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EDGE ARTICLE

Photo-induced imino functionalizations of alkenes *via* intermolecular charge transfer†

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A catalyst-free photosensitized strategy has been developed for regioselective imino functionalizations of alkenes *via* the formation of an EDA complex. This photo-induced protocol facilitates the construction of structurally diverse β-imino sulfones and vinyl sulfones in moderate to high yields. Mechanistic studies reveal that the reaction is initiated with an intermolecular charge transfer between oximes and sulfinates, followed by fragmentation to generate a persistent iminyl radical and transient sulfonyl radical. This catalyst-free protocol also features excellent regioselectivity, broad functional group tolerance and mild reaction conditions. The late stage functionalization of natural product derived compounds and total synthesis of some bioactive molecules have been demonstrated to highlight the utility of this protocol. Meanwhile, the compatibility of different donors has proved the generality of this strategy.

Introduction

Nitrogen-containing molecules are widely found in natural products and pharmaceuticals, and play an important role in organic synthesis.[1] Particularly, β-functionalized amino compounds display unique properties in terms of pharmaceutical activity and ligand design.[2] Given the availability and abundance of olefins, difunctionalization of alkenes has been recognized as a straightforward and powerful strategy for constructing complex molecules. Therefore, transition metal-catalyzed difunctionalization of olefins has been developed for the construction of a series of products containing β-functionalized amino structural units.[3] However, this method faces problems such as relatively harsh reaction conditions and the participation of precious metals (Fig. 1A).[3d–f,3h] Considering the problem of heavy metal residues and the applicability of the reactions, searching for gentler and non-toxic methods becomes necessary. Recently, photoredox catalysis has been employed to construct β-functionalized amino compounds *via* multicomponent alkene difunctionalization (Fig. 1A).[4] Nevertheless, unlike amino functionalizations of alkenes, olefin imino functionalization is still in the initial stage and mainly limited to intramolecular cyclization reactions.[3d,4a,5] Additionally, most of these photoredox protocols require the participation of noble metal photocatalysts. Under energy transfer

photocatalysis, various elegant bifunctional reagents have been developed to generate the required radical pairs for alkene difunctionalizations (Fig. 1B).[6] Although significant progress has been made, this energy transfer catalytic strategy relies on the design and synthesis of bifunctional reagents, and often requires multi-step synthesis for the introduction of other functional groups. Therefore, it is of great interest to develop a flexible and variable olefin difunctionalization method under mild conditions.

Considering the current problems, an alternative strategy is the direct photoexcitation of an electron donor–acceptor (EDA) complex. It is defined as a new molecular aggregate formed by an electron acceptor substrate A and a donor molecule D through non-bonding interactions.[7] The two components A and D may not absorb visible light themselves, but their *in situ* formed EDA complex does. And subsequent intramolecular single-electron transfer (SET) is triggered to generate radical intermediates under the excitation of visible light.[8] With regard to photochemical reactions involving EDA complexes, there are two reaction modes. On the one hand, the free radicals generated by the two substrates respectively could occur a direct radical–radical coupling reaction.[9] On the other hand, the free radical intermediates produced by the EDA complex are reacted by free radical trapping reagents.[5a,10] However, only a few protocols are able to incorporate the donor D and acceptor A motifs simultaneously onto the radical traps (Fig. 1C).[4a,10g,11]

Based on this point and our group's research on olefin functionalization,[12] we wonder whether the two free radicals produced by the EDA complex can both be utilized with alkenes as trap reagents. The studies by Narasaka,[13] Walton,[14] Leonori,[5] Yang[6j] and Glorius[6a,d,6g,i] have demonstrated oximes[15] as good nitrogen radical precursors. The β-amino sulfones display

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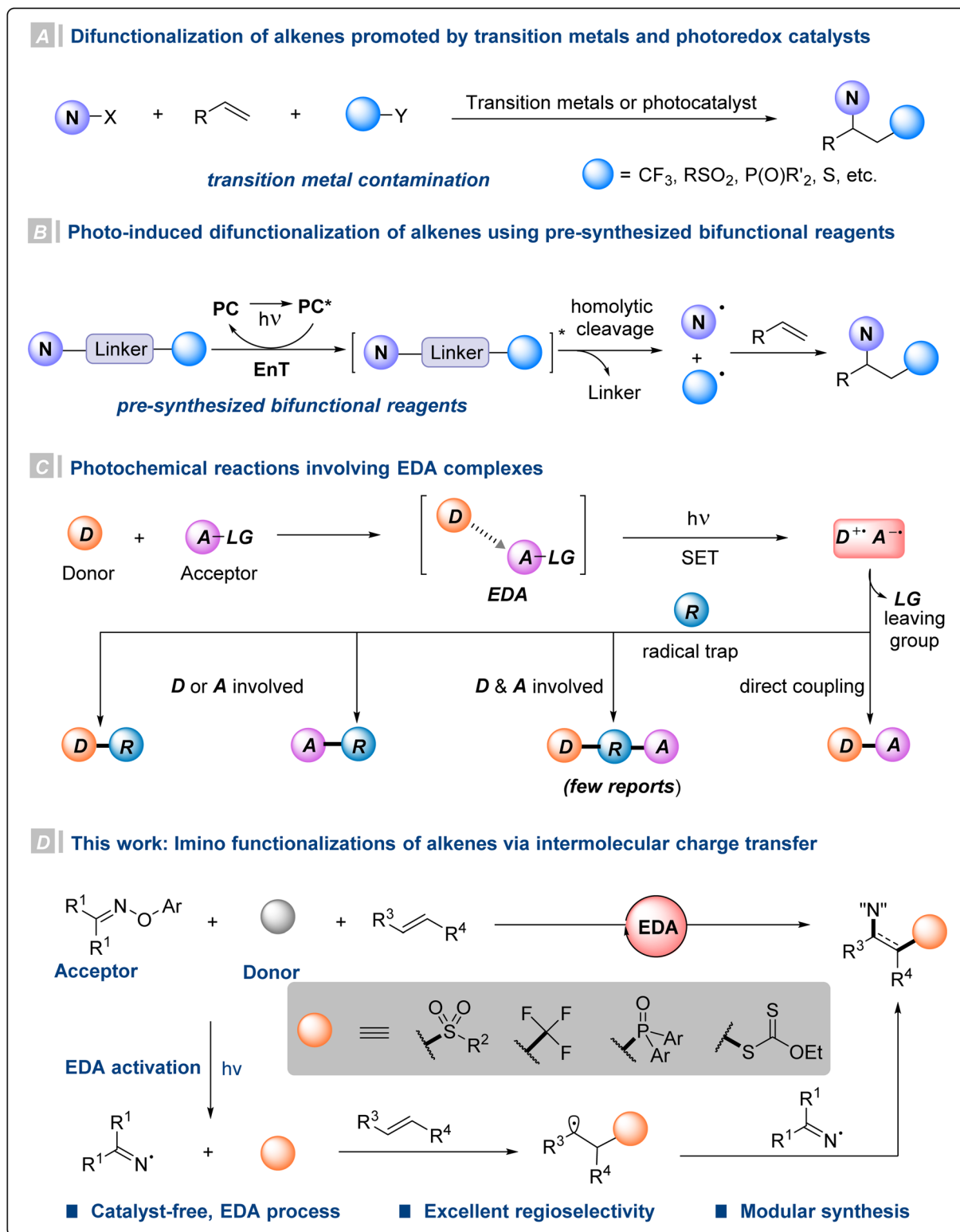
Fig. 1 Imino functionalizations of alkenes.

unique pharmaceutical activities that render them as good candidates in drug discovery research. Then we speculated that the electron-poor *O*-aryl oximes and electron-rich sulfinates could form EDA complexes and enable access to sulfonyl radicals and iminyl radicals upon exposure to visible light. Herein, we report a catalyst-free intermolecular radical sulfonylimination of alkenes *via* photochemical EDA activation. Preliminary mechanistic studies suggest that the initial radical

addition of the reactive transient sulfonyl radical with alkenes should be kinetically favored compared to that of the persistent iminyl radical. Meanwhile, this strategy can also be applied to other donors to construct structurally different β-amino compounds.

Results and discussion

To verify our hypothesis, *O*-aryl oxime **1a**, styrene **2a**, and sodium benzosulfonate **3a** were chosen as model substrates to optimize the reaction (Table 1). After careful evaluation of reaction parameters, β-imino sulfone **4a** was formed in 88% yield with **1a** as the benzophenone iminyl radical precursor under blue light irradiation (entry 1). Control experiments confirmed the essential roles of visible light and the substituents of *O*-aryl oximes (entries 2 and 3). Meanwhile, screening of light sources revealed that the wavelength (390–456 nm) had little effect on the further improvement of the reaction yield (entries 4–6). The evaluation of solvents showed that MeCN and DMSO had better performance on yields (entries 7–10 and Table S2 in the ESI†). This result inspired us to test the mixed solvents and it was found that the MeCN/DMSO solvent system in 9 : 1 v/v was the optimal choice (entries 1, 11 and 12).
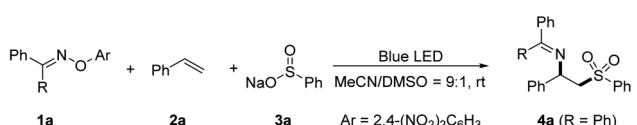
With the optimized conditions in hand, we systematically explored the substrate scope of this sulfonylimination approach (Fig. 2). A wide range of styrene derivatives all underwent the sulfonylimination reaction smoothly, delivering the corresponding β-imino sulfones with excellent regioselectivity. Styrenes bearing electron-donating or electron-withdrawing substituents at different positions of the aromatic rings were tolerated (**4a–4j**). Halogen and chloromethyl groups that are susceptible in an EDA reaction system could be well compatible in this protocol. Other terminal aryl alkenes, such as 2-

vinylnaphthalene and 2-vinylpyridine could also be applicable (**4k** and **4l**). Excitingly, 1,3-enyne could be easily accommodated, leaving the alkyne moiety untouched (**4m**). Next, a series of disubstituted and multi-substituted alkenes were investigated under our sulfonylimination conditions. 1,1-Disubstituted alkenes with different electronic properties and steric hindrance could provide β-imino sulfones with a tertiary alkyl-amine centre (**4n–4r**). The desired products (**4s–4w**) could also be obtained from the coupling of different 1,2-disubstituted and multi-substituted alkenes. Notably, high regio- and dia-stereoselectivities were obtained for unsymmetrical internal alkenes. The anti-geometries between sulfonyl and iminyl groups were confirmed by single crystal analysis of **4s** (CCDC: 2224155) and **4t** (CCDC: 2224158). Gratifyingly, two consecutive distinct quaternary carbon centers could be constructed simultaneously (**4w**). Subsequently, a series of sulfinates and *O*-aryl oximes were evaluated with 4-*tert*-butylstyrene. Moderate to excellent yields were obtained for phenylsulfinates with different substituents at the para position (**5a–5g**). This protocol was also compatible with other aromatic groups, such as naphthyl (**5h**), thienyl (**5i**), and pyridyl (**5j**). Besides, alkyl sulfi-nates also worked in this protocol with high reactivities and regioselectivities (**5k–5m**). It is worth noting that the cyclopropyl group could remain intact in the target product (**5m**). *O*-Aryl oximes derived from other diaryl ketones were also well accommodated in this sulfonylimination (**5n** and **5o**).

The synthetic utilization of this protocol in late-stage func-tionalization was further evaluated through direct sulfonylimi-nation of a range of complex alkene substrates (Fig. 3a). Natural products and drug-derived alkenes reacted smoothly to deliver the desired products in good yields (**6a–6d**). The ester groups, cyclic olefin and amides of complex olefins could be well maintained in this protocol. Ultimately, the synthesis of phar-maceuticals has been conducted to further demonstrate its synthetic utility.

Generally, *de novo* synthesis is used to synthesize drugs containing an amino-sulfone functionality. For changing key functional groups in drugs such as sulfonyl groups, it is often necessary to replace the corresponding substrate and re-synthesize from scratch. This greatly slows down the synthesis efficiency of drug molecules. Consequently, achieving modular and streamlined synthesis of drug molecules is critical for the rapid expansion of drug libraries. This sulfonylimination strategy was demonstrated efficaciously, which allowing different drugs to be synthesized in a concise manner (**10**, **15**, and **21**) with decent overall yields (35–53%, Fig. 3b). Only 3–4 steps were required to create these high functionalized mole-cules from simple starting materials. For drugs **15** and **21**, the reaction conditions for the introduction of amino and sulfone groups in traditional synthesis are relatively harsh (strong acid and strong base).[2e,i] Meanwhile, these groups can't be intro-duced at the same time. In the synthesis of these three drugs, the construction of key alkenes, the functionalization of alkenes, and subsequent simple modifications could bypass the one-to-one correspondence between drugs and starting substrates, and could efficiently synthesize drugs in a modular and gentle manner. In addition, this sulfonylimination strategy

Table 1 Optimization of reaction conditions[a]

Entry	Deviation from standard conditions	**4a**[b] (%)
1	None	88(82)[c]
2	Without light	—
3	R = Me or H	—
4	390 nm	76
5	427 nm	78
6	456 nm	65
7	MeCN	74
8	DMSO	46
9	THF	21
10	DCM	5
11	MeCN/DMSO = 2 : 1	77
12	MeCN/DCM = 9 : 1	73

[a] Conditions: **1a** (0.12 mmol), **2a** (0.10 mmol), **3a** (0.18 mmol), MeCN/DMSO (9 : 1, 1.0 mL), rt, 18 h. [b] Determined by HPLC with anthracene as the internal standard. [c] Isolated yield.
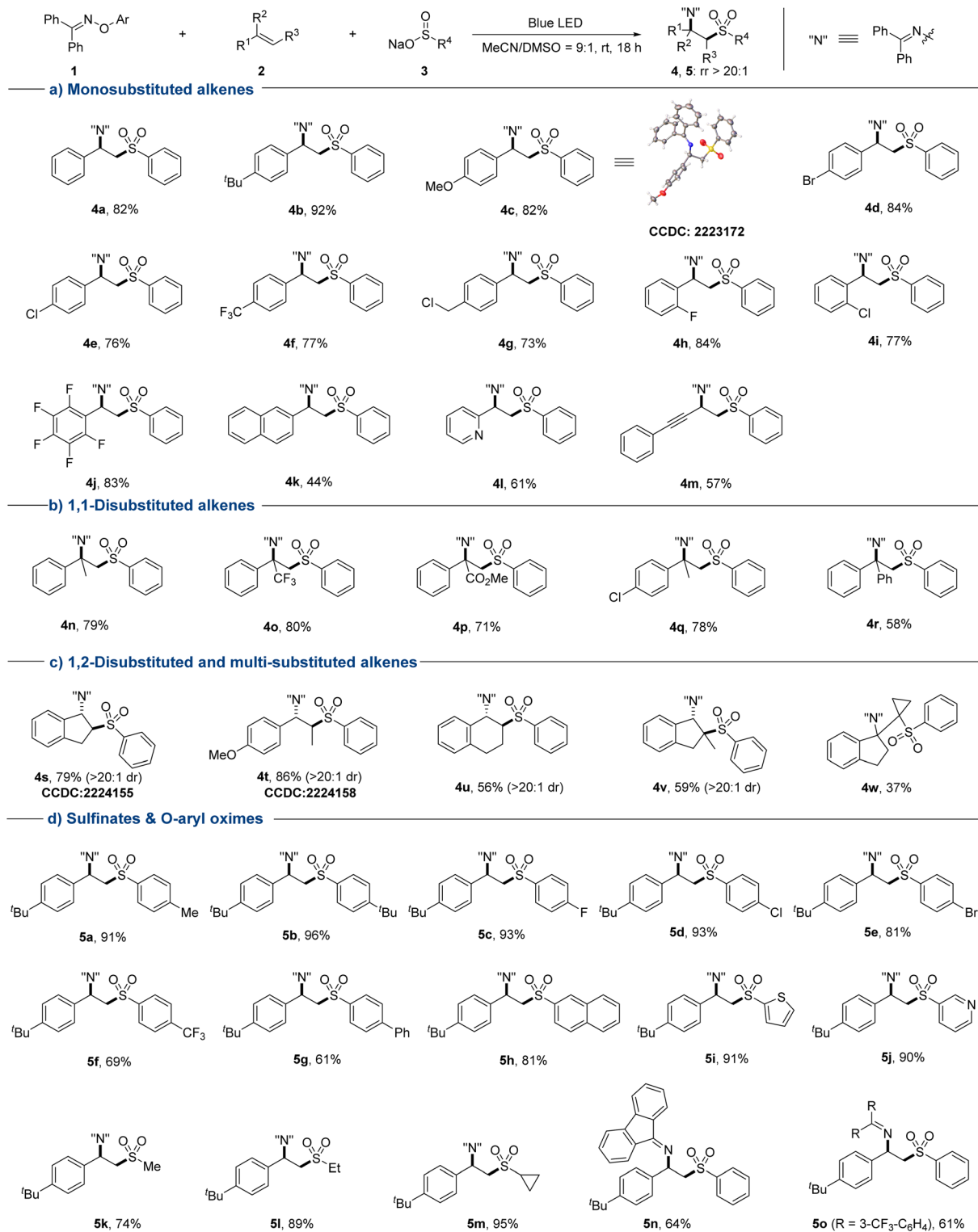
Fig. 2 Substrate scope of sulfonylimination of alkenes. Conditions: **1** (0.12 mmol), **2** (0.10 mmol), **3** (0.18 mmol), MeCN/DMSO (9 : 1, 1.0 mL), rt, 18 h. Isolated yields are given in all cases.
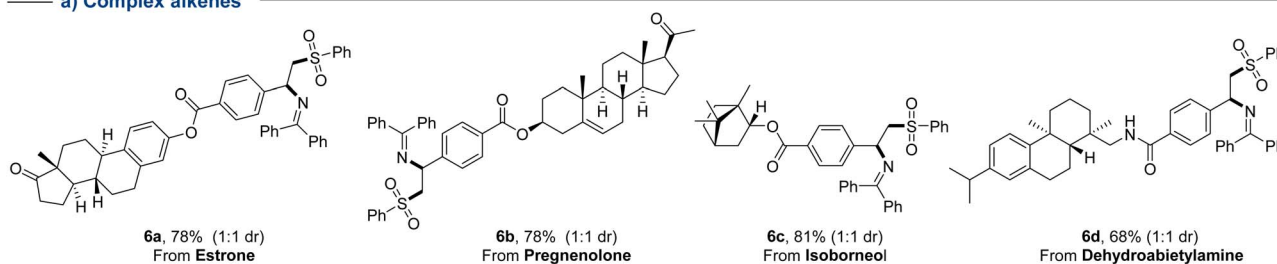
provided a way to quickly enrich the drug library, by only simply changing different oximes and sulfinates in a desired step.

To gain insight into the sulfonylimination mechanism, we performed a series of UV-vis spectroscopic measurements. An obvious increase in absorption intensity (400–500 nm) was observed by the addition of colorless **3a** into **1a**, accompanied by a certain degree of yellow color deepening. To further investigate the interaction between **1a** and **3a**, a series of

a) Complex alkenes

6a, 78% (1:1 dr)
From **Estrone**

6b, 78% (1:1 dr)
From **Pregnenolone**

6c, 81% (1:1 dr)
From **Isoborneol**

6d, 68% (1:1 dr)
From **Dehydroabietylamine**

b) Pharmaceuticals synthesis

(±)10, Matrix metalloprotease inhibitor precursor, 99%
(3 steps, 45% overall yields)

(±)15, Apremilast, 89%
(4 steps, 53% overall yields)

(±)21, Lapatinib analogue, 52%
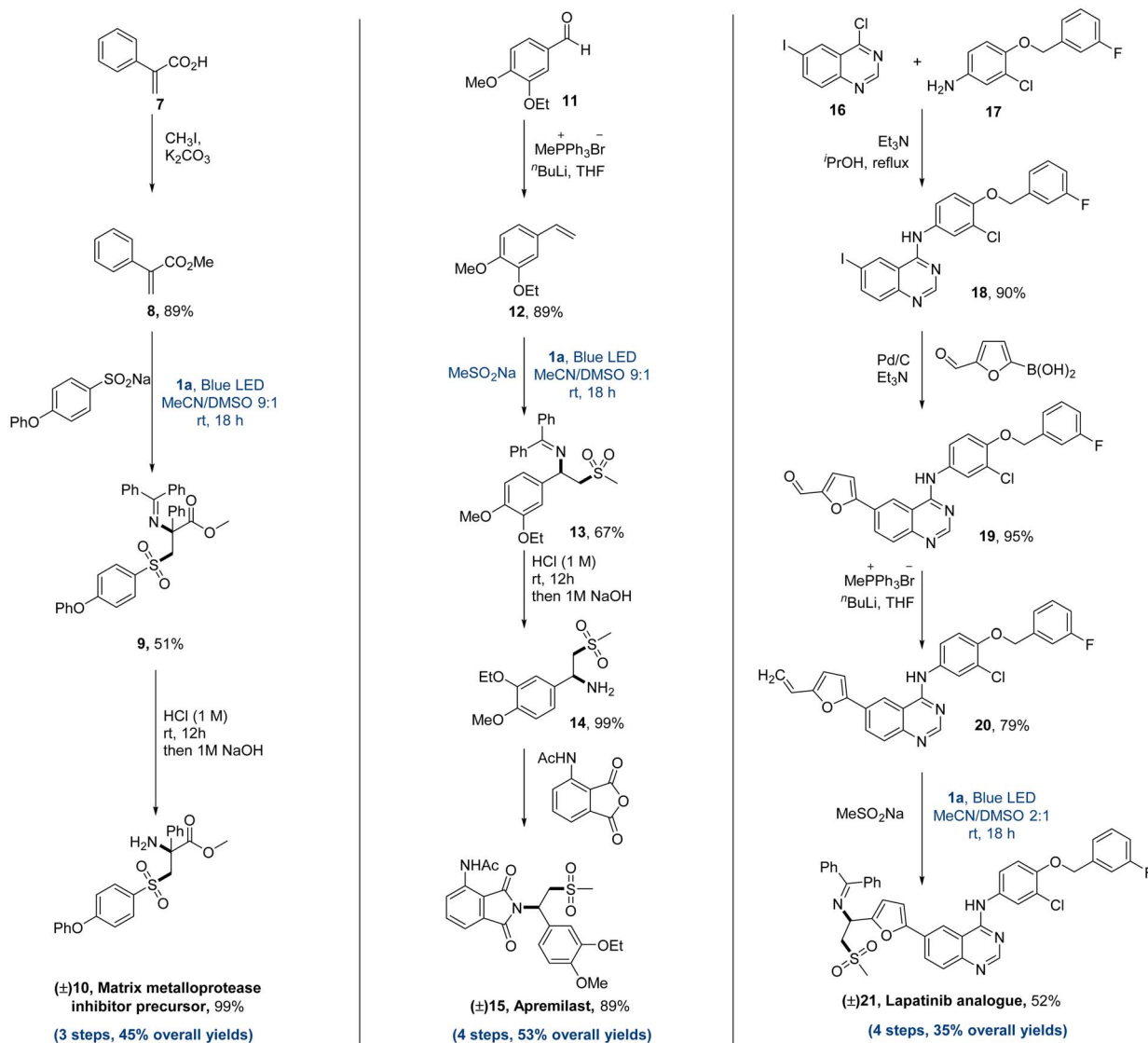(4 steps, 35% overall yields)

Fig. 3   Substrate scope of complex alkenes and synthesis of pharmaceuticals.

experiments were performed. The Job's plot measurement[16] revealed a 1:1 stoichiometry of the corresponding EDA complex (Fig. S2 in the ESI†). In addition, NMR titration further revealed the presence of weak interaction between **1a** an **3a** (Fig. S3 in the ESI†). And the association constant K_{EDA} between them was calculated to be 3.65 M^{-1} using the Benesi–

Hildebrand method[17] (Fig. S4 in the ESI†). This was proposed to result from the formation of an EDA complex (Fig. 4a). Next, free radical inhibition and capture experiments were performed. The addition of radical scavenger TEMPO (2,2,6,6-tetramethylpiperidinoxy) to the reaction mixture completely suppressed the reactivity. And in the presence of BHT,
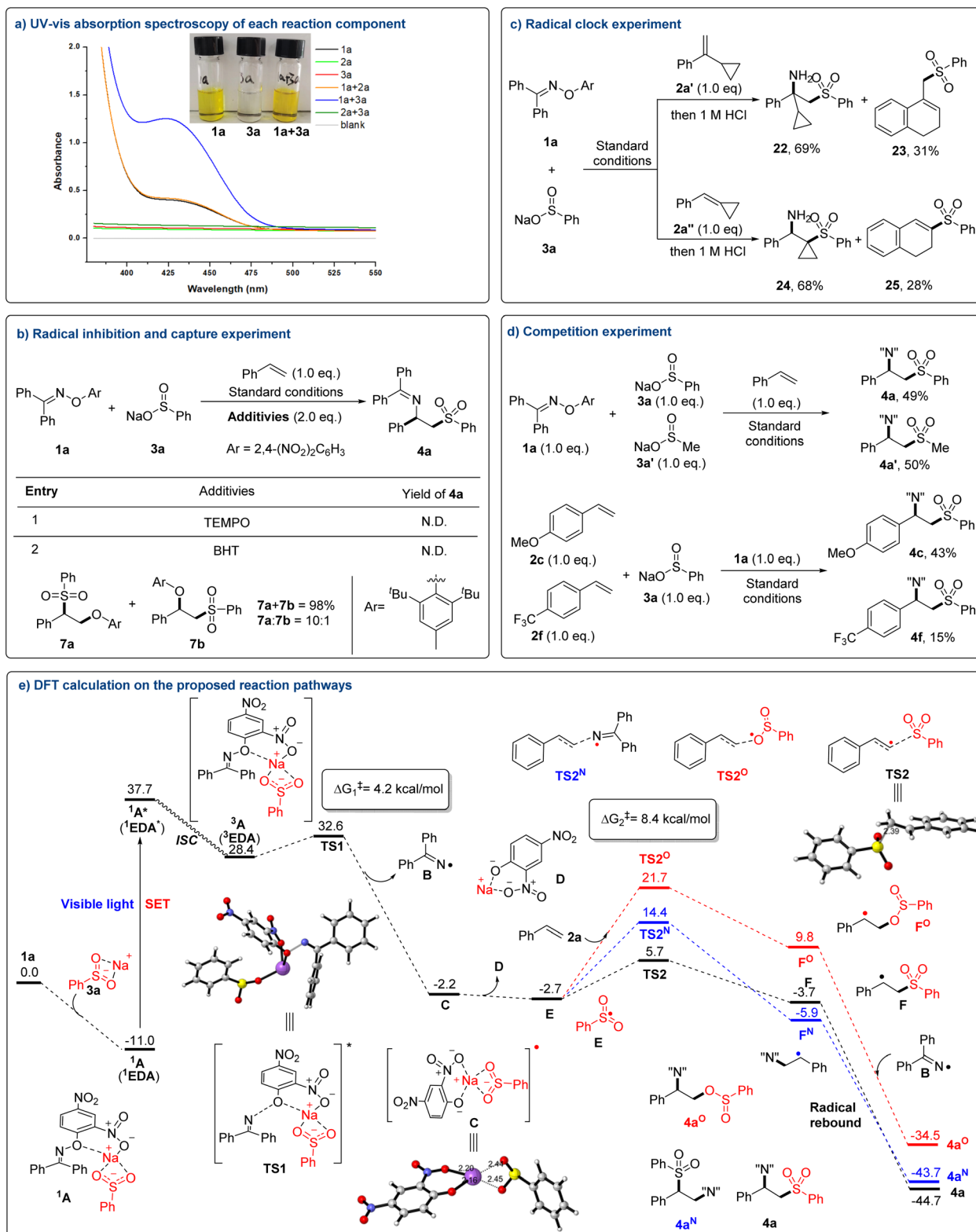
Fig. 4 Mechanistic studies and the proposed mechanism.

sulfonyletherification of olefin (**7a** : **7b** = 10 : 1) rather than the desired product **4a** was formed mainly (Fig. 4b). Radical clock experiments with different cyclopropanes led to the corresponding ring-opening products **23** and **25** (Fig. 4c). And

the products contained only sulfone functional groups, indicating that the order of addition of sulfone groups was preferential. These results hinted towards the radical nature of the reaction. Finally, different competitive experiments were

carried out separately (Fig. 4d). An evaluation of the reactivities of sulfinate **3a** and **3a′** gave the corresponding products **4a** and **4a′** with 49% and 50% yield, respectively. This indicated that the overall rate of the generation of corresponding free radicals is probably comparable between aryl and alkyl sulfinates *via* EDA activation. When different alkenes reacted simultaneously with sulfinate **3a**, more electron-rich product **4c** was more inclined to be formed over **4f**. This perhaps resulted from the stabilization of carbon radicals by increasing electron density.

Based on the aforementioned mechanistic studies and further DFT calculations, a plausible reaction mechanism is shown in Fig. 4e. First, the EDA complex **¹A** is formed *via* Coulomb interaction and π–π stacking between oxime **1a** and sulfinate **3a**. The existence of complex **¹A** is further supported by time-dependent density functional theory (TDDFT),[9c,18] which indicates that the excitation results in a single electron transfer (SET) from **3a** to **1a**. Then under the irradiation of visible light, the complex **¹A** in the ground state is excited to give the first singlet excited state **¹A***. The SET promotes the homolytic N–O
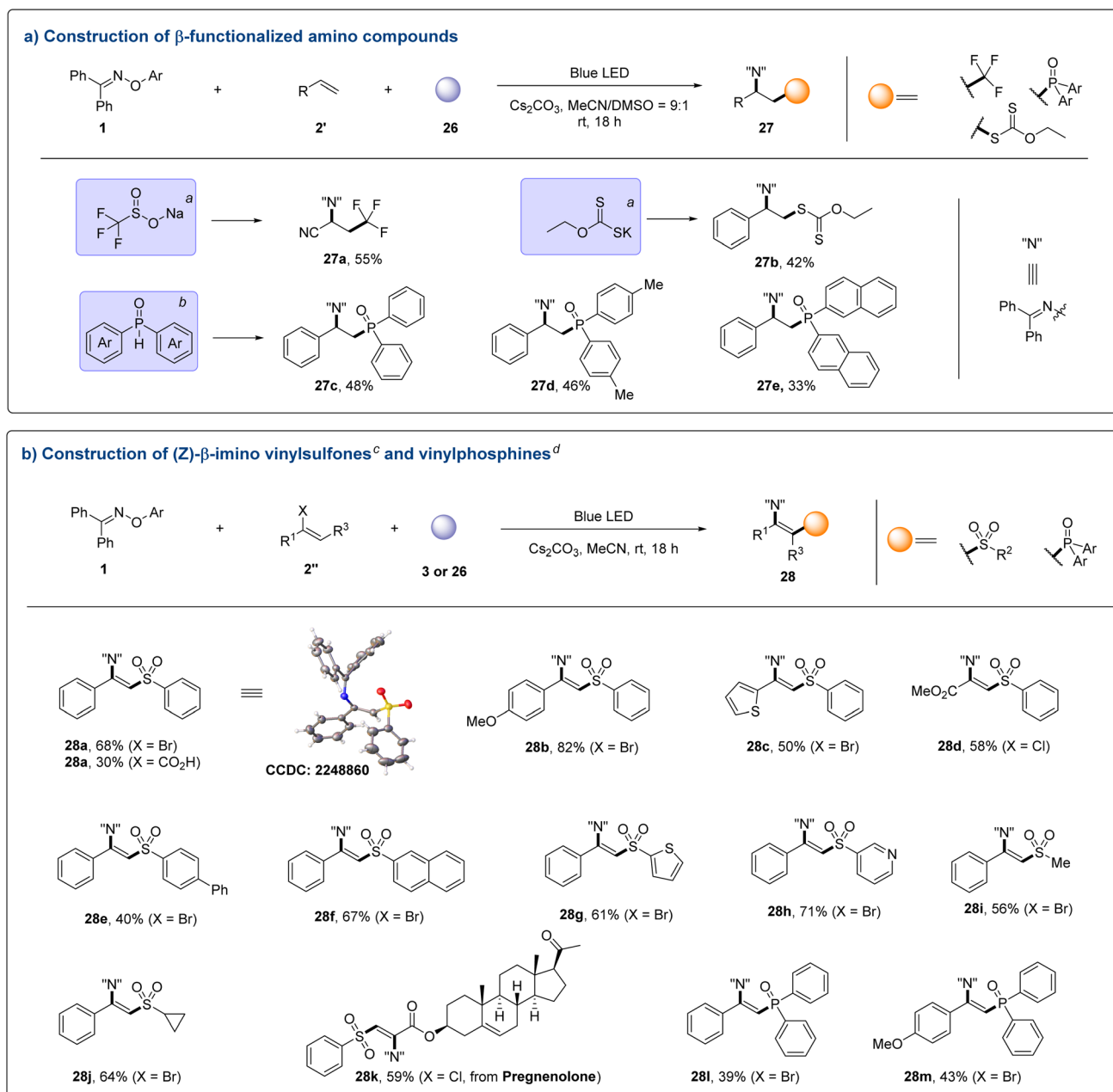

Fig. 5 Construction of β-amino compounds. Conditions: (a) **1** (0.12 mmol), **2′** (0.10 mmol), **26** (0.18 mmol), MeCN/DMSO (9 : 1,1.0 mL), rt, 18 h; (b) **1** (0.12 mmol), **2′** (0.10 mmol), **26** (0.18 mmol), Cs₂CO₃ (0.10 mmol), MeCN/DMSO (9 : 1, 1.0 mL), rt, 18 h; (c) **1** (0.12 mmol), **2′** (0.10 mmol), **3** (0.18 mmol), Cs₂CO₃ (0.10 mmol), MeCN (1.0 mL), rt, 18 h; (d) **1** (0.12 mmol), **2′** (0.10 mmol), **26** (0.18 mmol), Cs₂CO₃ (0.15 mmol), MeCN/DMSO (9 : 1, 1.0 mL), rt, 18 h. Isolated yields are given in all cases.

bond cleavage of **1a**. There are two possible mechanisms for N–O cleavage. It may occur in the first singlet excited state, directly giving persistent iminyl radical **B** (ref. 19) and ion pair intermediate **C**. Alternatively, the singlet $^1A^*$ undergoes intersystem crossing (ISC),[20] reaching the triplet ^3A, followed by N–O bond cleavage with a barrier of 4.2 kcal mol^{-1} (**TS1**). Although it is hard to determine which mechanism is actually involved, it is certain that iminyl radical **B** is generated under blue light irradiation. Subsequently, the resulting intermediate **C** undergoes intramolecular single electron transfer to deliver transient sulfonyl radical **E**. Through transition state **TS2** ($\Delta G_2^{\ddagger} = 8.4$ kcal mol^{-1}), the active radical **E** attacks alkene **2a** to produce C-centered radical **F**. In contrast, kinetically unfavorable radical additions between iminyl radical **B**, the sulphinic radical and alkene **2a** need to overcome a higher free energy barrier, 17.2 kcal mol^{-1} (via **TS2^N**) and 24.4 kcal mol^{-1} (via **TS2^O**), respectively. Finally, this C-centered radical **F** and the long-lived iminyl radical **B** participate in a radical–radical cross-coupling process to yield the desired β-imino sulfone product **4a**. Considering the large free energy difference between **TS2** and **TS2^N**, the formation of isomer **4a^N** can be kinetically suppressed, which theoretically explains the excellent regioselectivity of this transformation.

In order to test the generality of this EDA strategy, different donors were evaluated for the alkene difunctionalizations (Fig. 5a). Trifluoromethylimination of olefin could be achieved by using sodium trifluoromethanesulfonate as the donor (**27a**). As for potassium ethyl xanthate, the corresponding product could also be effectively obtained (**27b**). Organophosphorus compounds have a wide range of applications in the fields of organic synthesis, materials, coordination chemistry, medicine and agrochemicals due to their unique properties.[21] Specifically, β-aminophosphine derivatives have been widely used to build a diversity of ligands or organocatalysts.[2g,j,21f,g] Therefore, the ability to rapidly construct this building block is crucial for expanding the diversity of organophosphorus libraries. With diarylphosphine oxides as donors, the corresponding β-iminophosphines could be obtained in moderate yields (**27c–27e**).

Vinyl sulfones are excellent Michael acceptors and they have widespread applications in biological research as covalent protease inhibitors.[22] On the basis of the understanding of the reaction mechanism, this photo-induced intermolecular charge transfer strategy is further demonstrated in the construction of functionalized vinyl sulfones. After a quick reaction optimization (Tables S7–S10 in the ESI†), α-halogenated olefins bearing aromatic rings and an ester group all reacted smoothly (Fig. 5b), delivering the corresponding β-imino vinyl sulfones with acceptable yields (**28a–28d**). Interestingly, alpha carboxyl substituted olefin could be used to produce the desired product by decarboxylation (**28a**, X = CO$_2$H). For different substituted sulfinates, the reaction system could also be well compatible (**28e–28j**). Moreover, this protocol worked in the late-stage functionalization of complex alkenes through direct vinyl-sulfonylimination (**28k**). Meanwhile, the β-imino vinyl-phosphines could be obtained by using α-bromostyrene as the capture reagent (**28l** and **28m**).

Conclusions

In conclusion, a general strategy for imino functionalizations of alkenes has been developed by rationally utilizing the components involved in the formation of EDA. This strategy is photocatalyst-free, and features mild reaction conditions, excellent regioselectivity and broad functional group tolerance. With sulfinates as the donors, different substituted alkenes, even sterically encumbered tetra-substituted olefins could smoothly participate in the reaction. And it can rapidly construct structurally diverse β-imino sulfones, which provides a direct route for accessing this privileged motif. A series of experimental and computational studies suggest that an EDA complex between the electron-rich sulfinate and the electron-poor oxime was *in situ* formed, followed by the generation of a long-lived iminyl radical and a transient sulfonyl radical *via* intermolecular charge transfer. The large reactivity difference of these two radical species explains that the reaction has outstanding regional selectivity. Based on the understanding of the mechanism, different donors can also be compatible, and the corresponding β-aminovinyl compounds can also be obtained. This transition metal and catalyst free protocol provides a simple and tunable method to the corresponding β-amino compounds.

Data availability

The data that support the findings of this study are available in the ESI† of this article.

Author contributions

Q.-A. C. provided resources and supervision. Q.-A. C. and X.-X. Z. conceptualized the work. X.-X. Z. performed the investigations and the writing of original draft. X.-X. Z., H. Z., Y.-K. M., Y. L., Y.-Y. L., D.-W. J., and B.-S. W. analyzed the data. All authors contributed to the final version of the manuscript (writing, review and editing).

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

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