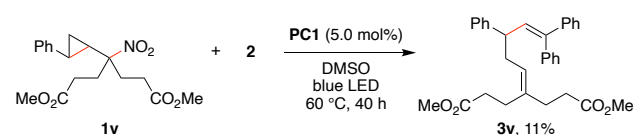TEMPO: < 5%
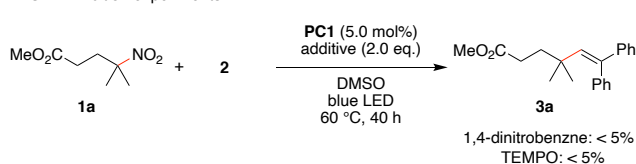
B. Stern–Volmer quenching experiments
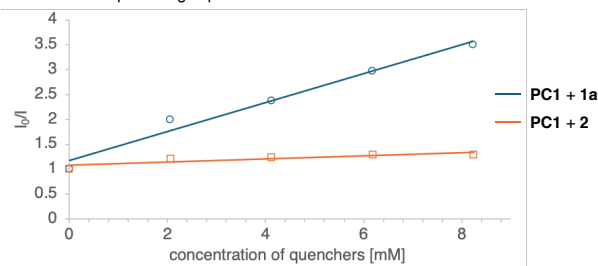
C. On/Off experiments

D. Radical clock experiments

3v, 11%

Based on these results, the proposed reaction mechanism is depicted in Scheme 3. The photoexcited **PC1** reduces the

nitroalkane via a SET, generating radical anion **I**. A nitrite ion is then eliminated, producing alkyl radical **II**, which subsequently adds across the alkene to form alkyl radical **III**. The alkyl radical is then oxidized by **PC1** to form a carbocation intermediate **IV**, which undergoes deprotonation to yield the denitrative alkenylation product. In contrast to the alkyl radical generation through C–N bond cleavage in the redox-neutral system described above, N–O bond cleavage preferentially occurred under photo-reductive conditions using terminal reductants, yielding the deoxygenative *N*-alkylation product with an electron-deficient alkene (Scheme 5). These results support the concept presented in Scheme 1D.

Scheme 4. Proposed mechanism
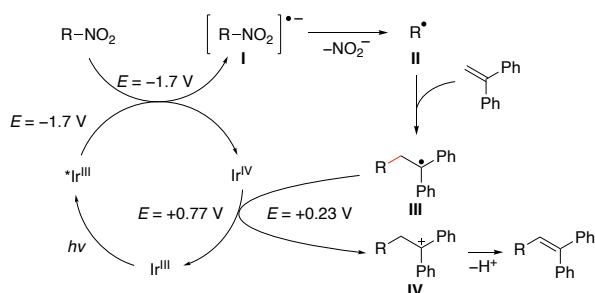
Scheme 5. Deoxygenative *N*-alkylation of nitroalkane*[a]***
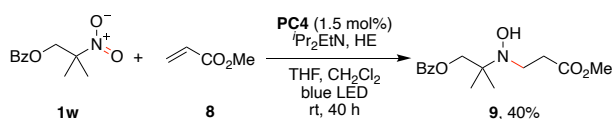
*[a]*Reaction was carried out with **1w** (1.0 mmol), **8** (2.0 mmol), **PC4** (15 µmol), *i*Pr₂EtN (1.0 mmol), Hantzsch ester (1.5 mmol) in THF (5 mL) and CH₂Cl₂ (5 mL) under blue-LED irradiation at rt for 40 h.

In summary, we have developed the catalytic denitrative C–C bond-forming reactions of nitroalkanes utilizing the photoredox system. This reaction can be applied to a wide range of nitroalkanes, which are conveniently synthesized by Michael and Henry reactions, as well as α-alkylation. The mechanistic studies indicate that nitroalkanes are reduced by the excited photocatalyst in a single electron manner to form alkyl radicals upon releasing a nitrite ion. This method is expected not only to enhance the synthetic utility of nitroalkanes but also to provide a new radical precursor in photoredox reactions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Detailed experimental procedures and analytical data (PDF)

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Author Contributions

Notes

The authors declare no competing financial interest.

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