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ARTICLE

ortho-Ethynyl group assisted regioselective and diastereoselective [2+2] cross-photocycloaddition of alkenes

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A highly regioselective and diastereoselective [2+2] cross-photocycloaddition between the electron-poor and electron-rich/electron-neutral alkenes under visible-light irradiation was developed. In the absence of an external photocatalyst, the substrates **1** and **4** reacted with rigid cyclic alkoxyethenes to generate *cis-anti*-head-to-head heterocoupled [2+2] products in high yields with regioselectivity and good diastereoselectivity. Meanwhile, the reactions of **1** and **4** with (*Z*)- and (*E*)-1,2-diphenylethenes yielded the desired products in good yields with a high ratio of d.r.. It is important to note that no geometric isomerization of olefins was observed during the reaction. Mechanistic studies and DFT calculations suggested that **1** and **4** having *ortho*-ethynyl and cyano groups as a self-photocatalyst play a very important role in the reaction and a five-membered ring diradical intermediate (Int1) was formed via an intramolecular radical addition. The obtained regioselectivity and diastereoselectivity were confirmed by X-ray structural analysis of the representative products.

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The cycloaddition reaction is a versatile and straight forward route to form cyclic compounds.^{1,2} In general, alkenes react with each other to construct two new single bonds at both carbon atoms of the double bond. Except for the Diels–Alder reaction, the [2+2] photocycloaddition of two alkenes is the most frequently used method to access cyclobutanes under ultraviolet or visible-light irradiation conditions.^{3,4,5} The cyclobutane-skeleton is widely found in natural products with remarkable biological activities.^{6,7} It is reported that the [2+2] photo-homodimerization of chalcones and cinnamic acid derivatives is a unique strategy to form cyclobutanes, which are used as building blocks for a variety of biologically active molecules and natural products.^{8–10} To overcome the competition of facile geometric isomerization of nonrigid alkenes, the stereo-controlled syntheses of complex cyclobutanes have focused on solid-state, molten-state, or host-guest template systems under UV-light irradiation.^{11–13}

For the regioselectivity of the cross-[2+2]-photocycloaddition, the reaction has the possibility of providing two regioisomers, which are referred to as head-to-head (HH) and head-to-tail (HT) products (Fig. 1a). Generally, a head-to-tail product is generated when R is an electron-donating group (EDG), while a head-to-head product is formed when R is an electron-withdrawing group (EWG) (Fig. 1b).^{6,14–17}

To achieve diastereoselectivity of the reaction, Yoon,^{18,19,20} Wu,⁹ and Beeler²¹ explored homo- and crossed-intermolecular [2+2] photocycloadditions of acyclic enone derivatives in the presence of Ir- or Ru-complex catalysts, providing *anti*-head-to-head major products with high diastereoselectivity in solution (Fig. 1c and 1d). Most recently, Weiss and co-workers used colloidal CdSe quantum dots (QDs) as photosensitizers and self-assembly scaffolds to drive homo- and hetero-intermolecular [2+2] photo cycloadditions of 4-vinylbenzoic acid derivatives with excellent regioselectivity and diastereoselectivity in THF for the preparation of *syn*-cyclobutane products (Fig. 1e).²²

To further investigate the enantioselective [2+2] photocycloadditions, Bach, Meggers, Yoon, *et al.* demonstrated the intermolecular [2+2] photocycloadditions in an *anti*-HH manner in the presence of hydrogen-bonding templates,^{23,24} chiral secondary amines,²⁵ chiral ligands of molecular catalysts,²⁶ and Lewis acid co-catalysts.^{27–29}

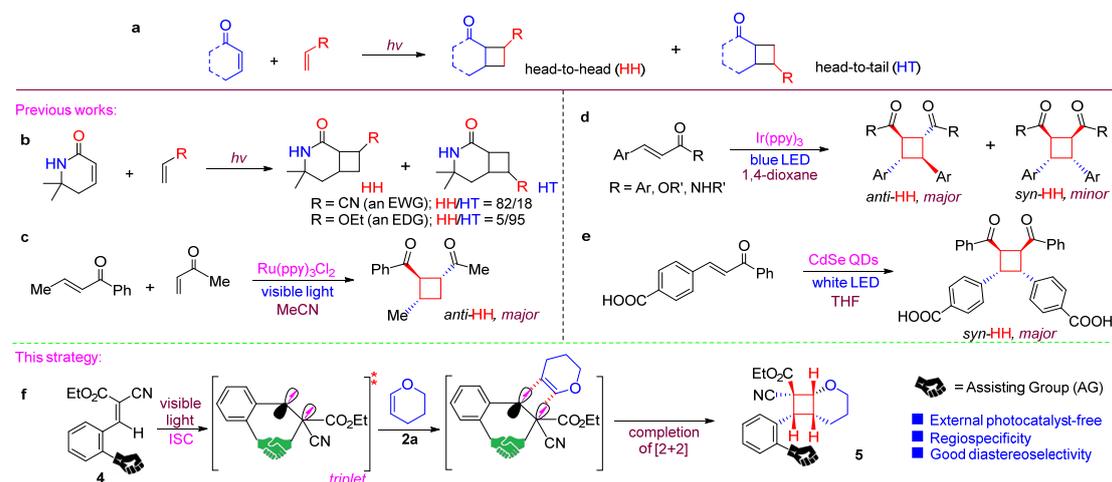


Fig. 1 Regio- and diastereoselectivity in [2+2] photocycloadditions.

In addition, the heterodimerization of two alkenes is highly dependent on the steric and electronic properties of the monomers. For the heterodimerization of two similar monomers, a photochemical approach could be complicated. Owing to the high diversity of the selectivity, construction of cyclobutane rings, especially regioselectivity and stereoselectivity, is a significant challenge in synthetic chemistry. In this strategy, molecular design of the substrate is based on the introduction of CN group as electron-acceptor for enhancing

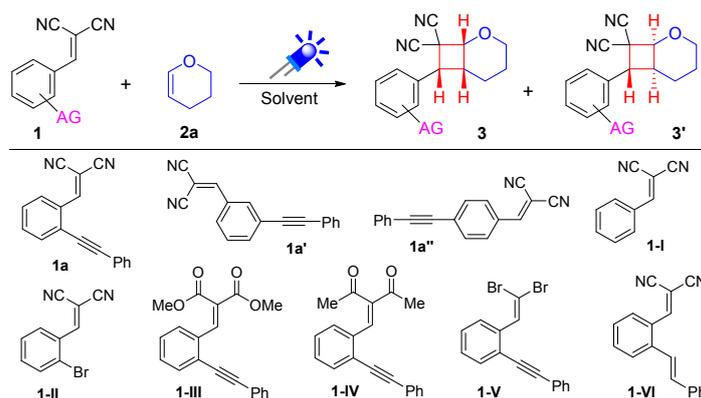
photoluminescence efficiency,^{30,31} *ortho*-ethynyl group installed on the conjugated system as visible-light photo-sensitizer for avoiding the external photocatalyst,^{32,33} and increasing the diastereoselectivity via a neighboring group participation (Fig. 1f). Here, we wish to describe the results of the intermolecular [2+2] photocycloaddition reactions between the electron-poor and electron-rich/electron-neutral alkenes induced by visible light irradiation without an additional photocatalyst to provide the corresponding products in good yields with high regioselectivity and diastereoselectivity.

Results

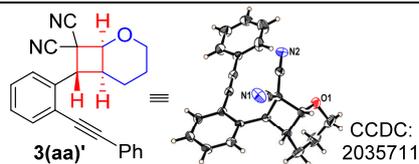
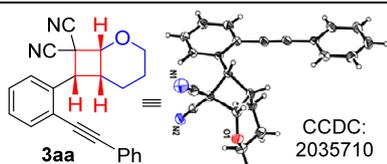
Molecular design of substrate 1. According to our strategy outlined in Fig. 1f, a representative substrate 2-(2-(phenylethynyl)benzylidene)malononitrile (**1a**) was prepared via a condensation of *ortho*-phenylethynyl benzaldehyde with malononitrile. Initially, when the reaction of **1a** with 3,4-dihydro-2*H*-pyran (**2a**, a rigid classical olefin) was carried out in the absence of additional photocatalyst (PC) in a solvent of 1,2-dichloroethane (DCE) under the irradiation of a blue light-emitting diode (LED, 410–415 nm) at room temperature for 8 h, a mixture of *cis-anti*-head-to-head (HH) heterocoupled [2+2] product (*rac*-**3aa**) and *trans-anti*-head-to-head one [*rac*-**3(aa)'**] was isolated in 36% and 5% yield, respectively (Table 1, entry 1). The structures of **3aa** and **3(aa)'** were characterized by ¹H and ¹³C nuclear magnetic resonance (NMR) spectroscopy and high-resolution mass spectrometry (HRMS), and they were unequivocally assigned by X-ray crystal diffraction analysis (ESI for detail). Subsequently, the position effect of ethynyl group in substrate **1** was investigated. As 2-(*meta*-(phenylethynyl)benzylidene)malononitrile (**1a'**) or 2-(*para*-(phenylethynyl)benzylidene)malononitrile (**1a''**) was used instead of 2-(*ortho*-(phenylethynyl)benzylidene)malononitrile (**1a**) to react with **2a** under the present reaction conditions, no any product was observed (Table 1, entries 2 and 3). Furthermore, the following substrates, such as **1-I**, **1-II**, **1-III**, **1-IV** and **1-V**, as shown in Table 1, were used to react with **2a** under the above reaction conditions, providing the unreacted starting materials in quantitative yields (Table 1, entries 4–8). Obviously, the electron-acceptor CN groups and an *ortho*-ethynyl moiety as assisting group, which are conjugated to a phenyl ring are essential in the reaction. It should be noted that **1-VI** exhibits no reactivity in the [2+2] cross-cycloaddition with **2a**, owing to the poor assistance of neighboring group (Table 1, entry 9).

Optimization of the reaction conditions: With **1a** in hand, a model reaction of **1a** with **2a** was chosen to optimize the reaction conditions. As shown in Table 1, a survey of LED sources with different wavelengths demonstrated that LED with 410–415 nm irradiation was the best choice without an additional photocatalyst, and only trace amounts of the products were detected when the reaction was irradiated by LED with wavelengths less than 254 nm or greater than 500 nm (Table 1, entries 10–15). A variety of solvents, such as acetone, DCE, dichloromethane (DCM), MeCN and dimethyl sulfoxide (DMSO) were examined, and DCE showed the highest reactivity (Table 1, entries 16–19 compared to entry 1). A number of external PCs, including *fac*-Ir(ppy)₃, Ru(bpy)₃Cl₂, Mes-Acr⁺ClO₄⁻, TPPT (2,4,6-triphenylpyrylium tetrafluoroborate), rose bengal and eosin Y, were used in the model reaction, and less yields of the products were obtained (ESI, Table S1), indicating that **1a** is an efficient self-photocatalyst in the reaction. To increase the target product yield, a series of molar ratios of **2a/1a** were subsequently investigated. The total yields of **3aa/3(aa)'** were increased from 41% in a 36/5 ratio to 63% in a 55/8 ratio as the molar ratio of **2a/1a** was raised from 2/1 to 10/1 (Table 1, entries 20–23). Encouragingly, when the model reaction was carried out with an excess amount of **2a** (1.0 mL, 55 equiv.) as well as solvent under neat conditions, **3aa** and **3(aa)'** were obtained in 79% and 11% yield, respectively (Table 1, entry 24). Furthermore, the optimal reaction time was found to be 8 h (ESI, Table S1).

Table 1 Optimization of the reaction conditions.



Entry	1	2a (equiv.)	Light source (nm)	Solvent	Yield (3a/3a', %) ^a
1	1a	2.0	410–415	DCE	36/5
2	1a'	2.0	410–415	DCE	0/0
3	1a''	2.0	410–415	DCE	0/0
4	1-I	2.0	410–415	DCE	0/0
5	1-II	2.0	410–415	DCE	0/0
6	1-III	2.0	410–415	DCE	0/0
7	1-IV	2.0	410–415	DCE	0/0
8	1-V	2.0	410–415	DCE	0/0
9	1-VI	2.0	410–415	DCE	0/0
10	1a	2.0	254	DCE	Trace
11	1a	2.0	365–370	DCE	22/3
12	1a	2.0	380–385	DCE	29/4
13	1a	2.0	420–425	DCE	35/5
14	1a	2.0	450–455	DCE	29/4
15	1a	2.0	530–535	DCE	Trace
16	1a	2.0	410–415	Acetone	29/4
17	1a	2.0	410–415	DCM	36/5
18	1a	2.0	410–415	MeCN	27/4
19	1a	2.0	410–415	DMSO	22/3
20	1a	4.0	410–415	DCE	36/5
21	1a	6.0	410–415	DCE	42/6
22	1a	8.0	410–415	DCE	48/7
23	1a	10.0	410–415	DCE	57/8
24	1a	55 (1.0 mL)	410–415	–	79/11



Reaction conditions: **1** (0.20 mmol), **2a** (0.40 mmol), DCE (1.0 mL), room temperature, air, under LED irradiation for 8 h. ^aIsolated yield.

Scope of substrate 1. With the optimized reaction conditions in hand, the scope of this transformation was investigated. First, 2-(2-(arylethynyl)benzylidene)malononitriles (**1**), derived from *ortho*-arylethynyl

arylaldehydes and malononitrile, reacted with 3,4-dihydro-2H-pyran (**2a**) smoothly to generate the corresponding products **3aa–3ua** in moderate to high yields with high stereoselectivity, as shown in Fig. 2. 2-(2-(Arylethynyl)benzylidene)malononitriles (**1**), having electron-donating groups ($R^2 = \text{MeO}$, Me, $t\text{Bu}$) or electron-withdrawing groups ($R^2 = \text{Ph}$, F, Cl, Br, CF_3 , CN) at the *para*-position of the benzene rings provided the desired products (**3ba–3ja**) with 55%–78% yields along with the formation of isomers [**3(aa)'**–**3(ja)'**] in ratios of 7/1 to 12/1. When the substituent ($R^2 = \text{MeO}$, Me) was placed at the meta-position of the phenyl rings, the reaction produced a mixture of stereoisomers [69% yield of **3ka** with 7/1 ratio of **3ka/3(ka)'**; 71% yield of **3la** with 8/1 ratio of **3la/3(la)'**]. It should be noted that a slightly lower reactivity of the *ortho*-position substituent ($R^2 = \text{MeO}$) on substrate **1m** was observed (61% of **3ma**). Subsequently, the scope of the substituted group (R^1) on substrates **1** was also examined (Fig. 2). The electron-rich group ($R^1 = \text{MeO}$, Me, OCH_2O) or electron-poor group ($R^1 = \text{F}$, Cl) on the aromatic rings delivered the corresponding major products (**3na–3ua**) in 65%–77% yields with 6/1 to 9/1 of d.r., neglecting the electron effect and steric hindrance effect. In addition, substrates (**1v–1x**) containing naphthyl or thiophenyl group reacted with **2a** to produce the target products **3va–3xa** in 59%–62% yields with high diastereoselectivity (7/1 to 9/1 ratios of d.r.). Remarkably, substrates **1** derived from *ortho*-(trimethylsilyl)ethynyl, *ortho*-(cyclopropyl)ethynyl, *ortho*-(*n*-butyl)ethynyl and *ortho*-(*n*-pentyl)ethynylbenzaldehyde (**1y–1z**) were also well tolerated in this transformation, and the desired products (**3ya–3z'a**) were obtained in 50%–81% yields with good diastereoselectivity. Furthermore, this intermolecular [2+2] cycloaddition of **1a** with **2a** was scaled up to 2.0 mmol for practical applications, generating **3aa** with a 71% yield.

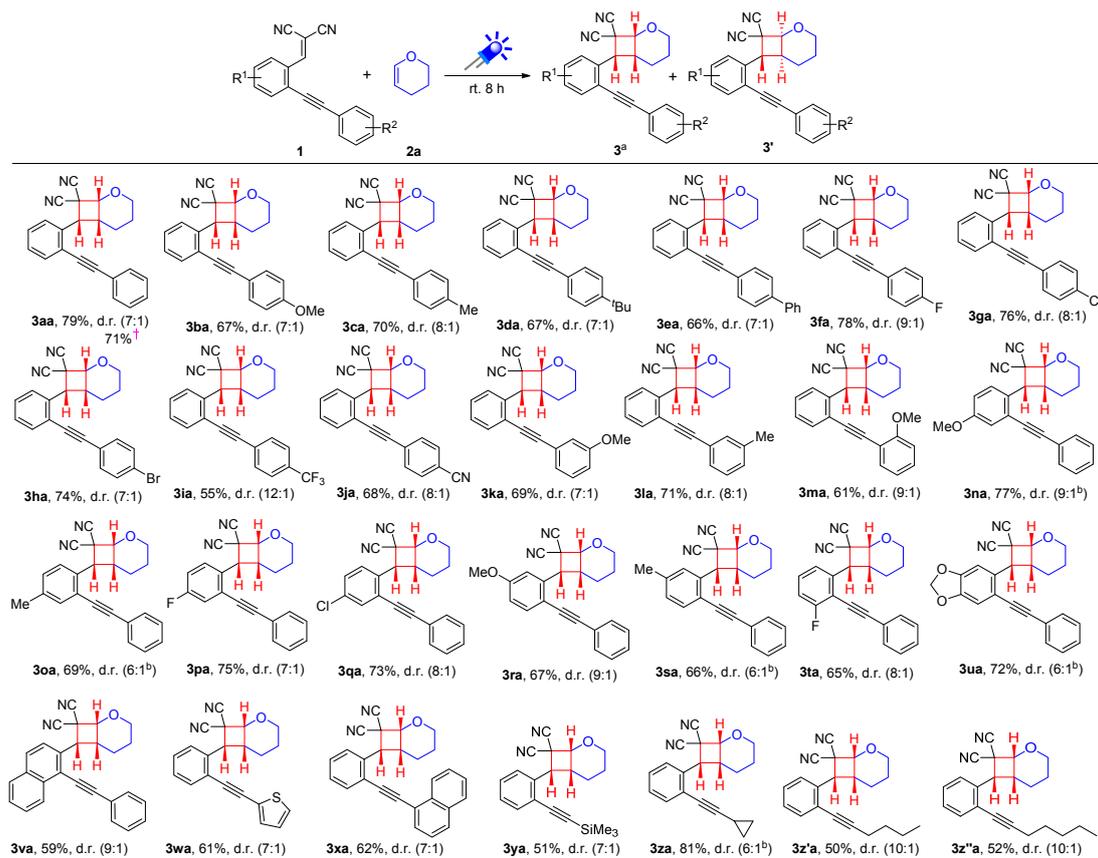


Fig. 2 Scope of substrate **1** [Reaction conditions: **1** (0.20 mmol), **2a** (1.0 mL), room temperature, air, under LED (410–415 nm) irradiation for 8 h. ^aIsolated yield; d.r. (**3/3'**) determined by ¹H NMR analysis of the unpurified reaction mixture. ^bNMR of **3'** are available in ESI; [†]2.0 mmol scale].

Scope of substrate 2. The scope of the electron-rich alkenes (**2**) was subsequently explored for their intermolecular [2+2] cycloaddition reactions with **1a** under the standard conditions. As shown in Fig. 3, a variety

of non-rigid classical alkoxyethenes including ethoxyethylene (**2b**), propoxyethylene (**2c**), *iso*-butoxyethylene (**2d**), *tert*-butoxyethylene (**2e**) and cyclohexyloxyethylene (**2f**) underwent cycloaddition with **1a** smoothly to afford the desired products (**3ab–3af**) in 55%–68% yields with high regioselectivity and diastereoselectivity. The structure of **3ab** was confirmed by X-ray crystal diffraction analysis. Meanwhile, the reactions of 2,3-dihydrofuran (**2g**) and 2-methoxy-3,4-dihydro-2*H*-pyran (**2h**) with **1a** also yielded the products **3ag** with 57% yield and 4/1 ratio of d.r. and **3ah** with 77% yield and 8/1 ratio of d.r., respectively. It should be noted that (*E*)-1-ethoxyprop-1-ene (**2i**) reacted with **1a** and **1h** to produce the target product **3ai** with 61% yield and 4/1 ratio of d.r. and **3hi** with 64% yield and 5/1 ratio of d.r., respectively.

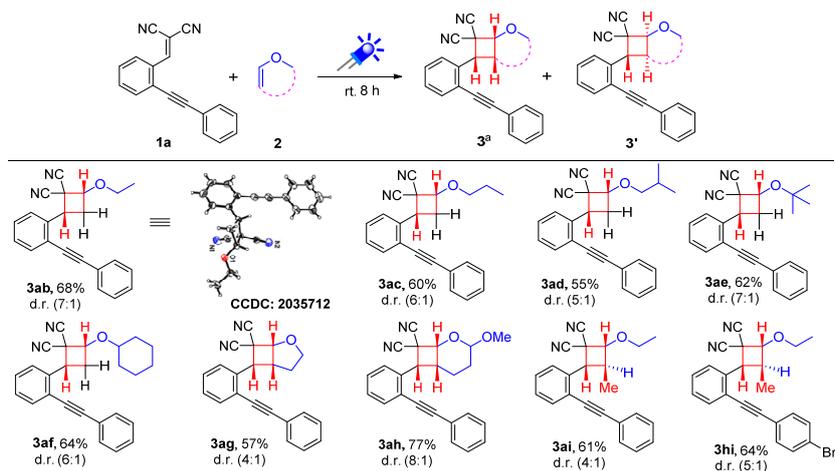


Fig. 3 Scope of substrate **2** [Reaction conditions: **1a** (0.20 mmol), **2** (1.0 mL), room temperature, air, under LED (410–415 nm) irradiation for 8 h. ^aIsolated yield; d.r. (**3/3'**) determined by ¹H NMR analysis of the unpurified reaction mixture].

Scope of substrate 4. Next, the scope of substrate (**4**), derived from *ortho*-(arylethynyl)arylaldehydes with ethyl 2-cyanoacetate, *tert*-butyl 2-cyanoacetate, and benzyl 2-cyanoacetate was investigated, and the results are summarized in Fig. 4. A variety of substrates **4**, including **4a–4h** reacted with 3,4-dihydro-2*H*-pyran (**2a**) smoothly to provide the corresponding major products **5aa–5ha**, respectively, in 60%–70% yields with moderate diastereoselectivity (2/1 to 5/1 of d.r.). It is important to note that the stereochemistry of the product *rac*-**5aa** in majority is a *cis-anti*-head-to-head and *rac*-**5(aa)'** in minority is a *trans-syn*-head-to-head. The

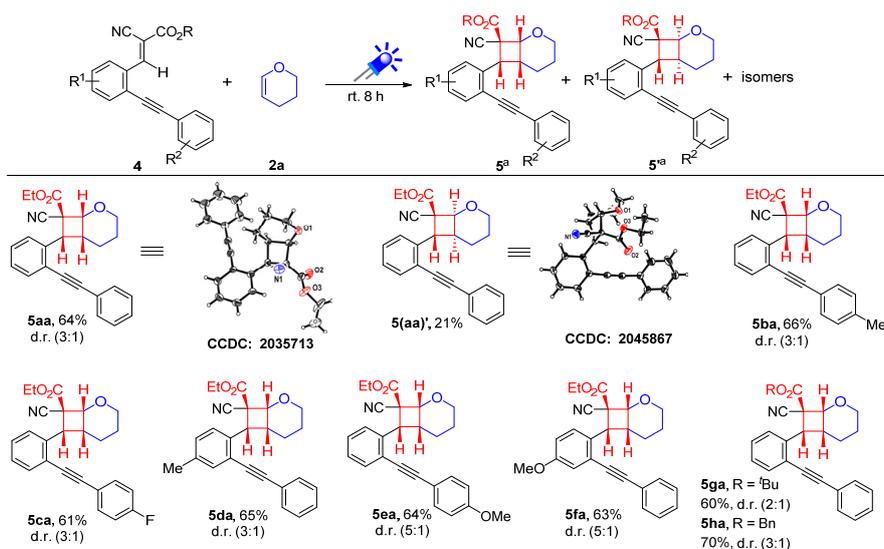


Fig. 4 Scope of substrate **4** [Reaction conditions: **4** (0.20 mmol), **2a** (1.0 mL), room temperature, air, under LED (410–415 nm) irradiation for 8 h. ^aIsolated yield; d.r. (**5/5'**) determined by ¹H NMR analysis of the unpurified reaction mixture].

structures of **5aa** and **5(aa)'** were confirmed by X-ray crystal diffraction analysis. The influence of the substituents ($R^2 = \text{Me, F, MeO}$) on the aromatic alkyne units, and the substituents ($R^1 = \text{Me, MeO}$) from the arylaldehydes on the reactions indicated that they are well tolerated, neglecting electronic effect and steric hindrance.

Scope of substrate 6. To further extend the scope of this [2+2] cycloaddition, the reactivity of electron-neutral alkenes containing styrene skeletons was explored, as described in Fig. 5. The reaction of styrene (**6a**) with **1a** generated the corresponding [2+2] product (*rac*-**7aa**, 50% yield, 7/1 of d.r.) in a (*cis*)-head-to-tail manner, which was indicated by X-ray crystal diffraction analysis. Other substituted styrenes, such as 1-phenyl styrene (**6b**), (*Z*)-1,2-diphenylethene (**6c**) and (*E*)-1,2-diphenylethene (**6d**) reacted with **1a** smoothly to produce the anticipated **7ab–7ad** as major products in 45%–69% yields and 7/1 to 8/1 ratios of d.r.. Furthermore, (*Z*)-1,2-diphenylethene (**6c**), (*E*)-1,2-diphenylethene (**6d**) and (*E*)-2-methyl styrene (**6e**) reacted with **4a** to yield the corresponding products **7bc** (77% yield, 7/1 ratio of d.r.), **7bd** (81% yield, 7/1 ratio of d.r.) and **7be** (75% yield, 8/1 ratio of d.r.), respectively. Importantly, the high regioselectivity and diastereoselectivity of the intermolecular [2+2] cycloaddition was confirmed by X-ray crystal structure analysis of the products **7bc**, **7bd** and **7be**, respectively.

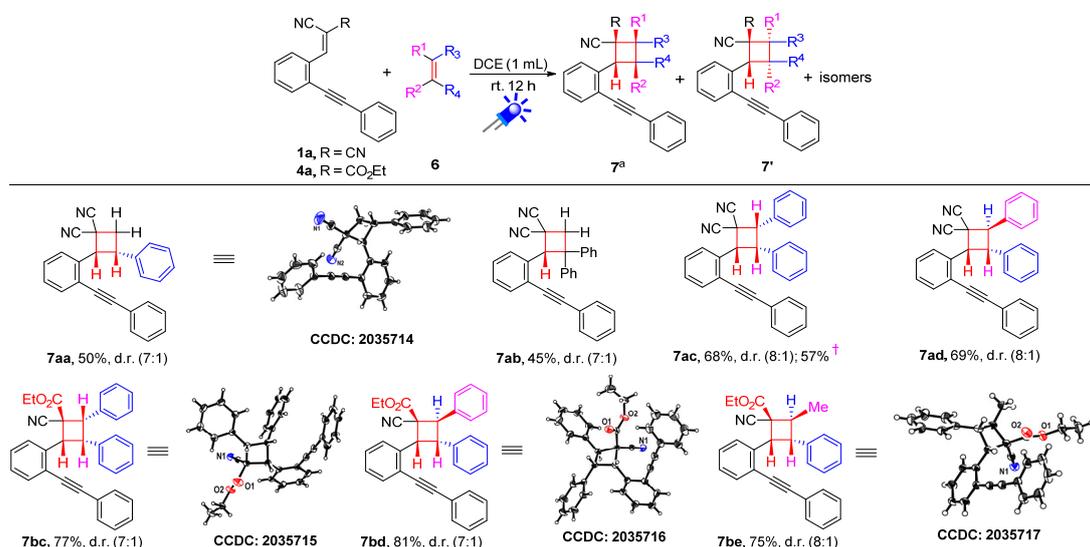


Fig. 5 Scope of substrate **6** [Reaction conditions: **6** (0.40 mmol), **1a** or **4a** (0.20 mmol), DCE (1.0 mL), room temperature, air, under LED (410–415 nm) irradiation for 12 h. [†]Isolated yield; d.r. (**7/7'**) determined by ¹H NMR analysis of the unpurified reaction mixture. [‡]2.0 mmol scale].

Homo-[2+2] photocycloaddition. To demonstrate the possibility of homo-[2+2] cycloaddition, the reaction of **1a** or **1i**, **4a** or **4d** was carried out in DCE in the absence of an electron-rich or an electron-neutral alkene partner under the irradiation of blue LED (410–415 nm) at room temperature for 12 h, generating a *cis*-head-to-tail product (**8aa** or **8ii**) or a *trans*-head-to-tail product (**9aa** or **9dd**) in 18%, 21%, 15% or 18% yield, respectively (Fig. 6). The structures of **8aa** and **9aa** were confirmed by X-ray crystal diffraction analysis. When the reaction of **2a** was performed in DCE without an electron-poor alkene and an external photocatalyst under the standard reaction condition, no homo-[2+2] cycloaddition product was detected.

Further transformation of the product. For further transformation of the alkynyl unit in this intermolecular [2+2] cycloaddition product, its synthetic application was demonstrated by follow-up chemistry with **7ac** as the starting material (Fig. 7). Encouragingly, an ICl/AgNO₃ co-catalyzed radical oxidation of **7ac** into 1,2-diketone (**10**) was achieved with 64% yield (Fig. 7a).³⁴ Furthermore, a corresponding benzoin *bis*-ether product (**11**) was obtained with 57% yield in methanol under visible light irradiation (Fig. 7b).³⁵

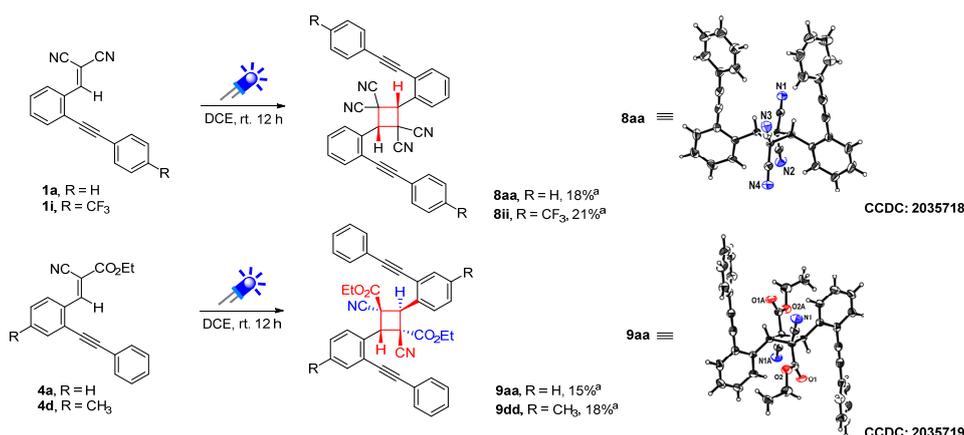


Fig. 6 Homo-[2+2] of substrate **1** or **4** [Reaction conditions: **1a/i** or **4a/d** (0.20 mmol), DCE (1.0 mL), room temperature, air, under LED (410–415 nm) irradiation for 12 h. ^aIsolated yield].

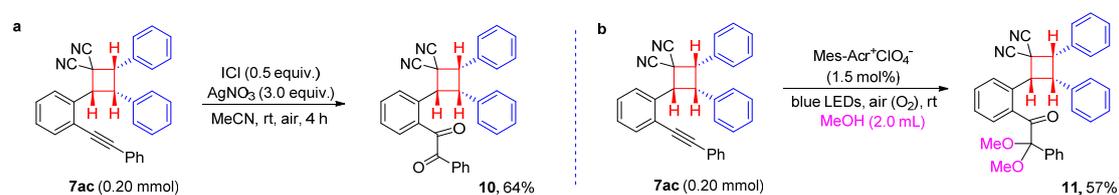


Fig. 7 Further transformation of **7ac**.

Furthermore, the ultraviolet-visible spectra of **1a** indicated that they had stronger absorption in the range of 410–415 nm and acted as photo-sensitizers, avoiding the external photocatalyst (ESI, Supplementary Figure 143). These results implied that the *ortho*-phenylethynyl group introduced into the substrates plays an important role in the reaction.

In this reaction, we speculated that the intermolecular [2+2] photocycloaddition proceeded through an energy transfer rather than an electron transfer. It was expected that isomerization would compete with crossed-[2+2] cycloaddition because triplet acyclic olefins would lead to isomerization.³⁶ Indeed, under our irradiation conditions, little geometric isomerization of **1** and **4**, as well as **2** and **6** was observed, which was confirmed by X-ray crystal structures of **5aa**, (**5aa**)', **7bc** and **7bd**.

In theory, a crossed [2+2] cycloaddition of two different unsymmetrical chain olefins can yield sixteen head-to-head and sixteen head-to-tail stereoisomers (ESI, Supplementary Scheme 1). As outlined above, the major products in all cases were found to be the (\pm)-(*trans,trans*)-*anti*-head-to-head (**I**) isomer derived from an electron-poor and an electron-rich olefin. Importantly, only head-to-head isomers were found and no head-to-tail isomers were observed, illustrating the regioselectivity of the reaction. Moreover, among the isolated head-to-head isomers, **I** was obtained in the majority and (\pm)-(*cis,trans*)-*syn*-head-to-head (**I'**) was isolated in the minority with good diastereoselectivity, demonstrating almost no geometric isomerization of the olefins during the [2+2]-cycloaddition.

Computational studies. To understand the high regioselectivity and diastereoselectivity of the crossed-[2+2]-photocycloaddition between the electron-poor and electron-rich alkenes, the density functional theory (DFT) calculations at the M06-D3/def2-TZVPP level³⁷ were performed using 2-(2-(phenylethynyl)benzylidene)malonitrile (**1a**) and 3,4-dihydro-2*H*-pyran (**2a**) as a model. The energy diagram for the suggested mechanism is display in Fig. 8. After photo-excitation of **1a**, an intersystem crossing to triplet (^T**1a**) takes place. The calculations show that ^T**1a** undergoes a ring closure process between the β -carbon of alkene moiety and the α -carbon of *ortho*-alkyne unit to form a five-membered ring diradical intermediate ^T**Int1**, which is exergonic by 5.1 kcal/mol. From ^T**Int1**, four different pathways leading to four different regio- and stereoisomers are considered, namely *cis*-HH, *trans*-HH, *cis*-HT, and *trans*-HT (Fig. 8). The optimized transition states for the first C–C bond formation is shown in the Supporting Information (ESI, Supplementary Figures 146–149). As shown in Fig. 8, this process turns out to be the rate-limiting step for the [2+2] cycloaddition. Importantly, the *cis*-HH pathway is the most favorable one, and the corresponding transition state ^T**TS1**_{*cis*-HH} was calculated to be 20.4 kcal/mol relative to ^T**Int1**, and the formation of ^T**Int2**_{*cis*-HH} is endergonic by 7.6 kcal/mol. Direct C–C bond formation between ^T**1a** and **2a** has a barrier of 21.9 kcal/mol, which is 1.5 kcal/mol higher than from ^T**Int1**. In addition, the *trans*-HH pathway (^T**TS1**_{*trans*-HH}) has a 1.3 kcal/mol higher barrier than the *cis*-HH pathway (^T**TS1**_{*cis*-HH}).

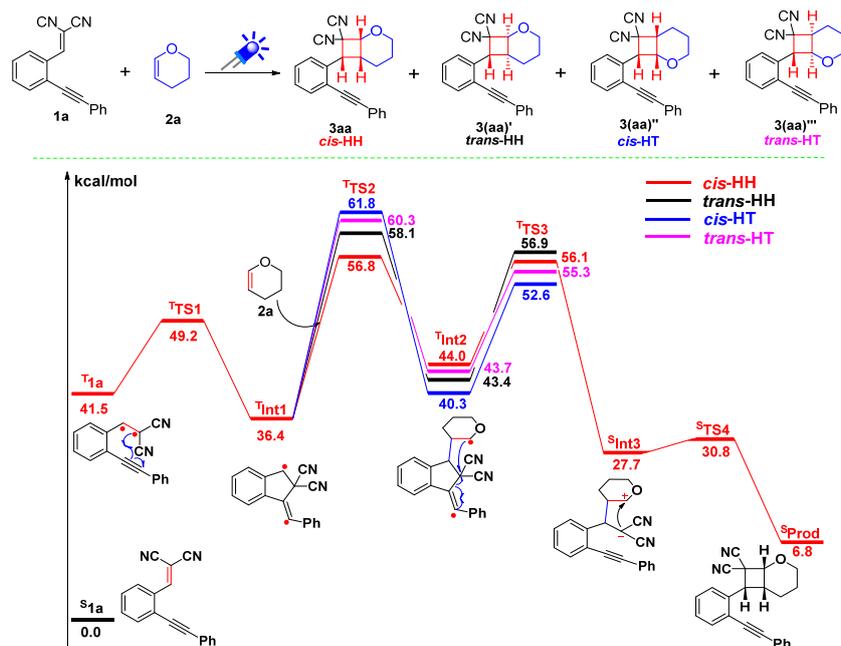


Fig. 8 Gibbs energy (in kcal/mol) diagram for the crossed-[2+2]-photocycloaddition between **1a** and **2a**. The left superscript **S** and **T** indicate the singlet and triplet state, respectively.

Furthermore, the alternative HT pathways have even higher barrier. These results are consistent with the experimental fact that only HH products were observed and the *ortho*-ethynyl moiety is crucial for this [2+2] reaction. The calculated barrier difference of 1.3 kcal/mol gives a product ratio of about 9:1 for **3aa** (*cis*-HH product): **3(aa)'** (*trans*-HH product), which is in excellent agreement with the experimental product ratio of 7.2:1. From T_{Int2} , the opening of the five-membered ring by C–C bond cleavage proceeds via T_{TS3} , which is coupled with a spin crossing from triplet to singlet downhill from T_{TS3} . This results in the formation of a zwitterionic intermediate **Int3**, which undergoes very facile C–C bond formation to form the final product **3aa**.

Proposed mechanism. Based on the control experiments and DFT calculations, as well as previous reports,^{3-6,9,38,39} a plausible mechanism is proposed in Fig. 9. First, **1a** is excited by the blue LED irradiation (410–415 nm) to generate the excited singlet species **1a***, which decays to its triplet exciplex **1a**** through an intersystem crossing (ISC) process with formed another **1a*** along with the formation of **1a** via an energy transfer (ET) step. The obtained **1a**** undergoes an intramolecular radical addition to afford a five-membered ring diradical intermediate **Int1**, which was trapped by 2,6-di-*tert*-butyl-4-methylphenol (BHT)⁴⁰ using **4a** as substrate instead of **1a** and the corresponding product was confirmed by X-ray crystal analysis (ESI, Supplementary Figure 144). The intermediate **Int1** reacts with **2a** to generate an intermediate **Int2**. Then, a ring opening of **Int2** through a carbon-carbon bond cleavage provides a zwitterionic intermediate **Int3** with the stabilization of carbanion with two CN groups, which was captured by ethyl diazoacetate/Fe(TPP)Cl as carbanion capturing agent,⁴¹ and the captured product was detected by high-resolution mass spectrum (HRMS) analysis (ESI, Supplementary Figure 145). Finally, **Int3** undergoes an intramolecular nucleophilic addition to form the desired cyclobutane derivative (**3aa**) through a facile carbon-carbon formation.

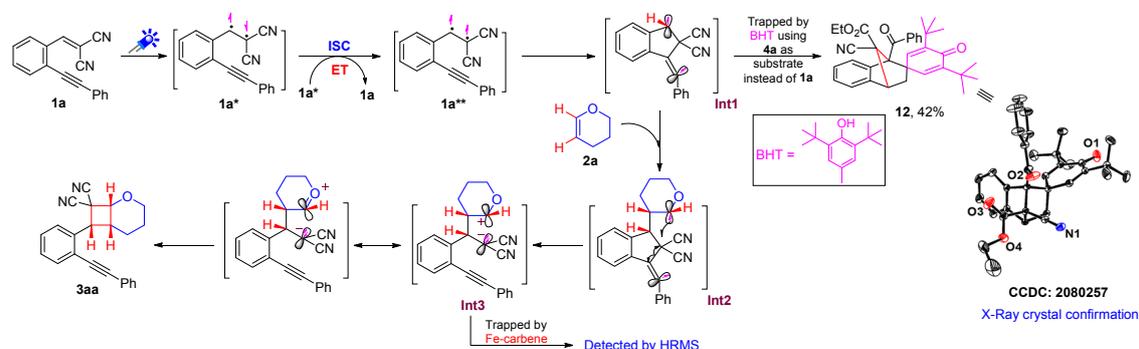


Fig. 9 Proposed mechanism for the formation of **3aa**.

In summary, we have developed a highly regioselective and diastereoselective intermolecular [2+2] photocycloaddition reaction between the electron-poor and electron-rich/electron-neutral alkenes under visible-light irradiation without an external photocatalyst. The reaction provides an efficient method for the synthesis of highly energy-rich and strained cyclobutanes. The electron-poor alkenes having *ortho*-ethynyl and cyano groups (**1** and **4**) undergo cycloaddition with the electron-rich and electron-neutral alkenes, including rigid cyclic and nonrigid acyclic alkoxyethenes (**2**), and styrenes (**6**) to generate the corresponding heterocoupled [2+2] products in high yields with regioselectivity and good diastereoselectivity. It should be noted that no geometric isomerization of the olefins is observed during the reaction. Mechanistic studies and DFT calculations suggest that **1** and **4** with *ortho*-ethynyl and cyano groups function as a self-photocatalyst to enhance the reactivity and exhibit high selectivity, which is confirmed by X-ray structural analysis of the representative products. Furthermore, the present strategy can overcome the problems of the low yield and low selectivity in the crossed [2+2] photocycloaddition between the different olefins in solution. Further studies to gain an in-depth understanding of the reaction mechanism and the new synthetic applications of this strategy are being conducted in our laboratory.

Methods

Representative procedure for the synthesis of 3aa. A 5 mL over-dried reaction vessel equipped with a magnetic stirrer bar was charged with 2-(2-(phenylethynyl)benzylidene)malononitrile (**1a**, 50.9 mg, 0.20 mmol), 3,4-dihydro-2*H*-pyran (**2a**, 1.0 mL). The reaction vessel was exposed to blue LED (410–415 nm, 3W) irradiation at room temperature in air with stirring for 8 h. After completion of the reaction, the mixture was concentrated to yield the crude product, which was further purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 20:1, V/V) to give the product **3aa** (54 mg, 79% yield) and product **3(aa)'** (8 mg, 11% yield). ¹H NMR (600 MHz, CDCl₃) δ 7.64–7.60 (m, 2H), 7.493–7.489 (m, 2H), 7.45–7.43 (m, 1H), 7.39–7.34 (m, 4H), 4.86 (d, *J* = 7.8 Hz, 1H), 4.45 (t, *J* = 12.0 Hz, 1H), 4.16 (d, *J* = 7.8 Hz, 1H), 3.89–3.87 (m, 1H), 3.54–3.48 (m, 1H), 2.18–2.15 (m, 1H), 1.87–1.81 (m, 1H), 1.70–1.68 (m, 1H), 1.61–1.55 (m, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 134.9, 133.6, 131.3, 128.9, 128.7, 128.6, 127.9, 127.0, 122.6, 122.2, 115.3, 114.8, 94.2, 87.2, 73.7, 64.6, 44.0, 40.1, 36.7, 22.1, 19.7. For ¹H NMR, ¹³C NMR, ¹⁹F NMR (if applicable) spectra of compounds **3fa**, **3ia**, **3pa**, **3ta**, **5ca**, see ESI for details.

Procedure for gram-scale synthesis of 3aa. A 20.0 mL oven-dried reaction vessel equipped with a magnetic stirrer bar was charged with 2-(2-(phenylethynyl)benzylidene)malononitrile (**1a**, 0.520 g, 2.0 mmol) and 3,4-dihydro-2*H*-pyran (**2a**, 5.0 mL). The reaction vessel was exposed to LED (410–415 nm, 3 W) irradiation at room temperature in air with stirring for 12 h. After completion of the reaction, the mixture was concentrated to yield the crude product, which was further purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 20:1) to give the desired product **3aa** (0.480 g, 71% yield).

Data availability

The authors declare that the data supporting the findings of this study are available within the article and its supplementary information files and from the authors upon reasonable request.

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Author contributions

L.W. and P.L. conceived the project and designed the experiments. X.X., H.P., M.H., X.G., Y.M., Z.W. and J.Y. performed the experiments, analyzed the data, and discussed the results. T.Z. and R.L. completed the DFT calculation work. L.W., X.X., P.L. and R.L. wrote the paper, Supplementary Methods, and related materials.

Competing interests

The authors declare no competing financial interests.

Additional information

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