Visible-Light-Induced Multicomponent Synthesis of γ-Amino Esters with Diazo Compounds

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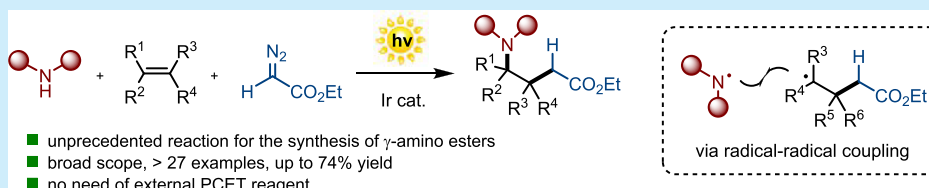ACCESS | Metrics & More | Article Recommendations | SI Supporting Information

- unprecedented reaction for the synthesis of γ-amino esters
- broad scope, > 27 examples, up to 74% yield
- no need of external PCET reagent

via radical-radical coupling

ABSTRACT: A visible-light-induced multicomponent reaction of ethyl diazoacetate, diarylamines, and styrene-type alkenes is described. This novel 1,2-difunctionalization of alkenes can be readily achieved under a simple operation and mild conditions, affording γ-amino esters as major products. The reaction proceeds through the generation of carbon-centered radicals from diazo compounds by a visible-light-promoted proton-coupled electron transfer (PCET) process. The carbon radicals then add to diverse alkenes, delivering new carbon radical species, and the final products are formed with N-centered radicals via a radical−radical coupling.

Diazo compounds have considerable synthetic potential because of their high reactivities and diverse applications. They are versatile building blocks in various reactions and functional group transformations.[1] Traditionally, diazo compounds are utilized as metal carbene precursors with a range of transition metal catalysts, such as rhodium, copper, iron, etc.[2] Typical transformations of metal carbenes involving X−H insertions (X = C, N, O, S, etc.),[3] cyclopropanation,[4] ring expansion,[5] and ylide formation[6] have been well established (Scheme 1a). However, the ability of diazo compounds to undergo free radical reactions, particularly radical addition to simple alkenes, is still underdeveloped.[7]
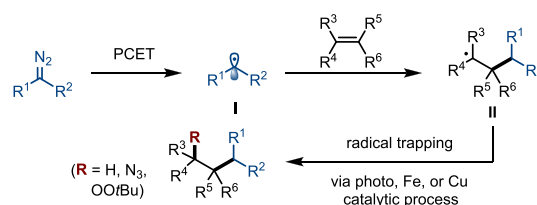
Proton-coupled electron transfer (PCET) is known to exist in numerous biological redox processes and is synthetically useful in the development of novel radical-mediated transformations.[8] Several research groups have recently used the PCET strategy to successfully convert diazo compounds into the corresponding carbon-centered radicals **I**, which can add to diverse alkenes with high regioselectivity to generate new carbon radical species **II**. The reactions were completed through either thiol-assisted hydrogen atom transfer or a radical trapping process with azides or peroxides (Scheme 1b).[9] Considering the fact that γ-aminobutyric acid (GABA) and its derivatives are privileged structural motifs present in living organisms and bioactive molecules,[10] we envisioned that the exploration of a multicomponent synthesis of γ-amino esters[11] from α-diazoacetate and amines would be highly rewarding. Notably, our previous work has demonstrated that N-centered radicals can be generated from diarylamines via photocatalytic oxidation.[12] We envisaged that under the appropriate photochemical conditions, a radical−radical

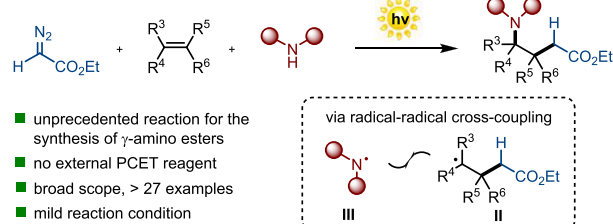## Scheme 1. Reaction of Diazo Compounds

a) Classical transformation of diazo compounds
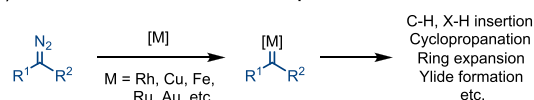
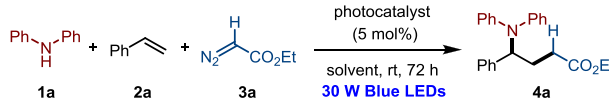**b) Functionalization of alkenes with diazo compounds via PCET process**

c) This work

- unprecedented reaction for the synthesis of γ-amino esters
- no external PCET reagent
- broad scope, > 27 examples
- mild reaction condition

via radical-radical cross-coupling

cross-coupling of the generated N-centered radicals **III** with the carbon radical species **II** would facilitate the production of the desired γ-amino esters (Scheme 1c). Such a multicomponent synthetic pathway is very attractive in organic synthesis as there is no need for an external PCET reagent.

With this hypothesis in mind, we start our investigation by using diphenylamine (**1a**), styrene (**2a**), and ethyl diazoacetate (**3a**) as model substrates in the presence of Ru(bpy)$_3$Cl$_2$ (5 mol %) as a photocatalyst under visible light irradiation (30 W blue LEDs), as shown in Table 1. Herein, the use of

Table 1. Optimization of Reaction Conditions[a]

entry	photocatalyst (5 mol %)	solvent	yield[b] (%)
1	Ru(bpy)$_3$Cl$_2$	MeCN	35
2	*fac*-Ir(ppy)$_3$	MeCN	trace
3	Ir(ppy)$_2$(dtbbpy)PF$_6$	MeCN	47
4	**Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$**[c]	**MeCN**	**51 (60)[c]**
5	Ru(bpz)$_3$PF$_6$	MeCN	0
6	Ru(phen)$_3$PF$_6$	MeCN	0
7	Ir(bpy)$_2$(dtbbpy)PF$_6$	MeCN	40
8	Eosin Y	MeCN	0
9	Mes-Acr$^+$ClO$_4^-$	MeCN	0
10	triphenylpyryllum	MeCN	0
11	Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$	DCM	0
12	Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$	DMSO	21
13	Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$	THF	trace
14	Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$	MeOH	18
15[d]	Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$	MeCN	0
16		MeCN	0

[a]Reaction conditions are as follows: **1a** (0.10 mmol), **2a** (0.30 mmol, 3.0 equiv), **3a** (0.45 mmol, 4.5 equiv), anhydrous solvent (5.0 mL), 30 W Blue LEDs, rt, 72 h, under a N$_2$ atmosphere. [b]Yields of isolated products. [c]Isolated yields in brackets were based on the recovered starting material. [d]Reaction was performed in the dark.

diarylamine as a nitrogen radical precursor is mainly based on the reported literature and our previous experimental results.[12,13] Gratifyingly, the desired γ-amino ester **4a** was afforded in a 35% yield when the reaction was performed at room temperature for 72 h (Table 1, entry 1). Encouraged by this result, we next investigated the influence of the photocatalyst (Table 1, entries 2−10). To our delight, Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ was found to be the optimal candidate with a 51% isolated yield of **4a** (Table 1, entry 4). The addition of additives to the reaction system proved to be ineffective.[14] Further optimizations were conducted by screening a variety of reaction solvents, such as DCM, DMSO, THF, and MeOH, but they all provided unsatisfying results (Table 1, entries 11−14, respectively). As anticipated, control experiments revealed that the multicomponent transformation does not proceed in the dark nor in the absence of a photocatalyst (Table 1, entries 15 and 16, respectively). Notably, the influence of the substrate ratio was also explored, which indicated that the optimal ratio of the diarylamine (**1a**), the styrene (**2a**), and the ethyl diazoacetate (**3a**) is 1:3:4.5.[14]

With the optimal reaction conditions in hand, we first investigated the scope of the amine substrates. As shown in Scheme 2, both symmetric and unsymetric diarylamines can work smoothly under the optimal reaction conditions to form

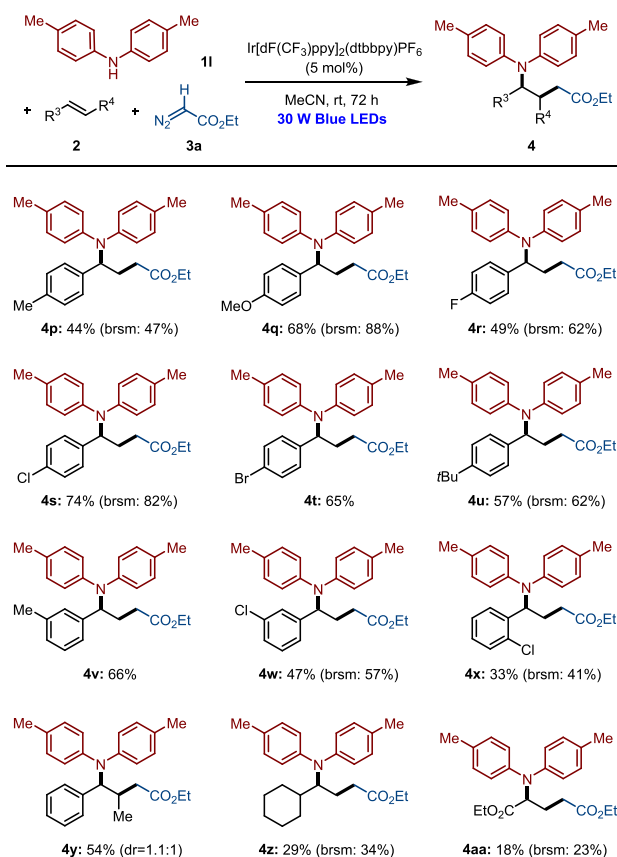### Scheme 2. Substrate Scope of Diarylamines[a,b]
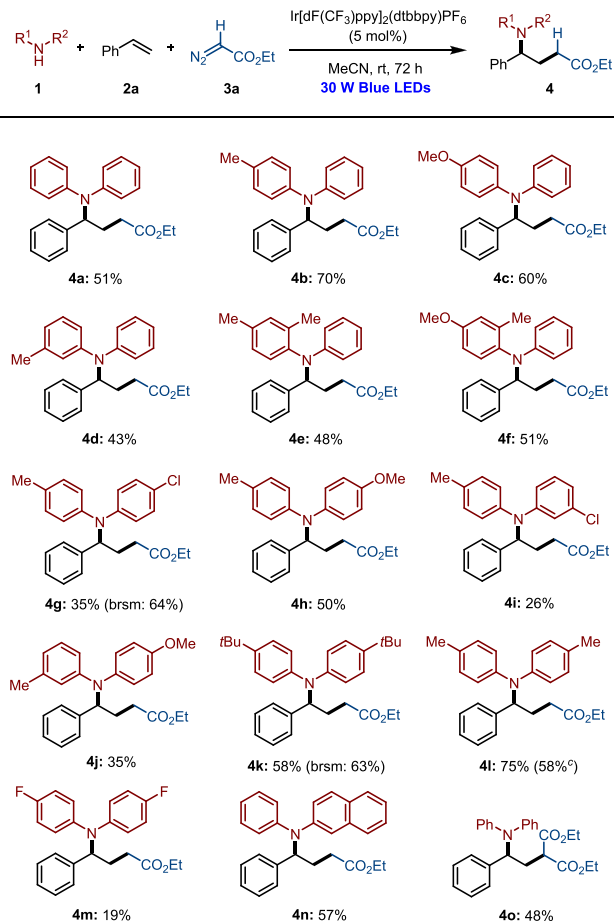
[a]Standard conditions are as follows: diarylamine **1** (0.10 mmol), styrene **2a** (0.30 mmol, 3.0 equiv), ethyl diazoacetate **3a** (0.45 mmol, 4.5 equiv), MeCN (anhydrous, 5.0 mL), 30 W Blue LEDs, rt, 72 h, under a N$_2$ atmosphere. [b]Yields of isolated products. Brsm, based on recovered starting material. [c]Reaction conditions are as follows: **1l** (1.0 mmol), **2a** (3.0 mmol, 3.0 equiv), **3a** (4.5 mmol, 4.5 equiv), MeCN (anhydrous, 20.0 mL), 455 nm (10 W) LED, rt, 38 h, under a N$_2$ atmosphere.

the desired γ-amino ester products in certain yields. It can be seen that diarylamines bearing various electron-donating groups in the *para*-position were more suitable compared to the electron-withdrawing groups (**4b−4c**). When one of the aryl groups was substituted at the *meta*-position, the corresponding product was obtained with a moderate yield (**4d**). Further investigations showed that diarylamines bearing two different substituents on one aromatic ring were also compatible. For example, the corresponding products **4e** and **4f** were delivered in 48% and 51% isolated yields, respectively. In addition, the diarylamines consisting of substituents on both aromatic rings presented interesting situations (**4g−4m**). It should be pointed out that chlorine- and fluorine-substituted secondary amines were well-tolerated under the reaction conditions to yield the corresponding products (**4g**, **4i**, and **4m**). Moreover, symmetrical diarylamines with substituents on two aromatic rings could furnish the desired products in low to good yields (**4k−4m**). The substrate containing a naphthyl group meets the need for the standard reactions to furnish product **4n** in a 57% yield. Furthermore, the use of diethyl 2-diazomalonate instead of ethyl diazoacetate produced **4o** in a

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48% yield, whereas the use of other diazo compounds was found to be ineffective.[14] To highlight the practicability of our method, a reaction was successfully performed on a larger scale (1.0 mmol), affording the desired product **4l** in a 58% yield.

What is more, to verify the effectiveness of the visible-light-induced multicomponent reaction, the scope of alkenes was further explored (Scheme 3). It could be seen that styrene

**Scheme 3. Substrate Scope of Alkenes**[a,b]

[a]Standard conditions are as follows: diarylamine **1** (0.10 mmol), styrene **2a** (0.30 mmol, 3.0 equiv), ethyl diazoacetate **3a** (0.45 mmol, 4.5 equiv), MeCN (anhydrous, 5.0 mL), 30 W Blue LEDs, rt, 72 h, under a N$_2$ atmosphere. [b]Yields of isolated products. Brsm, based on recovered starting material.

derivatives with electron-rich or electron-deficient groups on the *para*-position of aromatic ring performed well in this transformation. The desired products were obtained in moderate to good yields (**4p−4u**). Moreover, styrene derivatives with *meta*- or *ortho*-substituents were well-tolerated with the optimal reaction conditions (**4v−4x**). Importantly, the 1,2-disubstituted alkene **2y** was also examined and was found to be feasible for this multicomponent reaction, affording the desired γ-amino ester product (**4y**) in a moderate yield with high regioselectivity. To our delight, not only styrene-type substrates could be reacted but also an aliphatic olefin and diethyl fumarate, which were also transformed to the expected products under the optimized conditions with a slight depression of the reaction efficiency (**4z** and **4aa**, respectively).

Several control experiments were carried out before the reaction mechanism was proposed. As an alternative pathway, the sequence of cyclopropanation followed by a ring-opening reaction was considered. We first examined the reaction

between diphenylamine **1a** and the cyclopropane compound **5** that was generated by carbene insertion to styrene,[15] but no reaction was observed under the standard conditions (Scheme 4a). Such a result suggested that the reaction did not proceed

**Scheme 4. Investigation of the Reaction Mechanism**
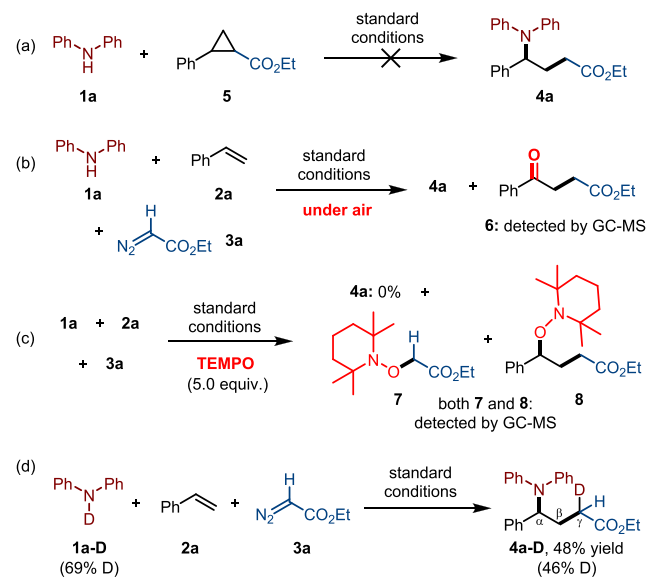
in a ring-opening manner under the photoredox conditions. When the model reaction was performed under air, the oxidized product **6** could be detected by GC-MS (Scheme 4b), mechanistically implicating a benzylic radical intermediate.[16] Further mechanistic investigations revealed that the addition of TEMPO (2,2,6,6-tetramethylpiperidinooxy) as a typical radical scavenger entirely abolished the desired multicomponent reaction, while the formation of radical trapping products **7** and **8** could be observed (Scheme 4c). We further explored whether the diarylamine underwent a nucleophilic addition reaction for C−N bond formation or a free radical cross-coupling process. Several nitrogen-centered nucleophiles or H$_2$O were added to the reaction system, but the corresponding nucleophilic addition products were not detected at all, which indicated that the involvement of cationic intermediates in the C−N bond formation is unlikely.[14]

To get a deeper insight into the mechanism and the efficiency of this multicomponent photoreaction, the oxidation potential of di-*p*-tolylamine (**1l**) was tested by using cyclic voltammetry. The measured redox potential of di-*p*-tolylamine $\left(E_{1/2}^{ox} = +0.92 \text{ V vs SCE}\right)$[14] is inside the redox window of the iridium photocatalyst Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ $\left(E_{1/2}^{*III/II} = +1.21 \text{ V vs SCE}\right)$,[17] revealing that our reaction may undergo a reductive quenching cycle of the photocatalyst and generate a key nitrogen-centered radical intermediate[18] from di-*p*-tolyl-amine. Such a result was consistent with our previous literature reports[12,13] and explained why only diarylamines are suitable substrates. The protons released from diarylamines participate in the process of coverting diazo compounds into carbon radicals via the PCET strategy. Isotopic labeling experiments were further performed to investigate the γ-hydrogen source of the product. When CD$_3$CN or D$_2$O was utilized in the reaction system, the nondeuterated product was observed. However, if the deuterated amine **1a-D** (with 69% D) was applied, the corresponding product **4a-D** was successfully obtained in a 48% isolated yield with 46% deuterium-incorporation (Scheme

4d), showing that the γ-hydrogen of the product may come from amine **1a** and that the presence of diphenylamine as a suitable hydrogen source promotes the key PCET step as well as the following reaction process.

On the basis of the above experimental results and previous literatures, a plausible mechanism for the multicomponent photocatalytic reaction was proposed, as depicted in Scheme 5.

Scheme 5. Proposed Reaction Mechanism
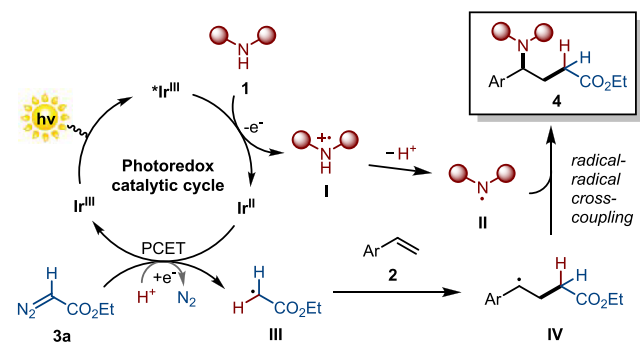
Upon irradiation with visible light, the iridium complex $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ is converted into its corresponding excited state Ir(III)*, which can oxidize the diarylamine **1** to generate a Ir(II) species and the radical cation **I**. The newly formed Ir(II) species then undergoes a single electron transfer to ethyl diazoacetate **3a** while returning Ir(III) to the catalytic cycle. The sequential release of one molecule of nitrogen with protonation produces a carbon-centered radical **III**, which further reacts with styrene derivative **2** to furnish a relatively stabilized benzylic radical **IV**. The nitrogen-centered radical intermediate **II**, which is delivered from the radical cation **I** after the release of a proton, undergoes a radical−radical cross-coupling reaction with benzylic radical **IV** to furnish the final product **4**.

In conclusion, we have established a novel and efficient multicomponent protocol for the synthesis of γ-amino esters under visible-light reaction conditions.[19] The transformation uses cheap and easily available diazo compounds, diarylamines, and alkenes as starting materials, showing the high synthetic efficiency as well as atom and step economy. The dual role of diarylamines as PCET reagents and free radical-trapping agents is the key to the success. The reaction is performed under a simple operation and mild conditions, making this synthetic method suitable for a diversity-oriented synthesis in drug discovery scenarios. Further development of new photocatalytic reactions is underway in our laboratory.

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02071.

Experimental details, characterization data, and copies of NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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