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Visible-Light-Promoted Polysubstituted Olefins Synthesis Involving Sulfur Ylides as Carbene Trapping Reagents

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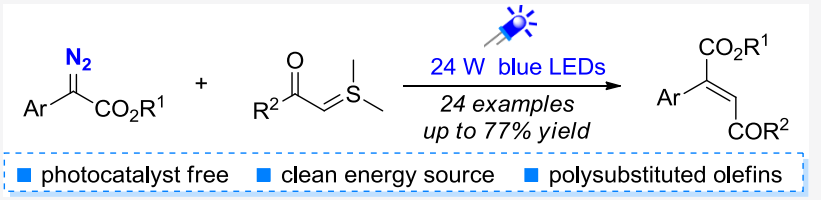

ABSTRACT: A blue-light-emitting diode (LED) promoted coupling of aryl diazoacetates with sulfur ylides is described. This protocol features mild conditions, good functional group tolerance, and broad substrate scope for both aryl diazoacetates with sulfur ylides. Under optimal reaction conditions, a wide range of trisubstituted olefins is obtained in moderate to good yield, which can be further transferred to other biologically important heterocycles after a two-step simple operation.

INTRODUCTION

Since the pioneering work disclosed by Johnson, Corey, and Chaykovsky, namely the Johnson−Corey−Chaykovsky reaction, sulfur ylides have been witnessed as one of the most important synthons in synthetic organic chemistry in the past 60 years.[1] In most of the reported contributions, sulfur ylides were always used as nucleophilic 1,1′-dipolar species to participate in cycloaddition reactions.[2] By using this strategy, a wide range of biologically important carbocycles and heterocycles can be accessed with high efficiency. Compared with those well-developed processes, synthetic applications of sulfur ylides under photochemical reaction conditions are relatively less exploited.

Generally, the transformation of sulfur ylides under photochemical reaction conditions can be roughly divided into the following two categories. The first one utilizes sulfur ylides as energy acceptors or electron donors. Under photochemical conditions, sulfur ylides could serve either as energy acceptors to form carbene species (Scheme 1a, left, ET, electron transfer)[3] or as single-electron reductants to generate radical cation intermediates (Scheme 1a, right, SET, single-electron transfer).[4] Those strategies have been successfully applied to the synthesis of many useful molecules, such as methyl malonate derivatives,[3] tetralones,[4a] 3-acyl oxindoles[4b] and indolines.[4c] The second one utilizes sulfur ylides as trapping reagents to react with photogenerated reactive species (Scheme 1b). In 2017, Chen and co-workers reported a visible-light-promoted indole synthesis using the formal [4 + 1]-cycloaddition of in situ generated *aza-ortho*-quinone methides with sulfur ylides as a key step.[5a] Shortly after this discovery, they further extended the strategy to the synthesis of 2,3-dihydrobenzofuran derivatives.[5b] However, some of these reported approaches utilized high-energy UV light, and visible-light-promoted sulfur ylides transformation largely relied on the use of photoredox catalysts (e.g., benzophenone, $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$, *fac*-$Ir(4'\text{-}CF_3ppy)_3$, or $Ru(phen)_3Cl_2$). Thus, continuously expanding the synthetic potential of sulfur ylides in photochemical transformation under sole visible light irradiation without an exogenous photoredox catalyst is still highly desirable.

In the past several decades, carbene generation from diazo compounds under thermal or transition-metal catalytic conditions has been well investigated.[6] Only recently, since 2018, photolysis of aryl diazoacetates under sole visible light irradiation has emerged as a promising new and sustainable approach to initiate free carbene-transfer reactions.[7,8] To date, the strategy has been elegantly applied to X−H insertion,[9] cyclopropanation and cyclopropenation,[10] and some other types of reactions.[11] In 2018, Zhou, He, and co-workers developed a blue-light-emitting diode (LED)-promoted cross-coupling of two distinct diazo compounds, leading to trisubstituted alkenes in high yields and stereoselectivities.[12a] In the same year, Maulide et al. reported a ruthenium-catalyzed cross-olefination of diazo compounds with sulfoxonium ylides as metal-carbene trapping reagents.[12b] Recently, *in situ* ylides formation from sulfides and aryl diazoacetates under blue LED irradiation was also achieved by Xiao,[13a] Koenigs[13b] and

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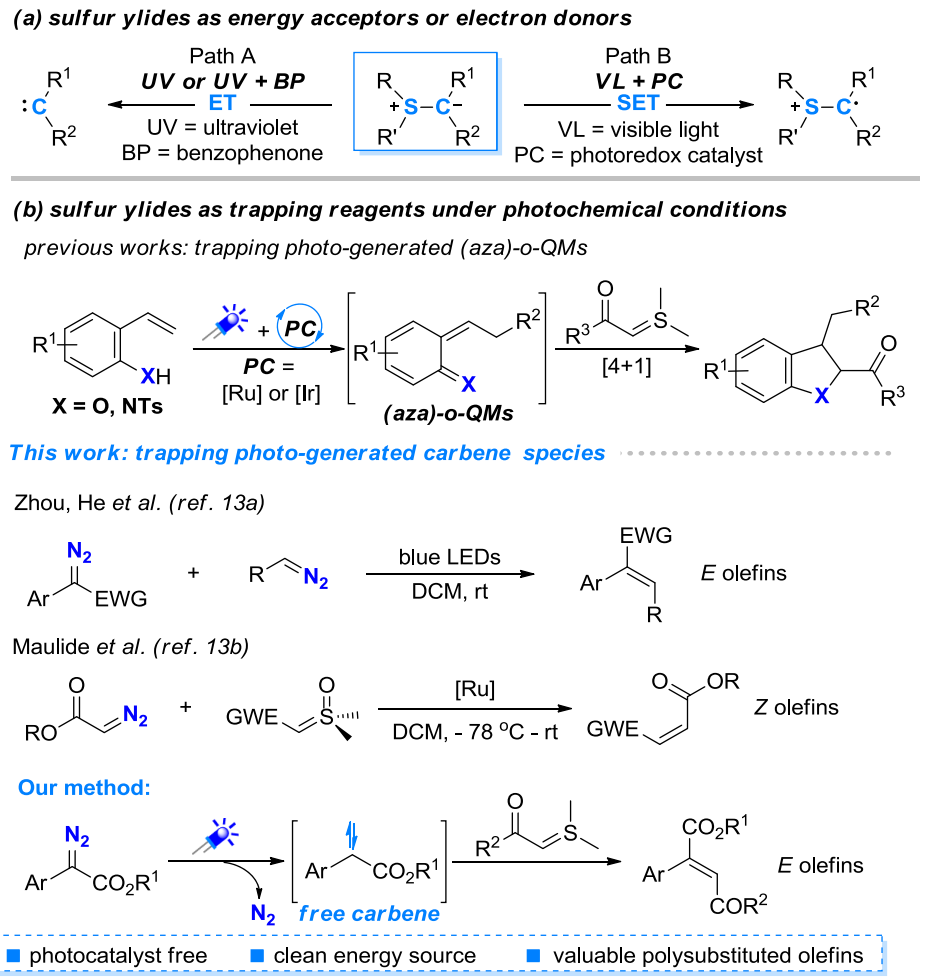
Scheme 1. Transformation of Sulfur Ylides under Photochemical Reaction Conditions and Our Reaction Design



Gryko.[13c] Inspired by these contributions, we envision that the photogenerated free carbene species from aryl diazoacetates might also be trapped by sulfur ylides. Within the frame of our continuing interests in visible-light-promoted fine chemical transformations,[14] we herein report the coupling reaction of aryl diazoacetates with sulfur ylides under blue LED irradiation, leading to various valuable polysubstituted olefins in single *E* configuration.

RESULTS AND DISCUSSION

We began our investigation by employing methyl 2-diazo-2-phenylacetate **1a** and sulfur ylide **2a** as model substrates. (Table 1). As shown in entry 1, upon irradiating the reaction mixture with 24 W blue LEDs for 7 h in DCM, the desired trisubstituted olefin **3aa** was obtained in 66% isolated yield as a single *E*-isomer. Encouraged by this preliminary result, we commenced with reaction optimization and investigated the effect of reaction solvents to further improve the yield. Replacement of DCM with other commonly used reaction media, such as CH_3CN, THF, EtOAc, and 1,4-dioxane, did not give better yields (Table 1, entries 2−5). Only a trace amount of **3aa** was observed when the reaction was performed in dimethyl formamide (DMF) and dimethyl sulfoxide (DMSO) (Table 1, entries 6 and 7). Further optimization identified dichloroethene (DCE) to be the best solvent candidate, affording **3aa** in 70% yield (Table 1, entry 8). Changing the ratio of **1a**:**2a** from 2:1 to 1:2 or 1.5:1 decreased the yield to 41 and 54%, respectively (Table 1, entries 9 and 10). Note that sulfoxonium ylide **2a′** can also serve as a carbene trapping reagent to form alkene **3aa**, albeit in a low yield (Table 1, entry 11). The control experiment revealed that visible light irradiation was essential for the product formation (Table 1, entry 10).

With the optimal reaction conditions in hand, we next evaluated the substrate scope with respect to both aryl diazoacetate and sulfur ylide components. It was found that the reaction showed a broad substrate scope and good functional group tolerance. As shown in Scheme 2, substrates **1a**−**e** bearing electron-neutral, electron-donating (e.g., −Me, −OMe), or electron-withdrawing (e.g., −F, −Br) substituents at the *para* position were tolerated well, affording trisubstituted olefins **3aa**−**ea** in moderate to good yield. Incorporation of ester functional groups proceeded well to afford products **3fa** and **3ga** in 68 and 43% yield, respectively. Apart from phenyl diazoacetate, substrate **1h** bearing a 2-naphthyl moiety was also an amenable substrate, giving the corresponding coupling product **3ha** in 40% yield. It was found that different ester groups in aryl diazoacetate **1** were well tolerated and the desired polysubstituted olefin products **3ia**−**ka** were obtained in 42−55% yields. Note that the relatively low yield in some cases might be due to the formation of the aryl diazoacetate homocoupling byproduct under visible light irradiation.

Next, we continued to investigate the generality of the process by reacting 2-diazo-2-phenylacetate **1a** with a

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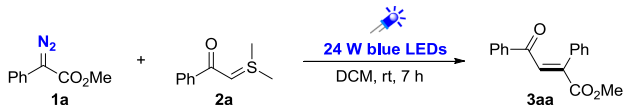
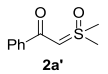
Table 1. Reaction Optimization[a]



entry	deviation from standard conditions	yield (%)[b]
1	None	66
2	CH_3CN instead of DCM	52
3	THF instead of DCM	33
4	EtOAc instead of DCM	50
5	1,4-dioxane instead of DCM	39
6	DMF instead of DCM	trace
7	DMSO instead of DCM	trace
8	DCE instead of DCM	70
9	DCE, **1a**:**2a**=1:2	41
10	DCE, **1a**:**2a**=1.5:1	54
11	 **2a'** instead of **2a**	32
11	DCE, in dark	N.R.

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.1 mmol) in the indicated solvent (1.0 mL), irradiation by 24 W blue LEDs at room temperature for 7 h under a N_2 atmosphere. [b]Isolated yield, *E*:*Z* > 19:1.

representative set of sulfur ylides **2** under the optimal reaction conditions (Scheme 2). The results revealed that both the electronic properties and substitution pattern of the aryl ring in the sulfur ylide **2** had no obvious effect on the reaction yields. Both electron-withdrawing (−F, −Cl, −Br, $-NO_2$) and electron-donating groups (−Me) at *para* or *meta*-positions of the aromatic ring reacted well, providing the trisubstituted olefin products **3ab**−**ag** in 52−65% yield. It should be pointed out that the alkyl-acyl-substituted sulfur ylide, such as **2h**, was not suitable, and only a trace amount of **3ah** was detected by gas chromatography−mass spectrometry (GC−MS) analysis.

To further explore the synthetic potential of this blue LED-promoted trisubstituted olefin synthesis protocol in the pharmaceutical industry, we introduced some natural isolates and drug-derived complex molecules, such as estrone, L-menthol, metronidazole, citronellol, and oleyl alcohol, into the starting materials of diazoalkane (Scheme 2). To our satisfaction, all of these diazoalkanes reacted well with **2a**, yielding the corresponding modified complex structures in moderate to good yields (**3la**−**pa**, 35−69% yields).

With the aim of showing the utility of the obtained trisubstituted olefins, we conducted some synthetic transformations in Scheme 3. It was found that the C=C bond in product **3aa** could be easily reduced, which offered us a good option to transfer the target trisubstituted olefins to a variety of other important heterocyclic compounds, such as pyridazine **4**[15a] and thiophene **5**,[15b] after a two-step simple operation (Scheme 3a). Treatment of **3aa** in BH_3. THF solution afforded diol, which could be transferred to the disubstituted tetrahydrofuran **6** in 87% yield and 1.4:1 d.r. over two steps.[15c] More significantly, a formal synthesis of the ET_A receptor radioligand **8** was achieved using the developed visible-light-promoted polysubstituted olefins synthesis as a key step (Scheme 3b).[16] Under optimal reaction conditions, the coupling of diazo compound **1q** with sulfur ylide **2i** afforded olefin **3qi** in 56% yield. Subsequently, the reduction of **3qi** gave 1,4-dicarbonyl **7** in 96% yield upon isolation, which is the key synthetic intermediate to the target molecule **8**.

A series of preliminary mechanistic experiments were conducted in Scheme 4 to gain some insight into the mechanism. Initially, the UV−vis absorbance spectra of 2-diazo-2-phenylacetate **1a** and sulfur ylide **2a** was conducted and both of the two starting materials presented an absorbance spectrum in the visible region (Scheme 4a). According to literature reports, both aryl diazoacetates and sulfur ylides could serve as carbene precursors under photo-irradiation.[3,8−13] Then, we conducted some control experiments to identify which substrates were activated under our optimal reaction conditions (Scheme 4b). It was reported that styrene is an efficient carbene trapping reagent under photochemical conditions.[9a] When 1.0 equivalent of styrene was added as a trapping reagent, the reaction afforded olefin **3aa** in 61% yield, together with 15% yield of cycloaddition adduct **9**. Moreover, we noticed that cyclopropane **10** was not formed even when the reaction of sulfur ylide **2a** with styrene was directly performed under standard reaction conditions. This result suggested that under current photochemical reaction conditions, only aryl diazoacetate **1** was selectively activated to form carbene intermediate, and sulfur ylide **2** did not undergo photolysis. Moreover, when 1.0 equivalent of radical scavenger 1,4-dinitrobenezene was added under standard conditions, **3aa** could be isolated in 61% yield. The result indicated that the radical pathway might not be the predominant reaction route in the current reaction system.

On the basis of the above experimental results and literature reports,[8−13] a plausible reaction mechanism was proposed in Scheme 4c. Under blue LEDs irradiation, selective photolysis of aryl diazoacetate yielded free carbene species with the release of nitrogen gas. Then, the nucleophilic attack of the negatively polarized carbon atom of sulfur ylide 2 to carbene intermediate, followed by elimination of dimethyl sulfide, gave the final trisubstituted olefins.

In summary, we have developed a green and efficient polysubstituted olefin formation protocol via blue-LED-promoted coupling of aryl diazoacetates with sulfur ylides. This reaction takes advantage of aryl diazoacetates as free carbene precursors and sulfur ylides as carbene trapping reagents without the need for an exogenous photoredox catalyst. Simple manipulation of the final olefin products allowed the facile construction of a wide range of important heterocycles, including pyrazole, pyrrole, isoxazole, and pyridazine derivatives. Moreover, the method can be applied as a key step to the formal synthesis of ET_A receptor radioligand 8. We envision this visible-light-promoted olefin formation strategy will find further applications in both organic synthesis and biomolecule studies.

EXPERIMENTAL SECTION

General Information. All reactions involving air- or moisture-sensitive reagents or intermediates were carried out in preheated glassware under an argon atmosphere using standard Schlenk techniques. All solvents and reagents were purified according to standard procedures or were used as received from chemical suppliers. The starting materials were synthesized according to literature procedures. The light employed in this work was bought from GeAo Chemical: model H106062, 24 W blue LED bulbs, light intensity, 24 mW/cm^2. Analytical thin-layer chromatography was performed using silica gel plates (Silica gel 60 F254) from Qingdao Puke Parting Materials Co. Visualization was by ultraviolet

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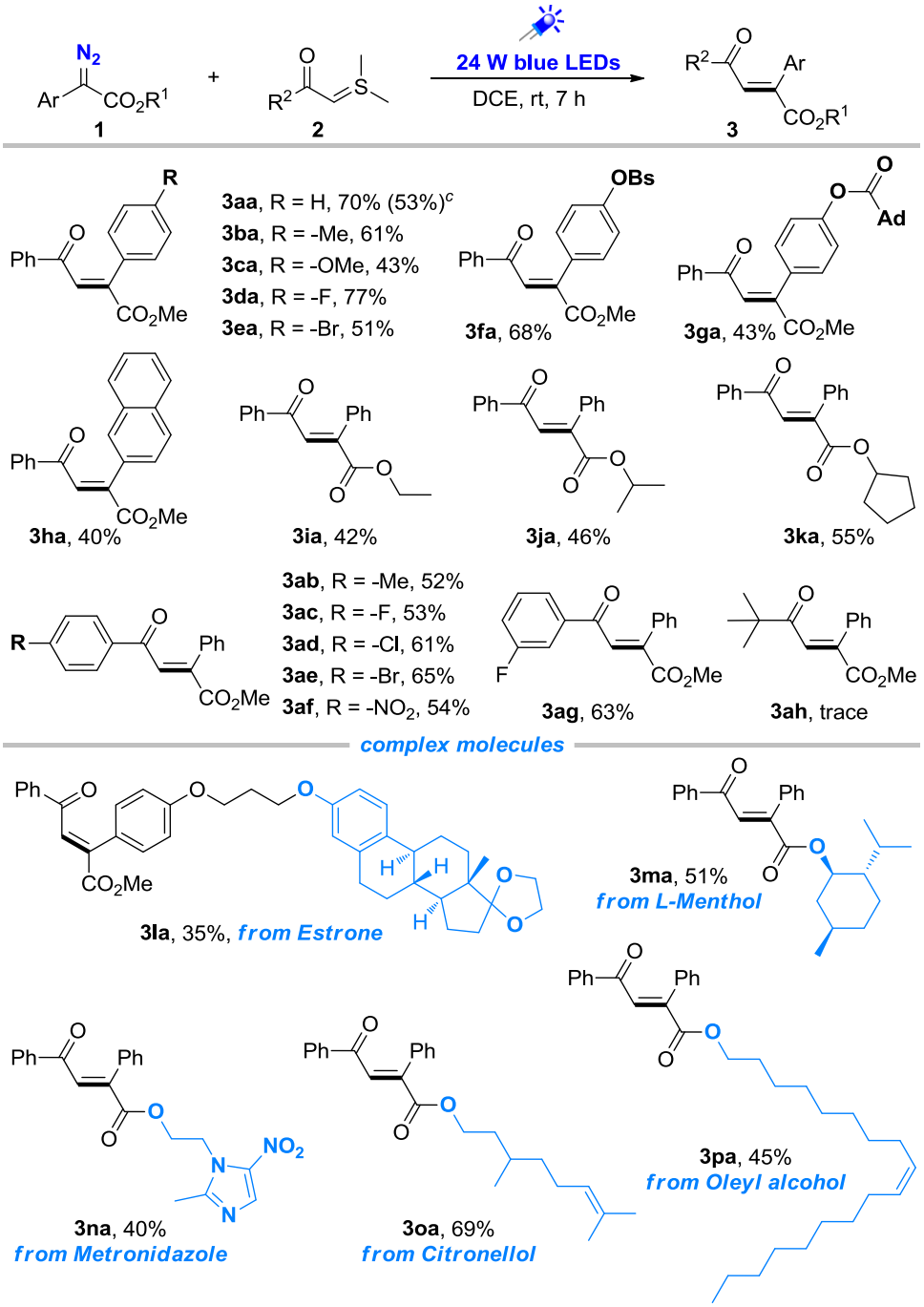
Scheme 2. Reaction Scope[a,b,c]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.1 mmol) in DCE (1.0 mL), irradiation by 24 W blue LEDs at room temperature for 7 h under a N_2 atmosphere. [b]Isolated yield, *E*:*Z* > 19:1 in all cases. [c]1.0 mmol scale reaction.

fluorescence (λ = 254 nm) and/or staining with phosphomolybdic acid or potassium permanganate ($KMnO_4$). Flash column chromatography was performed using 200−300 mesh silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM ECZ400R at 300 K. Spectra were calibrated relative to solvent's residual proton and carbon chemical shift: $CHCl_3$ (δ = 7.26 for ^{1}H NMR and δ = 77.0 for ^{13}C NMR). Data are reported as follows: chemical shift δ/ppm, integration (^{1}H only), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet or combinations thereof; ^{13}C signals are singlets unless otherwise stated), coupling constants *J* in Hz, assignment. Mass spectra were recorded on a Finnigan MAT 4200S, a Bruker Daltonics Micro Tof, a Waters-Micromass Quatro LCZ (ESI); peaks are given in *m*/*z* (% of basis peak). UV−vis spectrophotometer: UV−vis absorption spectra were recorded on an Agilent 8453 spectrophotometer in DCE (0.05 mol·mL^{-1}) at room temperature. Melting points were determined by Stuart SMP10 and are uncorrected. All reactions involving heating are carried out in an oil bath.

General Procedure for the Synthesis of Aryl Diazoacetates. DBU (1.4 equiv) was added to a mixture of esters (1.0 equiv) and *p*-toluenesulfonyl azide (1.2 equiv) in anhydrous acetonitrile (3 mL/mmol). The reaction mixture was stirred at room temperature overnight. Upon the complete consumption of the starting materials, the reaction mixture was diluted with an appropriate amount of water,

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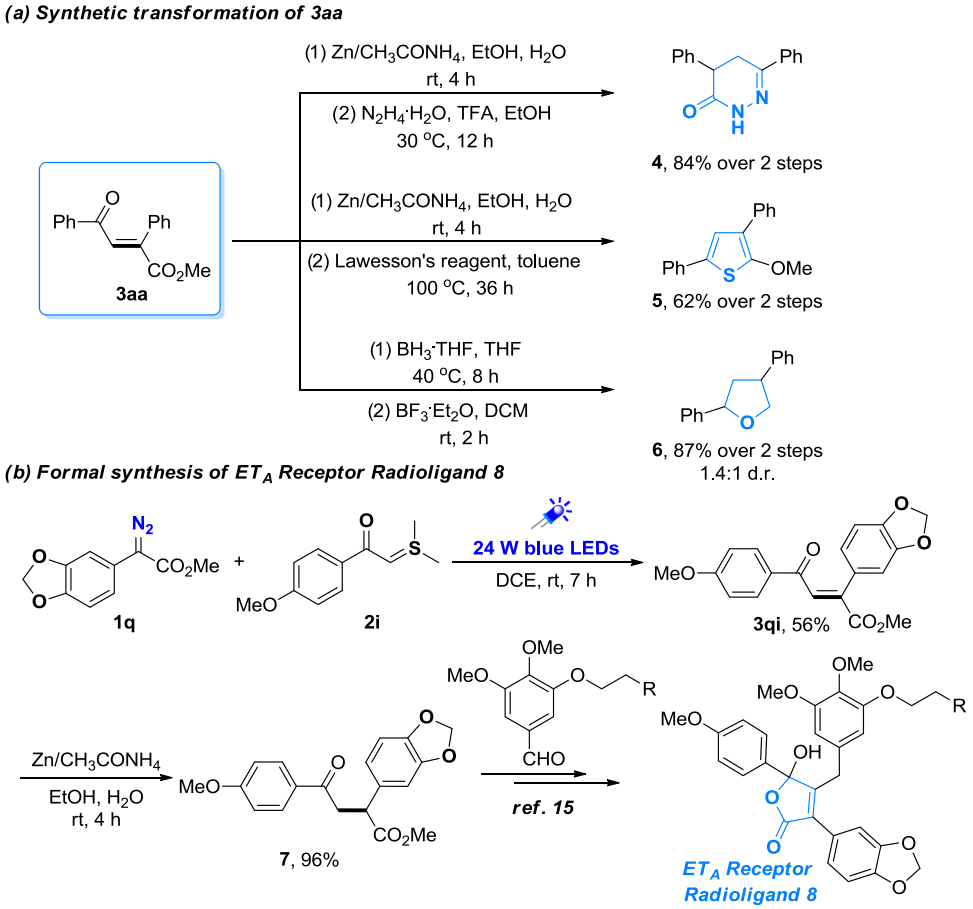
Scheme 3. Follow-Up Chemistry



followed by extraction with ethyl acetate. After washing with 10% NH_4Cl solution and brine, the combined organic extracts were dried over Na_2SO_4 and concentrated by rotary evaporation. The residue was purified by flash chromatography (petroleum ether/ethyl acetate = 60/1 to 30/1) to afford aryldiazoacetates. Aryl diazoacetates **1a–d**,[12a] **1e**,[9e] **1h**,[9e] **1i–j**,[12a] **1k**,[17d] **1m**,[17e] **1o**,[17f] and **1p**[11b] are known compounds.

*Methyl 2-(4-(((4-Bromophenyl)sulfonyl)oxy)phenyl)-2-diazoacetate (**1f**).* ^1H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.68 (s, 4H), 7.45–7.40 (m, 2H), 7.02–6.98 (m, 2H), 3.86 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 165.1, 147.0, 134.2, 132.6, 129.9, 129.7, 125.2, 124.9, 122.8, 52.1; IR (neat, cm^{-1}): 424*w*, 492*w*, 570*s*, 761*s*, 848*s*, 935*w*, 1004*m*, 1168*s*, 1369*s*, 1421*m*, 1507*s*, 1577*m*, 1689*s*, 1914*w*, 2114*s*, 2391*w*, 2946*m*, 3015*w*, 3094*m*. HRMS (ESI) exact mass calculated for $C_{15}H_{12}BrO_5S$: 382.9583 ($[M + H\text{-}N_2]^+$), found: 382.9586; mp: 167–169 °C.

*4-(1-Diazo-2-methoxy-2-oxoethyl)phenyl (3R,5R,7R)-Adamantane-1-carboxylate (**1g**).* ^1H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.49–7.43 (m, 2H), 7.09–7.05 (m, 2H), 3.86 (s, 3H), 2.10–2.02 (m, 9H), 1.82–1.73 (m, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 176.2, 165.6, 149.1, 125.0, 122.6, 122.2, 52.0, 41.0, 38.7, 36.4, 27.9. IR (neat, cm^{-1}): 502*m*, 553*m*, 640*w*, 675*s*, 774*s*, 857*s*, 1047*s*, 1108*w*, 1230*s*, 1291*m*, 1377*s*, 1437*s*, 1524*s*, 1602*w*, 1698*s*, 1724*s*, 1879*w*, 2105*s*, 2686*w*. HRMS (ESI) exact mass calculated for $C_{20}H_{23}O_4$: 327.1596 ($[M + H\text{-}N_2]^+$), found: 327.1585; mp: 134–136 °C.

*Methyl 2-Diazo-2-(4-(3-(((13S)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[a]phenanthrene-17,2′-[1,3]-dioxolan]-3-yl)oxy)propoxy)phenyl)acetate (**1l**).* ^1H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.36 (d, J = 9.0 Hz, 2H), 7.19 (dd, J = 8.8, 2.8 Hz, 1H), 6.94 (d, J = 9.0 Hz, 2H), 6.73–6.68 (m, 1H), 6.63 (d, J = 2.8 Hz, 1H), 4.18–4.08 (m, 4H), 3.96–3.88 (m, 4H), 3.84 (s, 3H), 2.86–2.78 (m, 2H), 2.34–2.28 (m, 1H), 2.26–2.19 (m, 3H), 2.07–1.99 (m, 1H), 1.94–1.83 (m, 2H), 1.81–1.73 (m, 2H), 1.68–1.57 (m, 2H), 1.54–1.30 (m, 6H), 0.88 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 166.2, 157.4, 156.7, 138.0, 132.8, 126.3, 125.9, 119.4, 115.2, 114.5, 112.0, 65.2, 64.6, 64.6, 64.2, 51.9, 49.3, 46.1, 43.6, 39.0, 34.2, 30.7, 29.8, 29.3, 27.0, 26.1, 22.3, 14.3; IR (neat, cm^{-1}): 831*w*, 1057*m*, 1143*m*, 1247*m*, 1429*w*, 1458*w*, 1504*w*, 1516*w*, 1548*w*, 1633*w*, 1654*w*, 1695*w*, 1733*w*, 1776*w*, 2087*s*, 2848*s*, 2925*s*. HRMS (ESI) exact mass calculated for $C_{32}H_{39}O_6$: 519.2741 ($[M + H\text{-}N_2]^+$), found: 519.2747; mp: 87–89 °C.

*2-(2-Methyl-5-nitro-1H-imidazol-1-yl)ethyl 2-Diazo-2-phenylacetate (**1n**).* ^1H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.97 (s, 1H), 7.47–7.33 (m, 4H), 7.26–7.14 (m, 1H), 4.75–4.52 (m, 4H), 2.46 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 164.4, 150.8, 138.4, 133.2, 129.0, 126.3, 124.4, 124.1, 62.7, 45.1, 14.2; IR (neat, cm^{-1}): 502*m*, 545*m*, 675*m*, 735*s*, 866*w*, 987*m*, 1065*s*, 1152*s*, 1238*s*, 1369*s*, 1472*s*, 1585*w*, 1724*s*, 2097*s*, 2964*w*, 3137*m*. HRMS (ESI) exact mass calculated for $C_{14}H_{14}N_3O_4$: 288.0979 ($[M + H\text{-}N_2]^+$), found: 288.0985; mp: 109–111 °C.

*(Z)-Octadec-9-en-1-yl 2-Diazo-2-phenylacetate (**1p**).* ^1H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.50–7.46 (m, 2H), 7.40–7.35 (m, 2H), 7.20–7.14 (m, 1H), 5.39–5.31 (m, 2H), 4.26 (t, J = 6.7 Hz, 2H), 2.01 (q, J = 7.3, 6.6 Hz, 4H), 1.70 (p, J = 6.7 Hz, 2H), 1.36–1.25 (m, 22H), 0.90–0.86 (m, 3H).; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 165.2, 129.9, 129.7, 128.9, 125.7, 125.6, 123.9, 65.1, 31.9, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 28.8, 27.2, 27.2, 25.8, 22.7, 14.1; IR (neat, cm^{-1}): 692*m*, 744*s*, 995*m*, 1160*s*, 1247*s*, 1359*m*, 1594*w*, 1706*s*, 2070*s*, 2842*m*, 2937*s*, 3077*w*. HRMS (ESI) exact mass calculated for $C_{26}H_{41}O_2$: 385.3107 ($[M + H\text{-}N_2]^+$), found: 385.3111.

General Procedure for the Synthesis of Sulfur Ylides. Dimethyl phenacyl sulfonium bromide (5.0 g, 0.019 mol) was dissolved in water (30 mL). The colored suspension was filtered, and

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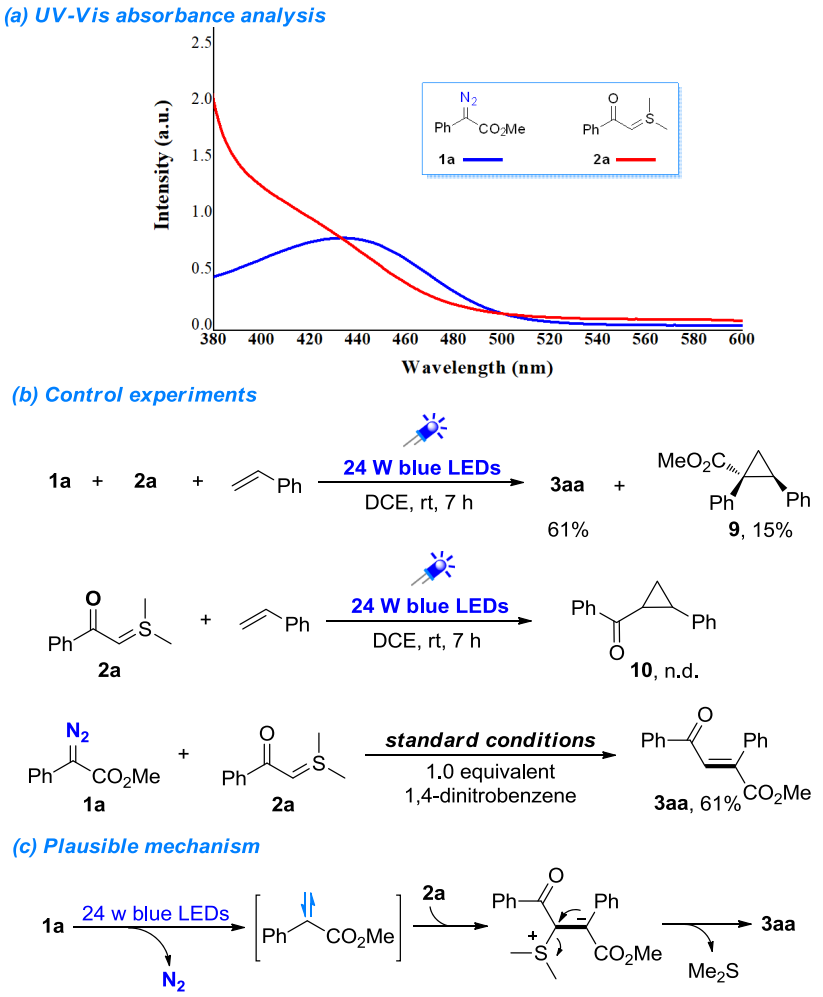
Scheme 4. Mechanism Studies



the clear filtrate was treated with 10% aqueous sodium hydroxide (50 mL, 0.125 mol). The solution was stirred and then extracted several times with chloroform. The chloroform extract was dried and evaporated to give an orange oil, which upon cooling immediately solidified to an orange solid (3.60 g, 100%). The infrared spectrum and NMR spectrum were identical to that of the previous phenacylide. Upon recrystallization of the solid, as before, a 95% yield of product was obtained. Sulfur ylides **2a**–**c**,[4c] **2d**–**e**,[5a] and **2g**–**h**[4c] are known compounds.

General Procedure for the Synthesis of Polysubstituted Olefins (*GP1*). To a 10 mL Schlenk flask equipped with a magnetic stir bar was added **1a** (0.2 mmol), **2a** (0.1 mmol), and dry DCE (1.0 mL). The resulting mixture was degassed using the "freeze–pump–thaw" procedure (3 times). Then, the solution was stirred at a distance of ~3 cm from a 24 W blue LED at room temperature for 7 h. The solvent was removed under vacuum, and the crude product was purified by flash chromatography on silica gel (silica: 200–300; eluant: petroleum ether/ethyl acetate (20:1 to 5:1)) to obtain the pure product **3aa** as a yellow oil in 70% yield.

Procedure for 1 mmol Reaction. To a 25 mL Schlenk flask equipped with a magnetic stir bar was added **1a** (2.0 mmol), **2a** (1.0 mmol), and dry DCE (10.0 mL). The resulting mixture was degassed using the freeze–pump–thaw procedure (3 times). Then, the solution was stirred at a distance of ~3 cm from a 24 W blue LED at room temperature for 12 h. The solvent was removed under vacuum, and the crude product was purified by flash chromatography on silica gel (silica: 200–300; eluant: petroleum ether/ethyl acetate (20:1 to 5:1)) to obtain the pure product **3aa** as a yellow oil in 53% yield (141.1 mg).

*(E)-Methyl 4-Oxo-2,4-diphenylbut-2-enoate (**3aa**).*[13a] **3aa** was synthesized according to *GP1*, with **1a** (35.2 mg, 0.20 mmol, 2.0 equiv) and **2a** (18.0 mg, 0.10 mmol, 1.0 equiv) in 1.0 mL of DCE for 7 h. Purification by silica gel chromatography (eluant: petroleum ether/ethyl acetate 20:1 to 5:1) afforded the desired **3aa**. Yellow oil, yield: 70% (18.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.86–7.79 (m, 2H), 7.70 (s, 1H), 7.52–7.47 (m, 1H), 7.39–7.34 (m, 2H), 7.24–7.18 (m, 5H), 3.86 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 193.5, 167.0, 140.4, 136.4, 136.2, 133.7, 133.6, 129.4, 128.9, 128.6, 128.5, 127.9, 52.9.

*(E)-Methyl 4-Oxo-4-phenyl-2-(p-tolyl)but-2-enoate (**3ba**).*[17a] **3ba** was synthesized according to *GP1*, with **1b** (38.0 mg, 0.20 mmol, 2.0 equiv) and **2a** (18.0 mg, 0.10 mmol, 1.0 equiv) in 1.0 mL of DCE for 7 h. Purification by silica gel chromatography (eluant: petroleum ether/ethyl acetate 20:1 to 5:1) afforded the desired **3ba**. Yellow oil, yield: 61% (17.1 mg); ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.86–7.80 (m, 2H), 7.67 (s, 1H), 7.52–7.47 (m, 1H), 7.40–7.34 (m, 2H), 7.13–7.08 (m, 2H), 7.02 (d, J = 7.7 Hz, 2H), 3.85 (s, 3H), 2.25 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 193.6, 167.2, 140.5, 138.5, 136.3, 135.8, 133.5, 130.7, 129.3, 128.9, 128.7, 128.5, 52.8, 21.2.

*(E)-Methyl 2-(4-Methoxyphenyl)-4-oxo-4-phenylbut-2-enoate (**3ca**).* **3ca** was synthesized according to *GP1*, with **1c** (41.2 mg, 0.20 mmol, 2.0 equiv) and **2a** (18.0 mg, 0.10 mmol, 1.0 equiv) in 1.0 mL of DCE for 7 h. Purification by silica gel chromatography (eluant: petroleum ether/ethyl acetate 20:1 to 5:1) afforded the desired **3ca**. Yellow oil, yield: 43% (12.7 mg); ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.86–7.80 (m, 2H), 7.61 (s, 1H), 7.51–7.46 (m, 1H), 7.39–7.34 (m, 2H), 7.21–7.12 (m, 2H), 6.80–6.67 (m, 2H), 3.86 (s,

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3H), 3.72 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 193.9, 167.3, 159.8, 140.0, 136.2, 135.4, 133.5, 130.9, 128.9, 128.5, 125.9, 113.4, 55.1, 52.8; IR (neat, cm^{-1}): 510*w*, 631*w*, 718*m*, 839*m*, 926*w*, 1030*s*, 1178*m*, 1247*s*, 1472*m*, 1515*s*, 1602*m*, 1655*m*, 1724*s*, 2834*w*, 2921*w*, 2964*w*; HRMS (ESI) exact mass calculated for $C_{18}H_{17}O_4$: 297.1127 ($[M + H]^+$), found: 297.1118.

*(E)-Methyl 2-(4-Fluorophenyl)-4-oxo-4-phenylbut-2-enoate (**3da**).* **3da** was synthesized according to *GP1*, with **1d** (38.8 mg, 0.20 mmol, 2.0 equiv) and **2a** (18.0 mg, 0.10 mmol, 1.0 equiv) in 1.0 mL of DCE for 7 h. Purification by silica gel chromatography (eluant: petroleum ether/ethyl acetate 20:1 to 5:1) afforded the desired **3da**. Yellow oil, yield: 77% (21.8 mg); ^1H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.85−7.80 (m, 2H), 7.72 (s, 1H), 7.54−7.49 (m, 1H), 7.41−7.36 (m, 2H), 7.22−7.17 (m, 2H), 6.94−6.88 (m, 2H), 3.87 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 193.4, 166.8, 139.4, 136.6, 136.1, 133.8, 131.4 (d, J = 8 Hz), 131.3, 129.6, 128.8 (d, J = 25 Hz), 115.0 (d, J = 21 Hz), 52.9; IR (neat, cm^{-1}): 519*w*, 640*m*, 710*s*, 857*s*, 961*w*, 1030*m*, 1152*m*, 1247*s*, 1455*m*, 1499*s*, 1568*m*, 1662*s*, 1733*s*, 2851*w*, 1964*m*, 3077*w*; HRMS (ESI) exact mass calculated for $C_{17}H_{14}FO_3$: 285.0927 ($[M + H]^+$), found: 285.0926.

*(E)-Methyl 2-(4-Bromophenyl)-4-oxo-4-phenylbut-2-enoate (**3ea**).* **3ea** was synthesized according to *GP1*, with **1e** (50.8 mg, 0.20 mmol, 2.0 equiv) and **2a** (18.0 mg, 0.10 mmol, 1.0 equiv) in 1.0 mL DCE for 7 h. Purification by silica gel chromatography (eluant: petroleum ether/ethyl acetate 20:1 to 5:1) afforded the desired **3ea**. Yellow oil, yield: 51% (17.5 mg); ^1H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.87−7.82 (m, 2H), 7.77 (s, 1H), 7.56−7.51 (m, 1H), 7.43−7.35 (m, 4H), 7.12−7.06 (m, 2H), 3.87 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 193.0, 166.5, 139.4, 136.8, 136.1, 133.9, 132.6, 131.2, 131.0, 128.9, 128.7, 52.9; IR (neat, cm^{-1}): 626*w*, 754*m*, 926*m*, 1010*m*, 1071*s*, 1176*s*, 1253*w*, 1314*w*, 1450*m*, 1597*s*, 1666*m*, 1723*s*, 2846*w*, 2918*m*, 2955*w*; HRMS (ESI) exact mass calculated for $C_{17}H_{14}BrO_3$: 345.0126 ($[M + H]^+$), found: 345.0135.

*(E)-Methyl 2-(4-(((4-Bromophenyl)sulfonyl)oxy)phenyl)-4-oxo-4-phenylbut-2-enoate (**3fa**).* **3fa** was synthesized according to *GP1*, with **1f** (82.0 mg, 0.20 mmol, 2.0 equiv) and **2a** (18.0 mg, 0.10 mmol, 1.0 equiv) in 1.0 mL of DCE for 7 h. Purification by silica gel chromatography (eluant: petroleum ether/ethyl acetate 20:1 to 5:1) afforded the desired **3fa**. Yellow oil, yield 68% (34.0 mg); ^1H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.83−7.77 (m, 2H), 7.73 (s, 1H), 7.62−7.52 (m, 5H), 7.44−7.37 (m, 2H), 7.19−7.14 (m, 2H), 6.86−6.81 (m, 2H), 3.87 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 193.1, 166.4, 149.4, 138.8, 137.3, 136.0, 133.9, 133.0, 132.4, 131.0, 129.9, 129.6, 128.9, 128.7, 121.9, 53.0; IR (neat, cm^{-1}): 530*m*, 607*s*, 684*w*, 761*m*, 865*s*, 980*m*, 1108*s*, 1147*s*, 1405*s*, 1507*m*, 1661*w*, 1765*m*, 1857*w*, 2961*w*, 3115*w*; HRMS (ESI) exact mass calculated for $C_{23}H_{18}BrO_6S$: 501.0007 ($[M + H]^+$), found: 500.9994.

*(3R,5R,7R)-4-((E)-1-Methoxy-1,4-dioxo-4-phenylbut-2-en-2-yl)-phenyl Adamantane-1-carboxylate (**3ga**).* **3ga** was synthesized according to *GP1*, with **1g** (70.8 mg, 0.20 mmol, 2.0 equiv) and **2a** (18.0 mg, 0.10 mmol, 1.0 equiv) in 1.0 mL of DCE for 7 h. Purification by silica gel chromatography (eluant: petroleum ether/ethyl acetate 20:1 to 5:1) afforded the desired **3ga**. Yellow oil, yield: 43% (19.1 mg); ^1H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.87−7.80 (m, 2H), 7.72 (s, 1H), 7.54−7.50 (m, 1H), 7.41−7.36 (m, 2H), 7.24−7.20 (m, 2H), 6.96−6.91 (m, 2H), 3.85 (s, 3H), 2.07−1.99 (m, 9H), 1.78−1.73 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 193.3, 175.6, 166.8, 151.2, 139.6, 136.6, 136.1, 133.8, 130.8, 130.5, 128.9, 128.6, 121.0, 52.9, 41.0, 38.7, 36.4, 27.8. IR (neat, cm^{-1}): 505*w*, 620*w*, 723*w*, 1044*s*, 1096*w*, 1147*s*, 1160*s*, 1366*w*, 1418*m*, 1520*m*, 1584*w*, 1774*m*, 1726*s*, 2845*m*, 1922*s*, 3063*w*; HRMS (ESI) exact mass calculated for $C_{28}H_{29}O_5$: 445.2015 ($[M + H]^+$), found: 445.2012.

*(E)-Methyl 2-(Naphthalen-2-yl)-4-oxo-4-phenylbut-2-enoate (**3ha**).* **3ha** was synthesized according to *GP1* with **1h** (45.2 mg, 0.20 mmol, 2.0 equiv), **2a** (18.0 mg, 0.10 mmol, 1.0 equiv) in 1.0 mL of DCE for 7 h. Purification by silica gel chromatography (eluant: petroleum ether/ethyl acetate 20:1 to 5:1) afforded the desired **3ha**. Yellow oil, yield: 40% (12.6 mg); ^1H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.85−7.82 (m, 2H), 7.79 (s, 1H), 7.77−7.66 (m, 4H), 7.47−7.40 (m, 3H), 7.35−7.30 (m, 3H), 3.88 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 193.5, 167.1, 140.5, 136.7, 136.2, 133.6, 131.2, 129.1, 128.9, 128.5, 128.2, 127.6, 127.5, 126.8, 126.6, 126.2, 52.9; IR (neat, cm^{-1}): 401*w*, 440*m*, 723*m*, 748*m*, 954*w*, 1044*w*, 1237*s*, 1456*w*, 1597*m*, 1661*m*, 1713*s*, 2112*w*, 2832*m*, 2909*m*, 3013*w*; HRMS (ESI) exact mass calculated for $C_{21}H_{17}O_3$: 317.1178 ($[M + H]^+$), found: 317.1175.

*(E)-Ethyl 4-Oxo-2,4-diphenylbut-2-enoate (**3ia**).* **3ia** was synthesized according to *GP1*, with **1i** (38.0 mg, 0.20 mmol, 2.0 equiv) and **2a** (18.0 mg, 0.10 mmol, 1.0 equiv) in 1.0 mL of DCE for 7 h. Purification by silica gel chromatography (eluant: petroleum ether/ethyl acetate 20:1 to 5:1) afforded the desired **3ia**. Yellow oil, yield: 42% (11.8 mg); ^1H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.85−7.79 (m, 2H), 7.67 (s, 1H), 7.51−7.46 (m, 1H), 7.38−7.33 (m, 2H), 7.21 (s, 5H), 4.33 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 193.8, 166.5, 140.7, 136.2, 136.0, 133.8, 133.6, 129.4, 128.9, 128.5, 127.8, 61.9, 14.1; IR (neat, cm^{-1}): 659*w*, 697*m*, 774*m*, 1031*m*, 1096*w*, 1173*m*, 1250*s*, 1379*w*, 1443*m*, 1674*m*, 171*s*, 1832*w*, 1909*m*, 3063*w*; HRMS (ESI) exact mass calculated for $C_{18}H_{17}O_3$: 281.1178 ($[M + H]^+$), found: 281.1174.

*(E)-Isopropyl 4-Oxo-2,4-diphenylbut-2-enoate (**3ja**).* **3ja** was synthesized according to *GP1*, with **1j** (40.8 mg, 0.20 mmol, 2.0 equiv) and **2a** (18.0 mg, 0.10 mmol, 1.0 equiv) in 1.0 mL of DCE for 12 h. Purification by silica gel chromatography (eluant: petroleum ether/ethyl acetate 20:1 to 5:1) afforded the desired **3ja**. Yellow oil, yield: 46% (13.5 mg); ^1H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.84−7.79 (m, 2H), 7.67 (s, 1H), 7.50−7.45 (m, 1H), 7.37−7.33 (m, 2H), 7.22−7.18 (m, 5H), 5.19 (p, J = 6.3 Hz, 1H), 1.32 (d, J = 6.3 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 194.0, 166.0, 141.0, 136.2, 135.7, 133.9, 133.5, 129.5, 129.0, 128.5, 127.8, 69.6, 21.7; IR (neat, cm^{-1}): 530*w*, 671*m*, 748*m*, 838*w*, 929*w*, 980*m*, 1096*s*, 1237*s*, 1366*m*, 1482*m*, 1661*m*, 1726*s*, 2845*m*, 2898*m*, 2986*m*, 3077*w*; HRMS (ESI) exact mass calculated for $C_{19}H_{19}O_3$: 295.1334 ($[M + H]^+$), found: 295.1328.

*(E)-Cyclopentyl 4-Oxo-2,4-diphenylbut-2-enoate (**3ka**).* **3ka** was synthesized according to *GP1*, with **1k** (46.0 mg, 0.20 mmol, 2.0 equiv) and **2a** (18.0 mg, 0.10 mmol, 1.0 equiv) in 1.0 mL of DCE for 7 h. Purification by silica gel chromatography (eluant: petroleum ether/ethyl acetate 20:1 to 5:1) afforded the desired **3ka**. Yellow oil, yield: 55% (17.6 mg); ^1H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.84−7.79 (m, 2H), 7.61 (s, 1H), 7.50−7.45 (m, 1H), 7.38−7.33 (m, 2H), 7.19 (s, 5H), 5.38−5.32 (m, 1H), 1.95−1.87 (m, 2H), 1.80−1.61 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 194.0, 166.2, 141.1, 136.2, 135.6, 133.9, 133.5, 129.4, 129.0, 128.5, 128.4, 127.8, 78.8, 32.6, 23.7; IR (neat, cm^{-1}): 631*w*, 675*s*, 770*m*, 900*w*, 944m, 1022*m*, 1168*s*, 1238*s*, 1437*m*, 1490*w*, 1602*m*, 1663*s*, 1715*s*, 2868*w*, 2964*s*, 3077*w*; HRMS (ESI) exact mass calculated for $C_{21}H_{21}O_3$: 321.1491 ($[M + H]^+$), found: 321.1486.

*(E)-Methyl 4-Oxo-2-phenyl-4-(p-tolyl)but-2-enoate (**3ab**).*[13a] **3ab** was synthesized according to *GP1*, with **1a** (35.2 mg, 0.20 mmol, 2.0 equiv) and **2b** (19.4 mg, 0.10 mmol, 1.0 equiv) in 1.0 mL of DCE for 7 h. Purification by silica gel chromatography (eluant: petroleum ether/ethyl acetate 20:1 to 5:1) afforded the desired **3ab**. Yellow oil, yield: 52% (14.6 mg). ^1H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.76−7.71 (m, 2H), 7.70 (s, 1H), 7.23−7.21 (M, 4H), 7.17 (d, J = 7.9 Hz, 2H), 3.86 (s, 3H), 2.36 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 193.1, 167.1, 144.7, 140.0, 136.8, 133.8, 129.3, 129.3, 129.1, 128.5, 127.9, 52.8, 21.7.

*(E)-Methyl 4-(4-Fluorophenyl)-4-oxo-2-phenylbut-2-enoate (**3ac**).*[17b] **3ac** was synthesized according to *GP1*, with **1a** (35.2 mg, 0.20 mmol, 2.0 equiv) and **2c** (19.8 mg, 0.10 mmol, 1.0 equiv) in 1.0 mL of DCE for 7 h. Purification by silica gel chromatography (eluant: petroleum ether/ethyl acetate 20:1 to 5:1) afforded the desired **3ac**. Yellow oil, yield: 53% (15.1 mg); ^1H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.87−7.79 (m, 2H), 7.64 (s, 1H), 7.25−7.16 (m, 5H), 7.04−6.99 (m, 2H), 3.86 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$,

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300 K): δ (ppm) = 192.1, 166.9, 165.9 (d, J = 254.7 Hz), 140.5, 136.0, 133.6, 132.6, 131.6 (d, J = 9.5 Hz), 129.3, 128.7, 128.0, 115.7 (d, J = 25 Hz), 52.9.

*(E)-Methyl 4-(4-Chlorophenyl)-4-oxo-2-phenylbut-2-enoate (**3ad**).*[17c] **3ad** was synthesized according to *GP1*, with **1a** (35.2 mg, 0.20 mmol, 2.0 equiv) and **2d** (21.4 mg, 0.10 mmol, 1.0 equiv) in 1.0 mL of DCE for 7 h. Purification by silica gel chromatography (eluant: petroleum ether/ethyl acetate 20:1 to 5:1) afforded the desired **3ad**. Yellow oil, yield: 61% (18.3 mg); ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.77−7.71 (m, 2H), 7.63 (s, 1H), 7.34−7.30 (m, 2H), 7.25−7.17 (m, 5H), 3.86 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 192.4, 166.8, 140.8, 140.1, 135.7, 134.5, 133.5, 130.3, 129.3, 128.9, 128.8, 128.0, 52.9.

*(E)-Methyl 4-(4-Bromophenyl)-4-oxo-2-phenylbut-2-enoate (**3ae**).*[13a] **3ae** was synthesized according to *GP1*, with **1a** (35.2 mg, 0.20 mmol, 2.0 equiv) and **2e** (25.8 mg, 0.10 mmol, 1.0 equiv) in 1.0 mL of DCE for 7 h. Purification by silica gel chromatography (eluant: petroleum ether/ethyl acetate 20:1 to 5:1) afforded the desired **3ae**. Yellow oil, yield: 65% (22.4 mg); ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.68−7.65 (m, 2H), 7.63 (s, 1H), 7.51−7.47 (m, 2H), 7.25−7.17 (m, 5H), 3.87 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 192.7, 166.8, 140.8, 135.7, 134.9, 133.5, 131.9, 130.4, 129.3, 128.8, 128.0, 52.9.

*(E)-Methyl 4-(4-Nitrophenyl)-4-oxo-2-phenylbut-2-enoate (**3af**).* **3af** was synthesized according to *GP1*, with **1a** (35.2 mg, 0.20 mmol, 2.0 equiv) and **2f** (22.5 mg, 0.10 mmol, 1.0 equiv) in 1.0 mL of DCE for 7 h. Purification by silica gel chromatography (eluant: petroleum ether/ethyl acetate 20:1 to 5:1) afforded the desired **3af**. Yellow oil, yield: 54% (16.8 mg); ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 8.17−8.11 (m, 2H), 7.92−7.87 (m, 2H), 7.62 (s, 1H), 7.23−7.15 (m, 5H), 3.89 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 192.4, 166.5, 150.2, 142.1, 140.6, 134.7, 133.3, 129.8, 129.4, 129.2, 128.1, 123.6, 53.1; IR (neat, cm^{-1}): 492*w*, 605*w*, 675*m*, 692*s*, 788*m*, 866*m*, 926*m*, 1022*m*, 1100*w*, 1264*s*, 1308*m*, 1342*s*, 1542*s*, 1628*m*, 1663*s*, 1698*m*, 2842*w*, 2972*m*, 3077*m*, 3111*w*; HRMS (ESI) exact mass calculated for $C_{17}H_{14}NO_5$: 312.0872 ($[M + H]^+$), found: 312.0865.

*(E)-Methyl 4-(3-Fluorophenyl)-4-oxo-2-phenylbut-2-enoate (**3ag**).* **3ag** was synthesized according to *GP1*, with **1a** (35.2 mg, 0.20 mmol, 2.0 equiv) and **2g** (19.8 mg, 0.10 mmol, 1.0 equiv) in 1.0 mL of DCE for 7 h. Purification by silica gel chromatography (eluant: petroleum ether/ethyl acetate 20:1 to 5:1) afforded the desired **3ag**. Yellow oil, yield: 63% (17.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.64 (s, 1H), 7.62−7.57 (m, 1H), 7.50−7.45 (m, 1H), 7.36−7.31 (m, 1H), 7.25−7.15 (m, 6H), 3.87 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 192.3, 166.8, 141.1, 138.2, 135.5, 133.5, 130.2 (d, J = 8 Hz), 129.3, 128.8, 128.0, 124.8 (d, J = 3 Hz), 120.6 (d, J = 22 Hz), 115.3 (d, J = 22 Hz), 52.9; IR (neat, cm^{-1}): 519*w*, 623*w*, 692*s*, 779*s*, 917*m*, 969*m*, 1090*w*, 1178*m*, 1256*s*, 1446*m*, 1490*m*, 1602*m*, 1698*m*, 1733*s*, 2851*w*, 2972*m*, 3068*w*; HRMS (ESI) exact mass calculated for $C_{17}H_{14}FO_3$: 285.0927 ($[M + H]^+$), found: 285.0920.

*(E)-Methyl 2-(4-(3-(((13S)-13-Methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[a]phenanthrene-17,2′-[1,3]dioxolan]-3-yl)oxy)propoxy)phenyl)-4-oxo-4-phenylbut-2-enoate (**3la**).* **3la** was synthesized according to *GP1*, with **1l** (109.2 mg, 0.20 mmol, 2.0 equiv) and **2a** (18.0 mg, 0.10 mmol, 1.0 equiv) in 1.0 mL of DCE for 12 h. Purification by silica gel chromatography (eluant: petroleum ether/ethyl acetate 20:1 to 5:1) afforded the desired **3la**. Yellow oil, yield: 35% (22.3 mg); ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.86−7.80 (m, 2H), 7.60 (s, 1H), 7.51−7.45 (m, 1H), 7.40−7.33 (m, 2H), 7.22−7.10 (m, 3H), 6.77−6.70 (m, 2H), 6.68 (dd, J = 8.6, 2.8 Hz, 1H), 6.61 (d, J = 2.7 Hz, 1H), 4.07 (td, J = 6.1, 4.0 Hz, 4H), 3.97−3.88 (m, 4H), 3.86 (s, 3H), 2.88−2.76 (m, 2H), 2.17 (dd, J = 6.7, 5.5 Hz, 2H), 2.06−1.99 (m, 1H), 1.89−1.75 (m, 3H), 1.62 (q, J = 6.8 Hz, 3H), 1.55−1.29 (m, 6H), 0.88 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 193.9, 167.3, 159.2, 156.6, 140.0, 138.0, 136.3, 135.4, 133.6, 132.8, 130.9, 129.0, 128.5, 126.3, 126.0, 119.4, 114.5, 114.0, 112.0, 65.2, 64.6, 64.4, 64.2, 52.8, 49.3, 46.1, 43.6, 39.0, 34.2, 30.7, 29.8, 29.2, 27.0, 26.1, 22.3, 14.3; IR (neat, cm^{-1}): 510*w*, 683*m*, 839*m*, 952*w*, 1030*s*, 1195*m*, 1213*s*, 1256*m*, 1351*w*, 1515*m*, 1577*m*, 1680*m*, 1741*s*, 2842*m*, 2937*s*, 3059*w*, 3432*s*; HRMS (ESI) exact mass calculated for $C_{40}H_{45}O_7$: 637.3165 ($[M + H]^+$), found: 637.3169.

*(E)-(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 4-Oxo-2,4-diphenylbut-2-enoate (**3ma**).* **3ma** was synthesized according to *GP1*, with **1m** (60.0 mg, 0.20 mmol, 2.0 equiv) and **2a** (18.0 mg, 0.10 mmol, 1.0 equiv) in 1.0 mL of DCE for 7 h. Purification by silica gel chromatography (eluant: petroleum ether/ethyl acetate 20:1 to 5:1) afforded the desired **3ma**. Yellow oil, yield: 51% (19.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.84−7.78 (m, 2H), 7.62 (s, 1H), 7.50−7.46 (m, 1H), 7.38−7.33 (m, 2H), 7.20 (s, 5H), 4.81−4.91 (m, 1H), 2.18−2.10 (m, 1H), 1.92−1.82 (m, 1H), 1.72−1.67 (m, 2H), 1.58−1.50 (m, 1H), 1.46−1.38 (m, 1H), 1.27−1.01 (m, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H), 0.80 (d, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 194.0, 166.1, 141.3, 136.3, 135.5, 133.9, 133.5, 129.4, 129.0, 128.5, 128.4, 127.8, 76.1, 46.9, 40.7, 34.1, 31.4, 26.4, 23.5, 22.0, 20.7, 16.4; IR (neat, cm^{-1}): 545*w*, 701*m*, 753*m*, 909*w*, 978*m*, 1108*w*, 1213*s*, 1386*m*, 1446*m*, 1594*s*, 1672*s*, 1733*s*, 2868*m*, 2921*s*, 2946*s*, 3050*w*; HRMS (ESI) exact mass calculated for $C_{26}H_{31}O_3$: 391.2273 ($[M + H]^+$), found: 391.2269.

*(E)-2-(2-Methyl-5-nitro-1H-imidazol-1-yl)ethyl 4-Oxo-2,4-diphenylbut-2-enoate (**3na**).* **3na** was synthesized according to *GP1*, with **1n** (63.0 mg, 0.20 mmol, 2.0 equiv) and **2a** (18.0 mg, 0.10 mmol, 1.0 equiv) in 1.0 mL of DCE for 7 h. Purification by silica gel chromatography (eluant: petroleum ether/ethyl acetate 20:1 to 5:1) afforded the desired **3na**. Yellow oil, yield: 40% (16.2 mg). ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.96 (s, 1H), 7.80−7.76 (m, 2H), 7.67 (s, 1H), 7.52−7.48 (m, 1H), 7.39−7.35 (m, 2H), 7.25−7.19 (m, 3H), 7.09−7.06 (m, 2H), 4.59 (q, J = 2.2 Hz, 4H), 2.04 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 192.9, 166.0, 151.1, 139.5, 137.7, 136.0, 133.8, 133.2, 133.2, 129.1, 128.9, 128.8, 128.6, 128.2, 64.1, 44.8, 13.7; IR (neat, cm^{-1}): 502*w*, 640*w*, 710*s*, 761*m*, 822*m*, 1039*m*, 1179*s*, 1273*s*, 1377*s*, 1429*m*, 1464*s*, 1533*m*, 1594*w*, 1663*m*, 1733*s*, 2834*w*, 2921*w*, 3050w, 3137*w*, 3441*s*; HRMS (ESI) exact mass calculated for $C_{22}H_{20}N_3O_5$: 406.1403 ($[M + H]^+$), found: 406.1402.

*(E)-3,7-Dimethyloct-6-en-1-yl 4-Oxo-2,4-diphenylbut-2-enoate (**3oa**).* **3oa** was synthesized according to *GP1*, with **1o** (60.0 mg, 0.20 mmol, 2.0 equiv) and **2a** (18.00 mg, 0.10 mmol, 1.0 equiv) in 1.0 mL of DCE for 7 h. Purification by silica gel chromatography (eluant: petroleum ether/ethyl acetate 20:1 to 5:1) afforded the desired **3oa**. Yellow oil, yield: 69% (25.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.89−7.76 (m, 2H), 7.67 (s, 1H), 7.51−7.46 (m, 1H), 7.36 (dd, J = 8.4, 7.1 Hz, 2H), 7.20 (s, 5H), 5.12−5.03 (m, 1H), 4.36−4.25 (m, 2H), 2.04−1.90 (m, 2H), 1.77−1.71 (m, 1H), 1.67 (s, 3H), 1.60 (s, 3H), 1.56−1.46 (m, 2H), 1.39−1.31 (m, 1H), 1.24−1.14 (m, 1H), 0.92 (d, J = 6.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 193.7, 166.5, 140.8, 136.2, 136.0, 133.8, 133.6, 131.4, 129.4, 128.9, 128.5, 128.5, 127.8, 124.5, 64.5, 36.9, 35.3, 29.5, 25.7, 25.4, 19.4, 17.7; IR (neat, cm^{-1}): 631*w*, 692*m*, 770*m*, 1013*m*, 1186*m*, 1247*s*, 1446*m*, 1585*w*, 1663*m*, 1715*s*, 2842*w*, 2921*m*, 2981*m*, 3050*w*; HRMS (ESI) exact mass calculated for $C_{26}H_{31}O_3$: 391.2273 ($[M + H]^+$), found: 391.2271.

*(E)-(Z)-octadec-8-en-1-yl 4-Oxo-2,4-diphenylbut-2-enoate (**3pa**).* **3pa** was synthesized according to *GP1*, with **1p** (82.5 mg, 0.20 mmol, 2.0 equiv) and **2a** (18.0 mg, 0.10 mmol, 1.0 equiv) in 1.0 mL of DCE for 12 h. Purification by silica gel chromatography (eluant: petroleum ether/ethyl acetate 20:1 to 5:1) afforded the desired **3pa**. Yellow oil, yield:45% (22.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.84−7.80 (m, 2H), 7.67 (s, 1H), 7.51−7.46 (m, 1H), 7.36 (dd, J = 8.4, 7.1 Hz, 2H), 7.20 (s, 5H), 5.41−5.29 (m, 2H), 4.26 (t, J = 6.7 Hz, 2H), 2.01 (q, J = 6.5 Hz, 4H), 1.70−1.65 (m, 2H), 1.32−1.25 (m, 22H), 0.88 (t, J = 6.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 193.8, 166.5, 140.8, 136.2, 136.0, 133.8, 133.6, 130.0, 129.8, 129.4, 128.9, 128.5, 127.8, 66.0, 31.9, 29.7, 29.7, 29.7, 29.5, 29.4, 29.3, 29.2, 28.5, 27.2, 25.9, 22.7, 14.1; IR (neat, cm^{-1}): 614*w*, 692*s*, 761*m*, 1004*m*, 1168*m*, 1247*s*, 1437*m*, 1602*w*, 1663*s*,

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1733*s*, 2851*s*, 2912*s*, 3050*w*; HRMS (ESI) exact mass calculated for $C_{34}H_{47}O_3$: 503.3525 ([M + H]$^+$), found: 503.3517.

Synthesis of Pyridazine (4).[15a] Step I: A solution of **3aa** (0.1 mmol) in ethanol (2 mL) was added to water (80 μL) containing 38 mg of ammonium acetate (0.5 mmol) at room temperature and stirred vigorously with 3 mg of zinc powder (0.0375 mmol) added in a period of 15 min. Stirring was continued for a further 4 h (monitored by TLC). The suspended material was removed by filtration and washed with ethanol. Then, the filtrate was evaporated under reduced pressure nearly to dryness and then ice-cold water was added to the residual material. After filtration, the crude product was recrystallized from 95% ethanol to give methyl 4-oxo-2,4-diphenylbutanoate in 92% yield (24.6 mg).

Step II: A solution of methyl 4-oxo-2,4-diphenylbutanoate (0.1 mmol) in EtOH (1.0 mL) was taken in an over-dried reaction tube, and trifluoroacetic acid (100 μL) was added via a syringe. After stirring at 30 °C for 5 min, hydrazine hydrate (10.0 μL, 0.2 mmol) was added. The mixture was stirred for 12 h. The reaction mixture was purified by flash chromatography on silica gel to afford the desired pyridazine **4**. White solid, yield: 91% (22.8 mg, known compound, 84% over two steps); ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 9.07 (s, 1H), 7.77−7.66 (m, 2H), 7.45−7.38 (m, 3H), 7.38−7.25 (m, 5H), 3.83 (dd, J = 9.2, 7.3 Hz, 1H), 3.35−3.16 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 168.2, 150.9, 137.1, 135.4, 129.9, 129.0, 128.7, 127.8, 125.8, 42.4, 30.5.

Synthesis of Thiophene (5).[15b] Step I: A solution of **3aa** (0.1 mmol) in ethanol (2 mL) was added to water (80 μL) containing 38.0 mg of ammonium acetate (0.5 mmol) at room temperature and stirred vigorously with 3 mg of zinc powder (0.0375 mmol) added in a period of 15 min. Stirring was continued for a further 1 h (monitored by TLC). The suspended material was removed by filtration and washed with ethanol. The filtrate was evaporated under reduced pressure nearly to dryness and then ice-cold water was added to the residual material. After filtration, the crude product was recrystallized from 95% ethanol to give methyl 4-oxo-2,4-diphenylbutanoate in 92% yield (24.6 mg).

Step II: Lawesson's reagent (81 mg) was added to a solution of methyl 4-oxo-2,4-diphenylbutanoate (26.8 g, 0.1 mmol) in toluene (1 mL), and the mixture was stirred at 100 °C for 36 h. After cooling, the mixture was filtered through Celite, the solvent was evaporated, and the product was isolated by column chromatography on silica gel (eluent hexane/AcOEt, 100:1) to give the product **5**. White solid, mp = 92−94 °C, yield: 67% (17.8 mg, 62% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.70−7.65 (m, 2H), 7.57−7.52 (m, 2H), 7.43−7.33 (m, 4H), 7.29−7.26 (m, 1H), 7.25 (s, 1H), 7.25−7.20 (m, 1H), 4.00 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 160.3, 134.5, 129.2, 128.9, 128.4, 126.8, 126.4, 124.8, 122.1, 61.8. IR (neat, cm^{-1}): 492*m*, 580*s*, 683*s*, 753*s*, 926*w*, 1004*m*, 1230*s*, 1499*s*, 1602*m*, 1724*w*, 2841*m*, 2921*m*, 3015*w*. HRMS (ESI) exact mass calculated for $C_{17}H_{15}OS$: 267.0838 ([M + H]$^+$), found: 267.0832.

Synthesis of Tetrahydrofuran (6).[15c] BH_3·THF (1.0 mol/L, 1 mL, 5.0 equiv) was added to a dry Schlenk tube containing **3aa** (26.8 mg, 0.1 mmol), and the solution was stirred at 40 °C for 4 h before being quenched with MeOH carefully. The resulting mixture was concentrated and dissolved in DCM (2 mL), and then the solution was treated with BF_3·Et_2O (25 μL, 2.0 equiv) at room temperature for 2 h. The reaction was quenched with saturated NH_4Cl and extracted with DCM (3 × 5 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated. The purification by preparative TLC (petrol ether/EtOAc = 30:1) gave disubstituted tetrahydrofuran **6** in 87% yield over two steps (22.4 mg, 1.4:1 d.r., known compound). For cis-isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.43−7.21 (m, 10H), 5.07 (dd, J = 10.2, 5.7 Hz, 1H), 4.36 (t, J = 8.2 Hz, 1H), 4.02 (t, J = 8.5 Hz, 1H), 3.64 (dq, J = 10.7, 8.2 Hz, 1H), 2.76 (ddd, J = 12.8, 7.3, 5.8 Hz, 1H), 2.01 (dt, J = 12.4, 10.5 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 142.6, 141.7, 128.6, 128.4, 127.4, 127.2, 126.6, 125.7, 81.8, 75.1, 46.0, 43.7. For trans-isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.39−7.21 (m, 10H), 5.23 (dd, J = 7.7, 5.8 Hz, 1H), 4.47 (dd, J = 8.4, 7.4 Hz, 1H), 3.95 (t, J = 8.2 Hz, 1H), 3.53 (p, J = 7.8 Hz, 1H), 2.48 (dt, J = 12.6, 7.7 Hz, 1H), 2.33 (ddd, J = 12.6, 8.3, 5.8 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 42.6, 141.7, 128.6, 128.4, 127.4, 127.2, 126.6, 125.7, 81.8, 75.1, 46.0, 43.7.

Formal Synthesis of ET_A Receptor Radioligand 8.[16] Step I: To a 10 mL Schlenk flask equipped with a magnetic stir bar was added **1q** (0.2 mmol), **2i** (0.1 mmol), and dry DCE (1.0 mL). The resulting mixture was degassed using the freeze−pump−thaw procedure (3 times). Then, the solution was stirred at a distance of ∼3 cm from a 24 W blue LED at room temperature for 7 h. The solvent was removed by vacuum, and the crude product was purified by flash chromatography on silica gel (silica: 200−300; eluant: petroleum ether/ethyl acetate (20:1 to 5:1)) to give the pure product **3qi** as a yellow oil in 56% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.84−7.79 (m, 2H), 7.59 (s, 1H), 6.88−6.84 (m, 2H), 6.74 (d, J = 1.7 Hz, 1H), 6.66 (dd, J = 9.7, 7.9 Hz, 2H), 5.90 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H).; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 192.23, 167.13, 163.98, 147.85, 147.22, 138.87, 136.53, 131.38, 129.25, 127.47, 123.62, 113.85, 109.83, 107.92, 101.14, 55.47, 52.80; IR (neat, cm^{-1}): 588*w*, 718*w*, 831*m*, 944*m*, 1030*m*, 1090*w*, 1168*m*, 1230*s*, 1429*m*, 1481*m*, 1594*m*, 1663*w*, 1724*m*, 2842*w*, 2912*w*, 2955*w*. HRMS (ESI) exact mass calculated for $C_{19}H_{17}O_6$: 341.1025 ([M + H]$^+$), found: 341.1039.

Step II: A solution of **3qi** (0.1 mmol) in ethanol (2 mL) was added to water (80 μL) containing 38 mg of ammonium acetate (0.5 mmol) at room temperature and stirred vigorously with 3.0 mg of zinc powder (0.0375 mmol) added in a period of 15 min. Stirring was continued for a further 4 h (monitored by TLC). The suspended material was removed by filtration and washed with ethanol. The filtrate was evaporated under reduced pressure nearly to dryness and then ice-cold water was added to the residual material. After filtration, the crude product was recrystallized from 95% ethanol to give **7** in 96% yield (24.6 mg). Note that compound **7** is the key synthetic intermediate to the target ET_A Receptor Radioligand **8**. ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.70−7.65 (m, 2H), 7.57−7.52 (m, 2H), 7.43−7.33 (m, 4H), 7.29−7.26 (m, 1H), 7.25 (s, 1H), 7.25−7.20 (m, 1H), 4.00 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 160.3, 134.5, 129.2, 128.9, 128.4, 126.8, 126.4, 124.8, 122.1, 61.8.

Synthesis of 9. To a 10 mL Schlenk flask equipped with a magnetic stir bar was added **1a** (0.2 mmol), **2a** (0.1 mmol), styrene (0.1 mmol), and dry DCE (2.0 mL).[13a] The resulting mixture was degassed using the freeze−pump−thaw procedure (3 times). Then, the solution was stirred at a distance of ∼3 cm from a 24 W blue LED at room temperature. Upon the completion of the reaction, monitored by TLC, the solvent was removed under vacuum. The crude product was purified by flash chromatography on silica gel (silica: 200−300; eluant:petroleum ether/ethyl acetate (20:1)) to obtain the pure product **3aa** as a yellow oil in 61% yield (16.2 mg) and **9** as colorless oil in 15% yield (3.8 mg). ^{1}H NMR of **9** (400 MHz, $CDCl_3$, 300 K): δ (ppm) = 7.13−7.07 (m, 3H), 7.05−6.99 (m, 5H), 6.78−6.73 (m, 2H), 3.63 (s, 3H), 3.11 (dd, J = 9.4, 7.3 Hz, 1H), 2.12 (dd, J = 9.3, 4.9 Hz, 1H), 1.86 (dd, J = 7.3, 4.9 Hz, 1H). ^{13}C{^{1}H} NMR of **9** (100 MHz, $CDCl_3$, 300 K): δ (ppm) = 174.2, 136.3, 134.7, 131.9, 128.0, 127.6, 127.6, 126.9, 126.2, 52.5, 37.3, 33.0, 20.4.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02500.

Mechanism studies, experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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