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Visible-light-promoted N–H functionalization of O-substituted hydroxamic acid with diazo esters†

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Herein we report an N–H functionalization of O-substituted hydroxamic acid with diazo esters under blue LED irradiation conditions. The present transformations could be performed efficiently under mild conditions without use of catalyst, additive and N₂ atmosphere. Interestingly, when THF and 1,4-dioxane were employed as the reaction solvents, an active oxonium ylide involved three-component reaction and an N–H insertion of carbene species into hydroxamate occurred, respectively.

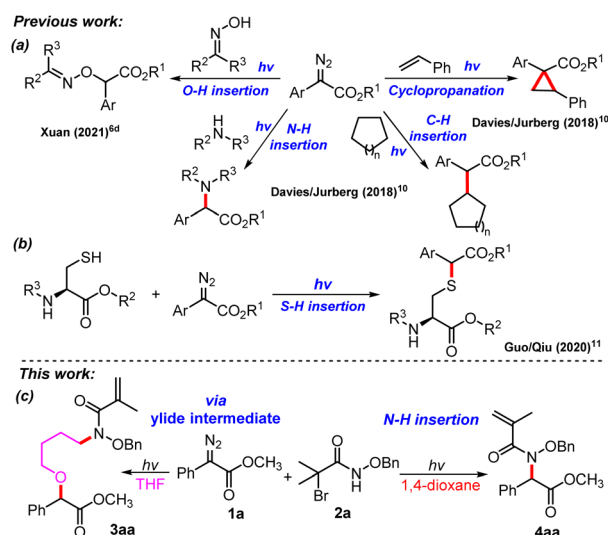
From recent decades, diazo compounds have been widely employed as an efficient reagent in numerous organic transformations.¹ For instance, they could be applied for constructing cyclopropane skeletons by transferring a carbene unit to a double bond with specific diastereoselectivity.² Moreover, diazo compounds could also be involved in transition metal catalysed carbene transfer reactions, which resulted in the development of various strategies for the construction of new C–C and C–X (X = N, O, S, Se, Si, Sn, Ge) bonds.³

Recently, visible light mediated transformations of donor/acceptor diazo compounds have been intensively studied.⁴ Until now, under visible light irradiation conditions, the conversion of donor/acceptor diazo compounds is mainly applied for cyclopropanation,⁵ insertion reaction of X–H (X = B, C, O, N, Si, S) bond^{6,7} via the formation of free carbene as an important intermediate, and some conversion that involves the formation of ylide intermediates.^{8,9} In 2018, Davies and Jurberg first revealed that aryldiazoacetates had absorption in the visible light region ($\lambda = 400\text{--}500\text{ nm}$).¹⁰ They found that aryldiazoacetates could occur cyclopropanation with styrene,¹⁰ O–H insertion reactions with oxime,^{6d} N–H insertion reactions with amines and C–H insertion reactions with cyclic alkanes or arenes (Scheme 1a). Subsequently, Guo and Qiu reported a visible light promoted S–H insertion reaction of aryl diazoacetates and cysteine residues in batch and flow (Scheme 1b).¹¹ Afterwards, photochemical multicomponent reactions involving aryldiazoacetates have been developed successively.¹²

As our research interests on the development of photochemical insertion reactions of X–H-containing molecules into aryl diazoacetates, herein we report a visible-light-promoted N–H functionalization of O-substituted hydroxamates with

aryldiazoacetates. It was found that when THF was the reaction solvent, a three-component coupling product was obtained, while when 1,4-dioxane was used as the solvent, an N–H insertion product was achieved (Scheme 1c). As a multicomponent-reaction between hydroxamic acid and diazo esters has been developed,¹³ this work will be a good supplement to the photochemical transformation of diazo compounds through the formation of free carbene as a key intermediate.

At the outset, we evaluated the reaction using methyl 2-diazo-2-phenylacetate **1a** and *N*-(benzyloxy)-2-methylpropanamide **2a** as the model substrates. Initially, under the irradiation of 30 W blue LEDs, the reaction was conducted in THF in the presence of NaHCO₃ (Table 1, entry 1), but only trace amount of product **3aa** was observed. Next, some stronger bases were employed in the reaction system. To our



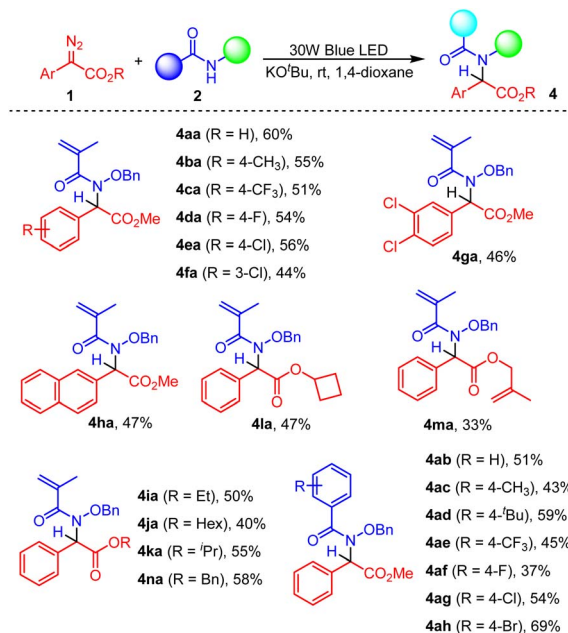
Scheme 1 Visible light induced carbene insertion reaction of diazo compounds.

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^a Reaction conditions: **1a** (0.2 mmol), **2a** (1.5 equiv.), base (1.2 equiv.), solvent (2 mL), 14 h, room temperature, 30 W blue LEDs ($\lambda \approx 440\text{--}450\text{ nm}$). ^b Isolated yields. ^c Without light irradiation. n.d. = no desired product was detected.



Scheme 3 Substrate scope with 1,4-dioxane as the solvent. Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), KO^tBu (0.24 mmol), 1,4-dioxane (2 mL), r.t., 30W blue LEDs ($\lambda \approx 440\text{--}450\text{ nm}$), 14 h. Isolated yield.

and THF gave rise to the product **3ea** in 87% yield. Additionally, the naphthyl-containing substrate **1j** was also compatible with this protocol, generating the corresponding product **3ja** in 79% yield. Subsequently, substituent modification of the ester group in aryl diazoacetates was investigated. The results showed that the replacement of methyl group with ethyl, *n*-hexyl, isopropyl, benzyl, cycloalkyl and other sensitive functional groups (**1q** and **1r**) was feasible, leading to the corresponding products **3ka–3ra** in good yields (51–91%). Unfortunately, the α -aryl diazo substrate **1s** was failed to react with **2a** and THF.

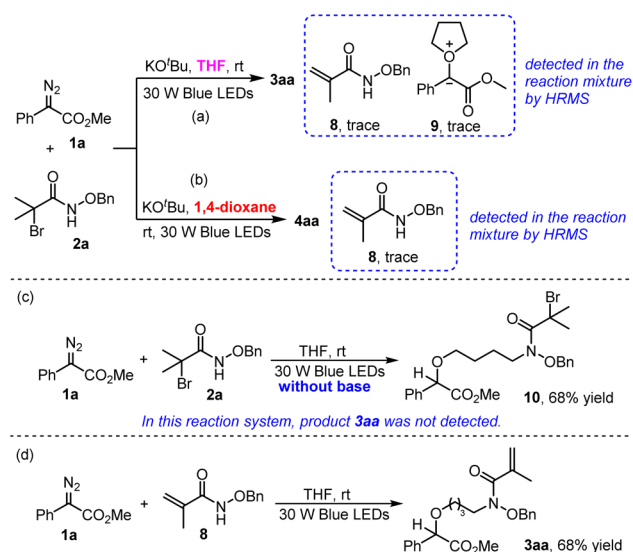
Then, we investigated the substrate scope of amide **2**. The fluoro-group containing **2b** was found to react with **1a** or **1n** smoothly, giving the corresponding products **3ab** and **3nb** in good yields. However, changing the OBn group to Bn group, no desired product **3ac** was detected. To our delight, the *tert*-butyl substituted amide **2d** worked well to produce product **3ad** in 58% yield. Unfortunately, when *N*-(benzyloxy)isobutyramide **2e** or *N*-(benzyloxy)-2-bromopropanamide **2f** were taken as the substrate, both of the reaction were failed, no desired products (**3ae**, **3af**) was observed. Additionally, aromatic amides bearing either electron-withdrawing or electron-donating groups were also tolerated, resulting in the formation of the corresponding products **3ag–3am** in good yields. Moreover, using tetrahydropyran as the reaction solvent, the corresponding product **5** was isolated in 51% yield. But, when 2-methyltetrahydrofuran or tetrahydrothiophene were taken as the reaction solvent, reactions were failed.

We further expanded the reaction scope of aryl diazoacetates **1** and hydroxamates **2** in 1,4-dioxane (Scheme 3). It was found that the incorporation of both electron-donating and electron-

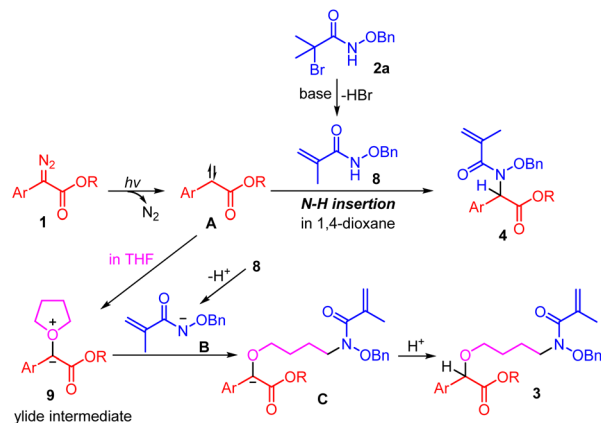
withdrawing groups on the phenyl ring of aryl diazoacetates generally afforded the corresponding N–H insertion product in 44–60% yields (Scheme 3, **4aa–4ga**). In addition, the reaction of methyl 2-diazo-2-(naphthalen-2-yl)acetate **1h** and *N*-(benzyloxy)-2-bromo-2-methylpropanamide **2a** also proceeded very well under the standard conditions, giving rise to **4ha** in 47% yield. Moreover, a series of aryl diazoacetates were also demonstrated to react with **2a** smoothly, leading to the formation of products **4la–4na**. As expected, various amides **2** reacted with methyl 2-diazo-2-phenylacetate **1a** successfully, giving rise to the corresponding products **4ab–4ah** in moderate yields. Different functional groups including F, Cl, Br, CF₃, Me, ^tBu were all tolerated under the reaction conditions.

As is shown in Scheme 4, a key intermediate **8** which was generated from an intramolecular elimination reaction of substrate **2a** was detected in the reaction mixture (both in THF and 1,4-dioxane) by HRMS. Additionally, in the THF reaction system, the ylide intermediate **9** was also detected by HRMS (Scheme 4a). When we performed the reaction of **1a** and **2a** in the absence of base (Scheme 4c), it was found that the N–H insertion reaction still worked but without *in situ* dehydrobromination occurring, product **10** could be obtained in 68% yield, while in this reaction system product **3aa** could not be detected. Then, we prepared *N*-(benzyloxy)methacrylamide **8** as the substrate, and under the irradiation with 30 W blue LEDs we conducted the reaction of **8** with **1a** in THF which resulted in the formation of product **3aa** in 68% yield (Scheme 4d).

Based on the results of control experiments and previous reports,¹² a plausible mechanism for this transformation is illustrated in Scheme 5. Initially, in the presence of base, *N*-(benzyloxy)-2-bromo-2-methylpropanamide **2a** was transformed into intermediate **8** through elimination of one molecular HBr. In the meantime, with the release of molecule nitrogen, a carbene intermediate **A** was generated from aryl diazoacetates **1** upon the irradiation with blue LEDs.^{4–6} When the reaction was performed in 1,4-dioxane, trapping of the carbene species **A** by



Scheme 4 Mechanistic studies.



Scheme 5 Possible reaction mechanism.

the intramolecular elimination product **8** afforded the N-H insertion product **4**. However, when THF was employed as the reaction solvent, an active oxonium ylide intermediate **9** would be generated. Then, intermolecular nucleophilic attack of the nitrogen anion **B** on the intermediate **9** would lead to the formation of intermediate **C**, which further delivered the final product **3**.

Conclusions

In summary, a visible light promoted N-H functionalization of O-substituted hydroxamic acids with diazo esters under mild conditions was developed. The reactions proceeded efficiently to afford two series of N-H functionalized products of O-substituted hydroxamic acids in moderate to excellent yields with good functional group compatibility. When 1,4-dioxane was applied as the solvent, N-H insertion of the photo-generated free carbene species into hydroxamic acid derivatives occurred directly. While, when the reaction was performed in THF, it was found that THF can participate in the reaction system through a formation of an active oxonium ylide intermediate. Taken THF as a covalent linker, this strategy can be applied in medicinal chemistry to providing a new approach for antibody-drug conjugation.¹⁴

Conflicts of interest

There are no conflicts to declare.

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