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COMMUNICATION

Photocatalytic Decarboxylative Alkenylation of α-Amino and α-Hydroxy Acid-derived Redox Active Esters by NaI/PPh$_3$ Catalysis

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Herein we report photocatalytic decarboxylative alkenylation reactions of *N*-(acyloxy)phthalimide derived from α-amino and α-hydroxy acids with 1,1-diarylethene, and with cinnamic acid derivatives through double decarboxylation, using sodium iodide and triphenylphosphine as redox catalyst. The reaction proceeds under mild irradiation condition with visible blue light (440 nm or 456 nm) in acetone solvent without recourse to transition-metal or organic dye based photoredox catalyst. The reaction proceeds *via* photoactivation of transiently self-assembled chromophore from *N*-(acyloxy)phthalimide and NaI/PPh$_3$. Solvation plays crucial role for the reactivity.

While most of the currently reported photoredox catalysis[1] entails the use of transition-metal-[2] or organic dye-[3] based photoredox catalysts to harvest photon energy of visible light, our recent work revealed that sodium iodide and triphenyl phosphine in combination with suitable substrates [*e.g.* *N*-(acyloxy)phthalimide or redox active esters (RAEs)][4] forms a transiently assembled chromophore in suitable solvent system, which absorbs visible light to deliver high energy radical species useful for organic synthesis.[5] We recently reported photocatalytic decarboxylative alkylation of silyl enol ether and *N*-heteroarene using NaI/PPh$_3$ photoredox catalytic system with broad substrate scope. In this work we report the application of NaI/PPh$_3$ photoredox catalysis for direct decarboxylative alkenylation[6] of α-amino and α-hydroxy acid-derived redox active esters with 1,1-diarylethenes,[7] and with cinnamic acid derivatives via double decarboxylation.[8] These transformations generate structure motifs of allylic amine[9] and allylic ether without using any transition metal under redox neutral conditions. Compared with previously reported catalytic condition using ruthenium-, iridium-, or organic dye-based photoredox catalysts for similar transformations,[10] the NaI/PPh$_3$ system is in advantage of its easy accessibility, low cost, as well as the green solvent system using low boiling-point acetone.[11]

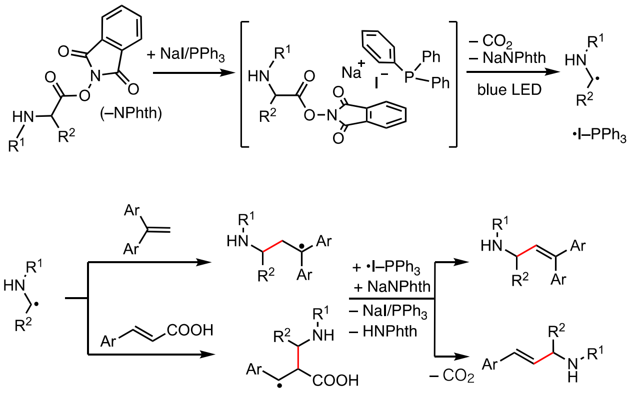

Figure 1. Working Hypothesis of Photocatalytic Decarboxylative Alkenylation using NaI/PPh$_3$ Catalysis.

Our working hypothesis using NaI/PPh$_3$ photoredox system for decarboxylative alkenylation of α-amino acid-derived RAEs is depicted in Figure 1. It is reported that NaI, PPh$_3$, and RAEs assemble to form a chromophore that absorbs visible light of blue range in acetone solvent.[5] We envisaged that photoactivation of this transiently formed chromophore will induce electron transfer from iodide to *N*-phthalimide moiety to further generate α-amino alkyl radical through extrusion of carbon dioxide for alkenylation reaction. PPh$_3$ will stabilize iodine radical to generate •I–PPh$_3$ species,[12] which resembles a photoredox catalyst in its oxidized form. The formed α-amino alkyl radical attacks 1,1-diarylethene and cinnamic acid to generate relatively stable benzylic radicals which were subsequently oxidized by •I–PPh$_3$ to produce alkenylation products after proton elimination and to regenerate NaI/PPh$_3$. Thus, the process delivers product of decarboxylative alkenylation, in which the carboxylate group in a carboxylic acid derivative is replaced by an alkene moiety.[6a] In this work, we successfully developed this transformation with substantial substrate scope and good functional group compatibility. The

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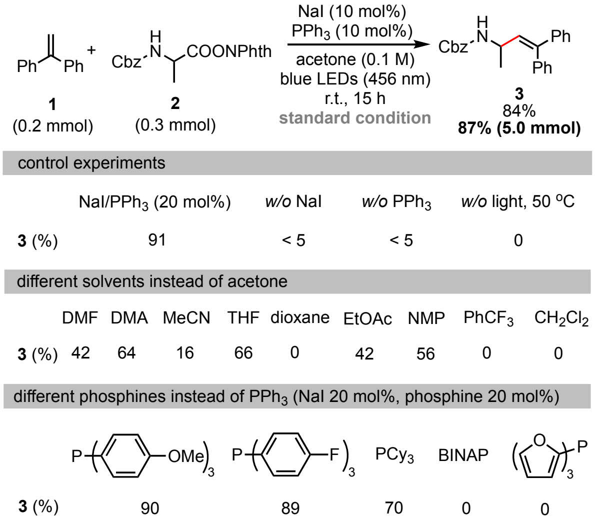
reaction reported herein further extended the synthetic scope of NaI/PPh_3 catalytic system for low-cost photoredox catalysis.



control experiments

	NaI/PPh_3 (20 mol%)	*w/o* NaI	*w/o* PPh_3	*w/o* light, 50 °C
3 (%)	91	< 5	< 5	0

different solvents instead of acetone

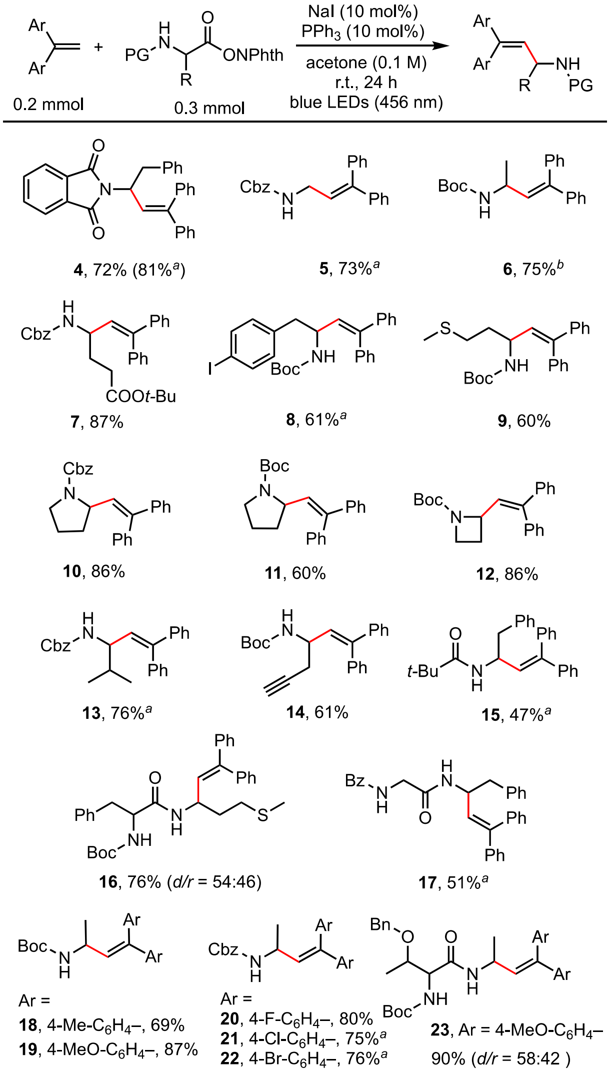
	DMF	DMA	MeCN	THF	dioxane	EtOAc	NMP	$PhCF_3$	CH_2Cl_2
3 (%)	42	64	16	66	0	42	56	0	0

different phosphines instead of PPh_3 (NaI 20 mol%, phosphine 20 mol%)

	$P(C_6H_4\text{-}OMe)_3$	$P(C_6H_4\text{-}F)_3$	PCy_3	BINAP	$P(C_4H_3O)_3$
3 (%)	90	89	70	0	0

Scheme 1 Key reaction parameters. Reaction conditions: **1** (0.2 mmol, 1.0 eq.), **2** (0.3 mmol, 1.5 eq.), NaI (10 mol%), PPh_3 (10 mol%), acetone (2.0 mL), irradiation with blue LEDs (456 nm) at room temperature for 15 h under argon atmosphere. Yield of isolated product.

Decarboxylative alkenylation was first performed using 1,1-diphenylethylene (**1**) and RAEs of Cbz-protected alanine (**2**) as coupling partners. After careful optimization of all reaction parameters, the desired product **3** was obtained in 84% isolated yield using a combination of NaI (10 mol%) and PPh_3 (10 mol%) as photocatalyst in acetone under 456 nm blue LEDs irradiation at room temperature. Measuring UV-Vis absorption spectrum revealed that a chromophore with absorption onset overlapping with wavelength of blue LEDs was formed in the reaction mixture (see the supplementary materials Figure S2 for details). Control experiments revealed that iodide, phosphine, and irradiation were all essential parameters. As noted in previous report,[5,13] solvation has heavy influence on the assembly of charge-transfer complex (CTC) through non-covalent interactions. As shown in Scheme 1 (second row), the reaction also proceeded in THF, NMP, DMA or DMF, albeit in lower yields. 1,4-Dioxane and $PhCF_3$, which were suitable solvent in NaI/PPh_3-catalyzed decarboxylative alkylation of *N*-heterocycles,[5] were totally ineffective. Because phosphine stabilizes iodine radical in the form of $R_3P–I\bullet$ species and facilitates intermolecular charge transfer, a series of phosphines with different electronic nature were examined (Scheme 1, third row). Tris(4-methoxyphenyl)phosphine and tris(4-fluorophenyl)phosphine gave no significant change in the yield of **3** compared with PPh_3. When tricyclohexylphosphine was used instead of PPh_3, the isolated yield of **3** was reduced to 70%. The reaction did not proceed when BINAP or tri(2-furanyl)phosphine was used as the catalyst. Investigation of other alkali iodides (see the supplementary materials for further details) showed that LiI, KI, RbI, and CsI gave slightly lower yields compared to NaI. ZnI_2 failed to serve as catalyst for this transformation as ZnI_2 did not form chromophore with **2** to absorb blue light under the reaction condition (see the supplementary materials Figure S2 for further details). It is interesting to note that tetrabutylammonium iodide, which is entirely ineffective in decarboxylative alkylation of silyl enol ethers,[5] also produced the desired product in 70% yield. Although we could not fully rationalize the observed cation effect on reaction efficiency, we speculate that the cation affects assembly of transient chromophore, electron transfer, and further diffusion of radical pair in a solvent cage. The reaction can be easily scaled up to gram scale without reducing its efficiency.



Scheme 2 Decarboxylative alkenylation of α-amino acid-derived RAEs. Reaction conditions: 1,1-diarylethylenes (0.2 mmol, 1.0 eq.), RAEs (0.3 mmol, 1.5 eq.), NaI (10 mol%), PPh_3 (10 mol%), acetone (2.0 mL), irradiation with blue LEDs (456 nm) at room temperature for 24 h under argon atmosphere. Yield of isolated product. [a] NaI (20 mol%), PPh_3 (20 mol%). [b] NaI (20 mol%), PPh_3 (20 mol%), THF (2.0 mL).

With the optimized reaction condition in hand, the scope of the reaction was investigated. As shown in Scheme 2, a wide range of natural and unnatural α-amino acid-derived RAEs and 1,1-diarylethylenes exhibited as suitable substrates with

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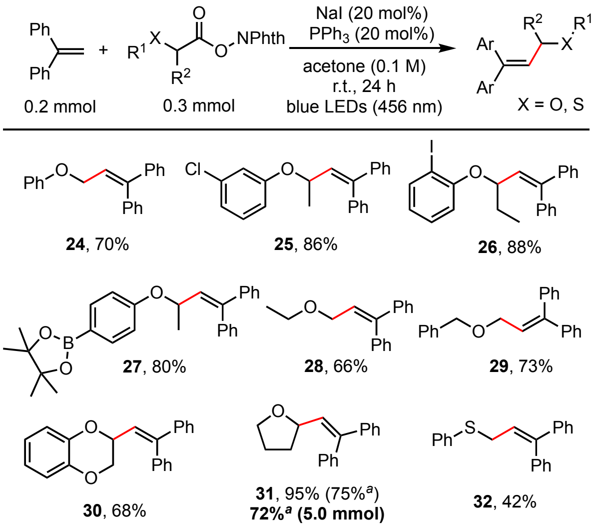
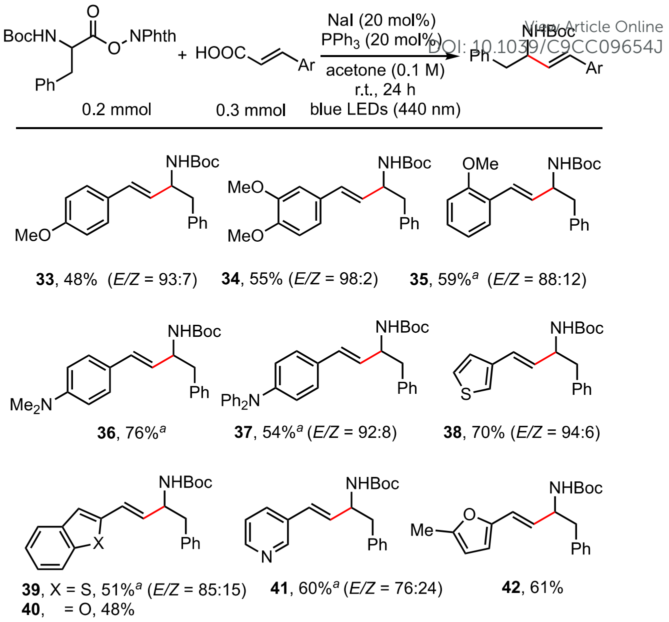
moderate to good yields obtained. A variety of functional groups, such as phthalimide (**4**), benzyloxycarbonyl (**5**, **13**), tert-butyloxycarbonyl (**6**), ester (**7**), aryl halides (**8**, **20**, **21**, **22**), and sulfide (**9**) were all well-tolerated. Terminal alkyne could also be tolerated affording the desired product (**14**) in 61% yield. RAs derived from proline (**10**, **11**) and 2-azetidinecarboxylic acid (**12**) reacted smoothly. 1,1-Diarylethylenes of different electronic properties were examined. Both electron-rich (**19**) and electron-deficient (**20**, **21**) alkenes could be used. It's worth noting that dipeptide-derived RAEs generated desired alkenylation products in good yields (**16**, **17**, **23**), suggesting the potential to use this method for modification of bioactive peptides.[14] For certain substrates, the catalyst loading was increased to 20 mol% (**4**) and the solvent was modified (**6**) to improve yields. The reaction did not proceed well with styrene and 1,1-dialkylethylene, probably because of much slower rate of radial addition to double bond of these alkenes compared with 1,1-diarylethylene.



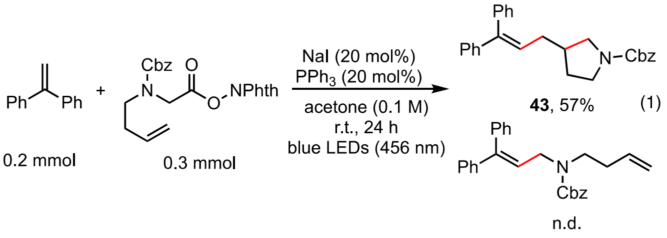
Scheme 3 Decarboxylative alkenylation of α-hydroxy acid and thioglycolic acid derivatives. Reaction conditions: 1,1-diphenylethylenes (0.2 mmol, 1.0 eq.), RAEs (0.3 mmol, 1.5 eq.), NaI (20 mol%), PPh_3 (20 mol%), acetone (2.0 mL), irradiation by blue LEDs (456 nm) at room temperature for 24 h under argon atmosphere. Yield of isolated product. [a] NaI (10 mol%), PPh_3 (10 mol%).

Besides α-amino acids, α-hydroxy acids were also amenable coupling partners (Scheme 3). RAEs derived from various *O*-protected α-hydroxy acids, including *O*-aryl, *O*-alkyl and *O*-benzyl substituents, reacted readily with 1,1-diphenylethylene to give alkenylation product in moderate to good yields (66-95%). Functionalities such as aryl chloride, aryl iodide, and even aryl pinacol boronate, which were useful for subsequent cross-coupling reactions,[15] were well tolerated as shown in entries **25**, **26,** and **27**. Cyclic α-alkoxy acids (**30**, **31**) also reacted well. This reaction is easily scaled up to gram scale without decreasing the yield. Thioglycolic acid-derived redox-active ester was also suitable for this transformation to construct allylic sulphide structure (**32**).



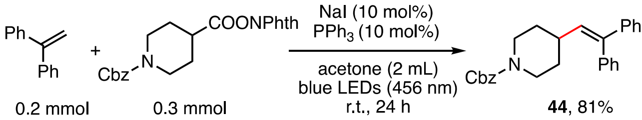
Scheme 4 NaI/PPh_3-catalyzed alkenylation of α-amino-acid derived RAEs via double decarboxylation. Reaction conditions: RAEs (0.2 mmol, 1.0 eq.), cinnamic acid derivatives (0.3 mmol, 1.5 eq.), NaI (20 mol%), PPh_3 (20 mol%), acetone (2.0 mL), irradiation with blue LEDs (440 nm) at room temperature for 24 h under argon atmosphere. Yield of isolated product. [a] DMA (2 mL) instead of acetone (2 mL).

As shown in the working hypothesis, alkenylation between α-amino acid-derived RAEs and cinnamic acids via dual decarboxylation also proceeded successfully without further optimization of the reaction condition. As shown in Scheme 4, cinnamic acid and its analogues reacted readily with RAEs derived from *N*-Boc-protected phenylalanine furnishing the desired products in moderate to good yields. Methoxy substituent on *para*- (**33**), *meta*- (**34**), and *ortho*-position (**35**) of cinnamic acid has no obvious effect on the reaction outcome. Dimethylamino (**36**) and diphenylamino (**37**) groups, which are sensitive to oxidant, were also compatible. This protocol is also applicable to acrylic acids possessing β-heteroarene-substituents, such as thiophene (**38**), benzothiophene (**39**), benzofuran (**40**), pyridine (**41**), and furan (**42**).



Scheme 5 Radical-clock Experiment

The reaction in Scheme 1 was totally suppressed when 2,2,6,6-tetramethylpiperding-1-oxyl (TEMPO) was added in 2 equivalent amounts as radical scavenger (see the supplementary materials). A radical-clock experiment was performed as shown in Scheme 5. A ring-closed product (**43**) was obtained in 57% yield. These results indicated that the decarboxylative alkenylation proceeds through a free radical pathway.[16] Finally, besides reaction with tertiary alkyl demonstrated in our previous work,[5] the reaction also proceeded well with RAEs that deliver secondary and primary normal alkyls (eq. 2 and 3), though the reaction with primary normal alkyl proceeded in relatively lower yield. The reaction did not proceed well with RAE derived from phenyl acetic acid.



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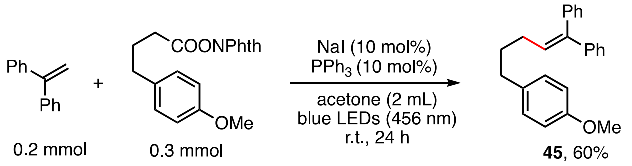

(3)

In conclusion, NaI/PPh_3 works as an easily accessible and low-cost redox catalyst for decarboxylative alkenylation of various RAEs derived from α-amino acids, α-hydroxy acids, and also thioglycolic acid with 1,1-diarylethenes. Cinnamic acid and its analogues were also used as alkenylation reagents through double decarboxylation. The reactions reported herein offers a low-cost and operationally simple method to synthesize compounds containing allylic amine and allylic ether structures from biomass-derived carboxylic acids.

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Conflicts of interest

The authors declare no competing interests.

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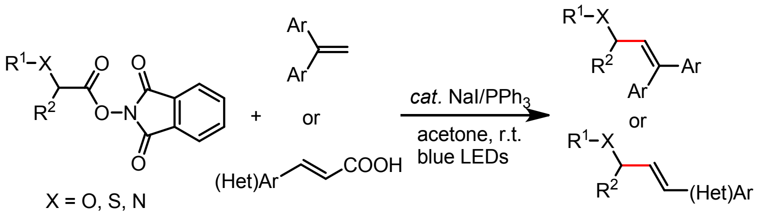

Photocatalytic Decarboxylative Alkenylation of α-Amino and α-Hydroxy Acid-derived Redox Active Esters by NaI/PPh$_3$ Catalysis