Hydroxyl-Diazomethylation of Alkenes *via* Photoredox Catalysis

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Abstract

α-Diazoesters belong to significantly important carbenoid precursors in synthetic chemistry, diazomethylation-based difunctionalization of alkenes is highly valuable but remain nontrivial. Herein, we reported a general and modular approach for the direct 1,2-hydroxyl-diazomethylation of alkenes through visible-light photoredox catalysis. This process exploits photocatalyzed strategy to convert alkenes to γ-hydroxyl-α-diazoesters using α-diazo iodonium salts as carbyne precursors, featuring wide substrate tolerance and broad late-stage diversifications. Mechanistic studies suggest that the formation of γ-carbocation-tethered α-diazoesters plays a crucial role in trapping H_2O to allow for this transformation.

Introduction

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Alkenes are abundant and easily accessible hydrocarbons which are commonly pervasive in both academia and industry, the development of versatile alkene 1,2-bifunctionalization strategies stands out as an appealing approach to forge structural complex molecules. In the past decades, the classical catalytical systems of alkene carboamination[1], diamination[2], trifluoromethylamination[3], trifluoromethylarylation[4], haloarylation[5], arylsulfonylation[6], dicarbonylation[7], and others[8] have been well-explored to form two stable covalent bonds in a single step. Surprisingly, none of these existed strategies could simultaneously embed two different chemo-active groups on both sides of the carbon-carbon double bonds, albeit high-active groups can easily expand the potential value-added modifications of alkenes through post-chemical transformations[9].

Hydroxyl units feature with versatile reactivities in organic synthesis, supported by a rich methodological toolbox[10] that encompasses oxidative, redox-neutral, and reductive trans-formations, etc. There is no doubt that the direct incorporation of hydroxyl group and another chemo-active group into carbon-carbon double bond presents a high-step economic strategy to access high-valuable functionalized alcohols. In this context, although the hydration of alkenes with H_2O to regioselectively assemble primary and secondary alcohols by Lewis acid- and transition metal-catalysis, has been well-established, the hydroxylation-based difunctionalization of alkenes remains a signficant challenge[11]. To date, the existing breakthrough in this field was typically limited to metal oxide- and nitroarene-mediated alkene dihydroxylation to produce 1,2-diols.[9b] There is enormous chemical space remaining to be explored to enable different hydroxylfunctionalization of alkenes.

Low-valent carbon species-involved chemical reactions have been one of the important cornerstones in morden synthetic strategy[12]. Up to now, much significant progress on transition metal- and photo-catalyzed cross-coupling between carbenoids and C-H, N-H, C-C, C=C, C≡C, and C-heteroatom bonds has been achieved[13]. By contrast, monovalent carbyne-based transformations have been rarely explored, mainly due to that carbyne species are not readily available[14]. In 1967, Strausz first reported that $Hg\{C(=N_2)CO_2Et\}_2$ could produce free carbyne radicals [:C(•)–R] under UV-Vis irradiation, this carbyne species feature with dual radical and carbene behaviour, such as Csp^3-H carbenoid insertion and carbene-alkene [1 + 2] cycloaddition (**Fig. 1a-I**)[15]. Since then, the exploration of alternative carbyne precursors has always kept going forward by chemists.

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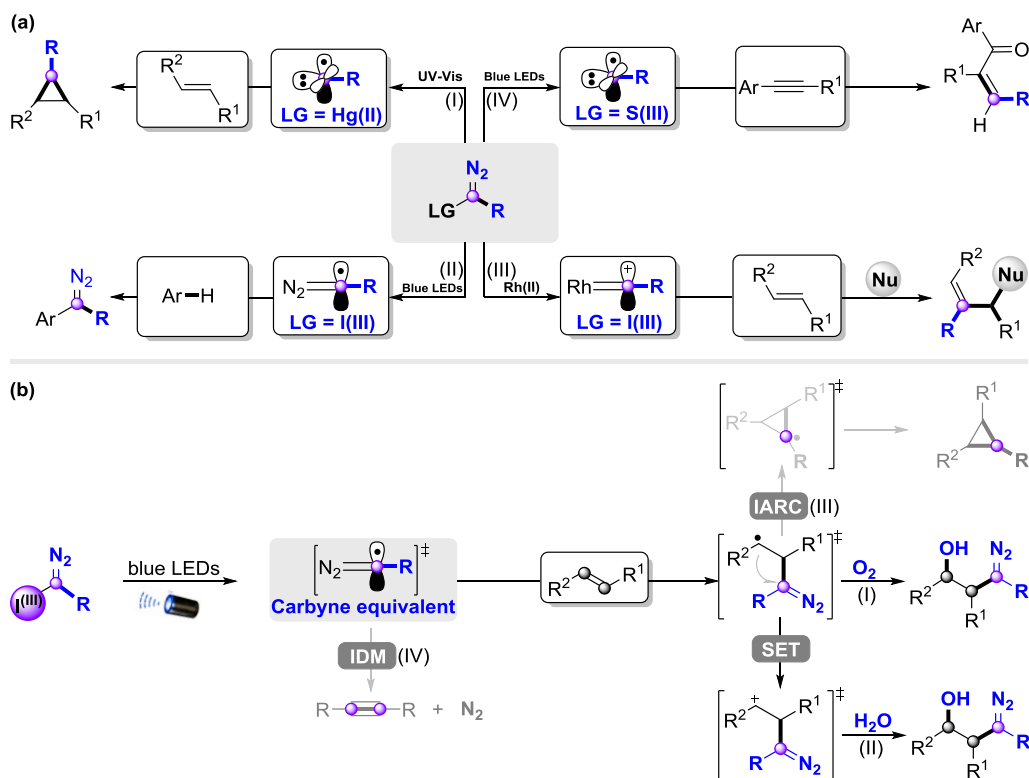
Fig. 1. Hydroxyl-diazomethylation strategy of alkenes (**a**) Versatile reactivities of α-diazo onium salts as carbyne precursors. (**b**) **This work:** Hydroxyl-diazomethylation of alkenes *via* photoredox catalysis.

In 2018, Gaunt and Seuro innonatively confirmed that α-diazo iodonium triflates could act as an another carbyne precursor to form diazomethyl radical [N₂=C(•)–R] by visible-light-mediated metal-photocatalysis, this α-diazo onium salts would react with arenes and methionine residues, allowing for aryl Csp²–H bond and protein diazomethylation, respectively (**Fig. 1a-II**)[16]. Subsequently, Seuro further found α-diazo iodonium salts could still cleavage C(sp²)-C(sp²) double bonds by transition metal-catalysis, followed by inserting a monovalent carbon unit into alkenes (**Fig. 1a-III**)[17]. Interestingly, Wang also developed a cross-coupling of alkynes with α-diazo sulfonium triflates to produce 1,4-dicarbonyl alkenes, in which free carbyne radicals instead of diazomethyl radicals were involved in a radical cyclization to alkynes under visible-light-promoted metal-free photocatalysis[18]. Considering these significant discoveries which mean that α-diazo onium salts can generate carbyne species by utilizing different catalysis systems, we questioned whether diazomethyl radical [N₂=C(•)–R] could be chemoselectively trapped by alkenes to form alkyl radicals under photocatalysis system.

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Then, the diazo-containing alkyl radicals could be further trapped again by molecular oxygen (**Fig. 1b-I**) or H$_2$O through radical-coupling or single electron transfer (SET) process followed by nucleophilic attack (**Fig. 1b-II**). If successful, it would unlock easy access to offer a conceptual complementary of diazomethylation-based difunctionalization of alkenes, namely, 1,2-hydroxyl-diazomethylation. Of course, this hypothesis faces several severe challenges, including intramolecular alkyl radical coupling (IARC) with diazomethyl moiety (**Fig. 1b-III**)[16], intermolecular dimerization (IDM)[15] of diazomethyl radicals (**Fig. 1b-IV**), and other side reactions.

Results and Discussion

Investigation of reaction conditions. Based on the above hypothesis and our continued interest in carbenoid transformations as well as alkene difunctionalizations[19], we first evaluated the feasibility of this idea by exploring the diazomethylation-based difunctionalization of styrene **1-1** with different α-diazo onium salts (**2-1** ~ **2-4**) in the presence of Ru(bpy)$_3$(PF$_6$)$_2$ (2 mol %) and NaHCO$_3$ (2.5 equiv.) under blue light-emitting diodes (LEDs) irradiation (**Fig. 2**). To our delight, it was found that the treatment of styrene **2-1** with α-diazo onium salt **2-2** did provide 68% yield of γ-phenyl-γ-hydroxyl-α-diazoester **3-1** in DMF (3. 0 mL) at 0 $^{\circ}$C for 1 h, in which hydroxyl- and diazomethyl-units were regioselectively installed at the C1- and C2-position of styrene, respectively. (**Fig. 2**, entry 1). In comparison, utilizing other α-diazo onium salts **2-1**, **2-3** and **2-4** as "diazomethyl radical" sources only gave us 32-48% yields of **3-1** (entries 2-4 *vs* entry 1). We then further tested a series of metal- or organo-photocatalysts including Mes-Acr$^+$(*t*-Bu), 4-CzIPN, [Ir(dtbpy)(ppy)$_2$]PF$_6$, Ru(phen)$_3$(PF$_6$)$_2$, and Ru(bpy)$_3$Cl$_2$, but none of them could improve the reaction yield over 68% (entries 5–11 *vs* entry 1). Considering that hypervalent iodine diazo reagents possibly suffered from decomposization under room temperature, we performed the hydroxyl-diazomethylation of alkene **1-1** with α-diazoester **2-2** utilizing Ru(bpy)$_3$(PF$_6$)$_2$ as photocatalysts under lower temperature, finding that decreasing the reaction temperature could significantly increase the reaction conversions (entries 12 and 13). Among them, running this transformation at -10 $^{\circ}$C brought us the most satisfactory yield of **3-1** (81%, entry 12 *vs* entry 1). Additionally, switching blue LEDs into green LEDs and white LEDs could not further increase the reaction conversions (entries 14–15 *vs* entry 12) [see Supporting Information (SI) for full optimization studies].
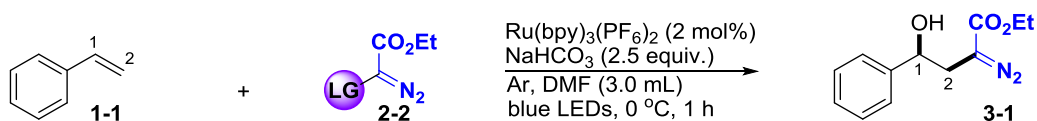
| entry	deviation from standard conditions	3-1 (%)
1	none	68
2	α-diazo onium salt **2-1** instead of **2-2**	32
3	α-diazo onium salt **2-3** instead of **2-2**	44
4	α-diazo onium salt **2-4** instead of **2-2**	48
5	Mes-Acr$^+$(t-Bu) instead of Ru(bpy)$_3$(PF$_6$)$_2$	18
6	4-CzIPN instead of Ru(bpy)$_3$(PF$_6$)$_2$	10
7	Mes-Acr$^+$ClO$_4^-$ instead of Ru(bpy)$_3$(PF$_6$)$_2$	16
8	[Ir(dtbpy)(ppy)$_2$]PF$_6$ instead of Ru(bpy)$_3$(PF$_6$)$_2$	25
9	Ir(ppy)$_3$ instead instead of Ru(bpy)$_3$(PF$_6$)$_2$	49
10	Ru(phen)$_3$(PF$_6$)$_2$ instead of Ru(bpy)$_3$(PF$_6$)$_2$	40
11	Ru(bpy)$_3$Cl$_2$ instead of Ru(bpy)$_3$(PF$_6$)$_2$	64
12	-10 ^{o}C instead of 0 ^{o}C	81
13	-20 ^{o}C instead of 0 ^{o}C	73
14	green LEDs instead of blue LEDs	55[a]
15	white LEDs instead of blue LEDs	62[a]

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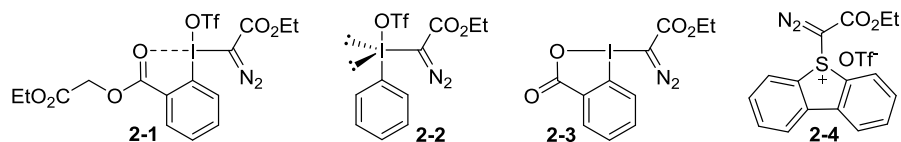
Fig. 2. Reaction development. All the reactions were performed using styrene **1-1** (0.20 mmol), hypervalent iodine diazoester **2-2** (0.3 mmol), NaHCO$_3$ (0.5 mmol) and Ru(bpy)$_3$(PF$_6$)$_2$ (2 mol %) in DMF (3.0 mL, ρ= 0.947 g/mL, 0.15% H$_2$O) at 0 ^{o}C for 1 h under blue LEDs radiation (40 W) and Ar atmosphere in a sealed tube in a sealed tube, followed by flash chromatography on SiO$_2$; [a]The reaction was performed at -10 ^{o}C.

Substrate scope. With the optimized conditions in hand (see **Fig. 2**, entry 12), we explored the scope of the reaction, initially evaluating the reactivity of various terminal alkenes **1** with hypervalent iodine diazoester **2-2**. As summarized in **Fig. 3**, various styrenes could regioselectively undergo 1,2-hydroxyl-diazomethylation to furnish γ-phenyl-γ-hydroxyl-α-diazoester **3-1**~**3-21** in moderate to excellent yields. Among them, 4-alkylstyrenes, 3-alkylstyrenes, 4-phenylstyrene, 4-acylaminostyrene, 4-acyloxylstyrene, 4-halostyrenes, 3-halostyrenes, and 2-halostyrenes could be easily converted to the desired hydroxyl-diazomethylation products **3-1**~**3-7**, **3-10**~3-**16** in 46-84% yields, in which the steric hindrance effects of substituent were not observed (**3-3** *vs* **3-4**, **3-15** *vs* **3-16**). Of note, 4-methoxylstyrene only produce a relatively lower yield of **3-8** (38%) possibly due to that 4-methoxylphenyl skeleton suffered from SET process and inhibited this transformation. Interestingly, when 4-sulfonylaminostyrene was subjected to the standard photocatalysis system, N-H bond diazomethylation also occurred to assemble *N*-(α-sulfonylamino)-α-diazoester-tethered hydroxylfunctionalization product **3-9** in 62% yield. Moreover, 3,4-difluorostyrene, 4-chloro-3-fluorostyrene, electron-deficient 4-trifluorostyrene, 4-nitrostyrene, 4-cyanostyrene, 1-vinylnaphthalene, 2-vinylnaphthalene, and even 2-vinylbenzofuran were also well-tolerable in this transformation to deliver the corresponding products **3-17**~**3-24** with 42-83% yields. To our satisfaction, switching styrene to terminal 1-alkylethene, buta-1,3-diene and isoprene could still regioselectively furnish the corresponding hydroxyl-diazomethylation products **3-25**~**3-28** in acceptable yields (19-69%). However, when 1,1-diarylethenes were employed as substrates, diazomethylation of alkenes was achieved, providing 21-55% yields of β, γ-unsaturated α-diazoesters **3-29**~**3-32** which were possibly derived from the dehydration of hydroxyl-diazomethylation

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products. It should be pointed out that the method could be still applied to structural complex menthol- and estrone-containing terminal alkenes, affording 1,2-hydroxyl-diazomethylation products **3-33** (53%) and **3-34** (43%), respectively.
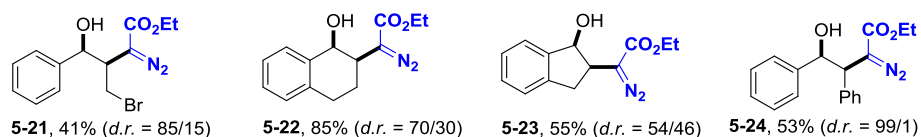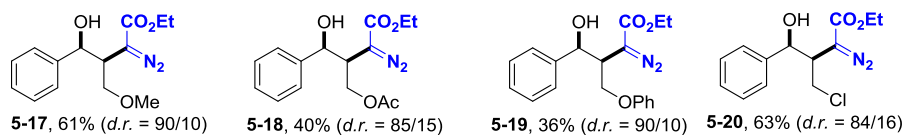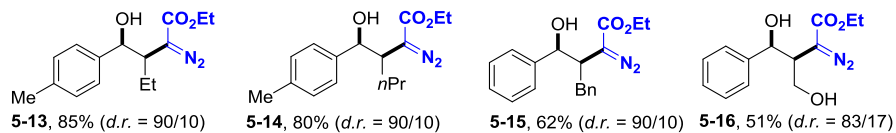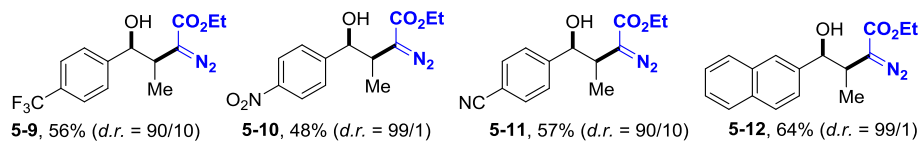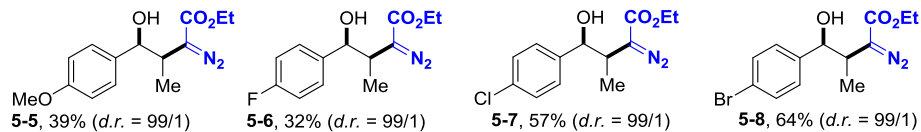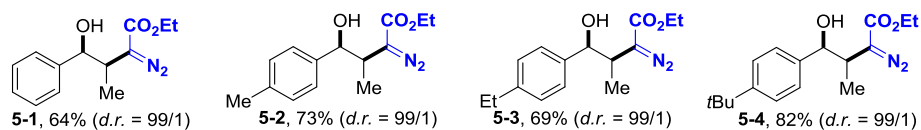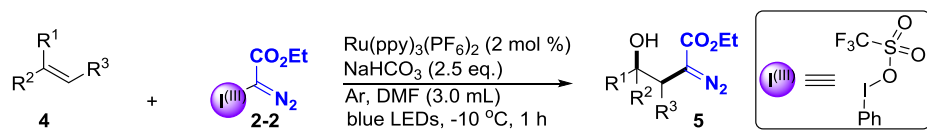

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X-ray of **3-7**
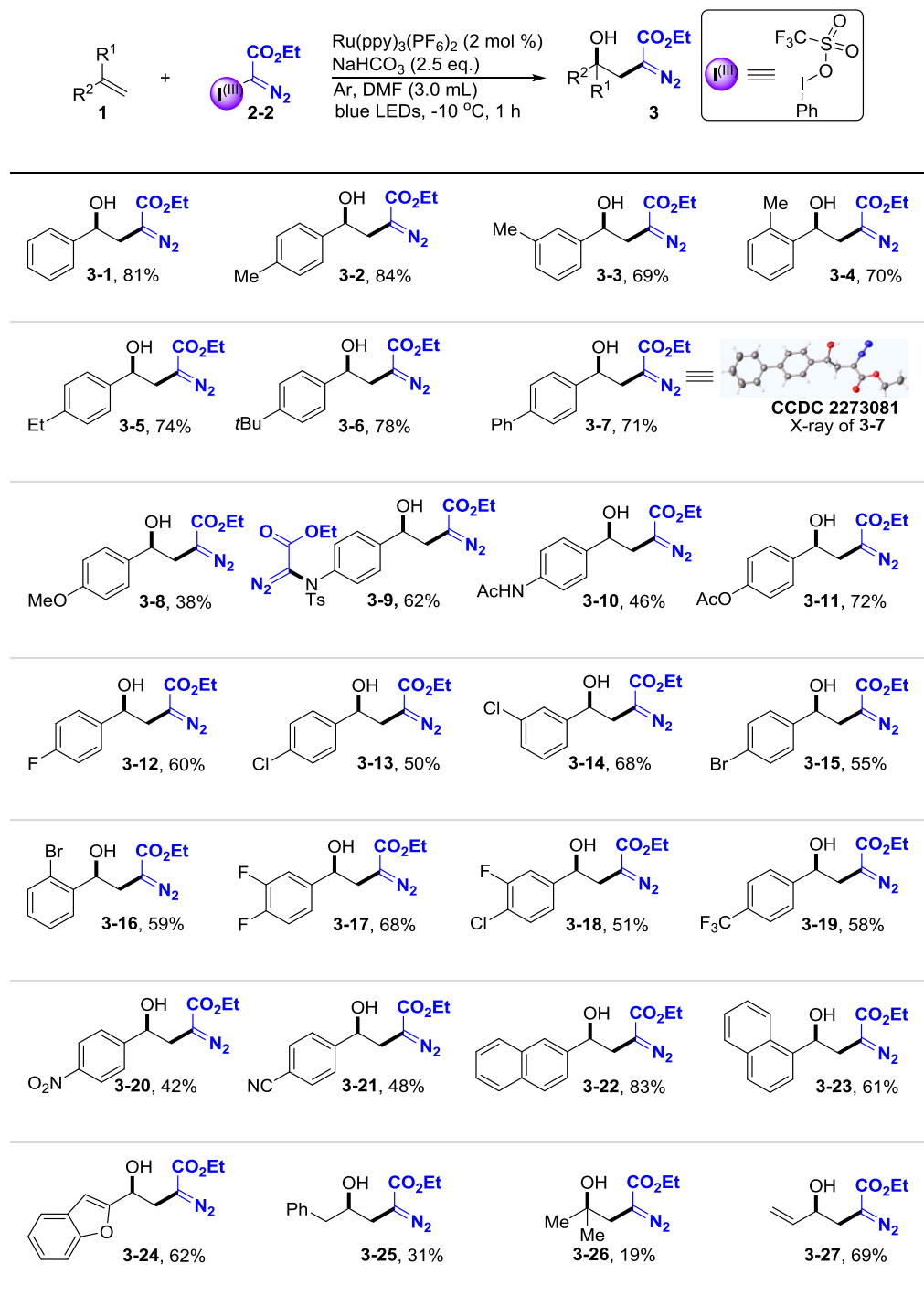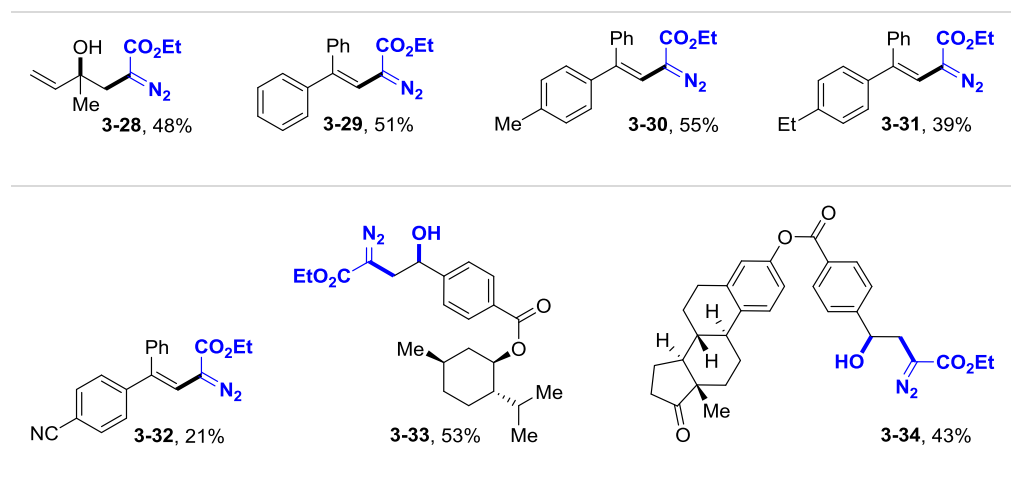
Fig. 3. Hydroxyl-diazomethylation of terminal alkenes. All the reactions were performed using terminal alkenes **1** (0.20 mmol), hypervalent iodine diazoester **2-2** (0.3 mmol), $NaHCO_3$ (0.5 mmol) and $Ru(bpy)_3(PF_6)_2$ (2 mol %) in DMF (3.0 mL, ρ= 0.947 g/mL, 0.15% H_2O) at -10 °C for 1 h under blue LEDs radiation (40 W) and Ar atmosphere in a sealed tube in a sealed tube, followed by flash chromatography on SiO_2.

To expand the scope of alkenes for photocatalytic hydroxy-diazomethylation, we subsequently focused on 1,2-bissubstituted internal alkenes (see **Fig. 4**). Remarkably, our protocol proved compatible with a broad range of 1-aryl-2-alkyl-alkenes, affording the corresponding products **5-1~5-15** in yields ranging from 32% to 82%, in which electron-rich aryl substituents brought us good to excellent yields (**5-1~5-4**, **5-12~5-15**), and electron-deficient aryl substituents led to lower reaction conversions (**5-6~5-11**). Meanwhile, 4-methoxyphenyl-substituted internal alkene only produced poor yield of **5-5** (39%). Gratifyingly, vinyl alkyl moiety bearing hydroxyl, methoxyl, acyloxyl, aryloxyl, and halo-substituents were well-tolerated in this transformation to give structural versatile γ-aryl-γ-hydroxyl-α-diazoester **5-16~5-21** with 36-63% yields. Moreover, cycloalkenes such as 1,2-dihydronaphthalene and 1H-indene were also suitable internal alkenes which could be converted to the desired products **5-22~5-23** in 85% and 55% yields, respectively.

More importantly, the potential breadth of utility of this methodology is further illustrated with 1,2-diarylalkene and 1,2-dialkylalkene, which are effective substrates for assembling **5-24** (53%) and **5-25** (28%). Of note, when 1-phenyl-1,3-diene was subjected to the standard photocatalysis system, although the hydroxyl-diazomethylation of 1,3-diene could occur to deliver the desired product **5-26** (35%), the reaction site were limited to 3,4-bisfunctionalization of terminal C=C double bonds. Finally, evaluating the reactivity of 1,1,2-

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trisubstituted alkenes **4-27** and **4-28** with hypervalent iodine reagent **2-2** indicated that a novel [3 +1] coupling-cyclization instead of 1,2-hydroxyl-diazomethylation occurred, producing cyclobutenes **5-27** (47%) and **5-28** (49%) with moderate yields, respectively.
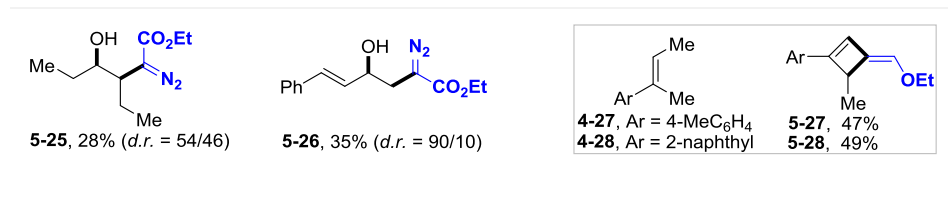
Fig. 4. Hydroxyl-diazomethylation of internal alkenes. All the reactions were performed using internal alkenes **4** (0.20 mmol), hypervalent iodine diazoester **2-2** (0.3 mmol), NaHCO$_3$ (0.5 mmol) and Ru(bpy)$_3$(PF$_6$)$_2$ (2 mol %) in DMF (3.0 mL, ρ= 0.947 g/mL, 0.15% H$_2$O) at -10 °C for 1 h under blue LEDs radiation (40 W) and Ar atmosphere in a sealed tube in a sealed tube, followed by flash chromatography on SiO$_2$.

Application. The post-synthetic modifications of the γ-hydroxyl-α-diazoester **3-1** were highlighted by a series of diazo- and hydroxyl-involved transformations (**Fig. 5**). In these respects, Rh or Pd-catalyzed cross-coupling of diazo-units of **3-1** with 4-methylbenzoic acid, aryliodine, benzyl bromide, aniline, and (4-methoxyphenyl)boronic acid could readily occur to produce α-arylcarbonyloxyl, γ-hydroxyl ester **6** (76%), α-aryl-γ-hydroxyl-α, β-unsaturated ester **7** (64%), γ-hydroxylethyl-β-aryl-α, β-unsaturated ester **8** (70%), α-amino-γ-hydroxyl-carboxylic acid ester **9** (62%), α-aryl-β, γ-unsaturated ester **10** (69%), respectively. Of course, Rh(III)-catalyzed amide-directed regioselective Csp^2-H carbenoid insertion of *N*-carbonyloxylbenzamide with **3-1** could smoothly proceed to assemble 3-alkoxylcarbonyl-3-hydroxylethylisoindolin-1-one **11** in 77% yield. In addition, γ-hydroxyl-α-diazoester **3-1** could also undergo dimerization in the presence of Rh(III)-catalysts to produce 2-(2-hydroxy-2-phenylethyl)-3-styrylmaleate **12** (54%). Finally, this skeleton molecules could be efficiently converted to 2-oxo-4-phenyl-2-butenoic acid ester **13** (62%) *via* cascade dehydration/oxidation under photocatalysis conditions.

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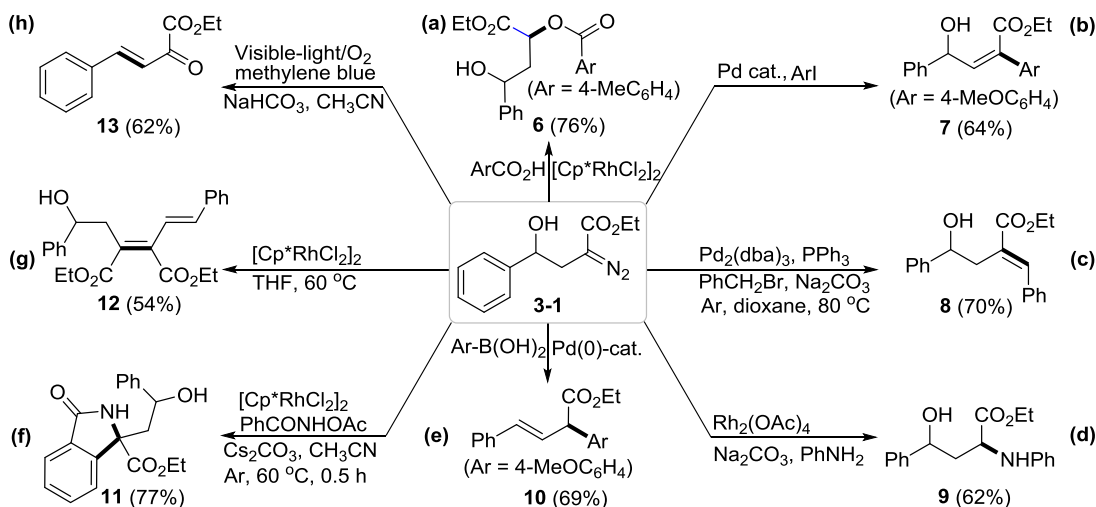
Fig. 5. Synthetic Applications. (**a**) Carboxyl O-H bond carbenoid insertion. (**b**) Cross-coupling of **3-1** with aryliodine. (**c**) Cross-coupling of **3-1** with benzyl bromide. (**d**) Amino N-H bond carbenoid insertion. (**e**) Cross-coupling of **3-1** with aryl boronic acid. (**f**) Aryl Csp^2-H bond carbenoid insertion/cyclization. (**g**) Homo-coupling of **3-1**. (**h**) Photocatalyzed dehydration/oxidation of **3-1**.

Mechanistic investigations. In order to ascertain the mechanism of the hydroxyl-diazomethylation of alkenes, we performed the reaction of **1a** with hypervalent iodine diazoester **2-2** in the presence of TEMPO (1.0 eq.) under the standard reaction conditions, the decreased hydroxyl-diazomethylation reactivity of **1a** with **2-2** indicates that this transformation is possibly triggered by SET process, which is confirmed by the observed HR-MS of TEMPO-trapped product **14** (**Fig. 6a**). Interestingly, when excessive H_2O (1.0 mL) was subjected to this photocatalysis system, benzyl ether **15** (27%) and hydroxy-diazomethylation product **3-1** (22%) could be simultaneously obtained, indicating that cationic-polar crossover between alcohols and benzylic cation intermediates possibly occurs (**Fig. 6b**). To further probe whether the hydroxyl oxygen atom of **3-1** is from molecular O_2 or H_2O, we conducted the hydroxy-diazomethylation of **1a** with **2-2** under pure O_2, and found that alkene **1a** and hypervalent iodine diazoester **2-2** basically remained intact. This result implies that O_2 possibly inhibits the initiating SET process, resulting in very poor reaction conversions (**Fig. 6c**). By contrast, when H_2O^{18} (10.0 eq.) was subjected to the standard reaction conditions with alkene **1a** and α-diazoester **2-2** under Ar atmosphere, the O^{18}-labeled product ^{18}O-**3-1** could be obtained in 28% yield (**Fig. 6d**). This result

highlights that hydroxyl oxygen atom of the hydroxyl-diazomethylation product **3-1** is from solvent H_2O instead of molecular O_2, further implying that carbocation intermediates were involved in this transformation.
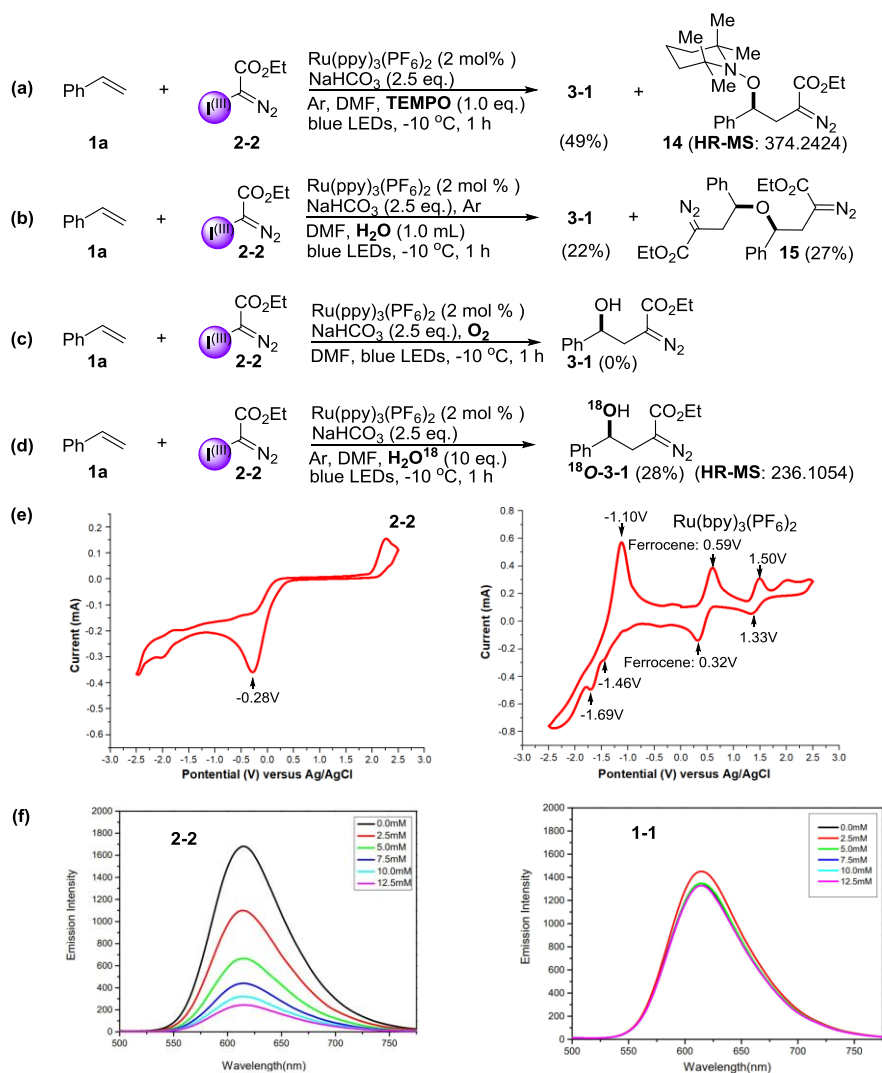
Fig. 6. Preliminary mechanism studies. (a) Radical trapping experiment. (b) Carbon cationic trapping experiment. (c) The effect of O_2 atmosphere on this transformation. (d) ^{18}O-labeled experiment. (e) Cyclic voltammetry measurements on **2-2** and photocatalysts. (f) Stern-Volmer fluorescent quenching experiments of $Ru(bpy)_3(PF_6)_2$ by **2-2** and **1-1**.

On the basis of the above-mentioned control experiments, a possible mechanism is proposed for this hydroxyl-diazomethylation of alkenes. As shown in **Fig. 7**, the reaction is initiated by reduction of hypervalent

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iodine diazoester **2-2** to diazomethyl radicals **D** [N$_2$=C(•)–CO$_2$Et] by a photoexcited Ru(II)-catalysts **B***, releasing I(I)-aryliodine **C** and Ru(III)-catalysts {[E red (**2-2**)]= -0.28 V *vs* standard silver/silver chloride electrode (SSCE); [E red (Ru(bpy)$_3$(PF$_6$)$_2$)] = -1.69 V *vs* SSCE (**Fig. 6e**), see SI for details}, this SET process is also supported by Stern−Volmer fluorescent quenching experiments of Ru(bpy)$_3$(PF$_6$)$_2$ (**B***) by **2-2** and **1-1**, which indicate that **2-2** efficiently quenches the excited state of photocatalysts Ru(bpy)$_3$(PF$_6$)$_2$ (**Fig. 6f**). Subsequently, **D** attacks alkene **1-1** *via* radical addition to produce γ-carboradical-tethered α-diazoester species **E**, followed by SET oxidation by the newly generated Ru(III)-catalysts to give γ-carbocation-tethered α-diazoester species **F**. Finally, carbocation intermediates **F** are trapped by H$_2$O to deliver γ-phenyl-γ-hydroxyl-α-diazoester **3-1**. However, given that γ-carboradical-tethered species **E** possibly react with molecular O$_2$ to produce superoxide radicals **G**,[20] which then undergo a cascade protonation and homolysis to afford **3-1**, but this alternative reaction mechanism can be fully excluded by the control experimental result from **Fig. 6c**.
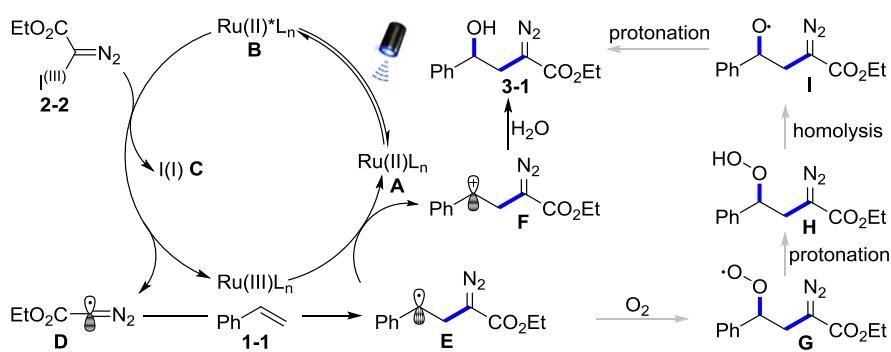
Fig. 7. Proposed reaction mechanism

Conclusion

In summary, we have developed an unprecedented visible-light-catalyzed regioselective 1,2-hydroxyl-diazomethylation of alkenes with hypervalent iodine diazoesters. A variety of alkenes including terminal alkenes and internal alkenes are applicable to this mild catalysis system for rapidly assembling valuable γ-hydroxyl-α-diazoesters, featuring simultaneously introducing two chemo-active hydroxyl group and diazomethyl group into carbon-carbon double bonds. We believe that this strategy will open a new window to

achieve diazomethylation-based difunctionalization of alkenes by utilizing various carbon and heteroatomic nucleophiles.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available.

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Methods

Reactions were run in an oven-dried 2 dram vial fitted with an oven-dried Teflon coated stir bar, and a Teflon cap under argon. The $Ru(bpy)_3(PF_6)_2$ that was used was stored in a freezer. The DMF utilized as solvent contains 0.15% H_2O.

Procedure. To a 10 mL vial equipped with a magnetic stir bar, was added alkenes **1** or **4** (0.20 mmol), α-diazoester **2-2** (139.8 mg, 0.30 mmol, 1.5 equiv), $Ru(bpy)_3(PF_6)_2$ (3.4 mg, 0.004 mmol, 2 mol %), $NaHCO_3$ (42.0 mg, 0.50 mmol, 2.5 equiv) and DMF (3.0 mL) under argon. The vial was placed into cold trap and stirred at -10 ℃ under blue LED irradiation with one Kessil LED (40 W, 456 nm, approximately 3 cm away from the reaction mixture) for 0.5-1 hour, followed by flash column chromatography on silica gel to yield the products **3** and **5**.

Data availability

The authors declare that the data supporting the findings of this study are available within the article, Supplementary Information (SI) and Source Data, as well as from the authors upon reasonable request. The X-ray crystallographic coordinates for structures **3-7** (CCDC 2273081) reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data-request/cif.

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Author contributions
W. Z. directed the research. Y. Z., X. Z., S. C., Z. L. and H. X. performed the experiments. Y. Z. and X. Z. contributed equally to this work. J. L. directed the analytical measurements. W. Z. wrote the manuscript. H. J. contributed to discussions.

Competing Interests

The authors declare that they have no competing interests.

Additional information

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