Master's Thesis

Synthesis of Azetidines based on Visible-light Photocatalytic [2+2] Aza Cycloaddition Between Alkenes and Imines

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Approved by

Advisor
Prof. Cheol-Min Park

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Abstract

The organic compounds which have four-membered ring structure are fascinating in organic chemistry, since they have been found in numerous bioactive molecules and used as useful synthon due to their ring strain. Among them, the azetidine which is nitrogen-containing four-membered heterocycle starts to gain in popularity as an interesting pharmacophore in current medicinal chemistry because of their desirable biological activity and improved metabolic stability. Also, as a synthon, their strained structure makes them excellent candidates for ring expansion reactions. In spite of their strong points, the lack of efficient synthetic method of azetidine is still remaining challenge.

Among the known synthetic strategies, the [2+2] photocycloaddition reaction between imine and alkene has emerged as prominent method, which can directly afford the functionalized azetidine. However, because of low reactivity between imines and alkenes, previous methods usually relied on UV irradiation in order to activate the imine or alkene. UV irradiation can excite both alkene and imine so that the C=N bond can undergo undesired relaxation pathways such as isomerization, fragmentation, or decomposition. Some research groups designed rigid imine and alkene substrates to solve that, but still UV light is hazardous, and it has limited the functional groups of substrates.

To break through these drawbacks, we developed the visible light induced photocatalytic [2+2] cycloaddition reaction between imine and alkene. The selective activation of alkene was achieved via redox mechanism to avoid the excitation of imine or other functional groups. Using blue LED as light source and acridinium catalyst as organophotocatalyst, a variety of azetidine compounds were synthesized in moderate to excellent yield without any by-product.

This redox neutral method gives product only and utilizes acridinium photocatalyst which is eco-friendly, cheap, and less toxic than metal photocatalysts. Therefore, it allows a highly atom economic reaction and it is highly desirable in green chemistry. Also, the constructed bicyclic azetidine moiety have great potential in biological activity and further modification.

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Abbreviations

Ph	Phenyl group
Me	Methyl group
iPr	Isopropyl group
^{t}Bu	Tert-butyl group
CO_2iPr	Isopropyl ester group
NO_2	Nitro group
UV	Ultraviolet radiation
PC	Photocatalyst
LED	Light emitting diode
SET	Single electron transfer
ISC	Intersystem crossing
EnT	Energy transfer
SCE	Saturated calomel electrode
S_N2	Bimolecular nucleophilic substitution
d.r.	Diastereomeric ratio
rt	Room temperature
N_2	Nitrogen atmosphere
TEA	Triethylamine
TFA	Trifluoroacetic acid
DMAP	p-Dimethylaminopyridine
TsCl	p-Toluenesulfonyl chloride
TsOH	p-Toluenesulfonic acid
TrCl	Triphenylmethyl chloride
n-BuLi	n-Butyllithium
LAH	Lithium aluminum hydride, $LiAlH_4$

CSA	Camphor sulfonic acid
PPI	Potassium phthalimide
Boc_2O	Di-tert-butyl dicarbonate
m-CPBA	meta-Chloroperxoybenzoic acid
NaI	Sodium iodide
NaH	Sodium hydride
Et_2O	Diethyl ether
THF	Tetrahydrofuran
MeCN	Acetonitrile
DMSO	Dimethyl sulfoxide
DMF	Dimethyl formamide
^1H NMR	Proton nuclear magnetic resonance

I. INTRODUCTION

1.1. Azetidine

The four-membered azaheterocycles, azetidines have got growing attention for their versatility in medicinal chemistry and many areas of chemistry[1]. Their molecular rigidity and robustness allow an efficient tuning of pharmacological properties and often improve the pharmacokinetic effects and biological activities. Also, their rigid conformations exhibit a wide range of bioavailability, and superior metabolic stability or ligand efficiency. The azetidine-bearing molecules have been found in natural products, approved drugs, and ligands for transition metals[2]. The representative examples are shown in Figure 1.

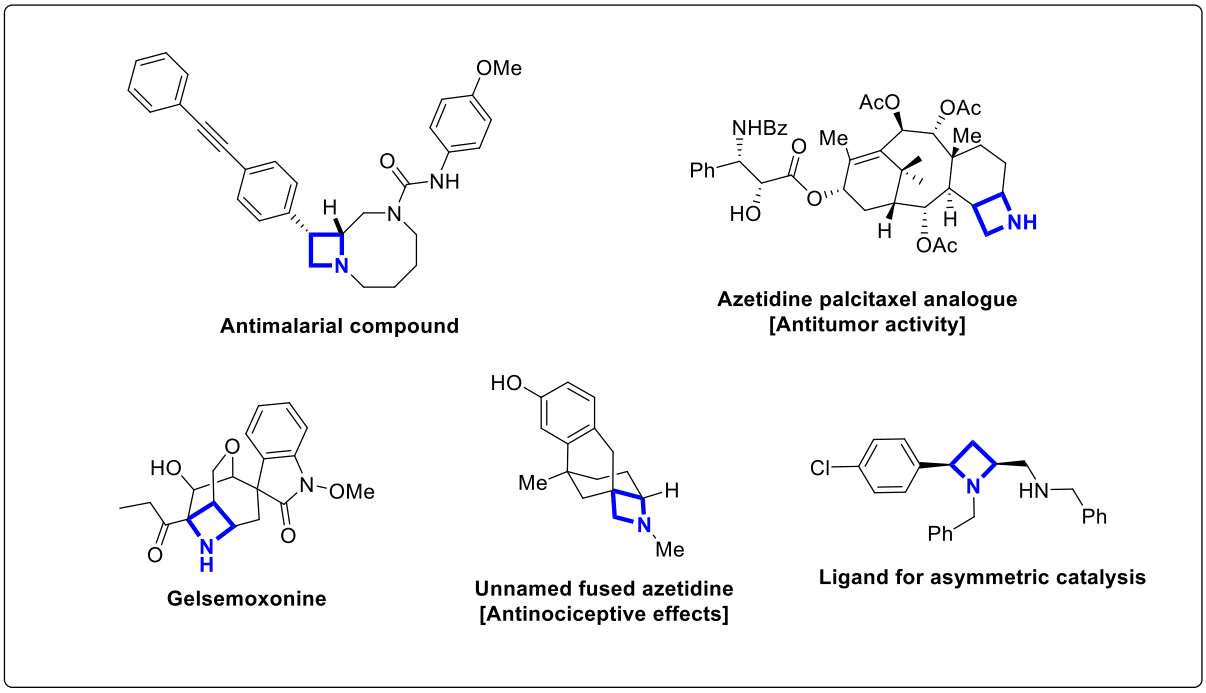


Figure 1. Representative examples of azetidine bearing molecules.

Azetidines have been widely used as a prominent synthon (Figure 2)[3]. Their ring strain energy is quite high, so they can serve as a valuable building blocks for several transformations. Activating the azetidine generally afforded acyclic amine via ring-opening reaction with electrophilic reagents or Lewis acid followed by addition of external nucleophile. Also, the azetidine can undergo the ring-expansion reaction to 5- or 6-membered and medium-sized heterocycles. It can be achieved by using Lewis acid, oxidant[4], transition metal or external nucleophile.

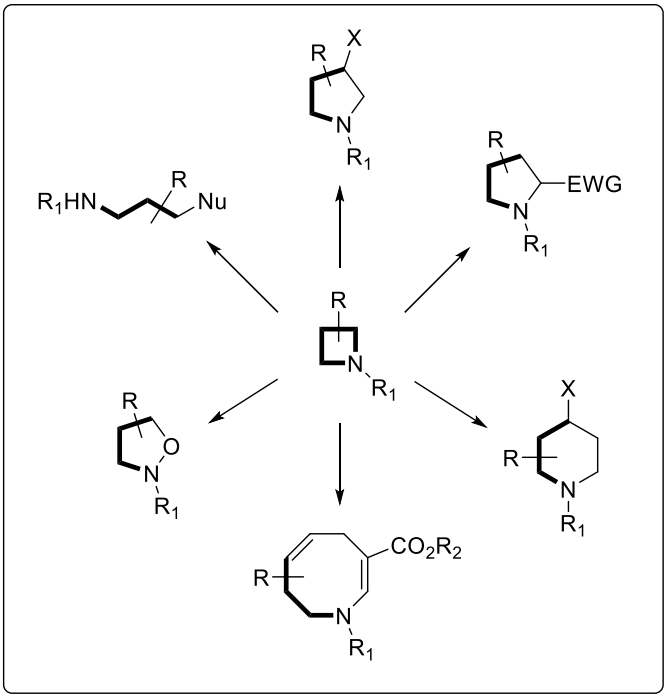


Figure 2. The application of azetidine in organic synthesis.

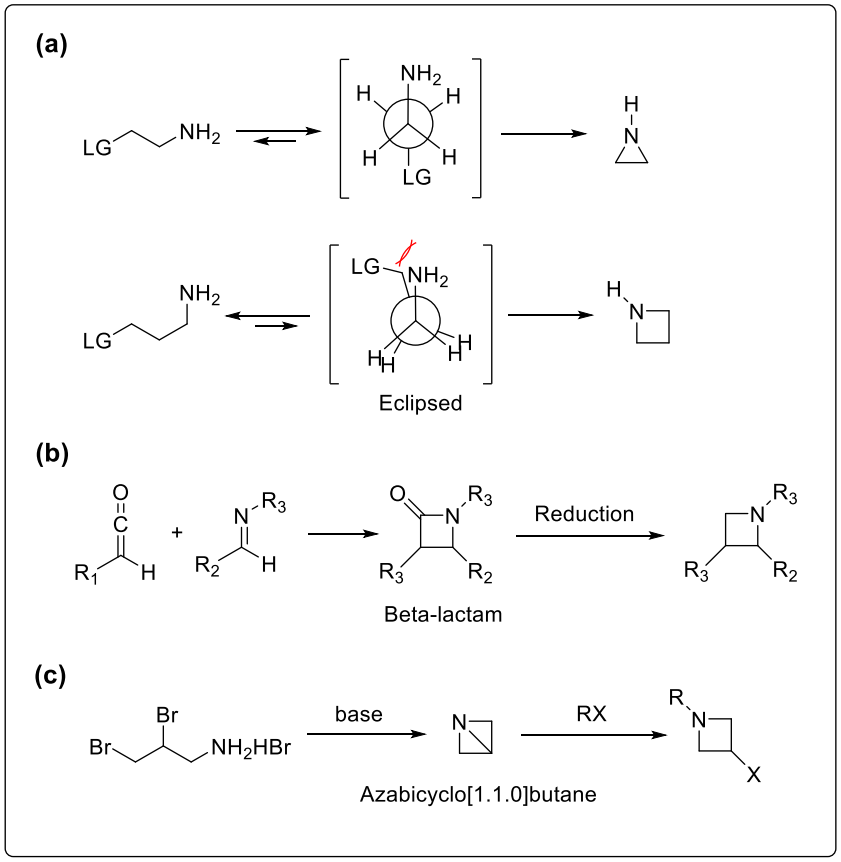
Many research groups have developed a number of synthetic methods for the azetidine which is attractive scaffold having broad range of utilization. The traditional methods mostly relied on lactam reduction or ionic processes like nucleophilic substitution reaction. Then, [2+2] photocycloaddition reaction between imine and alkene has been considered as the most efficient method for azetidine synthesis, which can directly synthesize the functionalized azetidine.

1.2. Traditional methods for azetidine synthesis

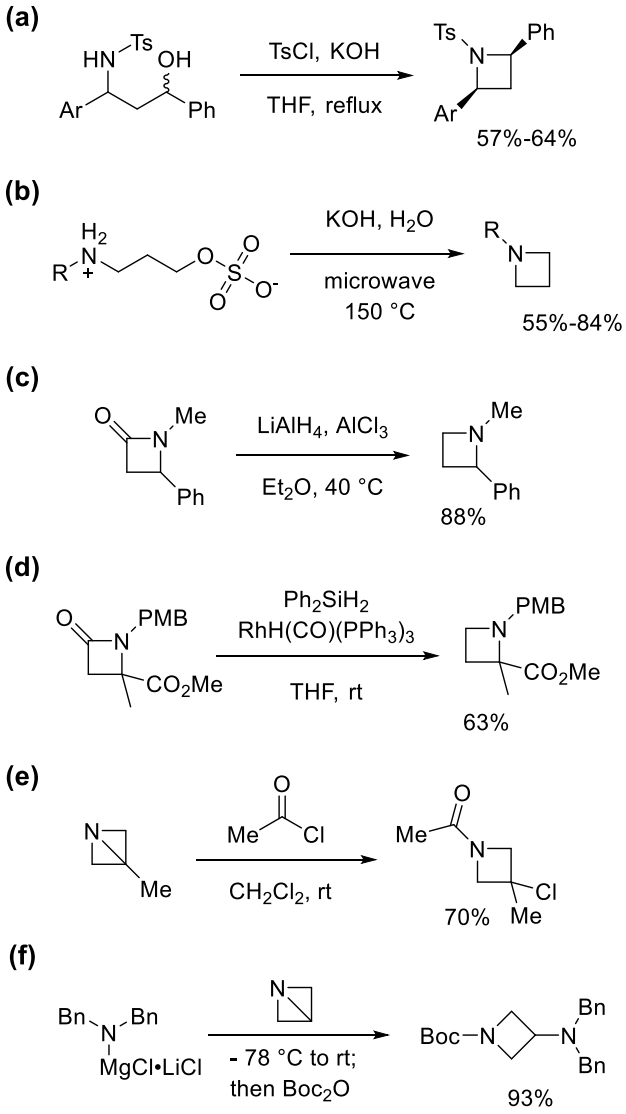
In the group of common azaheterocycles, the azetidine has been known as the hardest ring system to form. Although their inherent ring strain is a challenge in preparation, several methods were developed, in general, nucleophilic substitution, lactam reduction, and strain release reaction[5].

In case of the nucleophilic substitution reaction, the formation of the three-membered ring is favorable because it undergoes preferred conformation for S_N2 cyclization, but the four-membered ring has unfavorable eclipsed conformation so that the reaction generally requires much higher energy (Scheme 1a).

The β-lactam was generally synthesized via ketene and imine [2+2] cycloaddition known as Staudinger synthesis, then reduction of the β-lactam readily afforded azetidine. Also, the aza-bicyclobutane can be transformed to azetidine by using its ring strain (Scheme 1b, 1c).



Scheme 1. Traditional synthetic methods for azetidine (a) nucleophilic substitution, (b) β-lactam reduction, (c) strain release.



Scheme 2. Examples of traditional synthetic methods for azetidine.

However, these reactions need multiple steps and previous installation of the functional groups, and generally require harsh conditions like high temperature. As a result, they failed to incorporate the diverse products with a wide range of substituents; the several examples are shown in Scheme 2[6]. Thus, the mild and efficient synthetic methods for azetidine were highly desirable.

1.3. [2+2] photocycloaddition between imine and alkene using UV light

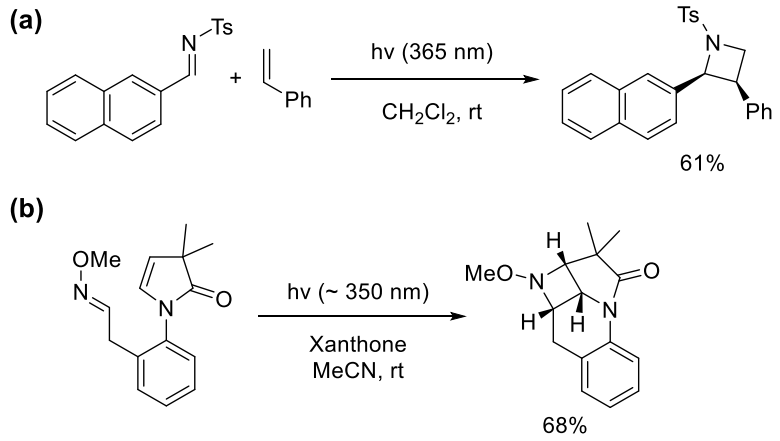
[2+2] photocycloaddition reaction between imine and alkene also known as aza Paternò-Büchi reaction can yield azetidine product. Especially, [2+2] photocycloaddition of imine and alkene needs substrates and the light only, and it can directly give product without any waste. Therefore, this reaction has been expected as the most efficient strategy for azetidine synthesis.

As a result of some researcher's effort, [2+2] photocycloaddition of imine and alkene could be

established using UV light which has high enough energy to excite the alkene. However, UV irradiation can't selectively activate the alkene. The excited C=N π bond of imine undergoes the radiationless decay processes such as isomerization or fragmentation[7] so that the imine has low chance to react with alkene[8].

This problem was solved by using rigid imine or alkene as substrates which were designed to avoid the relaxation pathways[9]. Also, the imine that has electron-withdrawing group on nitrogen could be adopted for this reaction.

Just irradiation of UV, without photocatalyst, can induce the azetidine product via π-π stacking between aryl groups of both imine and alkene substrates (Scheme 3a)[10]. In this reaction, the imine groups bearing tosyl or other protecting groups were used. Reaction between the enamide derivatives and imine groups was developed from Sivaguru group (Scheme 3b)[11]. Oxime, hydrazone, or hydrazine were used as imine group and cyclic enamide was alkene moiety. UV-sensitized xanthone transfers its energy to the substrate, then excited imine and alkene undergo intramolecular [2+2] cycloaddition.



Scheme 3. [2+2] photocycloaddition of imine and alkene via UV light irradiation.

But still this reaction has limited substrate range because of the UV light which is hazardous and has very high energy enough to decompose the susceptible functional groups. Thus, milder condition which can selectively activate the alkene and have broader substrate scope is highly demanded.

1.4. Visible light photocatalysis

Recently, visible light photocatalysis has drawn significant interest as unique and valuable catalytic process[12]. This process uses visible light as energy source which is inexpensive, abundant, safe, and sustainable. Since organic compounds generally do not absorb the visible light, photocatalyst which can absorb the light in visible region is selectively excited. Organic dyes or transition metal like ruthenium and iridium with polypyridyl complex are typical photocatalysts (Figure 3). Resulting excited photocatalyst can induce the reactive intermediate which has different reactivity patterns from

the polar or two-electron manifolds. Thus, synthetic methods using visible light photocatalysis can build the new covalent bonds even in low loading of catalyst, which were hard to be achieved using established protocols. In addition, visible light photocatalysis has a number of advantages against UV photocatalysis. Both organic molecules and photocatalysts can absorb the UV light which has high energy. As a result, UV irradiation can't selectively photoexcite the catalysts or particular functional groups and various side reactions can be caused.

However, in visible light photocatalysis, visible light can selectively excite the photocatalyst because it has lower energy. This excited catalyst can efficiently activate the substrate. This low energy demand of itself can broaden the available functional groups and decrease the possibility of side reactions. Also, it doesn't need specialized reactor or glassware, contrast to UV photochemistry[13]. Therefore, visible light photocatalysis has emerged as the most prominent tool for synthetic organic reactions.

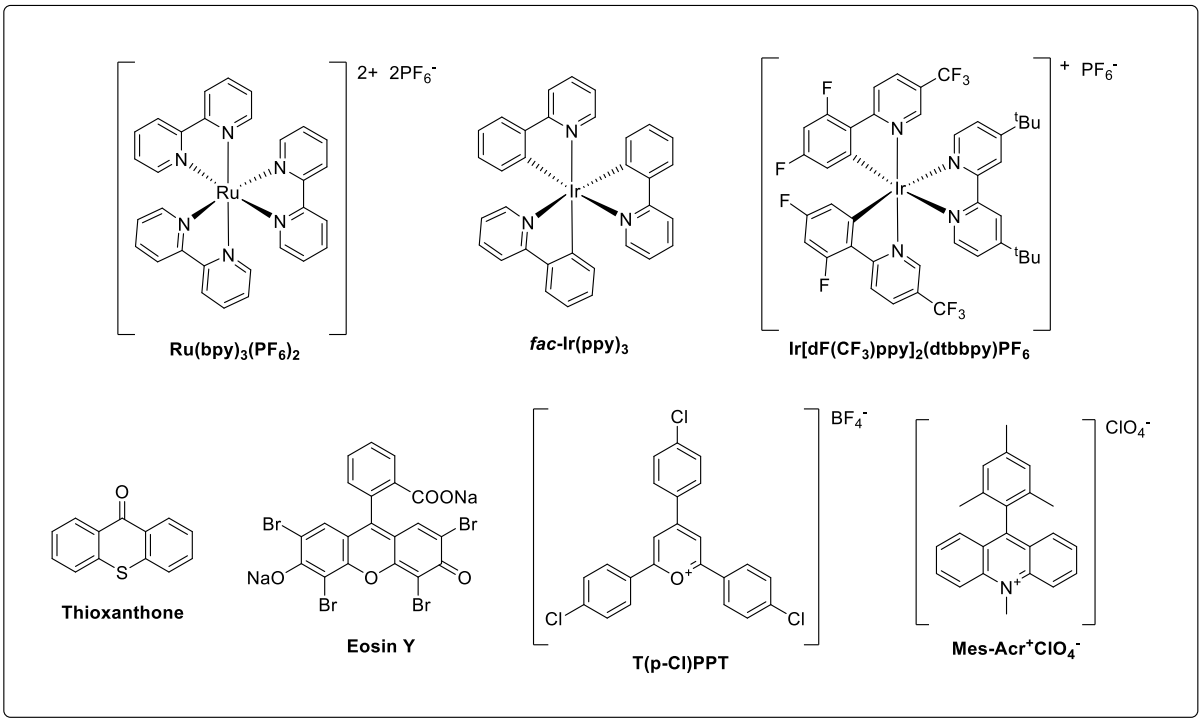


Figure 3. Typical photocatalysts.

1.4.1. General mechanism of visible-light photocatalysis

Absorption of light can provide an electronically excited photocatalyst, which means the electron is promoted to a higher energy level from the ground singlet state (**S0**) to a singlet excited state. Actually, this singlet excited state rapidly relaxes to the lowest energy level called the first singlet excited state (**S1**). This excited state can undergo radiative or nonradiative transition such as fluorescence or internal conversion to the ground state. Otherwise, it can proceed to a triplet excited

state (**T1**) via intersystem crossing (**ISC**). These excited states **S1** and **T1** can participate in reactions via energy transfer or electron transfer, but **T1** is more potent redox reagent and sensitizer due to sufficient lifetime.

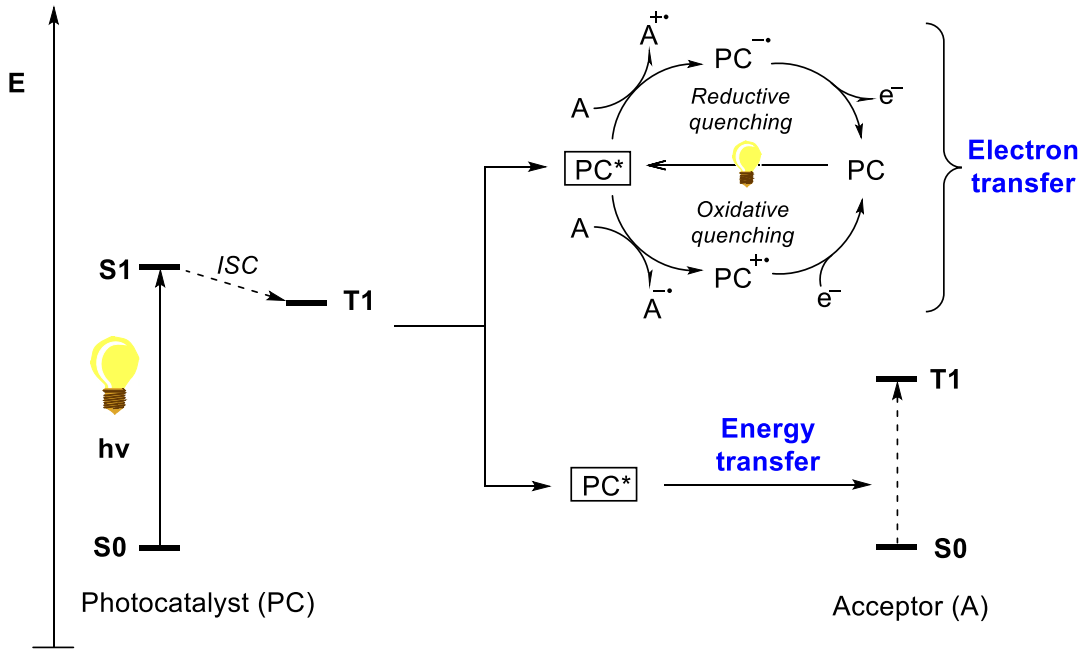


Figure 4. General mechanism of photocatalysis.[12]

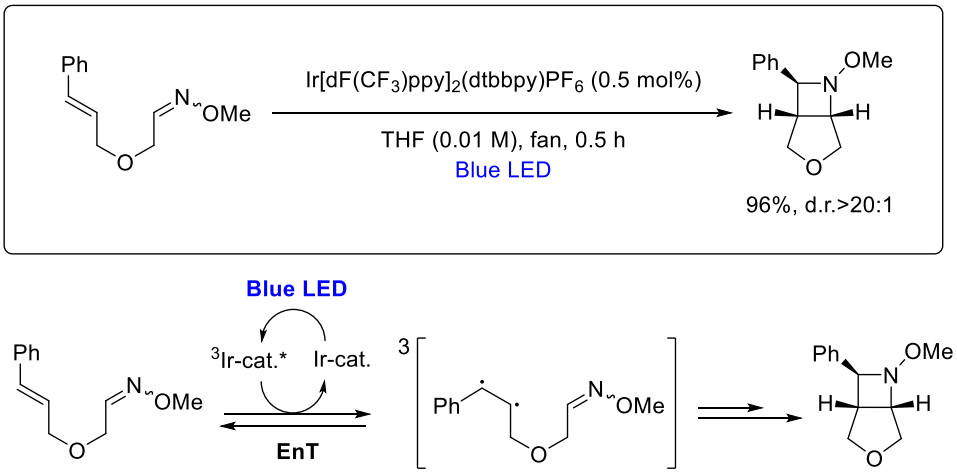
The electron transfer mechanism refers to the single electron transfer between the excited state photocatalyst and a ground state substrate. The photocatalysts can play a role as strong oxidant or reductant and this approach has greater benefits than methods requiring the stoichiometric amount of oxidant or reductant. In general, for successful electron transfer from donor to acceptor, their redox potentials have to match, which means the acceptors need to have a bigger redox potential than donors. If the reduction potential of excited state photocatalyst is bigger than oxidation potential of substrate, the photocatalyst gets an electron from the substrate. This process is called reductive quenching cycle since the photocatalyst starts its catalytic cycle as getting reduced. The opposite case is called oxidative quenching cycle.

When conducting one electron redox reactions, there is inevitable limitation. That is, the scope of the reaction is limited because the reduction of electron-rich substrate or the oxidation of electron-deficient substrate are hardly achieved in general conditions. However, energy transfer reaction can overcome this electrochemical constraint. This process depends not on redox properties but triplet energy level. In explanation above, excited **T1** state of the donor (photocatalyst) can transfer its energy to acceptor (substrate). Then, the acceptor is elevated to the triplet excited state (**T1** for A) from ground state. This excited substrate can undergo certain organic reactions. For this energy transfer process known as Dexter triplet-triplet energy transfer, the triplet energy level of donor should

be higher than acceptor.

1.4.2. [2+2] photocycloaddition between imine and alkene using visible-light

The prospect of conducting visible-light photocatalysis reactions has become the top interest from a number of research groups. Because utilization of this photocatalysis in organic reactions can provide direct C-C bond formation (C-N, C-O, and etc.) which were hard to be achieved using other traditional methods such as substitution reactions. Thus, we were engaged in developing the azetidine synthetic method which could directly afford functionalized azetidines using visible light photocatalysis. Visible light induced [2+2] photocycloaddition between imine and alkene will be the most efficient method for azetidine synthesis.



Scheme 4. [2+2] photocycloaddition of imine and alkene via energy transfer.

To the best of our knowledge, there is only one report, which is very recently published, about visible light photocatalysis [2+2] cycloaddition between imine and alkene from Schindler group (Scheme 4)[5]. On this paper, intramolecular aza Paternò-Büchi reaction was achieved via energy transfer mechanism using blue LED as light source and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ as a photocatalyst. Among the photocatalysts which absorb visible light, that was known to have the biggest triplet energy 60.8 kcal/mol. The alkene which has lower triple energy level than 60.8 kcal/mol could be selectively activated to diradical intermediate by this photocatalyst, so that the reaction was successfully applied to 24 examples, including styrene moiety which possesses a triplet energy of approximately 60 kcal/mol, up to 99% yield.

However, the limitations exist in this reaction. The imine part was still limited to oxime or hydrazone because of imine stability and they used iridium photocatalyst which is expensive and environmentally hazardous metal.

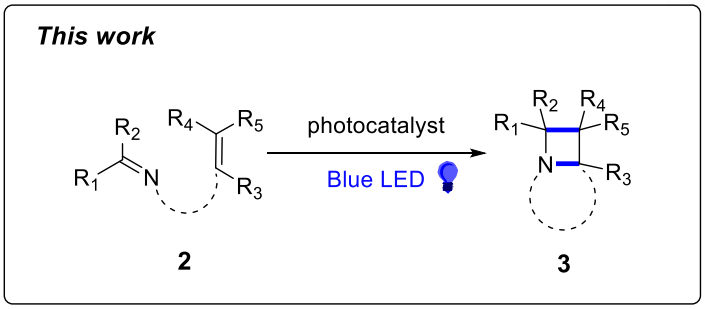


Figure 5. Our design.

Herein, we introduced more desirable metal-free photocatalytic [2+2] intramolecular aza-cycloaddition reaction which was achieved via electron transfer mechanism. The use of organophotocatalyst which is cheap and eco-friendly made it possible to selectively activate the alkene. Also, we tried to design the imine part away from the oxime or hydrazone so that multi-functionalized bicyclic azetidine could be readily synthesized.

II. RESULTS AND DISSCUSION

2.1. Research design and development

Firstly, we started our investigation on the imine part changing from oxime, hydrazone, sulfonamide, or other rigid imines. As a result, the iminomalonate was chosen which is stable, easy to prepare. The iminomalonate was synthesized from keto-malonate hydrate and easily purified by column chromatography[14]. Among the malonate groups, the isopropyl group was used because ethyl iminomalonate was easily hydrolyzed, and tert-butyl had low reactivity (Figure 6a). In addition, although iminomalonate was barely studied in photochemistry, we thought that it might be used as nitrogen radical precursor via oxidative photocatalytic quenching cycle since the malonate had electron withdrawing effect. Thus, there was a possibility that the [2+2] reaction between imine and alkene proceeded as the generated nitrogen radical attacked the alkene, followed by oxidation and cyclization (Figure 6b. eq. 1). However, unfortunately, cyclic voltammetry data revealed that the reduction potential of N-butyl iminomalonate was $E_{1/2}^{red}$ = - 1.9 V (vs. SCE in MeCN) and the oxidation potential wasn't detected, which meant reduction of the iminomalonate moiety is hard to occur and oxidation is nearly impossible by photocatalysts (Figure 6c).

In case of alkene, the styrene moiety looked good candidate for [2+2] reaction which would be initiated by alkene oxidation, because the β-alkylated styrene was known to have oxidation potential $E_{1/2}^{ox}$ = + 1.6 V (vs. SCE)[15]. On our initial expectation, the alkene was oxidized via reductive quenching cycle, then the generated radical cation was nucleophilic attacked by imine nitrogen, followed by reduction and cyclization to afford azetidine (Figure 6b. eq. 2).

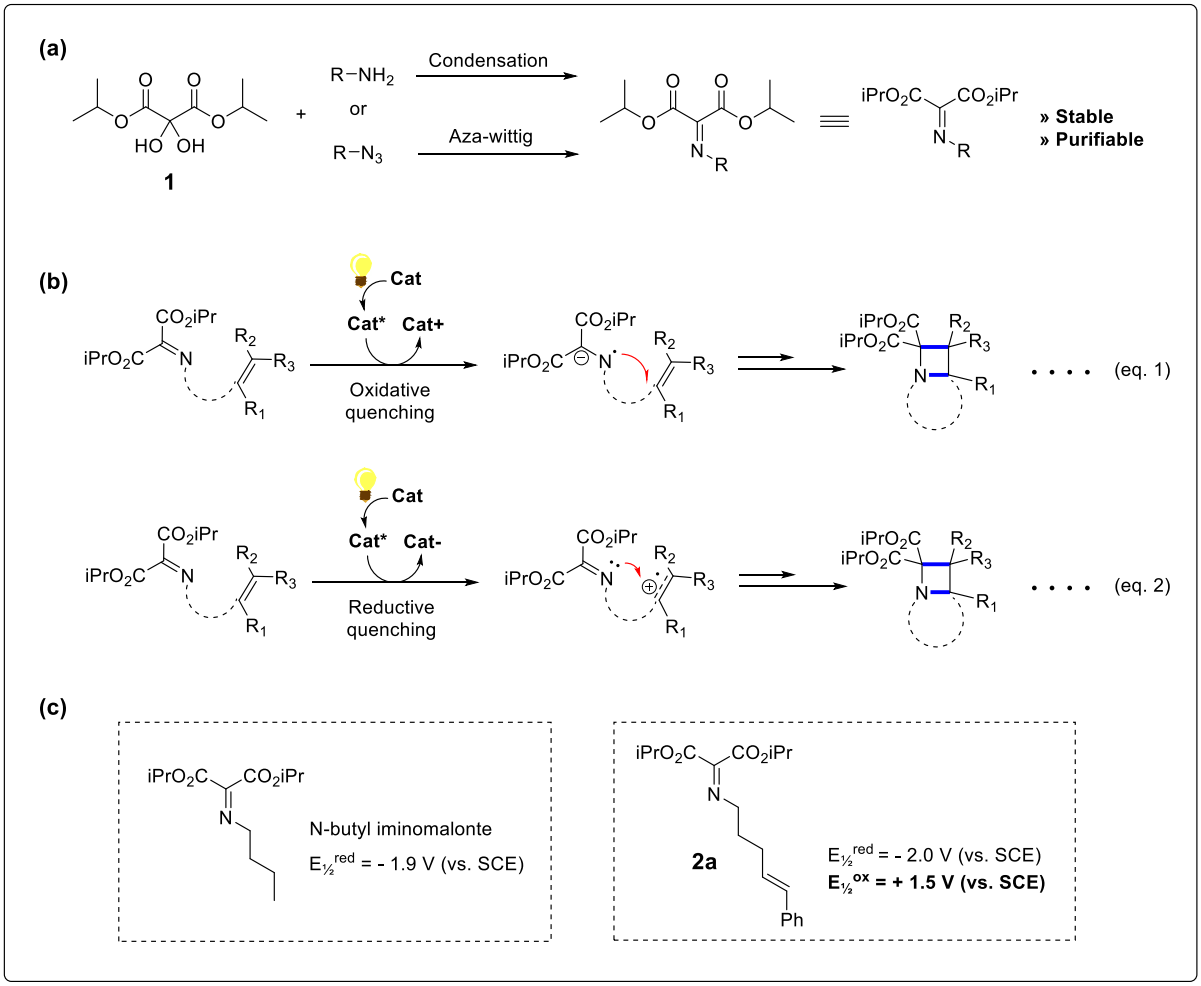
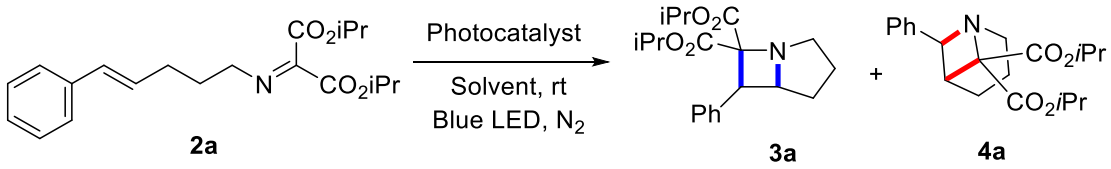


Figure 6. Reaction design and electrochemical property of substrates.

Accordingly, we synthesized **2a** as a basic substrate to test the reactivity of styrene and iminomalonate (Figure 6c). Before the photocatalysts screening, we measured redox potential of the substrate to find out its electrochemical properties. The result displayed reduction potential $E_{1/2}^{red}$ = – 2.0 V (vs. SCE in MeCN) and oxidation potential $E_{1/2}^{ox}$ = + 1.5 V (vs. SCE in MeCN), which means this substrate would be barely reduced but could be oxidized by some photocatalysts.

Thus, we envisioned the intramolecular [2+2] reaction between imines and alkenes which involved reductive quenching catalytic cycle based on visible light. As we expected, irradiation of **2a** with blue LED in the presence of some photocatalysts resulted in the formation of bicyclic azetidine products.

Table 1. Optimization table[a]



2a 3a 4a

Entry	Catalyst [5 mol%]	Solvent	Concentration	Yield (%)[b]	3 : 4
1	Rose Bengal	MeCN	0.1 M	NR	-
2	Eosin Y	MeCN	0.1 M	NR	-
3	Riboflavin	MeCN	0.1 M	NR	-
4	$Ru(bpy)_3(PF_6)_2$	MeCN	0.1 M	NR	-
5	*fac*-[$Ir(ppy)_3$]	MeCN	0.1 M	NR	-
6	$Ir(ppy)_2(dtbbpy)PF_6$	MeCN	0.1 M	NR	-
7	$Ir(Fppy)_2(dtbbpy)PF_6$	MeCN	0.1 M	Trace	-
8	$Ir(dFppy)_2(dtbbpy)PF_6$	MeCN	0.1 M	11	4.5 : 1
9	$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$	MeCN	0.1 M	17	2 : 1
10	$Ir[dF(CF_3)ppy]_2(bpy)PF_6$	MeCN	0.1 M	26	2 : 1
11	T(p-Cl)PPT	MeCN	0.1 M	70	4 : 1
12	Mes-$Acr^+ClO_4^-$	MeCN	0.1 M	> 99	4 : 1
13[c]	Mes-$Acr^+ClO_4^-$	DMSO	0.1 M	Trace	-
14[c]	Mes-$Acr^+ClO_4^-$	Toluene	0.1 M	51	16 : 1
15[c]	Mes-$Acr^+ClO_4^-$	Acetone	0.1 M	82	15 : 1
16[c]	Mes-$Acr^+ClO_4^-$	CH_2Cl_2	0.1 M	97	23 : 1
17[c]	Mes-$Acr^+ClO_4^-$	MeCN	0.1 M	> 99	10 : 1
18[c]	Mes-$Acr^+ClO_4^-$	MeCN	0.2 M	88	8 : 1
19[c]	Mes-$Acr^+ClO_4^-$	MeCN	0.02 M	> 99	1 : 0
20[c,d]	**Mes-$Acr^+ClO_4^-$**	**MeCN**	**0.02 M**	**> 99 (74[e])**	**16 : 1**
21	-	MeCN	0.02 M	NR	-
22[d,f]	Mes-$Acr^+ClO_4^-$	MeCN	0.02 M	NR	-

a. **2a** 0.05 mmol; 24 h; NR = No reaction
b. Yield was determined via ^1H NMR analysis versus an internal standard (1,1,2,2-Tetrachloroethane)
c. 48 h
d. Catalyst [2.5 mol%]
e. **2a** 0.1 mmol; isolated yield;
f. dark

Beginning with some typical photocatalysts such as $Ru(bpy)_3(PF_6)_2$, *fac*-$[Ir(ppy)_3]$, $Ir(ppy)_2(dtbbpy)PF_6$, Rose Bengal, Eosin Y and Riboflavin, these reactions didn't work at all (Table 1. entry 1 ~ 6). After that, several iridium-based photocatalysts were used, and they could deliver the desired product but in low yield (entry 7 ~ 10). Then, in use of T(p-Cl)PPT and Mes-$Acr^+ClO_4^-$, the desired products were obtained in excellent yield (entry 11, 12). These organophotocatalysts had high reduction potential E^*_{red}(cat*/cat•) = + 2.3 V (vs. SCE) and E^*_{red}(cat*/cat•) = + 2.0 V (vs. SCE), respectively, and these were high enough value to oxidize the **2a** [$E^{ox}_{1/2}$ = + 1.5 V (vs. SCE)]. Although T(p-Cl)PPT had higher reduction potential than Mes-$Acr^+ClO_4^-$, the reaction with Mes-$Acr^+ClO_4^-$ worked more efficiently. That's because, the pyrylium catalysts like T(p-Cl)PPT could be deactivated by primary amines which came from the hydrolysis of trace amount of iminomalonate. Therefore, Mes-$Acr^+ClO_4^-$ was selected as optimal catalyst.

In these reactions, to our surprises, two products were generated **3a** and **4a**. After the oxidation of styrene moiety, generated radical cation intermediate which had resonance between styrene α- and β-position could undergo nucleophilic addition of imine so that two kinds of bicyclic azetidine could be produced. We thought that if imine attacked β-position of the styrene, resulting product was **3a** which had 5-membered bicyclic structure, and if α-position, the 6-membered bridged bicyclic product **4a**. However, **4a** was readily reversed to starting material in the MeCN solution. Thus, we could get almost **3a** only as we kept longer reaction time up to 48 h.

Next, the effect of a variety of solvent was explored. Although MeCN and CH_2Cl_2 showed similar performance, MeCN was chosen as the most effective one because various types of substrates dissolved better in MeCN. Also, further optimization indicated that more diluted condition was effective, and 2.5 mol% catalyst loading could display quantitative yield. Since the yield of **4a** was in the range of error of ^{1}H NMR yield, the ratio between **3a** and **4a** wasn't accurate (entry 16, 17, 19, 20). In addition, **4a** couldn't be detected in isolation procedure which meant very trace amount of **4a** remained in those cases.

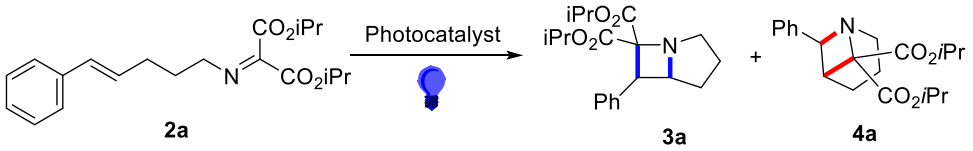
Finally, control experiments revealed that no product formation occurs in the absence of light or photocatalyst (entry 21, 22) and optimal condition was established as **2a** (1.0 equiv.), Mes-$Acr^+ClO_4^-$ (2.5 mol%), MeCN (0.02 M) under N_2 atmosphere at room temperature with irradiation of 12 W blue LED.

2.2. Plausible mechanism

The results above said that the photocatalysts which had lower reduction potential than 1.5 V (vs. SCE) was shown ineffective for reaction, and in use of higher reduction potential catalysts, the reaction worked well. Accordingly, we suggested that the reaction included oxidation of the **2a**, which was conducted by electron transfer with excited state photocatalyst. However, in several iridium photocatalysts, the cycloadduct was obtained, even though their reduction potential was lower. As we

looked into the reason, we found out that their triplet energy matched with **2a**.

Table 2. Reaction profile[a]



2a 3a 4a

Entry	Catalyst	E^*_{red}(cat*/cat$^-$)	E^*_{ox}(cat*/cat$^+$)	E_T (kcal/mol)	Yield[b] (%)
1	Mes-Acr$^+$ClO$_4^-$	**+ 2.06 V**	-	45	**> 99**
2	T(p-Cl)PPT	**+ 2.30 V**	-	53	**70**
3	Ir[dF(CF$_3$)ppy]$_2$(bpy)PF$_6$	+ 0.97 V	- 0.97 V	**60.4**	**26**
4	Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$	+ 1.21 V	- 0.89 V	**60.8**	**17**
5	Ir(dFppy)$_2$(dtbbpy)PF$_6$	+ 1.14 V	- 0.93 V	**55.4**	**11**
6	Ir(Fppy)$_2$(dtbbpy)PF$_6$	+ 1.07 V	- 1.04 V	53	Trace
7	*fac*-[Ir(ppy)$_3$]	+ 0.31 V	- 1.73 V	58	NR
8	Ir(ppy)$_2$(dtbbpy)PF$_6$	+ 0.66 V	- 0.96 V	49	NR
9	Ru(bpy)$_3$(PF$_6$)$_2$	+ 0.77 V	- 0.81 V	46	NR
10	Eosin Y	+ 0.79 V	- 1.06 V	44	NR
11	Rose Bengal	+ 0.99 V	- 0.68 V	41	NR

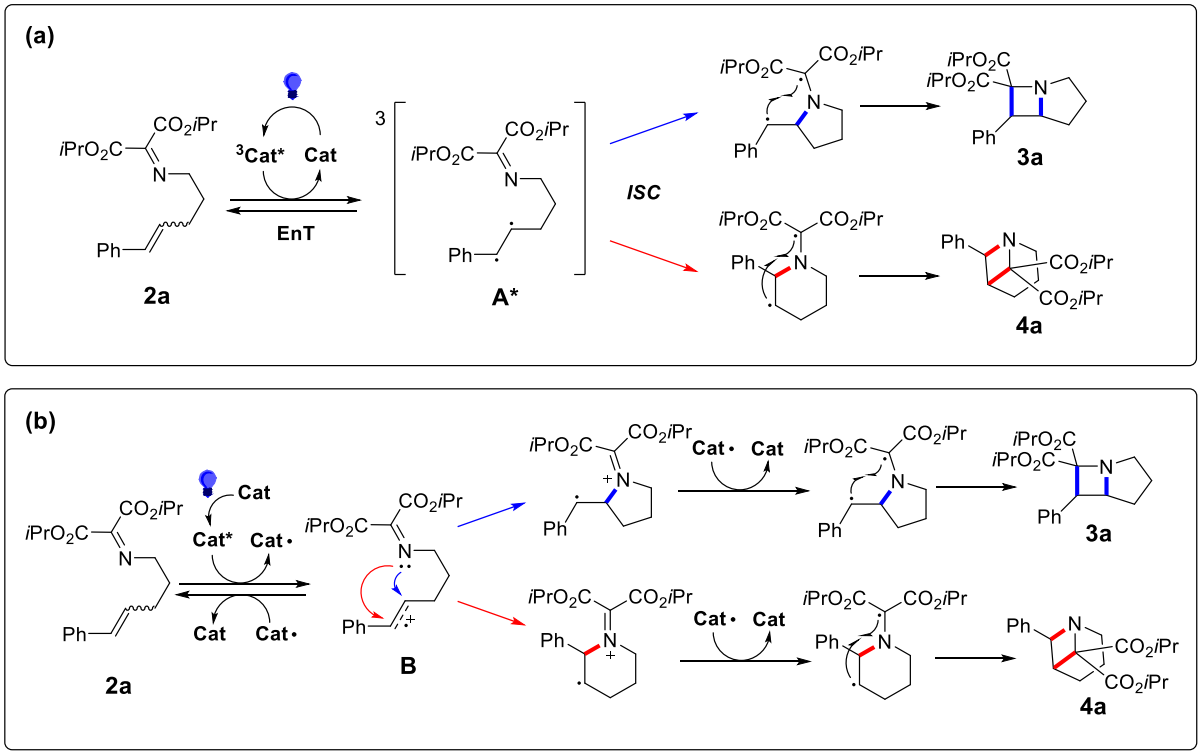
a. **2a** 0.05 mmol; MeCN (0.1 M); 24 h
b. **3** and **4** combined ^{1}H NMR yield (internal standard: 1,1,2,2-Tetrachloroethane)

In general, styrene moiety was known to possess triplet energy of approximately 60 kcal/mol.[16] Thus, in the case of iridium photocatalysts which have triplet energy around 60 kcal/mol, [2+2] reaction proceeded as the alkene was activated to diradical intermediate **A*** via energy transfer (Scheme 5a). This diradical intermediate **A*** can undergo relaxation pathways, so the E/Z isomerization can occur. Actually, the isomerization of remaining starting material was observed (Table 2. entry 3 ~ 6). The E:Z ratio was changed to 1:1, although the initial starting material has only E conformation. In addition, radical cation intermediate **B** could be also returned to starting material via back electron transfer, so that E:Z ratio 1:1 was observed even in trace amount of remaining starting material (entry 1, 2).

We could notice no reaction occurred when photocatalysts had lower value of both reduction potential and triplet energy (entry 8 ~ 11). However, there was an exceptional case, *fac*-[Ir(ppy)$_3$] which had triplet energy of 58 kcal/mol (entry 7), the starting material was recovered 100% with E:Z ratio 2.5:1.

Interestingly, those cases which energy transfer could occur showed much inferior performance to the reactions using Mes-Acr$^+$ClO$_4^-$ and T(p-Cl)PPT which could undergo redox mechanism. This result demonstrated the iminomalonate much prefers radical cation intermediate to diradical one for [2+2] cycloaddition. In other words, overall results said markedly low reactivity between triplet excited alkene and iminomalonate, which is contrast to the oxime or hydrazone moiety in reports from

other groups[5,10,11]. Additionally, Mes-Acr^{+}ClO$_4^{-}$ has triplet energy of 45 kcal/mol which is insufficient to activate the styrene.



Scheme 5. Proposed mechanism via (a) energy transfer, (b) electron transfer.

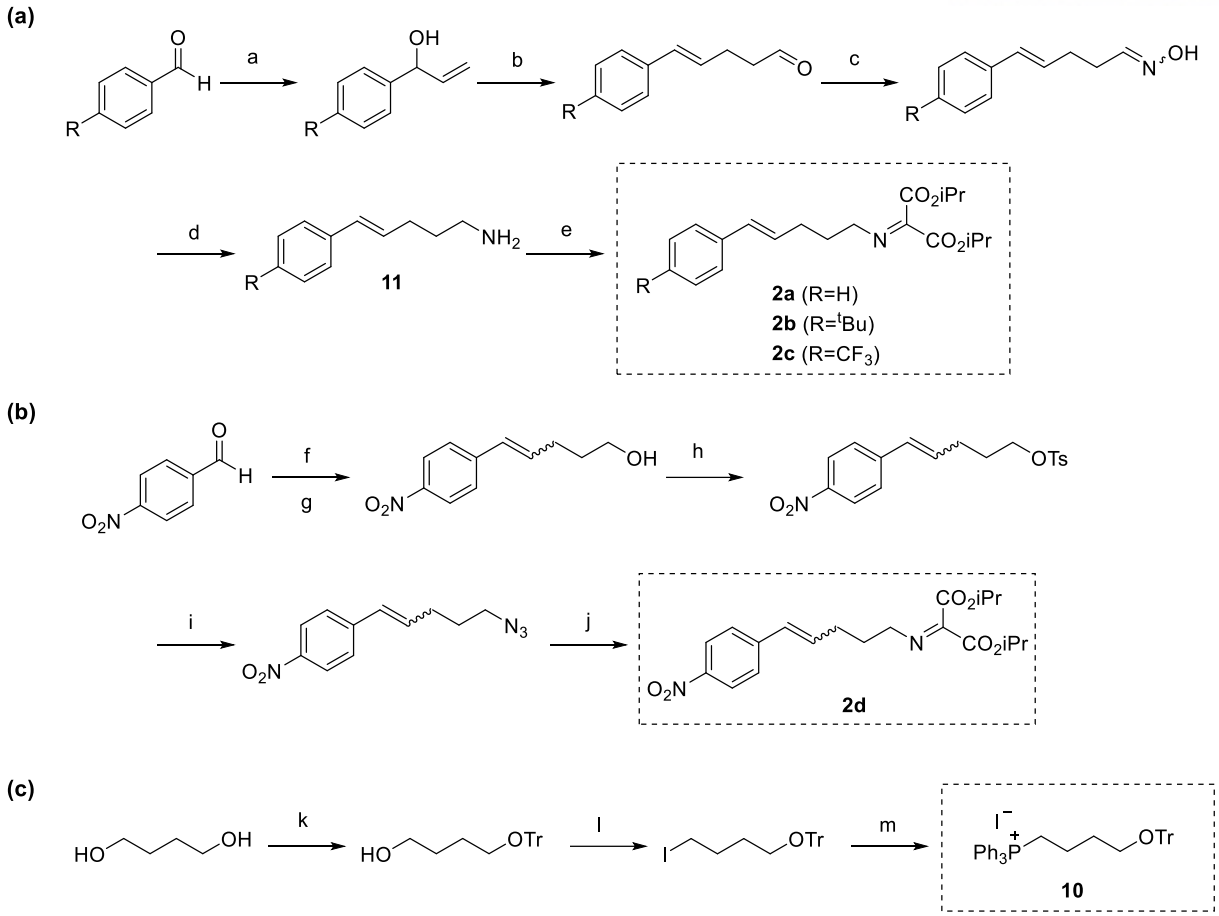
On the basis of these mechanistic investigations, we proposed feasible reaction mechanism as described in Scheme 5b. Firstly, blue LED irradiation[17] induces excited state of Mes-Acr^{+}ClO$_4^{-}$. This excited photocatalyst oxidizes the substrate via SET. Then imine moiety attacks radical cation intermediate **B**[18]. The generated iminium cation undergoes SET reduction[19] by cat· so that the photocatalytic cycle could be used again. Consequently, resulting diradical intermediate gives azetidine product by radical coupling each other.

2.3. Substrate synthesis

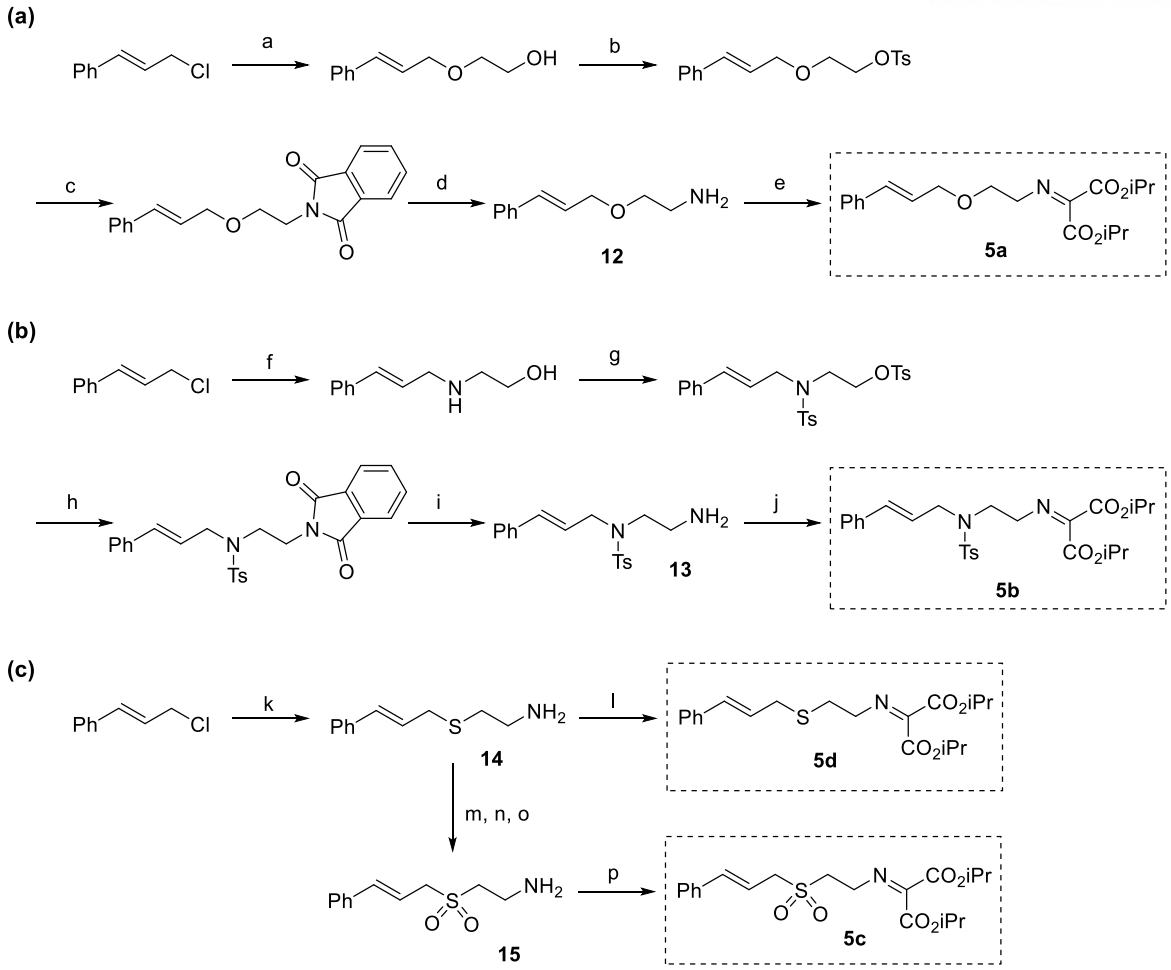
With our established condition, we tried to test the reactivity of several substrates in [2+2] photocycloaddition. Different kinds of iminomalonate were readily obtained by ketone-amine condensation. Amine intermediates were generally synthesized from reduction of oxime or Gabriel synthesis. In case of oxime reduction, firstly, the benzaldehyde or ketone was treated with vinyl magnesium bromide. Then, allylic alcohol underwent O-allylation and Claisen condensation simultaneously. Resulting tethered aldehyde was converted to oxime by hydroxylamine and followed by reduction to give amine. In case of **18**, the allylic alcohol intermediate was prepared by Corey-Chaykovsky type reaction.

In case of **2d** which has strong electron withdrawing group, the amine couldn't be prepared because p-NO_2 group made the alkene very electrophilic and intramolecular cyclization occurred[20]. As a solution, we used azide instead of amine, then aza-Wittig reaction could afford the **2d**. For azide intermediate, p-NO_2 benzaldehyde underwent Wittig reaction with **10**, followed by deprotection, tosylation, and azidation.

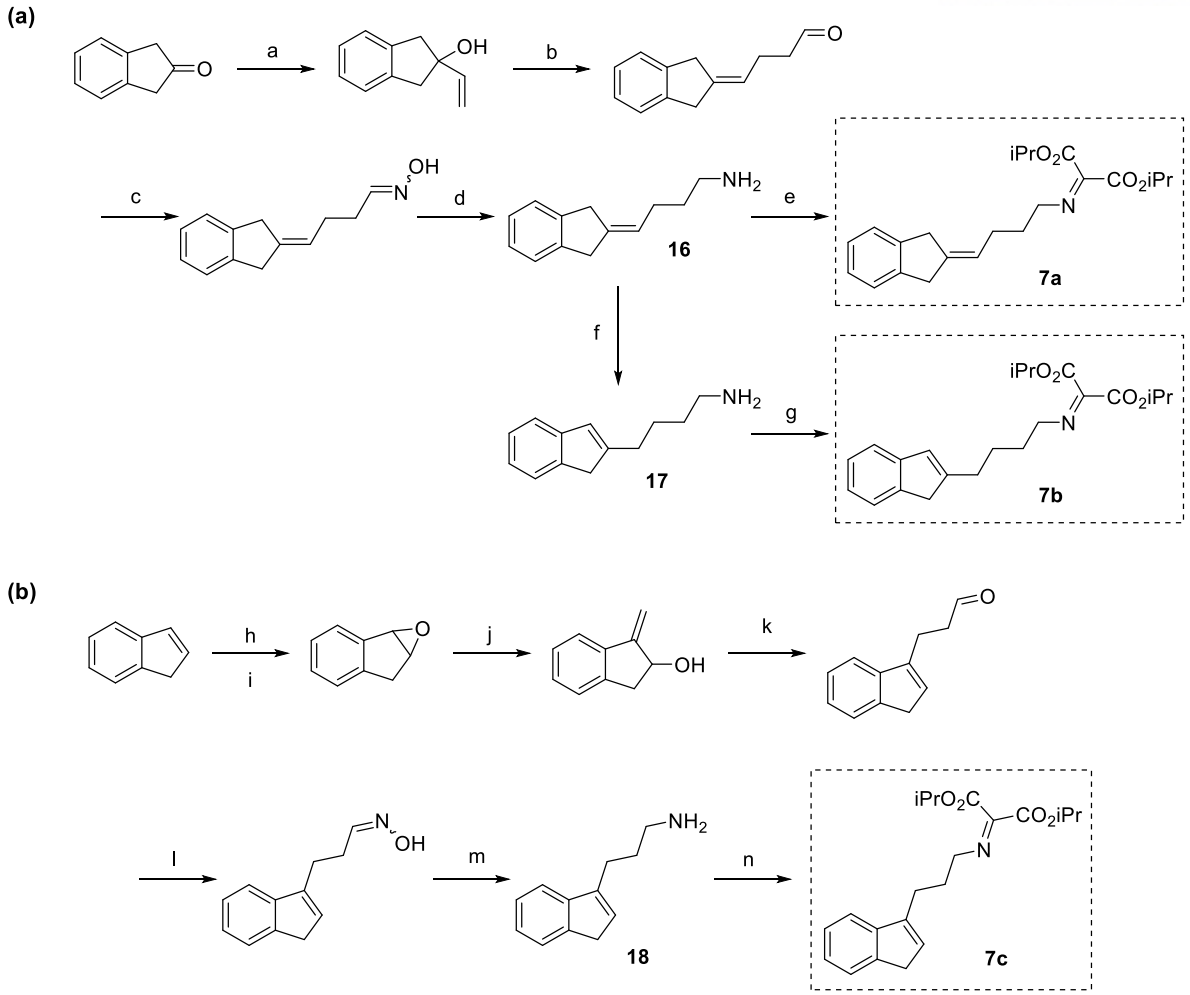
For Gabriel synthesis, methyl hydrazine was used instead of hydrazine, because hydrazine made side reaction like alkene reduction. Phthalimide intermediate was prepared via S_N2 reaction between tosylate and potassium phthalimide. Sulfur atom adopted substrate **5d** was synthesized differently using 2-Mercaptoethylamine, and **5c** was obtained from **15**, which **14** was converted to via processes of protection, oxidation, and deprotection. Overall synthetic scheme is described in Scheme 6~8. and detailed procedure is in Experimental section.



Scheme 6. Synthesis of iminomalonate with p-substituted styrene. Reagents and conditions: a) VinylMgBr, THF, 0 °C, b) $Hg(OAc)_2$, NaOAc, Butyl Vinyl Ether, 100 °C, 81% (R=H, 2 steps), 44% (R=CF_3, 3 steps), c) $NH_2OH{\cdot}HCl$, Pyridine, rt, 99% (R=H), 100% (R=CF_3), d) LAH, THF, 0 °C, 71% (R=H), 56% (R=CF_3), e) **1**, CSA, 4Å Molecular sieves, 100 °C, 84% (R=H), 55% (R=CF_3), f) **10**, n-BuLi, THF, - 30 °C, 75% (E:Z=1:4), g) TsOH, CH_2Cl_2/MeOH, rt, 76% (E:Z=1:4), h) TsCl, TEA, DMAP, CH_2Cl_2, rt, 87% (E:Z=1:4), i) NaN_3, DMF, rt, 97% (E:Z=1:1), j) PPh3, Toluene, 70 °C, 3 h, then **1**, Toluene, 100 °C, 92% (E:Z=20:1), k) TrCl, pyridine, CH_2Cl_2, rt, 92%, l) Imidazole, PPh_3, I_2, Et_2O/MeCN, 0 °C, 91%, m) PPh_3, Benzene, 90 °C, 85%

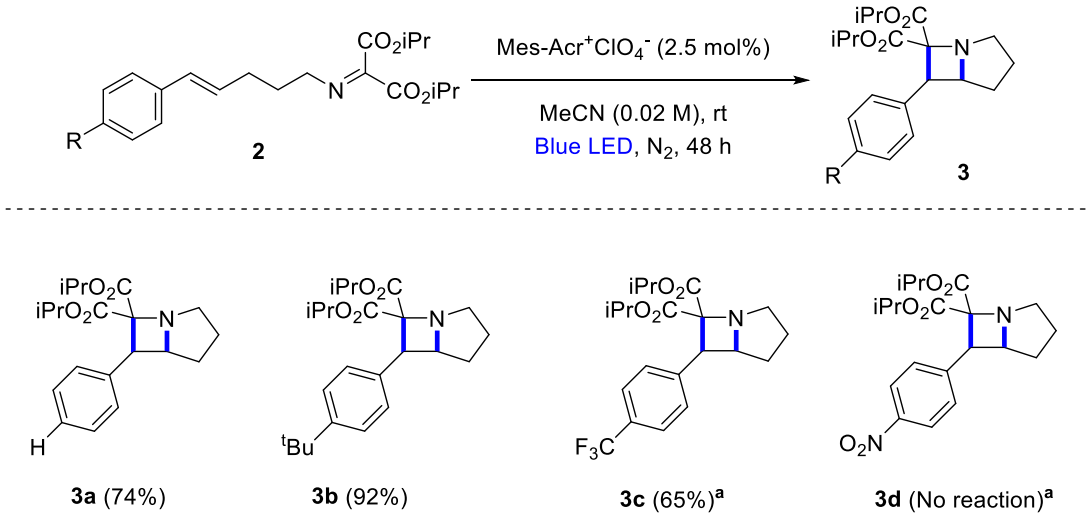


Scheme 7. Synthesis of heteroatom adopted iminomalonate. Reagents and conditions:
a) Ethylene glycol, NaH, NaI, THF, 70 °C, 63%, b) TsCl, TEA, DMAP, CH_2Cl_2, 0 °C, 96%, c) PPI, DMF, 90 °C, 82%, d) $MeNHNH_2 \cdot H_2SO_4$, TEA, MeOH, 70 °C, 79%, e) **1**, CSA, 4Å Molecular sieves, 100 °C, 74%, f) 2-Aminoethanol, MeCN, rt, 76%, g) TsCl, TEA, DMAP, CH_2Cl_2, rt, 95%, h) PPI, DMF, 90 °C, 90%, i) $MeNHNH_2 \cdot H_2SO_4$, TEA, MeOH, 70 °C, 58%, j) **1**, CSA, 4Å Molecular sieves, 100 °C, 59%, k) Cysteamine hydrochloride, $LiOH \cdot H_2O$, Ethanol/H_2O, 90%, l) **1**, CSA, 4Å Molecular sieves, 100 °C, 66%, m) Boc_2O, TEA, CH_2Cl_2, 0 °C, 97%, n) m-CPBA, THF, 0 °C, 96%, o) TFA, CH_2Cl_2, 0 °C, 98%, p) **1**, CSA, 4Å Molecular sieves, 100 °C, 72%



Scheme 8. Synthesis of iminomalonate with alkyl substituted alkene. Reagents and conditions: a) VinylMgBr, Toluene, 0 °C, 57%, b) $Hg(OAc)_2$, NaOAc, Butyl Vinyl Ether, 100 °C, 70%, c) $NH_2OH{\cdot}HCl$, Pyridine, rt, 91%, d) LAH, THF, 0 °C, 60%, e) **1**, CSA, 4Å Molecular sieves, 100 °C, 54%, f) KO^{t}Bu, DMSO, 0 °C, 57%, g) **1**, CSA, 4Å Molecular sieves, 100 °C, 58%, h) NBS, THF/H_2O, 0 °C, i) NaOH, Et_2O, rt, 90% (2 steps), j) $(CH_3)_3SI$, n-BuLi, THF, - 10 °C, 61%, k) $Hg(OAc)_2$, NaOAc, Butyl Vinyl Ether, 100 °C, 68%, l) $NH_2OH{\cdot}HCl$, Pyridine, rt, 92%, m) LAH, THF, 0 °C, 53%, n) **1**, CSA, 4Å Molecular sieves, 100 °C, 51%

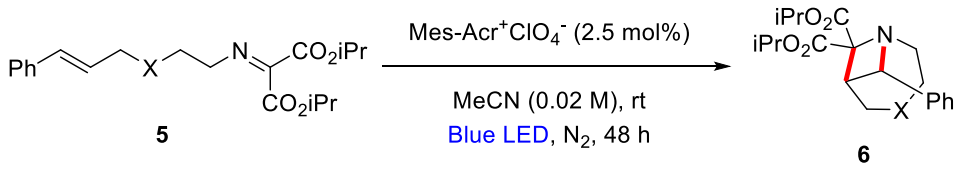
Table 3. Substrate scope 1

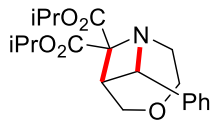


Condition: **2** (0.10 mmol), Mes-Acr$^+$ClO$_4^-$ (2.5 mol%), MeCN (0.02 M), N_2, rt, Blue LED, 48 h, isolated yield;
a. T(p-Cl)PPT (5 mol%) was used instead of Mes-Acr$^+$ClO$_4^-$

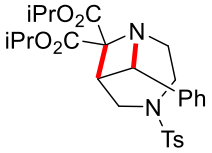
We investigated the reactivity of various kind of iminomalonate with our standard condition. Firstly, the electronic effect of the styrene was explored. As we expected, when the electron donating group was on aryl group, the standard condition afforded azetidine product **3b** in excellent yield. However, in case of the substrate which had electron withdrawing group such as CF_3 or NO_2, the reaction didn't work at all. We assumed these electron deficient substrates have higher oxidation potential than Mes-Acr$^+$ClO$_4^-$ and oxidation of the substrate couldn't proceed. So, T(p-Cl)PPT (5 mol%) was applied which is stronger oxidant than Mes-Acr$^+$ClO$_4^-$. As a result, **3c** was obtained in good yield. Although this reaction has electrochemical constraint which the oxidation of electron deficient substrate is hard, we can overcome it by using T(p-Cl)PPT and expand the range of available substrates. But, unfortunately, nitro group prevents formation of **3d** even in presence of T(p-Cl)PPT, implying there is still oxidation limitation.

Table 4. Substrate scope 2

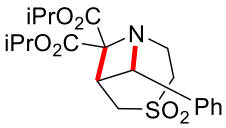




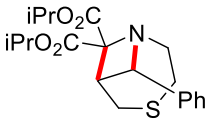
6a (58%)



6b (55%)[a]



6c (61%)[a]

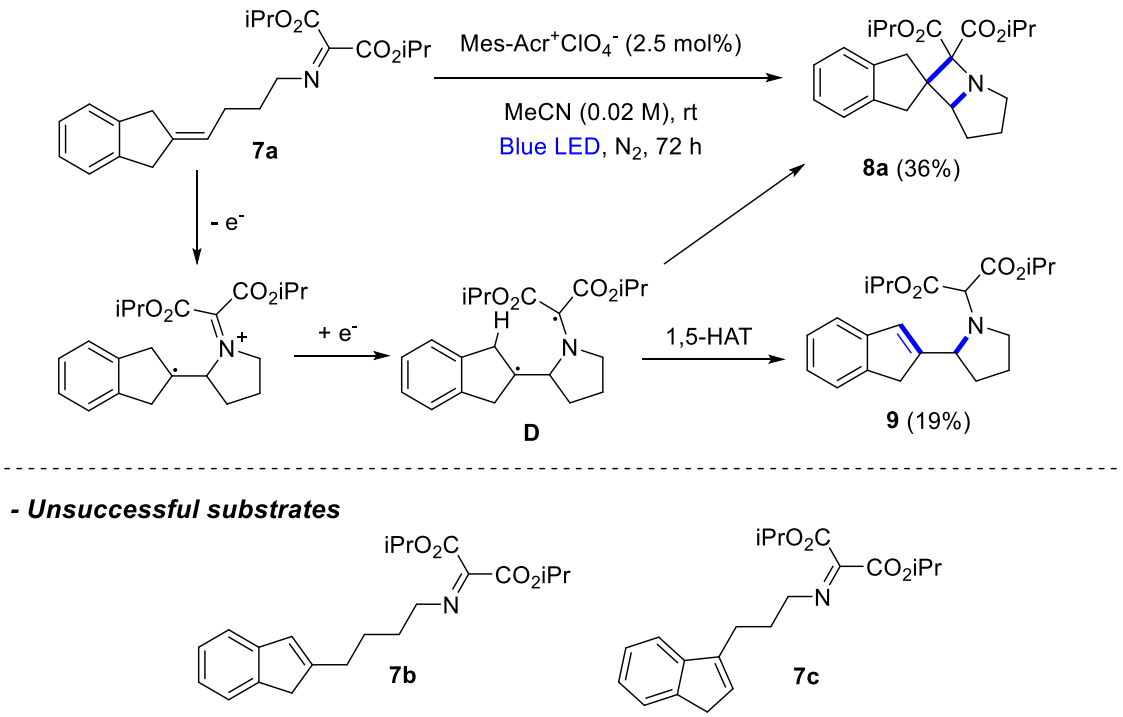


6d (No reaction)

Condition: **5** (0.10 mmol), Mes-Acr^{+}ClO$_4^{-}$ (2.5 mol%), MeCN (0.02 M), N_2, rt, Blue LED, 48 h, isolated yield;
a. 72 h

Next, we changed the tether between imine and alkene and prepared the substrates **5a**~**5d**. Surprisingly, the reaction only provided **6** which is the product from C-N bond formation on α-position of styrene. The heteroatom adopted bicyclic azetidines were obtained in moderate yield but the substrate with sulfide moiety **5d** wasn't successful. Probably, there was little chance of alkene oxidation because the sulfur atom could get oxidized and undergo back electron transfer. In contrast, the sulfone adopted azetidine **6c** could be generated, as the sulfone prevents that side reaction.

Table 5. Substrate scope 3



Condition: **7** (0.10 mmol), Mes-Acr$^+$ClO$_4^-$ (2.5 mol%), MeCN (0.02 M), N_2, rt, Blue LED, 72 h, isolated yield;

To further explore the scope, the tri-alkyl substituted alkene substrate **7a** was synthesized. **7a** gave azetidine product **8a** in 36% yield, and interestingly, **9** was observed in 19% yield. In our proposed mechanism, after C-N bond formation, the diradical intermediate **D** was generated, then direct radical-radical coupling provided **8a**. Otherwise, nitrogen alpha radical underwent 1,5-hydrogen atom transfer[21], so that **9** could be formed. As similar substrates, **7b** and **7c** which have indene moiety were tested, but they showed no reaction.

III. Conclusion

In summary, we have developed intramolecular [2+2] aza cycloaddition of alkene and imine via visible light photocatalysis, which can directly produce bicyclic azetidine derivatives up to 92% yield without any by-product. More variously functionalized azetidine can be accessed, as iminomalonate moiety is used as a new imine group which has different reactivity pattern from others. This mild protocol does not require transition metal or external redox reagents, so it has huge benefit over other methods utilizing UV light or metal photocatalyst and can be applied to the synthesis and modification of bioactive molecules.

IV. Experimental

General methods

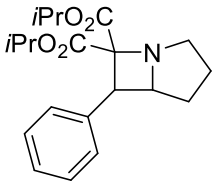
The reactions were carried out in oven dried glassware under N_2 atmosphere with dry solvents. All photocatalysis reactions were completed under argon atmosphere in glovebox. Organic solutions were evaporated under reduced pressure on a Büchi rotary evaporator using water bath. The reaction was monitored by analytical thin layer chromatography (TLC) using Merck TLC Silica gel 60 F254 precoated plate (0.2 mm thickness). After elution, plates were visualized using UV radiation (254 nm). Further visualization was possible by staining with solution of potassium permanganate, ceric molybdate, or ninhydrin. Flash column chromatography was performed with Silica Flash P60 silica gel (230-400 mesh). All reagents were obtained from commercial sources (Alfa Aesar, Sigma Aldrich, TCI Chemicals) and were used without further purification. Proton (1H) and carbon (13C) NMR spectra were recorded on a 400/100 MHz Agilent 400M FT-NMR spectrometer. NMR solvents were obtained from Cambridge Isotope Laboratories and the residual solvent signals were taken as the reference (0.0 ppm for 1H NMR spectra and 77.0 ppm for 13C NMR spectra in CDCl3). The signals observed are described as: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Coupling constants are reported as J value in Hz. High resolution mass analysis was performed with Bruker HCT Basic System coupled with Agilent 1200 Series. Cyclic voltammetry spectra were recorded on WizMAC WizECM – 1200 Premium. The reaction mixture of photocatalysis was irradiated with 12 W blue LED lamp. Systematic nomenclature for the compounds follows the numbering system as defined by IUPAC with assistance from CS Chemdraw® software.

General procedure A:

Visible-light photocatalysis for [2+2] cycloaddition between imine and alkene

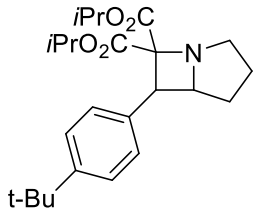
Photocatalyst Mes-Acr^{+}ClO$_4^{-}$ (2.5 mol%) were added to an oven-dried 8 ml-vial equipped with a stir bar and dissolved in MeCN (4 ml) under argon atmosphere. To this solution was added iminomalonate (0.1 mmol, 1.0 equiv.) in MeCN (1 ml), then resulting reaction mixture was irradiated by 12W blue LED lamp at room temperature. After completion of the reaction as monitored by TLC, the solution was concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel to give the desired azetidine product.

Diisopropyl 6-phenyl-1-azabicyclo[3.2.0]heptane-7,7-dicarboxylate (3a)



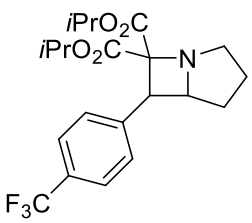
Prepared according to *General procedure A* using Diisopropyl (E)-2-((5-phenylpent-4-en-1-yl)imino)malonate **(2a)**, 74% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 5H), 5.17 (hept, *J* = 6.2 Hz, 1H), 4.61 (hept, *J* = 6.1 Hz, 1H), 4.33 (d, *J* = 8.6 Hz, 1H), 3.79 (ddd, *J* = 10.4, 7.3, 2.6 Hz, 1H), 3.13 (td, *J* = 8.1, 3.3 Hz, 1H), 2.42 (td, *J* = 9.2, 7.2 Hz, 1H), 1.97 - 1.75 (m, 3H), 1.49 - 1.42 (m, 1H), 1.34 - 1.29 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.25, 157.03, 136.70, 128.61, 127.55, 101.73, 77.97, 73.03, 67.14, 59.94, 52.59, 25.70, 22.81, 22.35, 22.21, 22.05, 21.90; MS (APCI): *m/z* 346.2 [M+H]$^{+}$.

Diisopropyl 6-(4-(tert-butyl)phenyl)-1-azabicyclo[3.2.0]heptane-7,7-dicarboxylate (3b)



Prepared according to *General procedure A* using Diisopropyl (E)-2-((5-(4-(tert-butyl)phenyl)pent-4-en-1-yl)imino)malonate **(2b),** 92% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 5.16 (hept, *J* = 6.1 Hz, 1H), 4.62 (hept, *J* = 6.1 Hz, 1H), 4.32 (d, *J* = 8.6 Hz, 1H), 3.77 (ddd, *J* = 10.5, 7.7, 2.5 Hz, 1H), 3.12 (td, *J* = 8.1, 3.2 Hz, 1H), 2.41 (td, *J* = 9.2, 6.9 Hz, 1H), 1.96 - 1.76 (m, 3H), 1.49 - 1.43 (m, 1H), 1.33 - 1.27 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.31, 157.09, 151.58, 133.70, 127.22, 125.52, 101.65, 77.81, 72.87, 67.09, 59.88, 52.61, 34.61, 31.29, 25.81, 22.80, 22.34, 22.22, 22.06, 21.88; MS (APCI): *m/z* 402.3 [M+H]$^{+}$.

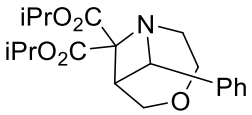
Diisopropyl 6-(4-(trifluoromethyl)phenyl)-1-azabicyclo[3.2.0]heptane-7,7-dicarboxylate (3c)



Prepared according to *General procedure A* using Diisopropyl (E)-2-((5-(4-(trifluoromethyl)phenyl)pent-4-en-1-yl)imino)malonate **(2c)**, and T(p-Cl)PPT (5 mol%) instead of Mes-Acr^{+}ClO$_4^{-}$ (2.5 mol%), 65% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 5.17 (hept, *J* = 6.3 Hz, 1H), 4.59 (hept, *J* = 6.2 Hz, 1H), 4.37 (d, *J* = 8.5 Hz, 1H), 3.80 (m, 1H), 3.10 (td, *J* = 8.2, 3.4 Hz, 1H), 2.43 (td, *J* = 9.4, 7.2 Hz, 1H), 1.96 - 1.76 (m, 3H), 1.46 - 1.40 (m,

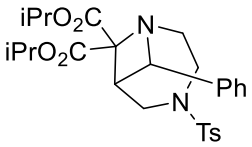
1H), 1.34-1.31 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.05, 156.61, 140.58, 130.82 (q, *J* = 32.5 Hz), 127.88, 125.63 (q, *J* = 3.7 Hz), 122.55 (q, J = 270 Hz), 102.07, 77.31, 73.40, 67.33, 60.03, 52.57, 25.86, 22.82, 22.37, 22.19, 22.03, 21.90; MS (APCI): *m/z* 414.2 $[M+H]^+$.

Diisopropyl 8-phenyl-4-oxa-1-azabicyclo[4.1.1]octane-7,7-dicarboxylate (6a)



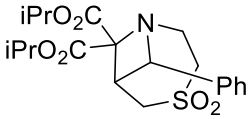
Prepared according to *General procedure A* using Diisopropyl 2-((2-(cinnamyloxy)ethyl)imino)malonate (**5a**), 58% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.37 (m, 3H), 7.34 – 7.31 (m, 2H), 5.46 (d, *J* = 9.3 Hz, 1H), 5.13 (hept, *J* = 6.2 Hz, 1H), 4.72 (m, 1H), 3.87 (dd, *J* = 11.4, 3.6 Hz, 1H), 3.79 (ddd, *J* = 11.9, 8.5, 2.9 Hz, 2H), 3.46 (d, *J* = 12.2 Hz, 1H), 3.29 (dt, *J* = 12.1, 2.0 Hz, 1H), 2.81 (td, *J* = 11.8, 3.8 Hz, 1H), 2.68 (dd, *J* = 9.2, 2.6 Hz, 1H), 1.32 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.00, 158.98, 136.65, 128.83, 128.74, 126.94, 102.83, 75.54, 72.69, 67.40, 67.22, 65.17, 58.03, 49.55, 22.34, 22.22, 22.13, 22.09; MS (APCI): *m/z* 362.2 $[M+H]^+$.

Diisopropyl 8-phenyl-4-tosyl-1,4-diazabicyclo[4.1.1]octane-7,7-dicarboxylate (6b)



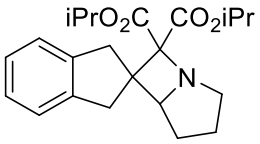
Prepared according to *General procedure A* using Diisopropyl 2-((2-((N-cinnamyl-4-methylphenyl)sulfonamido)ethyl)imino)malonate (**5b**), 55% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.41 (m, 7H), 7.28 – 7.26 (m, 2H), 5.54 (d, *J* = 9.3 Hz, 1H), 5.07 (hept, *J* = 5.8 Hz, 1H), 4.75 (hept, *J* = 6.1 Hz, 1H), 3.65 (dd, *J* = 11.1, 2.7 Hz, 1H), 3.38 (dt, *J* = 12.1, 2.8 Hz, 1H), 3.27 (d, *J* = 12.0 Hz, 1H), 2.85 (m, 2H), 2.52 (td, *J* = 11.8, 3.4 Hz, 2H), 2.40 (s, 3H), 1.30 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.92, 159.25, 144.01, 136.05, 131.02, 129.60, 129.02, 128.84, 127.97, 127.03, 101.63, 75.78, 72.75, 67.28, 57.72, 48.47, 46.43, 44.80, 22.39, 22.16, 22.13, 22.09, 21.45; MS (APCI): *m/z* 515.2 $[M+H]^{+\cdot}$

Diisopropyl 8-phenyl-4-thia-1-azabicyclo[4.1.1]octane-7,7-dicarboxylate 4,4-dioxide (6c)



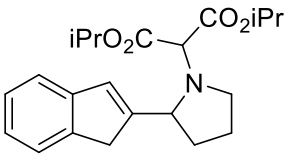
Prepared according to *General procedure A* using Diisopropyl 2-((2-(cinnamylsulfonyl)ethyl)imino)malonate (**5c**), 61% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.41 (m, 5H), 5.64 (d, *J* = 9.5 Hz, 1H), 5.12 (hept, *J* = 6.2 Hz, 1H), 4.74 (hept, *J* = 6.2 Hz, 1H), 3.61 (m, 1H), 3.39 (m, 3H), 3.21 (dd, *J* = 14.6, 5.6 Hz, 1H), 3.03 (m, 1H), 2.77 (dt, *J* = 14.6, 3.7 Hz, 1H), 2.68 (dd, *J* = 9.2, 2.6 Hz, 1H), 1.34 (m, 6H), 1.30 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.63, 158.86, 135.21, 129.38, 129.12, 127.48, 101.31, 76.52, 73.04, 67.70, 60.01, 51.12, 49.50, 47.86, 22.35, 22.16, 22.13, 22.08; MS (APCI): *m/z* 410.1 $[M+H]^{+\cdot}$

Diisopropyl 1',3'-dihydro-1-azaspiro[bicyclo[3.2.0]heptane-6,2'-indene]-7,7-dicarboxylate (8a)



Prepared according to *General procedure A* using Diisopropyl 2-((4-(1,3-dihydro-2H-inden-2-ylidene)butyl)imino)malonate **(7a)**, 36% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 - 7.16 (m, 4H), 5.16 (hept, *J* = 6.2 Hz, 1H), 4.35 (hept, *J* = 6.2 Hz, 1H), 3.73 (td, *J* = 9.0, 2.6 Hz, 1H), 3.44 (dd, *J* = 8.5, 3.9 Hz, 1H), 3.22 - 2.93 (m, 4H), 2.82 (td, *J* = 9.3, 7.6 Hz, 1H), 2.28 - 2.21 (m, 1H), 2.06 – 1.84 (m, 2H), 1.72 - 1.64 (m, 1H), 1.31 (dd, *J* = 6.3, 4.8 Hz, 6H), 1.18 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.06, 154.05, 140.80, 139.79, 126.75, 126.73, 124.52, 124.50, 89.08, 72.83, 67.14, 59.78, 51.09, 43.41, 38.75, 25.80, 22.94, 22.23, 22.20, 22.06, 21.80; MS (APCI): *m/z* 372.1 $[M+H]^+$.

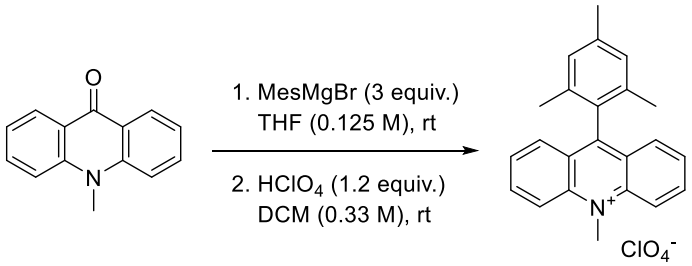
Diisopropyl 2-(2-(1H-inden-2-yl)pyrrolidin-1-yl)malonate (9)



Prepared according to *General procedure A* using Diisopropyl 2-((4-(1,3-dihydro-2H-inden-2-ylidene)butyl)imino)malonate **(7a)**, 19% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.4 Hz, 1H), 7.30 (d, *J* = 7.4 Hz, 1H) 7.23 (t, *J* = 7.4 Hz, 1H), 7.13 (td, *J* = 7.4, 1.3 Hz, 1H), 6.74 (s, 1H), 5.06 (m, 2H), 4.16 (s, 1H), 4.04 (t, *J* = 7.5 Hz, 1H), 3.36 (m, 3H), 3.03 (td, *J* = 8.5, 7.0 Hz, 1H), 2.13 - 2.05 (m, 1H), 1.94 - 1.76 (m, 3H), 1.23 (t, *J* = 6.0 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.62, 167.34, 151.19, 144.72, 143.57, 129.14, 126.23, 124.18, 123.76, 120.40, 68.80, 68.67, 64.94, 62.16, 48.26, 37.35, 32.77, 23.88, 21.88, 21.79, 21.65, 21.58; MS (APCI): *m/z* 372.1 $[M+H]^+$.

Synthesis of substrates:

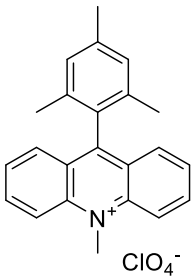
- Synthesis of photocatalyst Mes-Acr$^+$ClO4$^-$



Prepared with slightly modified procedure from previous report[S1]. To a solution of 10-methylacridin-9(10H)-one (220 mg, 1.0 equiv.) in THF (5.3 ml, total 0.125 M) was slowly added MesMgBr (3.15 ml, 1 M in THF, 3.0 equiv.) at rt under N2, then the mixture was stirred for 48 h. After completion (monitored by TLC, 10%MeOH/CH_2Cl_2 as eluent), the reaction was quenched with water (30 ml) and extracted three times with ethyl acetate (20 ml). The combined organic layer was dried over Na_2SO_4, concentrated, the red oil was obtained.

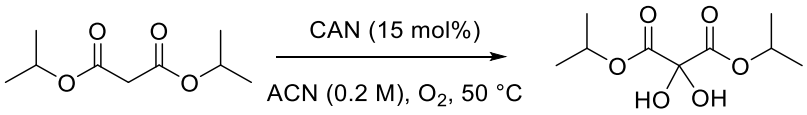
The oil was then dissolved in CH_2Cl_2 (3.2 ml, 0.33 M), and $HClO_4$ (108 ul, 70%, 1.2 equiv.) was added. The mixture was stirred at rt for 1 h, diethyl ether was added dropwise, and the yellow solid appeared. The yellow solid was then filtered, washed with ether to afford the acridinium photocatalyst, 380 mg, 88% yield.

9-mesityl-10-methylacridin-10-ium perchlorate (Mes-Acr$^+$ClO4$^-$)



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 9.2 Hz, 2H), 8.4 (ddd, *J* = 9.2, 6.7, 1.6 Hz, 2H), 7.87 (dd, *J* = 8.5, 1.4 Hz, 2H), 7.79 (ddd, *J* = 8.6, 6.6, 0.7 Hz, 2H), 7.16 (m, 2H), 5.10 (s, 3H), 2.49 (s, 3H), 1.74 (s, 6H); The compound was identified by spectral comparison with literature data[S1].

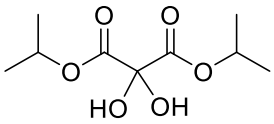
- Synthesis of diisopropyl 2,2-dihydroxymalonate



Prepared with slightly modified procedure from previous report[S2]. In a reaction flask, diisopropyl malonate (7.5 g, 1.0 equiv.) was dissolved in acetonitrile (200 ml, 0.2 M) and to the resulting solution ceric ammonium nitrate (3.3 g, 15 mol%) was added in one portion under constant stirring. The

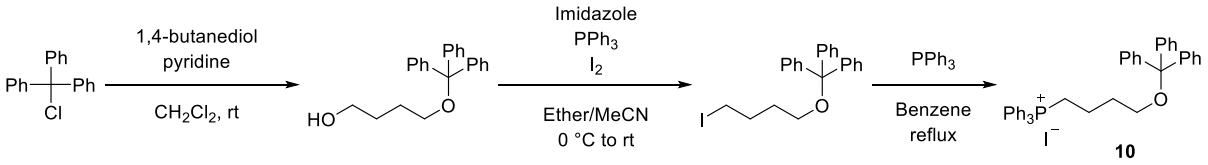
reaction vessel was fitted with O_2 balloon and heated to 50 °C. Progress of the reaction was monitored by checking the TLC of the reaction mixture. After confirming the consumption of the starting material, water was added to the reaction mixture and stirred until the reaction mixture became colorless. Next, the reaction mixture was extracted three times with ethyl acetate (equal volume). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was obtained and purified by column chromatography to give ketomalonate hydrate, 5.9 g, 70% yield.

Diisopropyl 2,2-dihydroxymalonate



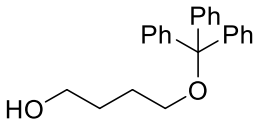
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16 (hept, *J* = 6.3 Hz, 2H), 4.78 (s, 2H), 1.3 (d, *J* = 6.3 Hz, 12H); The compound was identified by spectral comparison with literature data[S2].

- Synthesis of Wittig reagent (10)



To a vigorously stirred solution of 1,4-butanediol (13.5 g, 10 equiv.) in CH_2Cl_2 (150 ml, 0.1 M) were added Trityl Chloride (4.2 g, 1.0 equiv.) and pyridine (1.3 g, 1.1 equiv.) at room temperature. After 90 min, the solution was washed three times with brine (50 ml). The organic phase was dried over Na_2SO_4 and the solvents were evaporated in vacuo. The residue was purified by silica gel flash column chromatography to afford 4-(trityloxy)butan-1-ol (4.1 g, 82%) as a white solid.

4-(trityloxy)butan-1-ol

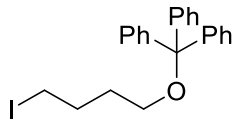


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (m, 6H), 7.27 (m, 9H), 3.64 (d, *J* = 6.4 Hz, 2H), 3.12 (t, *J* = 5.7 Hz, 2H), 1.71 - 1.61 (m, 5H); The compound was identified by spectral comparison with literature data[S3].

To a solution of 4-(trityloxy)butan-1-ol (4.1 g, 1.0 equiv.) in Et_2O/MeCN (62 ml, 0.2 M, 3:1) were added imidazole (2.5 g, 3.0 equiv.) and triphenylphosphine (4.9 g, 1.5 equiv.) at room temperature. The solution was cooled to 0 °C and iodine (4.7 g, 1.5 equiv.) was added in portions over 5 min. After 30 min at 0 °C, the solution was allowed to warm to room temperature overnight. After 1 h at room temperature, the solution was diluted with Et_2O (50 ml). The precipitate was filtered off and washed

with Et_2O. The filtrate was washed two times with a saturated aqueous $Na_2S_2O_3$ solution (50 ml) and dried over Na_2SO_4. The solvents were evaporated in vacuo and the residue was purified by silica gel flash column chromatography to afford ((4-iodobutoxy)methanetriyl)tribenzene (4.7 g, 86%) as a white solid.

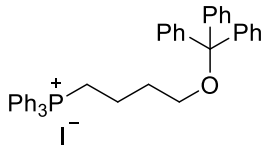
((4-iodobutoxy)methanetriyl)tribenzene



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 6H), 7.26 (m, 9H), 3.16 (t, *J* = 7.0 Hz, 2H), 3.09 (t, *J* = 6.2 Hz, 2H), 1.94 (p, *J* = 7.1 Hz, 2H), 1.71 (m, 2H); The compound was identified by spectral comparison with literature data[S3].

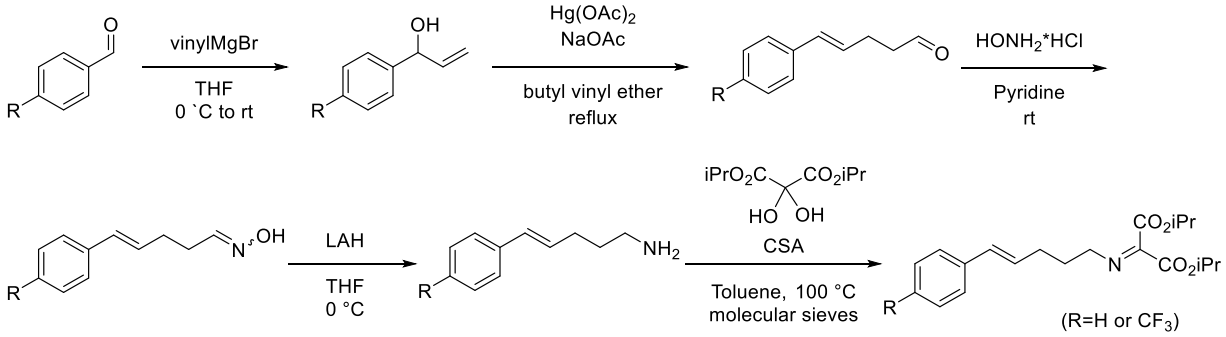
To a solution of ((4-iodobutoxy)methanetriyl)tribenzene (4.7 g, 1.0 equiv.) in benzene (50 ml, 0.2 M) was added triphenylphosphine (5.6 g, 2.0 equiv.) at room temperature. The solution was heated under reflux for 30 h, and then allowed to cool to room temperature. The phosphonium salt was filtered off, washed three times with benzene (30 ml), and dried under vacuum to afford **10** (6.4 g, 85%) as a white solid.

triphenyl(4-(trityloxy)butyl)phosphonium iodide (10)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 - 7.60 (m, 15H), 7.36–7.16 (m, 15H), 3.68 (m, 2H), 3.16 (m, 2H), 2.05 (m, 2H), 1.83 (m, 2H); The compound was identified by spectral comparison with literature data[S3].

- Synthesis of p-substituted iminomalonate

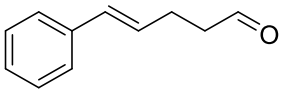


Corresponding benzaldehyde (1.0 equiv.) was dissolved in dry THF (0.4 M). The solution was cooled to 0 °C and vinyl magnesium bromide (1 M in THF, 1.1 equiv.) was added dropwise. After 15 min, the

reaction mixture was allowed to warm to rt and stirred at rt for 1 h. The reaction was quenched by addition of sat. aq. NH4Cl (equal volume), the phases were separated, and the aqueous phase was extracted three times with EtOAc (equal volume), then dried over Na_2SO4, filtered and concentrated in vacuo to yield the allylic alcohol as pale-yellow liquid.

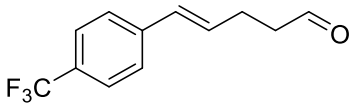
Under argon atmosphere, Hg(OAc)2 (10 mol%), NaOAc (10 mol%), and allylic alcohol (1.0 equiv.) were dissolved in n-butyl vinyl ether (0.8 M). The reaction mixture was stirred at reflux for 17 h. The mixture was cooled to rt and poured into sat. aq. $NaHCO_3$ solution (equal volume) and extracted three times with EtOAc (equal volume). The combined organic layers were dried over anhydrous MgSO4, filtered, and evaporated. Column chromatography afforded aldehyde compound as a yellow liquid.

(E)-5-phenylpent-4-enal



Prepared according to right above procedure using benzaldehyde, 81% yield (2 steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (t, *J* = 1.3 Hz, 1H), 7.35 – 7.19 (m, 5H), 6.43 (d, *J* = 15.8 Hz, 1H), 6.20 (dt, *J* = 15.8, 6.6 Hz, 1H), 2.63 (m, 2H), 2.56 (m, 2H); The compound was identified by spectral comparison with literature data[S4].

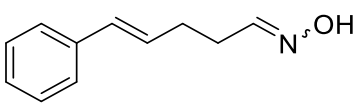
(E)-5-(4-(trifluoromethyl)phenyl)pent-4-enal



Prepared according to right above procedure using 4-trifloromethyl benzaldehyde, 44% yield (2 steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (t, *J* = 1.2 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H), 6.46 (d, *J* = 15.9 Hz, 1H), 6.31 (dt, *J* = 15.8, 6.5 Hz, 1H), 2.66 (m, 2H), 2.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.28, 140.65, 131.02, 129.91, 129.01 (q, *J* = 32.3 Hz), 126.16, 125.45 (q, *J* = 3.8 Hz), 122.84 (q, J = 271 Hz), 43.03, 25.42; MS (APCI): *m/z* 229.3 $[M+H]^+$.

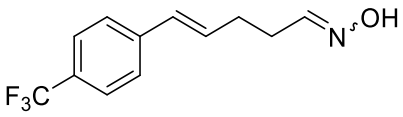
A solution of aldehyde (1.0 equiv.) in 0.5 M of pyridine was cooled with an ice bath. hydroxylamine hydrochloride (1.2 equiv.) was added slowly with stirring. After the reaction was completed (monitored by TLC), pyridine was evaporated, and the residue was purified by flash chromatography to give oxime as a colorless oil.

(4E)-5-phenylpent-4-enal oxime



Prepared according to right above procedure using (E)-5-phenylpent-4-enal, 99% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.35 – 7.18 (m, 5H), 6.78 (t, *J* = 5.3 Hz, 1H), 6.44 (d, *J* = 15.8 Hz, 1H), 6.20 (dt, *J* = 15.8, 6.7 Hz, 1H), 2.57 (q, *J* = 7.2 Hz, 2H), 2.42 (q, *J* = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.88, 137.34, 130.98, 128.72, 128.51, 127.14, 126.05, 29.30, 24.55; MS (APCI): *m/z* 176.0 $[M+H]^+$.

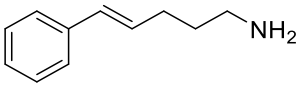
(4E)-5-(4-(trifluoromethyl)phenyl)pent-4-enal oxime



Prepared according to right above procedure using (E)-5-(4-(trifluoromethyl)phenyl)pent-4-enal, quantitative yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 8.1 Hz, 2H), 6.79 (t, *J* = 5.3 Hz, 1H), 6.47 (d, *J* = 15.9 Hz, 1H), 6.30 (dt, *J* = 15.7, 6.5 Hz, 1H), 2.59 (q, *J* = 6.9 Hz, 2H), 2.45 (q, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.55, 140.77, 131.53, 129.76, 128.97 (q, *J* = 32.5 Hz), 126.17, 125.45 (q, *J* = 3.8 Hz), 122.84 (q, J = 270 Hz), 29.28, 24.31; MS (APCI): *m/z* 244.1 $[M+H]^+$.

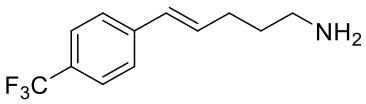
To a mixture of LAH (2.2 equiv.) in THF (0.3 M) at 0 °C, was added dropwise a solution of oxime (1.0 equiv.) in THF over 15 min under nitrogen. The reaction was warmed up to room temperature. After the reaction was completed (monitored by TLC), the reaction was cooled down to 0 °C, and quenched with H2O (x ul) and an aqueous solution of NaOH (2x ul, 15%) then H2O (3x ul) (for x mg of LAH). Crude material was dried over Na2SO4 and filtered. The filtrate was purified by short column chromatography.

(E)-5-phenylpent-4-en-1-amine (11a)



Prepared according to right above procedure using (4E)-5-phenylpent-4-enal oxime, 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 - 7.17 (m, 5H), 6.40 (d, *J* = 15.8 Hz, 1H), 6.22 (dt, *J* = 16.0, 6.9 Hz, 1H), 2.76 (t, *J* = 7.1 Hz, 2H), 2.26 (q, *J* = 7.2 Hz, 2H), 1.63 (p, *J* = 7.2 Hz, 2H), 1.33 (brs, 2H); The compound was identified by spectral comparison with literature data[S5].

(E)-5-(4-(trifluoromethyl)phenyl)pent-4-en-1-amine (11c)

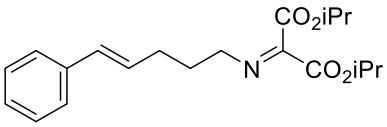


Prepared according to right above procedure using (4E)-5-(4-(trifluoromethyl)phenyl)pent-4-enal oxime, 56% yield; There were inseparable mixture which could be isolated in next step, so (E)-5-(4-(trifluoromethyl)phenyl)pent-4-en-1-amine, **11c** was used as crude.

General procedure B (condensation reaction to give iminomalonate, slightly modified procedure from previous report[S2])

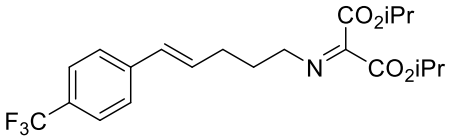
Diisopropyl 2,2-dihydroxymalonate (1.0 equiv.) was taken in a flask with toluene (0.2 M) and freshly activated 4 Å molecular sieves. To this solution corresponding amine (1.0 equiv.) was added followed by CSA (5 mol%). The reaction mixture was heated at 100 °C for 2 h. After confirming the completion of the reaction (monitored by TLC), the reaction mixture was allowed to cool to room temperature. Toluene was removed under reduced pressure and the crude material was purified by column chromatography to give iminomalonate.

Diisopropyl (E)-2-((5-phenylpent-4-en-1-yl)imino)malonate (2a)



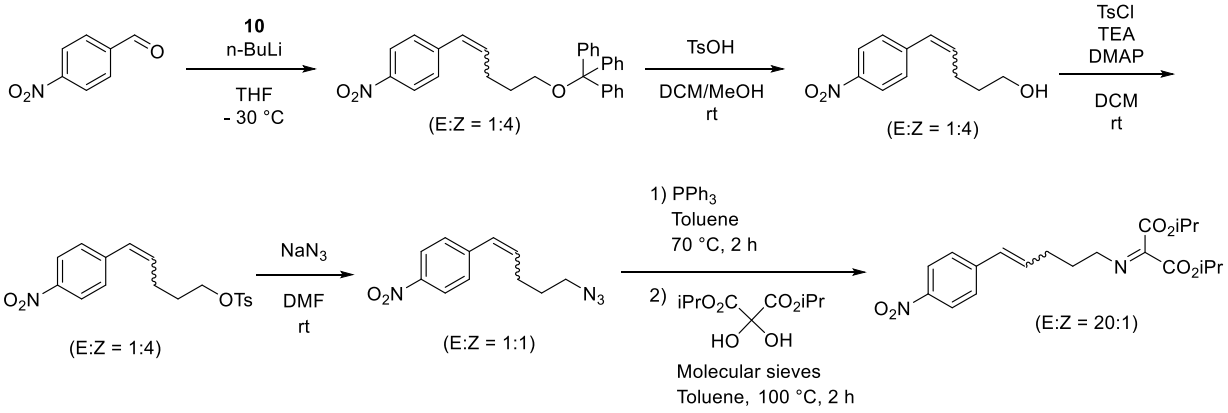
Prepared according to *General procedure B* using (E)-5-phenylpent-4-en-1-amine **(11a)**, 84% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 - 7.26 (m, 4H), 7.21 – 7.16 (m, 1H), 6.40 (dt, *J* = 15.8, 1.5 Hz, 1H), 6.20 (dt, *J* = 15.8, 6.9 Hz, 1H), 5.21 (m, 2H), 3.65 (t, *J* = 7.1 Hz, 2H), 2.28 (m, 2H), 1.93 (p, *J* = 7.2 Hz, 2H), 1.33 (d, *J* = 6.3 Hz, 6H), 1.30 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.16, 160.48, 154.31, 137.57, 130.61, 129.56, 128.44, 126.92, 125.93, 70.53, 70.11, 54.93, 30.69, 29.48, 21.64, 21.59; MS (APCI): *m/z* 346.3 $[M+H]^+$.

Diisopropyl (E)-2-((5-(4-(trifluoromethyl)phenyl)pent-4-en-1-yl)imino)malonate (2c)



Prepared according to *General procedure B* using (E)-5-(4-(trifluoromethyl)phenyl)pent-4-en-1-amine **(11c)**, 55% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H), 6.43 (d, *J* = 15.9 Hz, 1H), 6.31 (dt, *J* = 15.8, 6.7 Hz, 1H), 5.21 (m, 2H), 3.65 (t, *J* = 7.0 Hz, 2H), 2.32 (m, 2H), 1.95 (p, *J* = 7.1 Hz, 2H), 1.33 (d, *J* = 6.3 Hz, 6H), 1.31 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.09, 160.43, 154.41, 141.06, 141.04, 132.50, 129.40, 128.74 (q, *J* = 32.5 Hz), 126.05, 125.39 (q, *J* = 3.9 Hz), 122.89 (q, J = 270 Hz), 70.57, 70.17, 54.78, 30.69, 29.23, 21.63, 21.56; MS (APCI): *m/z* 414.3 $[M+H]^+$.

- Synthesis of p-nitro iminomalonate

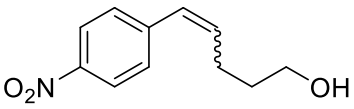


To a solution of phosphonium salt (**10**, 1.5 equiv.) in THF (0.1 M) was added n-BuLi (2.5 M in hexane, 1.5 equiv.) at - 30 °C. The orange solution was stirred for 15 min at - 30 °C and a solution of p-nitro benzaldehyde (1.0 equiv.) in THF was added dropwise. The resulting solution was stirred for 15 min at 0 °C and then allowed to warm to room temperature for 30 min. The solution was treated with a saturated aqueous NaHCO3 solution (equal volume) and diluted with EtOAc (equal volume). The aqueous phase was extracted with EtOAc three times (equal volume). The combined organic phases were dried over Na_2SO_4 and the solvent was evaporated in vacuo. The residue was purified by silica

gel flash column chromatography to give (((5-(4-nitrophenyl)pent-4-en-1-yl)oxy)methanetriyl)tribenzene as an inseparable E/Z mixture.

p-TsOH·H_2O (0.1 equiv.) was added in portions to a solution of (((5-(4-nitrophenyl)pent-4-en-1-yl)oxy)methanetriyl)tribenzene (1.0 equiv.) in CH_2Cl_2/MeOH 2:1 (0.3 M) at room temperature and the reaction mixture stirred for 2 h. After addition of a sat. NaHCO3 solution (equal volume), the aqueous layer was separated and extracted three times with CH_2Cl_2 (equal volume). The combined extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography to give 5-(4-nitrophenyl)pent-4-en-1-ol as a separable E/Z mixture (E:Z=1:4).

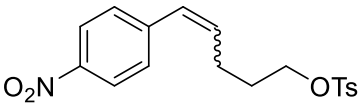
5-(4-nitrophenyl)pent-4-en-1-ol



Prepared according to right above procedure, 57% yield (2 steps); E isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (m, 2H), 7.46 (m, 2H), 6.46 (m, 2H), 3.73 (t, *J* = 6.5 Hz, 2H), 2.39 (td, *J* = 7.6, 5.5 Hz, 2H), 1.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.46, 144.15, 135.54, 128.61, 126.37, 123.95, 62.14, 31.81, 29.49; Z isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (m, 2H), 7.43 (m, 2H), 6.49 (dt, *J* = 11.7, 1.9 Hz, 1H), 5.88 (dt, *J* = 11.7, 7.4 Hz, 1H), 3.69 (t, *J* = 6.4 Hz, 2H), 2.44 (qd, *J* = 7.4, 1.9 Hz, 2H), 1.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.19, 144.22, 136.03, 129.35, 127.63, 123.51, 62.11, 32.46, 25.15; MS (APCI): *m/z* 208.0 $[M+H]^+$.

To a solution of 5-(4-nitrophenyl)pent-4-en-1-ol (E:Z=1:1, 1.0 equiv.), triethylamine (1.2 equiv.), and 4-(dimethylamino)pyridine (5 mol%) in CH_2Cl_2 (0.1 M) at 0 °C was added p-toluenesulfonyl chloride (1.1 equiv.) in three portions. The reaction mixture was brought to room temperature and stirred for 2 h. Then sat. aq. $NaHCO_3$ (equal volume) was added, and the mixture was vigorously stirred for 15 min at rt. The aqueous layer was extracted three times with CH_2Cl_2 (equal volume). The combined extract was dried over Na_2SO_4, and the solvent was evaporated in vacuo. The residue was purified by column chromatography to give 5-(4-nitrophenyl)pent-4-en-1-yl 4-methylbenzenesulfonate as E/Z mixture (E:Z=1:1).

5-(4-nitrophenyl)pent-4-en-1-yl 4-methylbenzenesulfonate



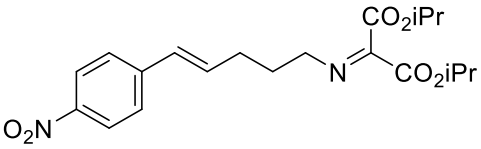
Prepared according to right above procedure, 87% yield; E isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (m, 2H), 7.80 (m, 2H), 7.41 (m, 2H), 7.34 (m, 2H), 6.41 (d, *J* = 15.9 Hz, 1H), 6.3 (dt, *J* = 15.8, 6.7 Hz, 1H), 4.09 (m, 2H), 2.44 (s, 3H), 2.34 (m, 2H), 1.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.59, 144.83, 143.77, 133.75, 132.98, 129.85, 129.50, 127.86, 126.47, 123.92, 69.45, 28.91, 28.12, 21.62; Z isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (m, 2H), 7.75 (m, 2H), 7.37 - 7.32 (m, 4H), 6.49 (dt, *J* = 11.7, 1.9 Hz, 1H), 5.76 (dt, *J* = 11.7, 7.4 Hz, 1H), 4.07 (t, *J* = 6.2 Hz, 2H), 2.45 (s, 3H), 2.38 (qd, *J* = 7.4, 1.9 Hz, 2H), 1.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.33, 144.88, 143.80,

134.27, 132.99, 129.83, 129.32, 128.44, 127.79, 123.53, 69.43, 28.84, 24.70, 21.62; MS (APCI): *m/z* 362.0 $[M+H]^+$.

A solution of 5-(4-nitrophenyl)pent-4-en-1-yl 4-methylbenzenesulfonate (E:Z=1:1, 1.0 equiv.) and sodium azide (1.1 equiv.) in DMF (0.2 M) was allowed to stir at rt for 9 h. Subsequently, ethyl acetate (equal volume) was added to the reaction mixture and it was washed three times with water (equal volume). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give azide intermediate as a colorless liquid, which was used in the next reaction without further purification.

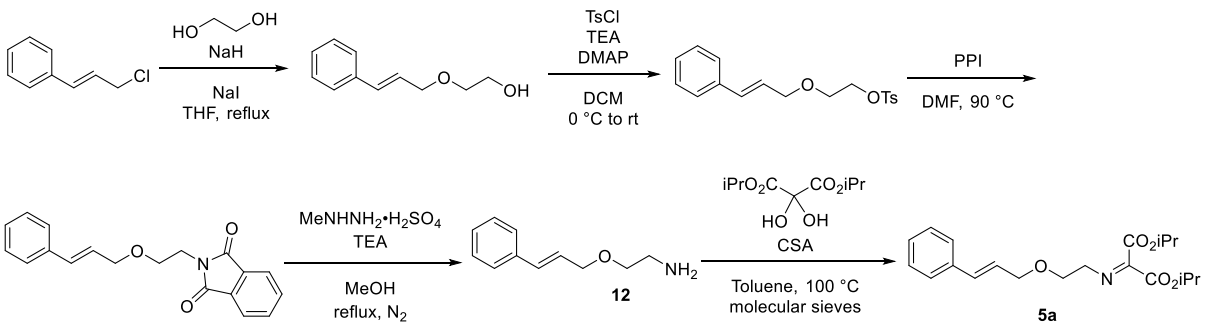
Triphenylphosphine (1.0 equiv.) in anhydrous toluene (0.2 M) was added to a solution of azide intermediate (1.0 equiv.) in anhydrous toluene dropwise. The solution was stirred for 30 min at room temperature, warmed up to 70°C and stirred at 70°C for 2 hours. The resulting freshly prepared solution of the Staudinger reagent was transferred to an oven-dried flask charged with molecular sieves and diisopropyl 2,2-dihydroxymalonate (1.0 equiv.) in anhydrous toluene. The pale-yellow mixture was stirred at room temperature for 1 hour, and then heated to reflux for 2 hours. The mixture was cooled to room temperature and concentrated in vacuo. The solid was filtered off and the filtrate was evaporated in vacuo. The crude material was purified by column chromatography to give **2d** which has only E conformation.

Diisopropyl (E)-2-((5-(4-nitrophenyl)pent-4-en-1-yl)imino)malonate (2d)



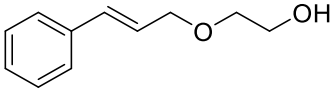
Prepared according to right above procedure using 5-(4-nitrophenyl)pent-4-en-1-yl-4-methylbenzenesulfonate, 92% yield (2 steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 6.46 (m, 2H), 5.23 (m, 2H), 3.66 (t, *J* = 6.9 Hz, 2H), 2.35 (q, *J* = 6.9 Hz, 2H), 1.97 (p, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 6.0 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.03, 160.39, 154.48, 146.52, 144.08, 135.05, 128.87, 126.39, 123.93, 70.61, 70.17, 54.66, 30.81, 29.07, 21.65, 21.57; MS (APCI): *m/z* 391.0 $[M+H]^+$.

- Synthesis of oxygen atom adopted iminomalonate



A flask was charged with ethylene glycol (372.4 mg, 1.5 equiv.) and THF (30 ml, 0.13 M). NaH (160.0 mg, 60%, 1.0 equiv.) was added at 0 °C and the solution was stirred at 0 °C for 0.5 h. Upon addition of trans-cinnamyl chloride (610.5 mg, 1.0 equiv.) and NaI (60 mg, 0.1 equiv.), the solution was allowed to warm to room temperature and then refluxed for 8 h. The resulting mixture was cooled to room temperature and treated with brine (equal volume). The organic layer was separated, and the aqueous layer was extracted three times with diethyl ether (equal volume). The combined organic layer was dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified on a silica gel column to give 2-(cinnamyloxy)ethan-1-ol, 451 mg, 63% yield.

2-(cinnamyloxy)ethan-1-ol

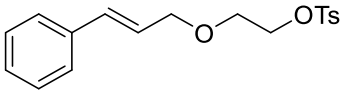


Prepared according to right above procedure using (E)-cinnamyl chloride, 63% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 2H), 7.32 (m, 2H), 7.26 (m, 1H), 6.62 (dt, *J* = 15.9, 1.5 Hz, 1H), 6.30 (dt, *J* = 15.9, 6.1 Hz, 1H), 4.21 (dd, *J* = 6.1, 1.4 Hz, 2H), 3.78 (q, *J* = 5.4 Hz, 2H), 3.62 (m, 2H), 1.99 (brs, 1H); The compound was identified by spectral comparison with literature data[S6].

General procedure C (Tosylation reaction)

To a solution of alcohol intermediate (1.0 equiv.), triethylamine (1.2 equiv.), and 4-(dimethylamino)pyridine (5 mol%) in CH_2Cl_2 (0.1 M) at 0 °C was added p-toluenesulfonyl chloride (1.1 equiv.) in three portions. The reaction mixture was brought to room temperature and stirred for 12 h. Sat. aq. $NaHCO_3$ (equal volume) was added, and the mixture was vigorously stirred for 15 min at rt. The aqueous layer was extracted three times with CH_2Cl_2 (equal volume). The combined organic layer was dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified on a silica gel column to give p-toluenesulfonate derivatives.

2-(cinnamyloxy)ethyl 4-methylbenzenesulfonate



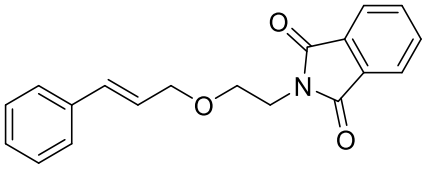
Prepared according to *General procedure C* using 2-(cinnamyloxy)ethan-1-ol, 96% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.37 – 7.23 (m, 7H), 6.54 (dt, *J* = 15.9, 1.5 Hz, 1H), 6.18 (dt, *J* = 15.9, 6.0 Hz, 1H), 4.20 (dd, *J* = 5.4, 4.1 Hz, 2H), 4.11 (dd, *J* = 6.0, 1.5 Hz, 2H), 3.67 (dd, *J* = 5.3, 4.2 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.77, 136.46, 133.03, 132.81, 129.79, 128.56, 127.97, 127.80, 126.48, 125.29, 71.79, 69.29, 67.42, 21.61; MS (APCI): *m/z* 333.1 $[M+H]^+$.

General procedure D (Phthalimide substitution reaction)

A suspension of p-toluenesulfonate derivatives (1.0 equiv.) and potassium phthalimide (1.05 equiv.) in DMF (1 M) was heated to 90°C for 2 hours. Upon completion, H_2O (equal volume) was added to the crude reaction mixture. The aqueous layer was then extracted three times with ethyl acetate (equal

volume). The organic layers were collected and washed two times with brine (equal volume). The organic phase was then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography to give phthalimide derivatives.

2-(2-(cinnamyloxy)ethyl)isoindoline-1,3-dione

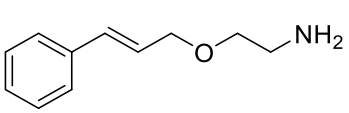


Prepared according to *General procedure D* using 2-(cinnamyloxy)ethyl 4-methylbenzenesulfonate, 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (m, 2H), 7.69 (m, 2H), 7.32 - 7.19 (m, 5H), 6.55 (d, *J* = 15.9 Hz, 1H), 6.21 (dt, *J* = 15.9, 6.0 Hz, 1H), 4.16 (d, *J* = 6.0 Hz, 2H), 3.93 (t, *J* = 5.8 Hz, 2H), 3.74 (t, *J* = 5.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.26, 136.58, 133.89, 132.55, 132.10, 128.48, 127.62, 126.45, 125.67, 123.24, 71.30, 66.81, 37.53; MS (APCI): *m/z* 308.3 $[M+H]^+$.

General procedure E (Gabriel synthesis)

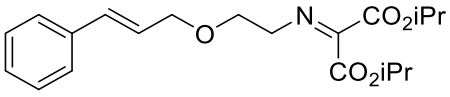
To a solution of phthalimide derivatives (1.0 equiv.) in MeOH (0.11 M) was treated with $MeNHNH_2 \bullet H_2SO_4$ (3.0 equiv.) and TEA (6.0 equiv.) and stirred with reflux. After the reaction was completed (TLC monitoring), the solvent was removed, the crude material was dissolved in CH_2Cl_2 (equal volume), add sat. aq. $NaHCO_3$ solution (equal volume). The separated aqueous layer was washed with CH_2Cl_2 additional two times. The collected organic layer was dried over Na_2SO_4, then purified by column chromatography.

2-(cinnamyloxy)ethan-1-amine (12)



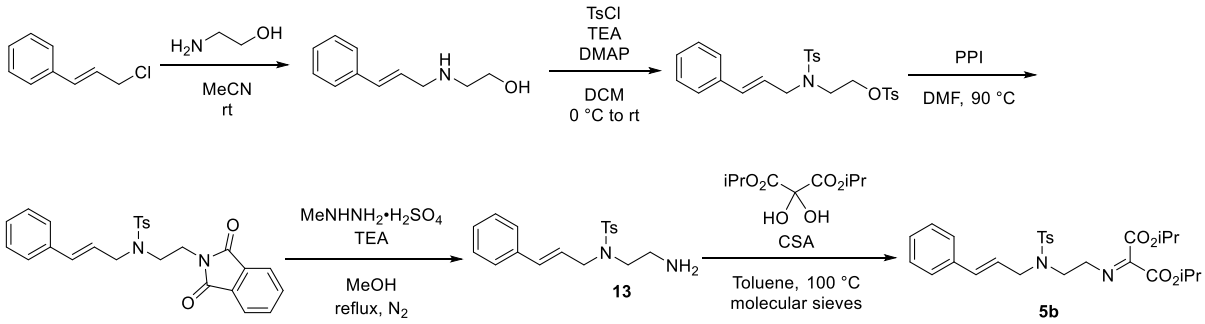
Prepared according to *General procedure E* using 2-(2-(cinnamyloxy)ethyl)isoindoline-1,3-dione, 79% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.22 (m, 1H), 6.62 (d, *J* = 15.9 Hz, 1H), 6.30 (dt, *J* = 15.9, 6.1 Hz, 1H), 4.18 (d, *J* = 6.1 Hz, 2H), 3.53 (t, *J* = 5.2 Hz, 2H), 2.91 (t, *J* = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.56, 132.58, 128.54, 127.71, 126.48, 125.80, 71.63, 70.65, 41.25; MS (APCI): *m/z* 178.1 $[M+H]^+$.

Diisopropyl 2-((2-(cinnamyloxy)ethyl)imino)malonate (5a)



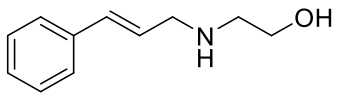
Prepared according to *General procedure B* using 2-(cinnamyloxy)ethan-1-amine **(12)**, 74% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.2 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.22 (m, 1H), 6.60 (d, *J* = 15.9 Hz, 1H), 6.27 (dt, *J* = 15.8, 6.0 Hz, 1H), 5.23 (m, 2H), 4.18 (dd, *J* = 6.0, 1.5 Hz, 2H), 3.84 (t, *J* = 3.7 Hz, 4H), 1.33 (d, *J* = 6.3 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.62, 160.49, 155.41, 136.64, 132.49, 128.50, 127.63, 126.46, 125.86, 71.68, 70.57, 70.22, 68.72, 54.91, 21.65, 21.58; MS (APCI): *m/z* 362.3 $[M+H]^+$.

- Synthesis of nitrogen atom adopted iminomalonate



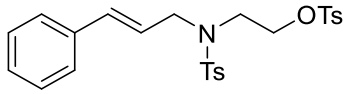
To a solution of ethanolamine (2.7 g, 15.0 equiv.) in acetonitrile (30 ml, 0.1 M) at room temperature was added dropwise a solution of trans-cinnamyl chloride (458 mg, 1.0 equiv.) in acetonitrile. After 5 hours, the mixture partitioned between ethyl acetate and saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted three times with ethyl acetate, and the combined organic layer were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography to give 2-(cinnamylamino)ethan-1-ol (406 mg, 76%).

2-(cinnamylamino)ethan-1-ol



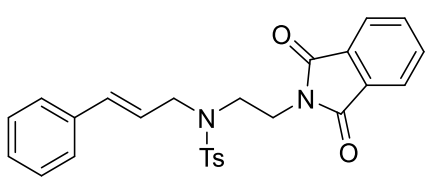
Prepared according to the right above procedure, 76% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 4H), 7.26 – 7.21 (m, 1H), 6.55 (d, *J* = 15.9 Hz, 1H), 6.29 (dt, *J* = 15.8, 6.4 Hz, 1H), 3.72 (m, 2H), 3.48 (d, *J* = 6.4 Hz, 2H), 2.98 (brs, 2H), 2.86 (t, *J* = 5.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.87, 131.85, 128.55, 127.63, 127.49, 126.28, 60.79, 51.37, 50.60; MS (APCI): *m/z* 178.2 $[M+H]^+$.

2-((N-cinnamyl-4-methylphenyl)sulfonamido)ethyl 4-methylbenzenesulfonate



Prepared according to *General procedure C* using 2-(cinnamylamino)ethan-1-ol, TsCl (2.2 equiv.), TEA (2.4 equiv.), and DMAP (1.0 equiv.), 95% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.67 (m, 4H), 7.32 – 7.25 (m, 9H), 6.43 (d, *J* = 15.9 Hz, 1H), 5.91 (dt, *J* = 15.8, 6.9 Hz, 1H), 4.14 (t, *J* = 6.2 Hz, 2H), 3.93 (dd, *J* = 6.9, 1.2 Hz, 2H), 3.42 (t, *J* = 6.2 Hz, 2H), 2.43 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.00, 143.75, 136.24, 135.93, 134.80, 132.49, 129.90, 129.85, 128.59, 128.09, 127.91, 127.27, 126.55, 123.27, 68.50, 51.62, 45.79, 21.65, 21.51; MS (APCI): *m/z* 486.1 $[M+H]^+$.

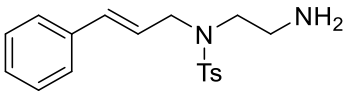
N-cinnamyl-N-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-4-methylbenzenesulfonamide



Prepared according to *General procedure D* using 2-((N-cinnamyl-4-methylphenyl)sulfonamido)ethyl 4-methyl benzene sulfonate, 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.77 (m, 2H), 7.68 – 7.63 (m, 4H), 7.29 – 7.22 (m, 5H), 7.17 (m, 2H),

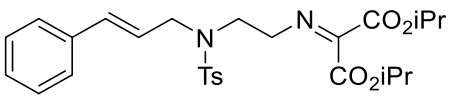
6.51 (dt, *J* = 15.8, 1.2 Hz, 1H), 6.07 (dt, *J* = 15.8, 6.9 Hz, 1H), 4.10 (dd, *J* = 6.9, 0.9 Hz, 2H), 3.84 (t, *J* = 5.8 Hz, 2H) 3.47 (t, *J* = 5.8 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.16, 143.22, 136.85, 136.03, 134.40, 134.27, 133.81, 132.04, 129.62, 128.57, 127.95, 127.14, 126.50, 123.81, 123.54, 123.19, 50.37, 44.77, 36.15, 21.48; MS (APCI): *m/z* 461.1 $[M+H]^+$.

N-(2-aminoethyl)-N-cinnamyl-4-methylbenzenesulfonamide (13)



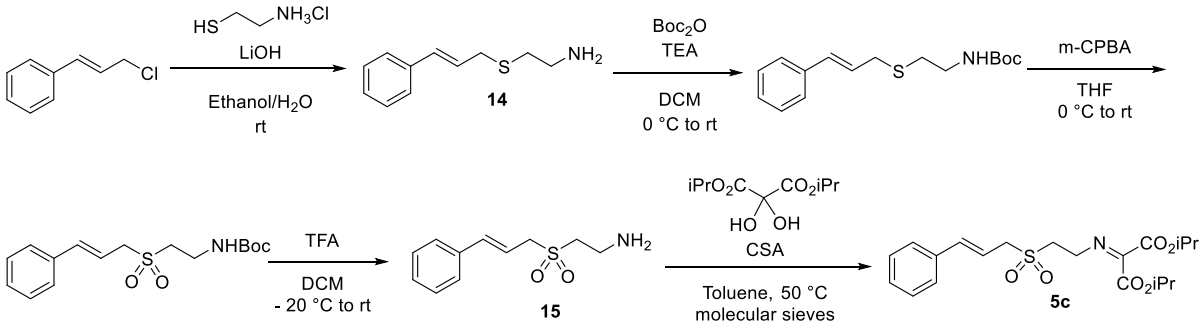
Prepared according to *General procedure E* using N-cinnamyl-N-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-4-methylbenzenesulfonamide, 58% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.71 (m, 2H), 7.30 – 7.21 (m, 7H), 6.44 (d, *J* = 15.9 Hz, 1H), 5.93 (t, *J* = 15.8, 6.8 Hz, 1H), 3.97 (dd, *J* = 6.8, 1.3 Hz, 2H), 3.39 (brs, 2H), 3.27 (t, *J* = 6.2 Hz, 2H), 2.96 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.50, 136.53, 135.98, 134.19, 129.79, 128.56, 127.98, 127.31, 126.45, 123.67, 51.07, 49.45, 40.17, 21.48; MS (APCI): *m/z* 331.0 $[M+H]^+$.

Diisopropyl 2-((2-((N-cinnamyl-4-methylphenyl)sulfonamido)ethyl)imino)malonate (5b)



Prepared according to *General procedure B* using N-(2-aminoethyl)-N-cinnamyl-4-methylbenzenesulfonamide (**13**) at 50 °C, 59% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.1 Hz, 2H), 7.31 – 7.21 (m, 7H), 6.45 (d, *J* = 15.8 Hz, 1H), 5.96 (dt, *J* = 15.8, 6.8 Hz, 1H), 5.17 (hept, *J* = 6.3 Hz, 2H), 4.01 (dd, *J* = 6.8, 1.3 Hz, 2H), 3.86 (t, *J* = 7.1 Hz, 2H), 3.50 (t, *J* = 7.1 Hz, 2H), 2.42 (s, 3H), 1.30 (d, *J* = 6.3 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.48, 160.28, 155.50, 143.40, 136.79, 136.12, 134.21, 129.73, 129.70, 128.50, 128.46, 127.89, 127.32, 127.29, 126.49, 126.47, 123.85, 70.65, 70.59, 54.95, 51.51, 47.15, 21.59, 21.56, 21.48; MS (APCI): *m/z* 515.0 $[M+H]^+$.

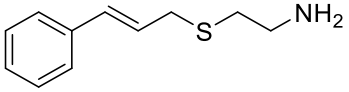
- Synthesis of sulfone adopted iminomalonate



An aqueous solution of LiOH•H_2O (50.4 mg, 2.1 equiv.) in H_2O (1 ml) was added to a solution of cysteamine hydrochloride (114.0 mg, 1.0 equiv.) and trans-cinnamyl chloride (153 mg, 1.0 equiv.) in ethanol (3 ml) at rt then stirred for 1 h. Ethanol was removed in vacuo and the resulting oily solution

was extracted three times with CH_2Cl_2 (equal volume), dried over Na_2SO_4 and filtered. This crude material was purified by column chromatography to give **14** (174 mg, 90%).

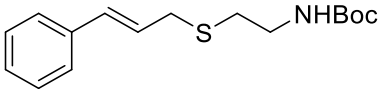
2-(cinnamylthio)ethan-1-amine (14)



Prepared according to right above procedure, 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 2H), 7.32 (m, 2H), 7.24 (m, 1H), 6.44 (d, *J* = 15.7 Hz, 1H), 6.18 (dt, *J* = 15.6, 7.4 Hz, 1H), 3.31 (dd, *J* = 7.4, 1.1 Hz, 2H), 2.88 (t, *J* = 6.4 Hz, 2H), 2.61 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.61, 132.22, 128.58, 127.58, 126.28, 125.92, 40.99, 34.91, 34.00; MS (APCI): *m/z* 194.2 $[M+H]^+$.

To a solution of **14** (174.0 mg, 1.0 equiv.) in CH_2Cl_2 (4.5 ml, 0.2 M) at 0 °C was added Boc_2O (216.1 mg, 1.1 equiv.) and Et_3N (100.2 mg, 1.1 equiv.). The mixture was stirred 1 h at rt and was then washed with water and brine (equal volume). The phases were separated, and the organic phase was dried over Na_2SO_4, filtered and concentrated under vacuum. Purification over silica gel afforded the product (260 mg, 97% yield) as a colorless oil.

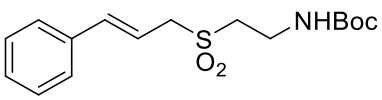
Tert-butyl (2-(cinnamylthio)ethyl)carbamate



Prepared according to right above procedure, 97% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (m, 2H), 7.31 (m, 2H), 7.25 (m, 1H), 6.47 (d, *J* = 15.6 Hz, 1H), 6.16 (dt, *J* = 15.2, 7.4 Hz, 1H), 4.87 (brs, 1H), 3.32 (d, *J* = 7.3 Hz, 4H), 2.63 (t, *J* = 6.5 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.73, 136.57, 132.58, 128.56, 127.62, 126.33, 125.47, 79.40, 39.47, 33.84, 30.81, 28.39; MS (APCI): *m/z* 194.2 $[M\text{-Boc}]^+$.

To a solution of tert-butyl (2-(cinnamylthio)ethyl)carbamate (220.0 mg, 1.0 equiv.) in tetrahydrofuran (7.5 ml, 0.1 M) was added m-chloroperoxybenzoic acid (776.3 mg, 50%, 3.0 equiv.) at 0 °C. The mixture was stirred at room temperature for 1 h. The solvent was removed in vacuo and the residue was dissolved in ethyl acetate. The solution was washed two times with sat. aq. $NaHCO_3$, water, brine, and dried over anhydrous Na_2SO_4. Filtration of the drying agent and removal of the solvent in vacuo afforded the crude sulfone, which was purified by column chromatography to give pure product (250.0 mg, quantitative yield).

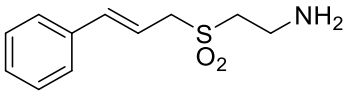
Tert-butyl (2-(cinnamylsulfonyl)ethyl)carbamate



Prepared according to right above procedure, quantitative yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.40 (m, 2H), 7.37 – 7.30 (m, 3H), 6.73 (d, *J* = 15.6 Hz, 1H), 6.24 (dt, *J* = 15.2, 7.6 Hz, 1H), 5.19 (brs, 1H), 3.89 (dd, *J* = 7.6, 1.3 Hz, 2H), 3.65 (q, *J* = 6.0 Hz, 2H), 3.21 (t, *J* = 6.0 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.71, 139.48, 135.39, 128.81, 128.74, 126.77, 114.84, 80.09, 58.40, 51.05, 34.34, 28.32; MS (APCI): *m/z* 270.0 $[M\text{-}^t\text{Bu}]^+$.

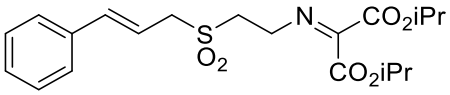
To a solution of Tert-butyl (2-(cinnamylsulfonyl)ethyl)carbamate (230.0 mg, 1.0 equiv.) in CH_2Cl_2 (3.5 ml, 0.2 M), TFA (710 ul, 1 M) was added dropwise at 0 °C; then the reaction mixture was stirred at room temperature for 0.5 h. After the reaction was finished (monitored by TLC), 1N NaOH solution (15 ml) was added slowly and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with 1N HCl solution (15 ml) and this acidified aqueous layer was basified by 1N NaOH solution until PH > 8. Then it was extracted three times with ethyl acetate (10 ml). Finally, combined organic layer was dried over Na_2SO_4 and solvent was evaporated to give 2-(cinnamylsulfonyl)ethan-1-amine (**15**) of 156 mg, 98% yield.

2-(cinnamylsulfonyl)ethan-1-amine (15)



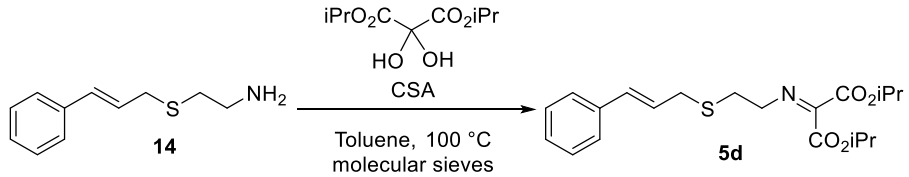
Prepared according to right above procedure, 98% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.41 (m, 2H), 7.37 – 7.28 (m, 3H), 6.72 (d, *J* = 15.9 Hz, 1H), 6.27 (dt, *J* = 15.8, 7.6 Hz, 1H), 3.96 (d, *J* = 7.5 Hz, 2H), 3.26 (dd, *J* = 7.0, 5.1 Hz, 2H), 3.11 (dd, *J* = 7.0, 5.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.01, 135.51, 128.74, 128.72, 126.71, 115.46, 58.77, 54.16, 35.85; MS (APCI): *m/z* 226.0 $[M+H]^+$.

Diisopropyl 2-((2-(cinnamylsulfonyl)ethyl)imino)malonate (5c)

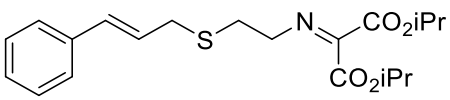


Prepared according to *General procedure B* using 2-(cinnamylsulfonyl)ethan-1-amine (**15**) at 50 °C, 72% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.41 (m, 2H), 7.36 – 7.29 (m, 3H), 6.87 (d, *J* = 15.9 Hz, 1H), 6.27 (dt, *J* = 15.5, 7.6 Hz, 1H), 5.25 (m, 2H), 4.09 (t, *J* = 6.1 Hz, 2H), 4.03 (t, *J* = 7.5 Hz, 2H), 3.37 (t, *J* = 6.0 Hz, 2H), 1.35 (dd, *J* = 6.2, 3.0 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.55, 160.20, 155.76, 139.45, 135.74, 128.66, 128.58, 126.75, 115.52, 71.00, 70.92, 58.95, 50.59, 48.39, 21.63, 21.40; MS (APCI): *m/z* 410.1 $[M+H]^+$.

- Synthesis of sulfur atom adopted iminomalonate



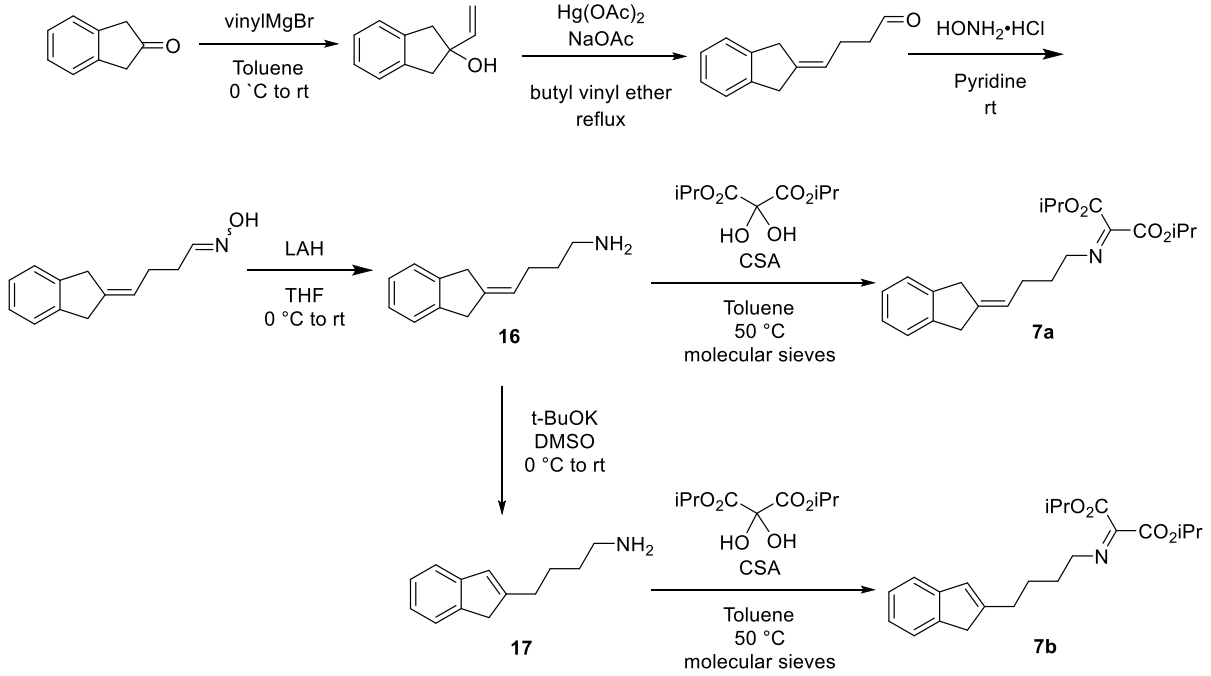
Diisopropyl 2-((2-(cinnamylthio)ethyl)imino)malonate (5d)



Prepared according to *General procedure B* using 2-(cinnamylthio)ethan-1-amine (**14**), 66% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 2H), 7.30 (m, 2H), 7.23 (m, 1H), 6.47 (d, *J* = 15.7 Hz, 1H), 6.17 (dt, *J* = 15.6, 7.4 Hz, 1H), 5.21 (m, 2H), 3.83 (dd, *J* = 7.8, 6.5 Hz, 2H),

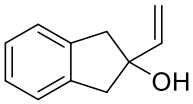
3.35 (dd, *J* = 7.4, 1.1 Hz, 2H), 2.86 (dd, *J* = 7.8, 6.5 Hz, 2H), 1.33 (dd, *J* = 6.3, 1.6 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.57, 160.48, 154.87, 136.63, 132.56, 128.53, 127.55, 126.34, 125.60, 70.66, 70.35, 55.44, 34.53, 30.26, 21.66, 21.59; MS (APCI): *m/z* 378.1 $[M+H]^+$.

- Synthesis of iminomalonate 7a, 7b



2-indanone (1.0 equiv.) was dissolved in dry Toluene (0.4 M). The solution was cooled to 0 °C and vinyl magnesium bromide (1 M in THF, 1.1 equiv.) was added dropwise. After 15 min, the reaction mixture was allowed to warm to rt and stirred at rt for 1 h. The reaction was quenched by addition of sat. aq. NH_4Cl (equal volume), the phases were separated, and the aqueous phase was extracted three times with ethyl acetate (equal volume). The combined organic phases were washed with brine (equal volume), dried over Na_2SO_4, filtered and concentrated in vacuo, then purified by column chromatography to yield 2-vinyl-2,3-dihydro-1H-inden-2-ol.

2-vinyl-2,3-dihydro-1H-inden-2-ol

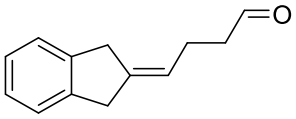


Prepared according to right above procedure, 57% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.17 (m, 4H), 6.18 (dd, *J* = 17.3, 10.7 Hz, 1H), 5.41 (dd, *J* = 17.3, 1.2 Hz, 1H), 5.15 (dd, *J* = 10.7, 1.2 Hz, 1H), 3.20 (d, *J* = 16.5 Hz, 2H), 2.99 (d, *J* = 16.2 Hz, 2H), 1.81 (brs, 1H); The compound was identified by spectral comparison with literature data[S7].

Under argon atmosphere, $Hg(OAc)_2$ (10 mol%), NaOAc (10 mol%), and 2-vinyl-2,3-dihydro-1H-inden-2-ol (1.0 equiv.) were dissolved in n-butyl vinyl ether (0.8 M). The reaction mixture was stirred at reflux for 12 h. The mixture was then poured into sat. $NaHCO_3$ aq. and extracted with ethyl acetate

three times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated. Column chromatography afforded 4-(1,3-dihydro-2H-inden-2-ylidene)butanal.

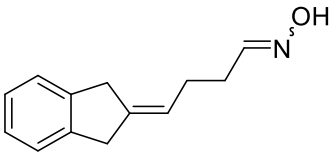
4-(1,3-dihydro-2H-inden-2-ylidene)butanal



Prepared according to right above procedure, 70% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (t, *J* = 1.3 Hz, 1H), 7.25 – 7.15 (m, 4H), 5.43 (tp, *J* = 7.2, 2.5 Hz, 1H), 3.66 (d, *J* = 11.4 Hz, 4H), 2.55 (td, *J* = 6.9, 1.4 Hz, 2H), 2.41 (q, *J* = 6.9, 1.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.28, 141.98, 141.74, 140.25, 126.42, 126.39, 124.65, 124.45, 120.74, 43.55, 39.26, 35.89, 22.31; MS (APCI): *m/z* 187.1 $[M+H]^+$.

A solution of 4-(1,3-dihydro-2H-inden-2-ylidene)butanal (1.0 equiv.) in 0.5 M of pyridine was cooled with an ice bath. hydroxylamine hydrochloride (1.2 equiv.) was added with stirring. After the reaction was completed (monitored by TLC), the solvent was evaporated, and the residue was purified by flash chromatography to give 4-(1,3-dihydro-2H-inden-2-ylidene)butanal oxime as a white solid.

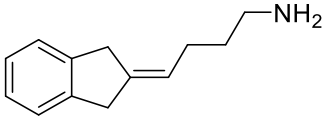
4-(1,3-dihydro-2H-inden-2-ylidene)butanal oxime



Prepared according to right above procedure, 91% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (brs, 1H), 7.23 – 7.14 (m, 4H), 6.75 (t, *J* = 5.4 Hz, 1H), 5.44 (tp, *J* = 7.3, 2.4 Hz, 1H), 3.68 (s, 2H), 3.63 (s, 2H), 2.49 (td, *J* = 7.4, 5.4 Hz, 2H), 2.27 (q, *J* = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.32, 151.74, 142.08, 141.82, 140.10, 126.40, 126.36, 124.65, 124.47, 121.40, 39.27, 35.94, 25.99; MS (APCI): *m/z* 202.1 $[M+H]^+$.

To a mixture of LAH (2.2 equiv.) in THF (0.3 M) at 0 °C, was added dropwise a solution of 4-(1,3-dihydro-2H-inden-2-ylidene)butanal oxime (1.0 equiv.) in THF over 15 min under nitrogen. The reaction was warmed up to room temperature. After the reaction was completed (monitored by TLC), the reaction was cooled down to 0 °C, and quenched with H_2O (x ul) and an aqueous solution of NaOH (2x ul, 15%) then H_2O (3x ul) (for x mg of LAH). Crude material was dried over Na_2SO_4 and filtered. The filtrate was purified by column chromatography to give 4-(1,3-dihydro-2H-inden-2-ylidene)butan-1-amine (**16**).

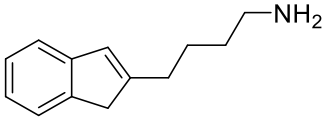
4-(1,3-dihydro-2H-inden-2-ylidene)butan-1-amine (16)



Prepared according to right above procedure, 60% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.14 (m, 4H), 5.44 (tp, *J* = 7.2, 2.4 Hz, 1H), 3.67 (s, 2H), 3.61 (s, 2H), 2.91 (brs, 2H), 2.77 (t, *J* = 7.3 Hz, 2H), 2.12 (q, *J* = 7.2 Hz, 2H), 1.61 (p, *J* = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.18, 141.98, 139.01, 126.31, 126.28, 124.62, 124.44, 122.29, 41.44, 39.25, 35.87, 32.35, 26.83; MS (APCI): *m/z* 188.2 $[M+H]^+$.

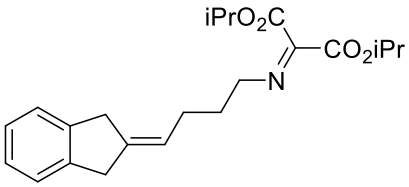
To a mixture of 4-(1,3-dihydro-2H-inden-2-ylidene)butan-1-amine (1.0 equiv.) in DMSO (0.1 M) at 0 °C, t-BuOK (2.0 equiv.) was added. The reaction mixture was warmed to rt, and vigorously stirred. After reaction was completed, the mixture was quenched with H_2O then extracted with CH_2Cl_2. The residue was purified by column chromatography to give 4-(1H-inden-2-yl)butan-1-amine (**17**).

4-(1H-inden-2-yl)butan-1-amine (17)



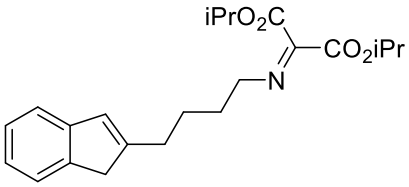
Prepared according to right above procedure, 57% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.4 Hz, 1H), 7.24 (m, 2H), 7.09 (t, *J* = 7.3 Hz, 1H), 6.50 (s, 1H), 3.29 (s, 2H), 2.72 (t, *J* = 7.0 Hz, 2H), 2.49 (t, *J* = 7.5 Hz, 2H), 1.68 – 1.47 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.46, 145.59, 143.05, 126.31, 126.22, 123.57, 123.37, 119.86, 42.01, 40.99, 33.48, 31.02, 26.28; MS (APCI): *m/z* 188.2 $[M+H]^+$.

Diisopropyl 2-((4-(1,3-dihydro-2H-inden-2-ylidene)butyl)imino)malonate (7a)



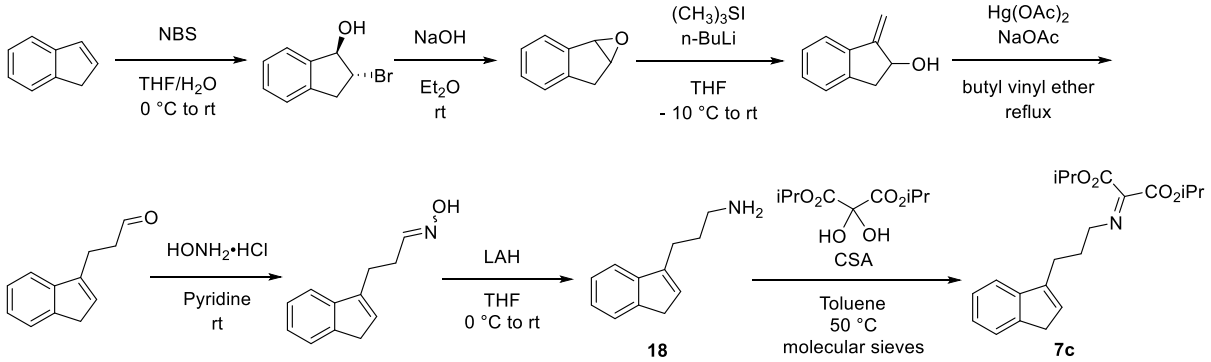
Prepared according to *General procedure B* using 4-(1,3-dihydro-2H-inden-2-ylidene)butan-1-amine (**16**), 54% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 - 7.14 (m, 4H), 5.44 (tp, *J* = 7.7, 2.9 Hz, 1H), 5.23 (m, 2H), 3.67 - 3.60 (m, 6H), 2.15 (q, *J* = 7.4 Hz, 2H), 1.85 (p, *J* = 7.3 Hz, 2H), 1.33 (t, *J* = 6.5 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.16, 160.52, 154.17, 142.15, 142.00, 139.34, 126.29, 126.27, 124.61, 124.42, 122.02, 70.49, 70.06, 55.06, 39.25, 35.85, 29.67, 27.26, 21.65, 21.60; MS (APCI): *m/z* 372.3 $[M+H]^+$.

Diisopropyl 2-((4-(1H-inden-2-yl)butyl)imino)malonate (7b)



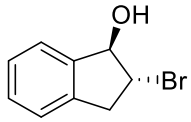
Prepared according to *General procedure B* using 4-(1H-inden-2-yl)butan-1-amine (**17**), 58% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.3 Hz, 1H), 7.24 (m, 2H), 7.09 (t, *J* = 7.3 Hz, 1H), 6.50 (s, 1H), 5.23 (m, 2H), 3.63 (t, *J* = 6.9 Hz, 2H), 3.29 (s, 2H), 2.51 (t, *J* = 7.5 Hz, 2H), 1.82 (m, 2H), 1.67 (p, *J* = 7.6 Hz, 2H), 1.33 (dd, *J* = 6.3, 1.4 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.17, 160.49, 154.18, 150.06, 145.53, 143.03, 126.47, 126.20, 123.59, 123.36, 119.88, 70.53, 70.09, 55.31, 40.97, 30.83, 29.66, 26.70, 21.67, 21.60; MS (APCI): *m/z* 372.3 $[M+H]^+$.

- Synthesis of iminomalonate 7c



Indene (1.0 equiv.) was dissolved in THF/H_2O (1:1, 0.5 M) at room temperature. N-bromosuccinimide (1.1 equiv.) was added over the course of 5 minutes at 0 °C. The reaction was allowed to stir open to air for 1 h. The yellow organic layer was separated, and the aqueous layer was washed three times with ethyl acetate (equal volume). The combined organic layers were washed with saturated sodium thiosulfate (equal volume) and brine (equal volume). The solution was dried with Na_2SO_4 and concentrated in vacuo. The resulting crude material was purified by short column chromatography to give trans-2-bromo-1-indanol.

Trans-2-bromo-1-indanol



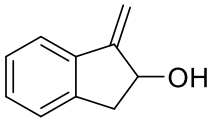
Prepared according to right above procedure, 69% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 1H), 7.30 (m, 2H), 7.23 (m, 1H), 5.32 (t, *J* = 5.9 Hz, 1H), 4.29 (td, *J* = 7.4, 5.9 Hz, 1H), 3.59 (dd, *J* = 16.2, 7.2 Hz, 1H), 3.23 (dd, *J* = 16.2, 7.4 Hz, 1H), 2.32 (d, *J* = 6.0 Hz, 1H); The compound was identified by spectral comparison with literature data[S8].

Trans-2-bromo-1-indanol (1.0 equiv.) was dissolved in dry Et_2O (0.3 M) at room temperature. Freshly ground sodium hydroxide powder (2.5 equiv.) was added portionwise to the reaction. The flask was sealed to prevent loss of Et_2O and any addition of water, and the reaction was allowed to stir for 4 h until the reaction mixture became slightly brown in color. H_2O was then added to dissolve the NaBr precipitate. The aqueous and organic layers were separated, and the organic layer was washed three times with saturated sodium bicarbonate (equal volume) and brine (equal volume). The resulting organic layer was dried with Na_2SO_4 and concentrated in vacuo. This indene oxide crude material was directly used in next step without further purification.

To – 10 °C suspension of trimethyl sulfonium iodide (3.0 equiv.) in dry THF (0.1 M) was added n-BuLi (2.9 equiv.). After 30 min, indene oxide crude (1.0 equiv.) in THF was introduced, producing a milky suspension. The reaction was allowed to warm to 0 °C, over about 30 min and then to r.t and stirred for 2 h. The reaction was quenched with water at 0 °C, extracted with ethyl acetate and the

combined organic layer dried over Na_2SO_4. Then, column chromatography of the crude afforded 1-methylene-2,3-dihydro-1H-inden-2-ol.

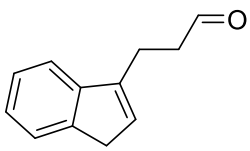
1-methylene-2,3-dihydro-1H-inden-2-ol



Prepared according to right above procedure, 91% yield (2 steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.48 (m, 1H), 7.31 – 7.22 (m, 3H), 5.61 (d, *J* = 2.0 Hz, 1H), 5.33 (d, *J* = 1.8 Hz, 1H), 4.94 (s, 1H), 3.33 (dd, *J* = 16.6, 7.3 Hz, 1H), 2.88 (dd, *J* = 16.6, 4.1 Hz, 1H), 1.82 (brs, 1H); The compound was identified by spectral comparison with literature data[S9].

Under argon atmosphere, $Hg(OAc)_2$ (10 mol%), NaOAc (10 mol%), and 1-methylene-2,3-dihydro-1H-inden-2-ol (1.0 equiv.) were dissolved in n-butyl vinyl ether (0.8 M). The reaction mixture was stirred at reflux for 12 h. The mixture was then poured into sat. $NaHCO_3$ aq. and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated. Column chromatography afforded 3-(1H-inden-3-yl)propanal.

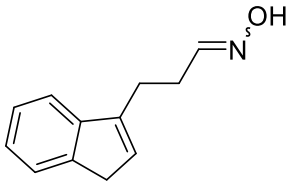
3-(1H-inden-3-yl)propanal



Prepared according to right above procedure using 1-methylene-2,3-dihydro-1H-inden-2-ol, 68% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (t, *J* = 1.3 Hz, 1H), 7.46 (d, *J* = 7.4 Hz, 1H), 7.37 – 7.29 (m, 2H), 7.22 (td, *J* = 7.3, 1.3 Hz, 1H), 6.20 (t, *J* = 1.9 Hz, 1H), 3.33 (d, *J* = 1.9 Hz, 2H), 2.92 – 2.81 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.92, 144.77, 144.37, 142.51, 128.38, 126.12, 124.86, 123.85, 118.73, 41.92, 37.78, 20.19; MS (APCI): *m/z* 173.1 $[M+H]^+$.

A solution of 3-(1H-inden-3-yl)propanal (1.0 equiv.) in 0.5 M of pyridine was cooled with an ice bath. hydroxylamine hydrochloride (1.2 equiv.) was added with stirring. After the reaction was completed (monitored by TLC), the solvent was evaporated, and the residue was purified by flash chromatography to give 3-(1H-inden-3-yl)propanal oxime as a white solid.

3-(1H-inden-3-yl)propanal oxime

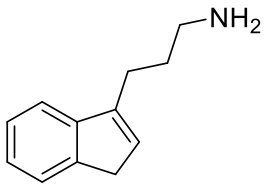


Prepared according to right above procedure using 3-(1H-inden-3-yl)propanal, 92% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (brs, 1H), 7.45 (d, *J* = 7.3 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 6.82 (t, *J* = 4.6 Hz, 1H), 6.25 (s, 1H), 3.33 (s, 2H), 2.80 – 2.72 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.69, 144.98, 144.42, 142.90, 128.36, 126.09, 124.76, 123.81, 118.79, 37.81, 24.04, 23.34; MS (APCI): *m/z* 188.1 $[M+H]^+$.

To a mixture of LAH (2.2 equiv.) in THF (0.3 M) at 0 °C, was added dropwise a solution of 4-(1,3-dihydro-2H-inden-2-ylidene)butanal oxime (1.0 equiv.) in THF over 15 min under nitrogen. The

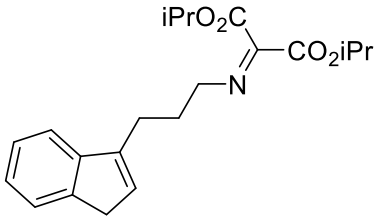
reaction was warmed up to room temperature. After the reaction was completed (monitored by TLC), the reaction was cooled down to 0 °C, and quenched with H_2O (x ul) and an aqueous solution of NaOH (2x ul, 15%) then H_2O (3x ul) (for x mg of LAH). Crude material was dried over Na_2SO_4 and filtered. The filtrate was purified by column chromatography to give 3-(1H-inden-3-yl)propan-1-amine (**18**).

3-(1H-inden-3-yl)propan-1-amine (18)



Prepared according to right above procedure, 53% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.3 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 1H) 7.29 (t, *J* = 7.4 Hz, 1H), 7.20 (m, 1H), 6.22 (t, *J* = 1.8 Hz, 1H), 3.33 (d, *J* = 1.8 Hz, 2H), 2.80 (t, *J* = 7.0 Hz, 2H), 2.60 (td, *J* = 7.6, 2.0 Hz, 2H), 1.85 (p, *J* = 7.3 Hz, 2H); The compound was identified by spectral comparison with literature data[S10].

Diisopropyl 2-((3-(1H-inden-3-yl)propyl)imino)malonate (7c)



Prepared according to *General procedure B* using 3-(1H-inden-3-yl)propan-1-amine (**18**), 56% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dt, *J* = 7.3, 0.9 Hz, 1H), 7.36 (dt, *J* = 7.5, 1.0 Hz, 1H) 7.29 (m, 1H), 7.19 (t, *J* = 7.3, 1.2 Hz, 1H), 6.23 (p, *J* = 1.8 Hz, 1H), 5.22 (hept, *J* = 6.3 Hz, 2H), 3.69 (t, *J* = 7.1 Hz, 2H), 3.32 (d, *J* = 2.0 Hz, 2H), 2.62 (m, 2H), 2.15 (p, *J* = 7.2 Hz, 2H), 1.34 (d, *J* = 6.3 Hz, 6H), 1.30 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.16, 160.52, 154.32, 145.19, 144.40, 143.44, 128.10, 125.97, 124.54, 123.70, 118.91, 70.55, 70.13, 55.19, 37.71, 28.13, 25.40, 21.63, 21.60; MS (APCI): *m/z* 358.3 $[M+H]^+$.

S1. Green Chem., 2019, 21, 5368.

S2. J. Am. Chem. Soc., 2017, 139 (32), 11184.

S3. Org. Lett. 2007, 9 (12), 2285.

S4. Adv. Syn. Cat., 2019, 361 (8), 1792.

S5. J. Am. Chem. Soc., 2014, 136 (25), 8915.

S6. J. Org. Chem., 2005, 70 (26), 10720.

S7. Organic Process Research and Development, 2003, 7 (2), 155.

S8. Synlett, 2019, 30 (4), 437.

S9. Tet. Lett., 1994, 35 (30), 5449.

S10. J. Org. Chem., 1993, 58 (24), 6650.

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