Doctoral Thesis

Synthesis of Heterocycles via Various Synthetic Methods

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Advisor

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Abstract

Heteroatom-containing molecule chemistry is one of the important sources of novel compounds with various biological activities, especially due to the unique ability of the resulting compounds to bind reversibly to proteins, like the structure of peptides.[1] Because of this importance, the synthetic community has been focused on developing various synthetic methodologies in simpler and milder reaction pathways compared to previously reported methodologies.

In Chapter 1, the synthesis of cyclobutenes using alkyne-alkene [2+2] cycloaddition based on visible light photosynthesis is described. Compared to previously reported UV-activated alkyne-alkene [2+2] cycloaddition reactions, this study proceeded under much milder conditions using blue light in the visible light region. Diverse cyclobutenes were synthesized based on intermolecular [2+2] cycloaddition using alkynes and alkenes. Furthermore, 1,3-dienes were also generated via intramolecular [2+2] cycloaddition using various enynes.

In Chapter 2, the synthesis of γ-lactams using electrochemical C(sp^3)-H functionalization based on hydrogen atom transfer is described. The typical synthesis of γ-lactams is nucleophilic addition to N-acyliminium (NAI) intermediates generated by the elimination of leaving groups at the nitrogen's alpha positions of lactams. Unlike the previous typical synthesis, this study describes a coupling reaction with electron-deficient alkenes or N-sulfonyl imines and nitrogen's alpha radical on lactams to generate various functionalized γ-lactams.

In Chapter 3, the synthesis of dithioacetals using a gold catalyst via hydrothiolation of vinyl sulfides is described. This method not only produces symmetrical dithioacetals, but also unsymmetrical dithioacetals with broad substrate scope. In this study, both activated and unactivated vinyl sulfides were demonstrated for hydrothiolation. Moreover, the reaction is not limited to aryl thiols, as aliphatic thiols were also used to display broad compatibility for reaction conditions.

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Abbreviations

Tf	Triflate
DMF	Dimethylformamide
DCE	1,2-Dichloroethane
Ppy	2-Phenylpyridine
SET	Single Electron Transfer
DFT	Density Functional Theory
MeCN	Acetonitrile
n.r.	No Reaction
THF	Tetrahydrofuran
m.p.	Melting Point
NMR	Nuclear Magnetic Resonance
HRMS	High Resolution Mass Spectroscopy
BDE	Bond dissociation energy
BHT	2,6-Di-tert-butyl-4-methylphenol
Bn	Benzyl group
^{t}Bu	Tert-butyl group
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	Dichloromethane
DMA	Dimethylformamide
Et	Ethyl
G	Graphite
GC	Glassy carbon

HAT	Hydrogen atom transfer
$LiClO_4$	Lithium perchlorate
Me	Methyl
MeOH	MeOH
TsCl	p-Toluenesulfonyl chloride
Ms	Methanesulfonyl
mmol	millimole
m/z	Mass-to-charge ratio
NAI	N-acyliminium
NaN_3	Sodium azide
$^nBu_4NN_3$	Tetrabutylammonium azide
$^nBu_4NBF_4$	Tetrabutylammonium tetrafluoroborate
$^nBu_4NPF_6$	Tetrabutylammonium hexafluorophosphate
NHPI	N-hydroxy phthalimide
Nu	Nucleophile
OAc	Acetate
OTf	trifluoromethanesulfonate
Ph	Phenyl
PPh_3	Triphenylphosphine
r.t.	Room temperature
SCE	Saturated calomel electrode
SET	Single electron transfer
TBHP	tert-butyl hydroperoxide
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl

THF	Tetrahydrofuran
TMS	trimethylsilyl
Ts	p-toluenesulfonyl
EnT	Energy Transfer
eT	Electron Transfer
PC	Photocatalyst
DIPEA	Diisopropylethylamine
EtOAc	Ethyl Acetate
HFIP	Hexafluoroisopropanol
TFA	Trifluoroacetic acid
BHT	2,6-Di-tert-butyl-4-methylphenol
TLC	Thin Layer Chromatography
TMS	trimethylsilyl
DCE	1,2-dichloroethane
EWG	electro-withdrawing group
Ar	aryl
UV	ultra-violet
ppy	2-phenylpyridine
bpy	2,2’-bipyridine
pic	picolinic
dF	di-fluoro
dtbbpy	di-tert-butyl-2,2’-dipyridyl
Ac	acetyl/acetic
Cy	cyclohexyl group

Chapter 1.

Alkyne–Alkene [2 + 2] cycloaddition based on visible light photocatalysis

1.1. Introduction

1.1.1 Cyclobutene

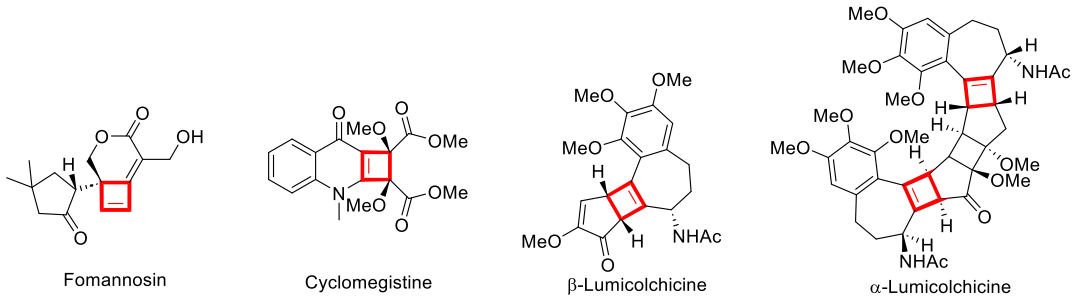


Figure 1-1. Natural products containing a cyclobutene scaffolds

Cyclobutene is an all-carbon, four-membered ring containing one double bond. Many naturally occurring biologically and pharmaceutically active structure contain this carbon structure (Figure 1-1).[2] The preparation of cyclobutenes has garnered attention from the synthetic community due to the importance of synthetic intermediates and their presence in complex natural products. However, synthesizing cyclobutenes with complex substituents is challenging due to their inherent ring strain, which makes them unstable.

1.1.2. Preparation of cyclobutene via [2+2] cycloaddition

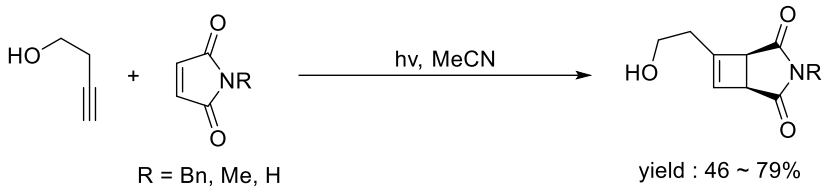
The preparation of cyclobutenes has gained attention from the synthetic community due to their presence in complex natural products. This process has been developed using light sources, such as UV light, as an energy source. Various synthesis methods have also been developed using Lewis acids and transition metals as reaction catalysts. However, these methods have limitations as they require specific functional groups to activate the substrates.

1.1.2.1. Photochemical [2+2] cycloaddition

Several [2+2] photocycloaddition works have been reported, utilizing ultraviolet (UV) to visible light as an energy source to prepare cyclobutenes. UV-activated [2+2] cycloaddition with alkynes and alkenes has been an essential tool for this purpose. However, the use of UV light as an energy source has faced limitations, which has driven the synthetic community to search for alternative synthesis methods.

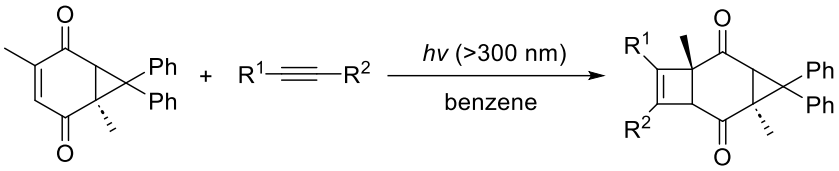
1.1.2.1.1. Direct excitation by UV light

Thermal [2+2] cycloaddition of alkenes with alkynes is a thermally forbidden process, which led to the development of methods based on direct excitation by UV light. In 2019, Donnelly et al. reported synthesis of cyclobutene alcohol in gram scale using this approach (Scheme 1-1).[3] The generated cyclobutene alcohols underwent Prins cyclization to form single diastereomers. The product succinimide was synthesized by the [2+2] cycloaddition of maleimide with propargyl alcohol in acetonitrile solvent. The imide can be converted to the corresponding products using flow photochemistry. Despite its broad accessibility, the use of UV light as an energy source has limitations, which have driven the synthetic community to seek alternative synthesis methods.



Scheme 1-1. Synthesis of cyclobutene reported by Donnelly et al.

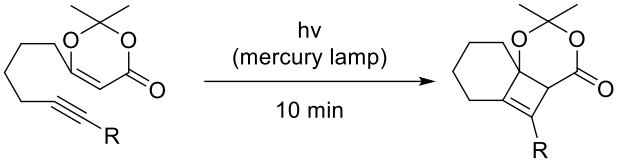
Oshima group reported the synthesis of [2+2] photocycloadducts using variously substituted alkenes and alkynes by irradiation of a homobenzoquinone deriviative (Scheme 1-2).[4] In a radical trapping experiment using benzeneselenol, the authors supported the detailed mechanism, which involves the generation of two biradicals during the reaction.



Scheme 1-2. [2+2] photocycloaddition of homobenzoquinone derivative

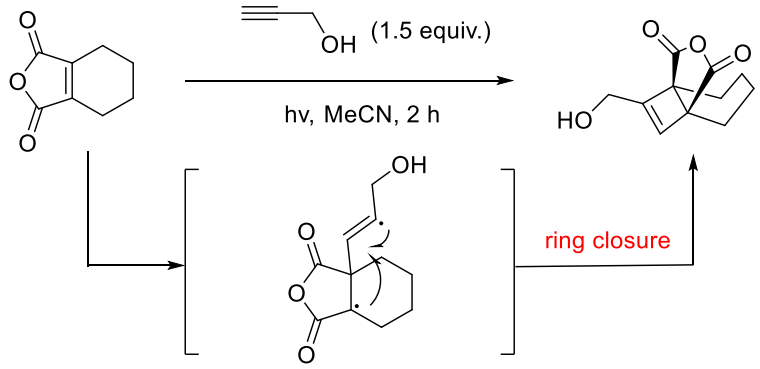
Scheme 1-3 illustrates an intramolecular photocycloaddition that results in the formation of cyclobutene photoadduct containing H or TMS as function R.[5] The substrate used was an acetylenic dioxanone, which, under irradiation of mercury lamp, led to the formation of the cyclobutene core-

containing product. Remarkably, the reaction showed complete disappearance of the starting material in a very short period, only 10 minutes.



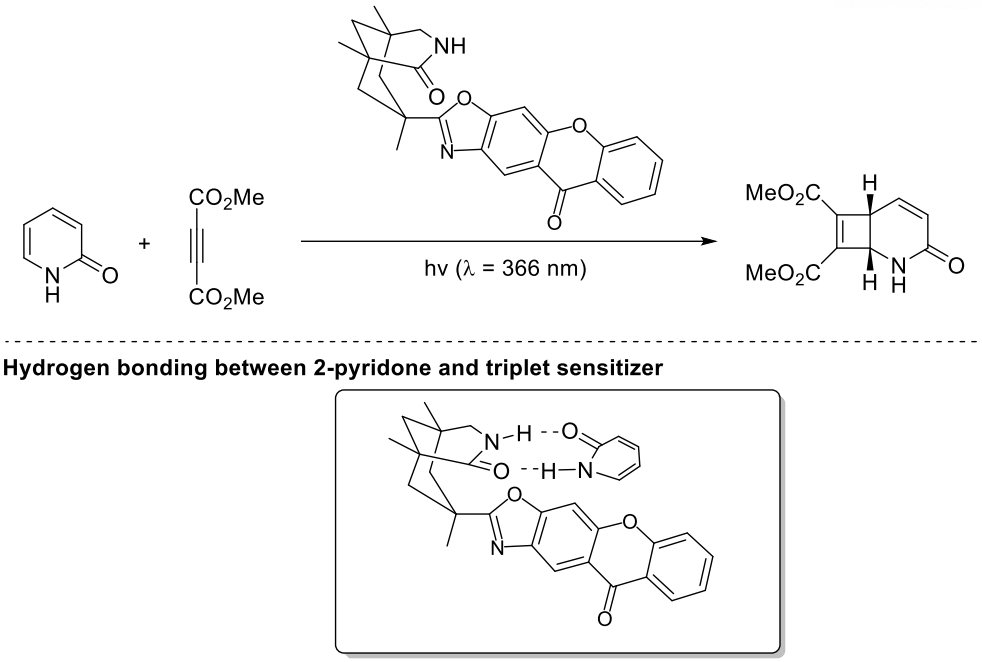
Scheme 1-3. Intramolecular photocycloaddition of dioxenones with alkynes

A highly efficient [2+2] photocycloaddition reaction between tetrahydrophthalic anhydride and propargyl alcohol under mercury lamp irradiation, which resulted in good yield of the cyclobutene product (Scheme 1-4).[6] The reaction proceeds via a triplet biradical intermediate, followed by ring closure to form the desired product. In addition to propargyl alcohol, a variety of alkyne substrates have been used in intermolecular [2+2] photocycloaddition reactions to form the desired cycloadducts with high yields.



Scheme 1-4. Intermolecular [2+2] photocycloaddition reaction of tetrahydrophthalic anhydride

Using a low catalyst loading, Maturi et al. carried out an intermolecular [2+2] photocycloaddition reaction with high enantioselectivity, using a chiral triplet sensitizer (Scheme 1-5).[7] This was the first time that intermolecular [2+2] photocycloadditions could be carried out with a catalytic amount of a chiral triplet sensitizer. The substrate and catalyst undergo hydrogen bonding, followed by fast addition of the alkyne to the excited substrate.

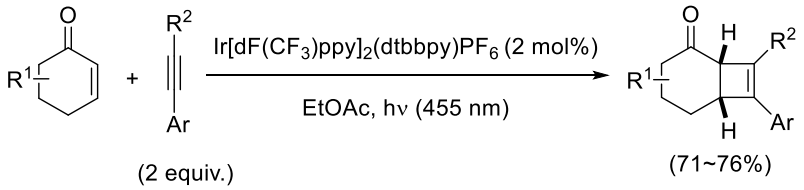


Scheme 1-5. Intermolecular [2+2] photocycloaddition between 2-pyridones and acetylenedicarboxylates

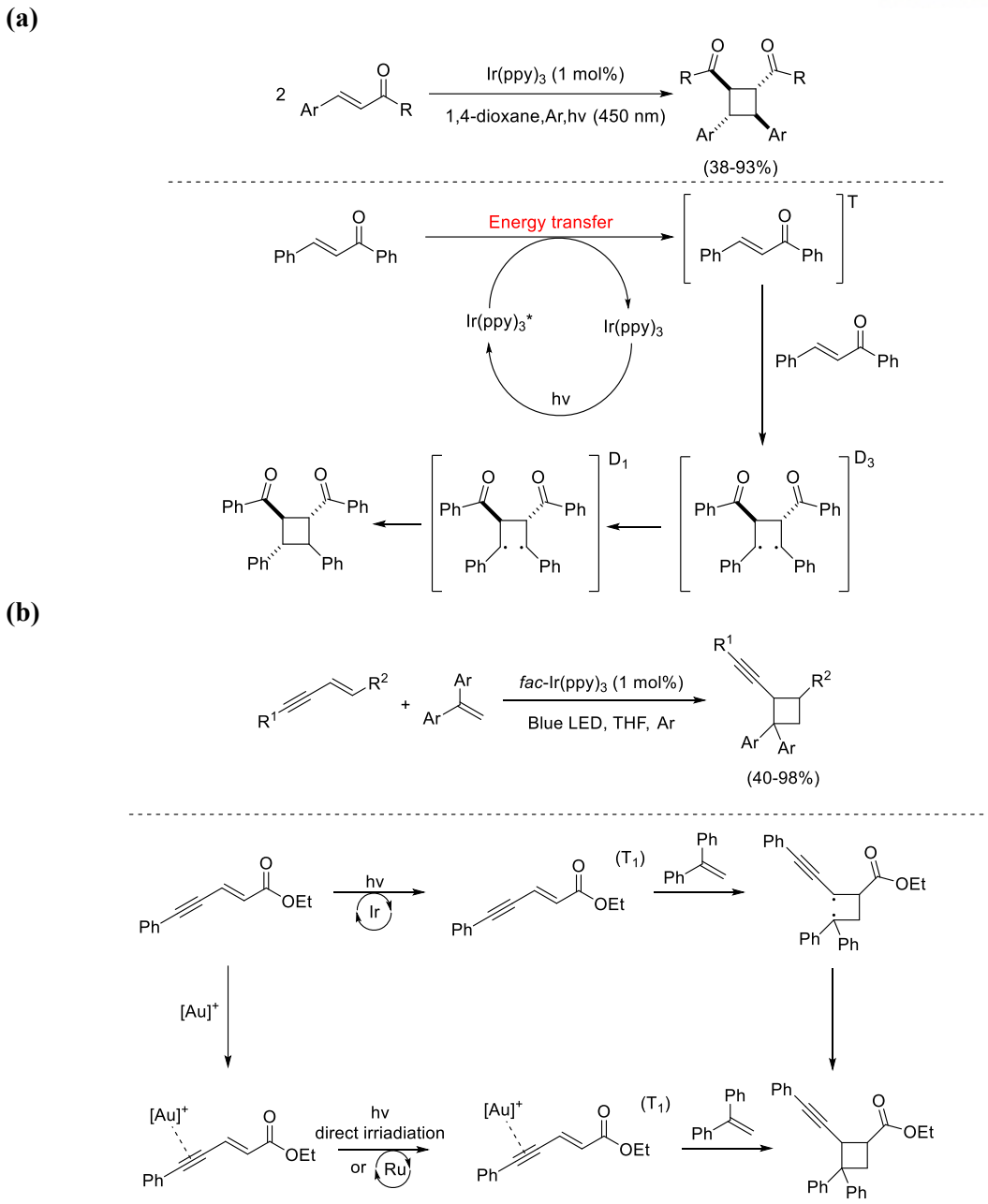
1.1.2.1.2. Visible light mediated [2+2] cycloaddition

Several studies have reported on alkene-alkene [2+2] cycloaddition reactions for the synthesis of cyclobutanes in both intermolecular and intramolecular reactions using the energy transfer (EnT) process. However, compared to alkene-alkene studies, the development of alkyne-alkene [2+2] cycloaddition reactions with visible light are still underdeveloped.

Recently, the Glorius group reported on an energy-transfer enabled dearomative [2+2] cycloaddition using Ir-based visible light photocatalysis (Scheme 1-6).[8] By using cyclic enones, fused cyclobutenes were formed via cycloaddition with electron-rich alkynes. The corresponding highly strained cyclobutene adducts were isolated as products of a formal [2+2] cycloaddition in good yields and with excellent diastereoselectivity.



Scheme 1-6. Energy transfer enabled dearomative [2+2] cycloaddition

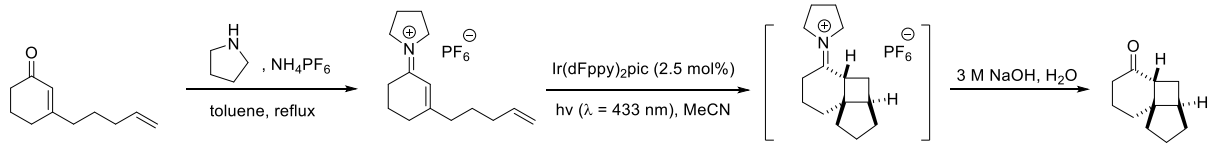


Scheme 1-7. [2+2] photocycloaddition by Wu group.

Several alkene-alkene [2+2] cycloaddition reactions for the under visible light irradiation has been reported. Wu group reported intermolecular [2+2] dimerization reaction of acyclic olefins to produce cyclobutanes in a highly regioselective and diastereoselective manner in a 1,4-dioxane solution under visible light conditions (Scheme 1-7, (a)).[9] Both electron-donating and electron-withdrawing substituted starting materials were tolerated, and series of aryl substituents also worked well to afford

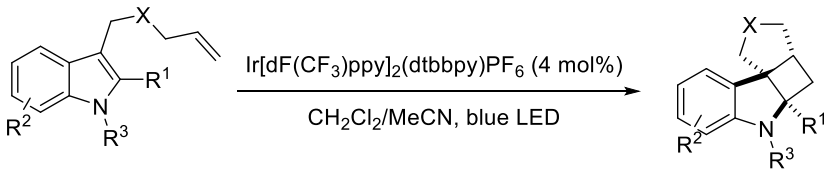
corresponding dimer products. The cyclobutene products are mainly in an anti-head-to-head configuration. Later in 2018, same group reported synthesis of alkynyl cyclobutanes by visible light photocatalysis (Scheme 1-7, (b)).[10] The reaction was conducted via an intermolecular cross [2+2] cycloaddition of enynes with alkenes to form alkynyl cyclobutanes. Nonaromatic enynes could be sensitized by *fac*-Ir(ppy)$_3$ using energy transfer method. When the Lewis acid PPh_3AuNTf_2 was added to the reaction condition, the photo-sensitization could work with $Ru(bpy)_3(PF_6)_2$ under visible light irradiation.

Bach group has reported on the use of eniminium ions in [2+2] photocycloaddition reactions under visible light conditions (Scheme 1-8).[11] The photoexcitied intermediates were found to undergo intramolecular [2+2] photocycloadditions to produce the desired product in good yields. The use of an Ir-based complex with a sufficiently high triplet energy was found to be an efficient catalyst, with only 2.5 mol loading needed for the reaction. In the intermolecular Ir-catalyzed [2+2] photocycloaddition, ketone products were produced, which were then subjected to hydrolysis with a 3 M NaOH solution for work-up.



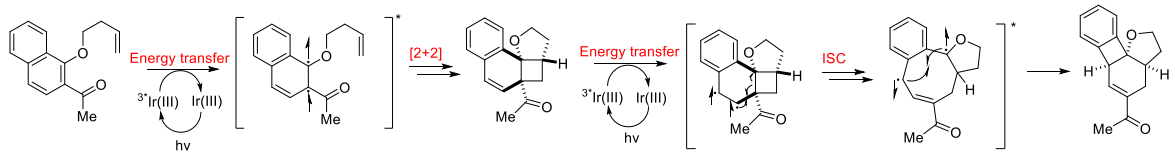
Scheme 1-8. Visible light induced [2+2] photocycloaddition of eniminium ions by Bach group

You group reported on the intramolecular dearomatization of indole derivatives based on visible-light-mediated [2+2] cycloaddition via an energy transfer mechanism (Scheme 1-9).[12] Throughout the reaction scope, the substrates substituted with electron-withdrawing groups were found to be more beneficial for the reaction results. To understand the reactivities of the substrates, the authors calculated Mulliken spin populations and triplet-singlet energy gaps.



Scheme 1-9. Intramolecular [2+2] cycloaddition of indole derivatives by You group

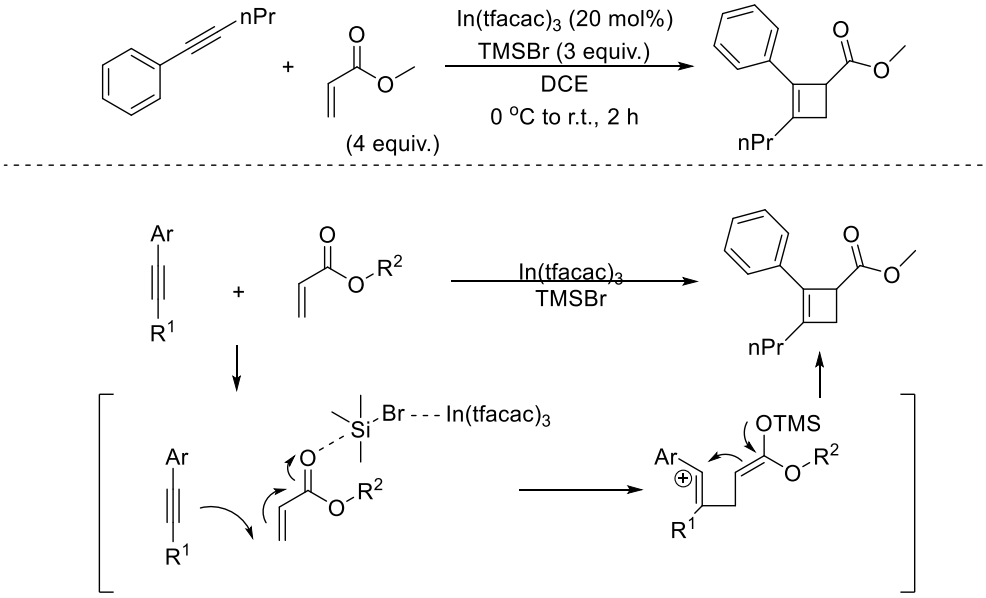
In Scheme 1-10 shows the mechanism of dearomative cascade photocatalysis via energy transfer which is reported by Glorius group in 2018.[13] This strategy was conducted in complex molecule synthesis. Starting from simple naphthol arene structure, divergent converted products were made using catalyst selective energy transfer.



Scheme 1-10. [2+2] photochemical dearomatization by Glorius group.

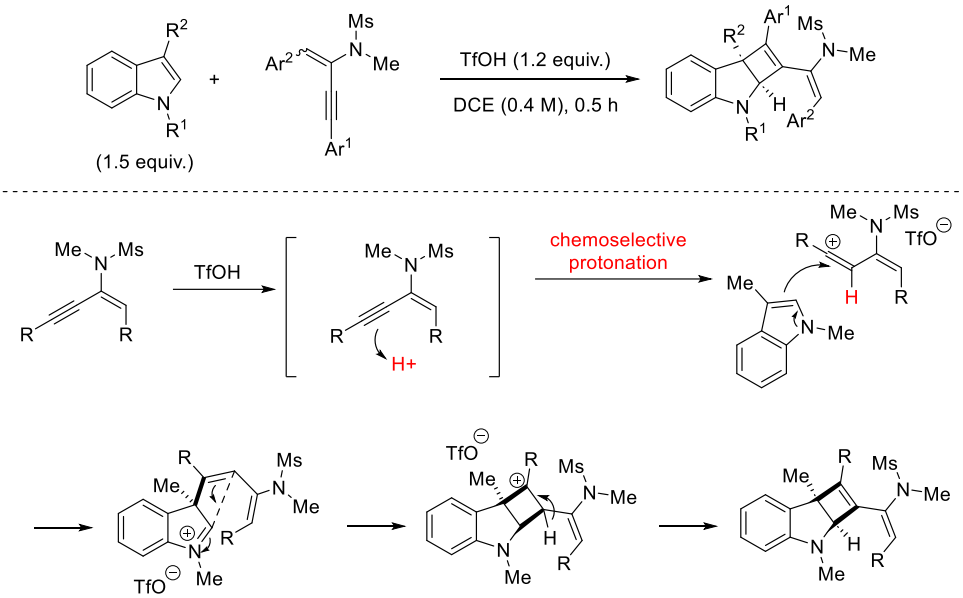
1.1.2.2. Lewis Acid (LA) Catalyzed Reactions

Lewis acids have explored as alternative methods for the synthesis of cyclobutenes. However, the requirement of specific functional groups on the substrates for activation remains a challenge. In 2017, Loh group reported a Lewis acid-catalyzed [2+2] cycloaddition reaction using aryl alkynes and acrylates as reagents (Scheme 1-11).[14] The reaction involves the formation of a combined Lewis acid complex through the reaction of indium catalyst and TMSBr. The combined Lewis acid then activates the acrylate partner, which is subsequently attacked by the aryl alkyne acting as a nucleophile to form an enolate intermediate. Finally, an intramolecular nucleophilic attack occurs to produce the desired cyclobutene product. The plausible reaction pathway was supported by DFT calculation to provide a detailed mechanism study.



Scheme 1-11. Lewis acid catalyzed [2+2] cycloaddition by Loh gorup

Park group reported a dearomative [2+2] cycloaddition using conjugated alkynes and electron-rich indoles (Scheme 1-12).[15] The optimized conditions allowed for the reaction of 25 cross-conjugated ynenamides and 6 indole derivatives. The [2+2] cycloadducts were generated through the cycloaddition of indole with different ynenamide substrates. The reaction began with the chemoselective protonation of the alkyne, which produced a vinyl cation intermediate. Then, a regioselective Friedel-Crafts alkenylation of an indole was followed by the subsequent ring closure of the alkene at the indole iminium ion.



Scheme 1-12. Lewis acid catalyzed [2+2] cycloaddition by Park group

1.1.2.3. Transition Metal (TM) Catalyzed Reactions

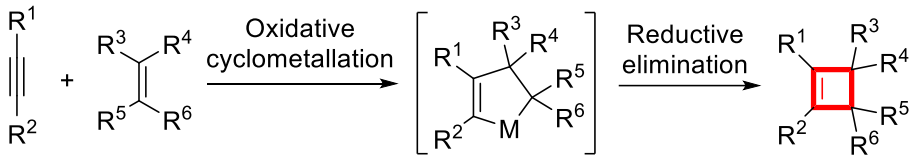
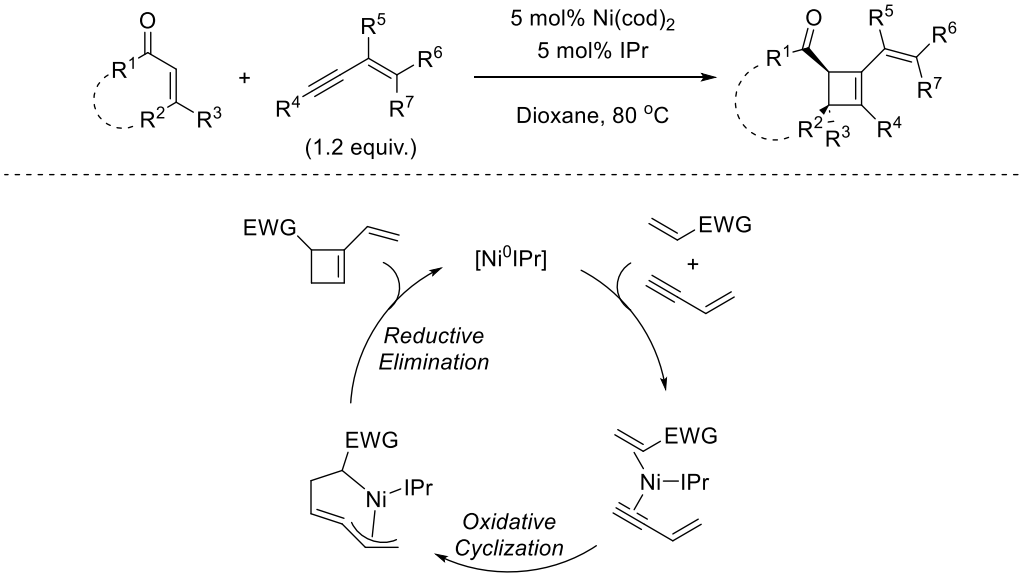


Figure 1-2. Reaction mechanism of transition metal (TM) catalyzed [2+2] cycloaddition.

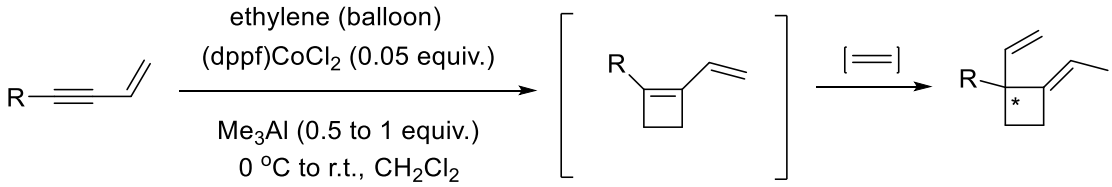
Many interesting reports of [2+2] cycloadditions have emerged in the field of transition metal-catalyzed reactions. Typically, the reaction mechanism involves the formation of a five-membered ring intermediate by the oxidative cyclometallation of transition metal catalyst, followed by the production of a cyclobutene via the reductive elimination of the five-membered ring intermediate (Figure 1-2).

In 2012, Ogoshi group reported on a transition metal-catalyzed [2+2] cycloaddition using nickel as the catalyst (Figure 1-13).[16] This study demonstrated the intermolecular [2+2] cycloaddition of conjugated enynes with alkenes. During the reaction, an η^3-butadienyl coordination nickelacycle intermediate was isolated as an intermediate complex, which was produced from the oxidative cyclization of the nickel catalyst, conjugated enyne, and alkene.



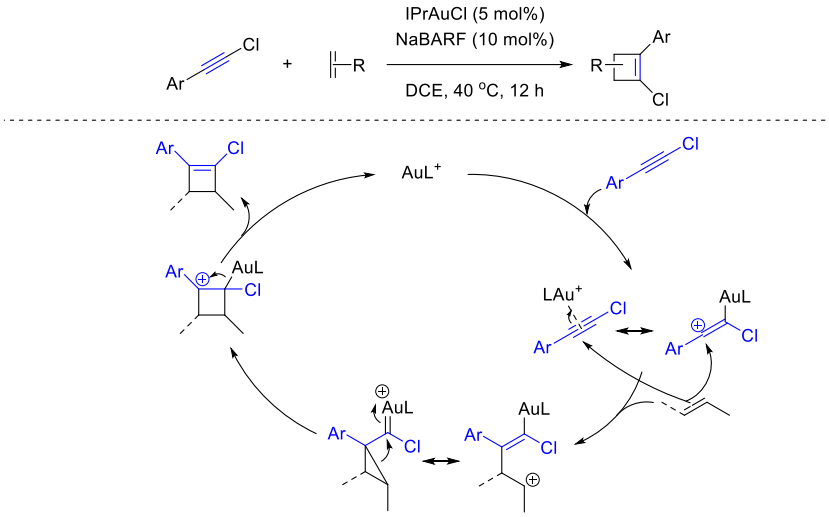
Scheme 1-13. Ni-catalyzed intramolecular [2+2] cycloaddition

Scheme 1-14 illustrates cobalt catalysis of a [2+2] cycloaddition using 1,3-enynes and ethylene (balloon) followed by a hydrovinylation of generating vinylcyclobutene to give highly substituted cyclobutanes having a chiral, all-carbon quaternary center in the ring.[17] Starting material which are 1,3-enyens and ethylene, both inexpensive. Throughout the reaction three highly selective carbon-carbon bond can be formed in one pot using a single chiral cobalt catalyst.



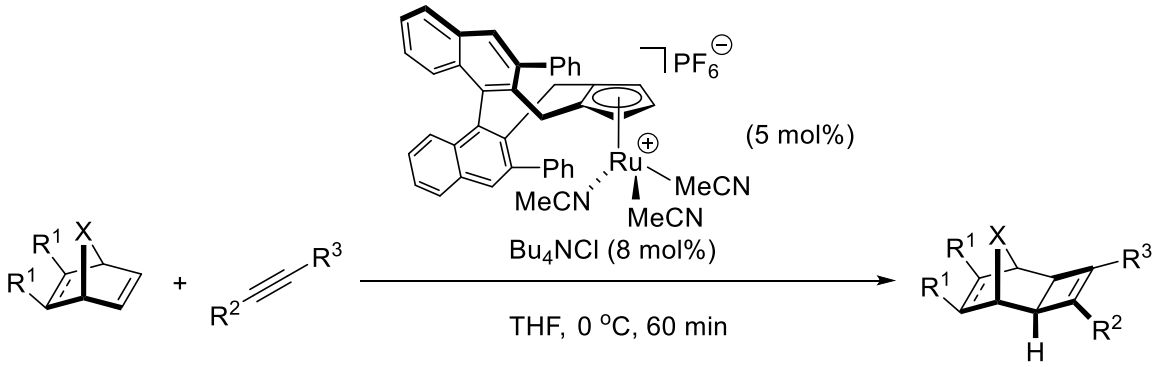
Scheme 1-14. Co-catalyzed intermolecular [2+2] cycloaddition

Gold-catalyzed intermolecular [2+2] cycloaddition using alkyne and alkene was reported in 2018 (Scheme 1-15).[18] Initially, gold activation of alkyne forms gold complex or its polarized resonance complex, vinyl cation. Then, a nucleophilic attack by an alkene to obtain mesomeric cationic intermediates. The intermediate goes to ring enlargement and followed by E1-type elimination of the gold catalyst to give cyclobutene product. The scope range is wide, from various disubstituted alkenes to monosubstituted alkenes, gives the corresponding products with moderate to excellent yields.



Scheme 1-15. Au-catalyzed [2+2] cycloaddition

Cramer group reported [2+2] cycloaddition using Ru(II) catalyst (Scheme 1-16).[19] A chiral neutral Ru(II) complex provided excellent catalytic reactivity to produce strained chiral cyclobutene. Also, larger scale reaction was proceeded in more concentrated condition and lower catalyst loading to obtain 91% of desired product.



Scheme 1-16. Ru-catalyzed [2+2] cycloaddition

1.1.3. Electron transfer (ET) and Energy transfer (EnT).

Visible light photocatalysis can be divided into two pathways: electron transfer and energy transfer (Figure 1-3). In the electron transfer pathway, the photocatalyst undergoes a single electron transfer from the excited state to the reagent or substrate upon irradiation with visible light. This generates a radical ion, and there are two mechanistic cycles: the oxidative quenching cycle and the reductive quenching cycle. In the oxidative cycle, the excited photocatalyst is first oxidized and then reduced to regenerate the photocatalyst. The reductive quenching cycle works in the opposite way.

In the energy transfer pathway, the reaction proceeds through energy transfer between an energy donor and acceptor. First, the photocatalyst absorbs light and is excited from its ground state. Next, the excited state of the photocatalyst turns into the triplet state through intersystem crossing. Then, energy transfer occurs from the photocatalyst to the substrate, resulting in the substrate being excited from its ground singlet state to an active triplet state. The resulting excited substrate will undergo an organic transformation. This pathway is dependent on the triplet state energy of both the photocatalyst and substrate.

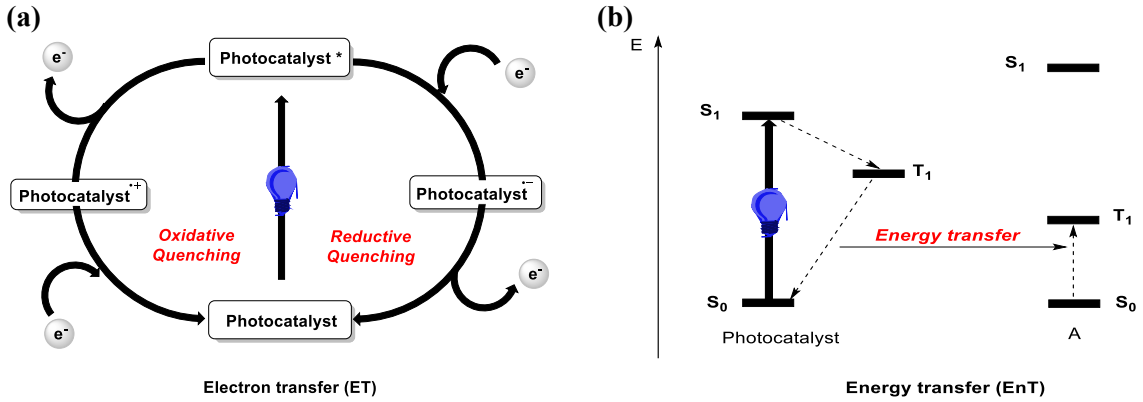
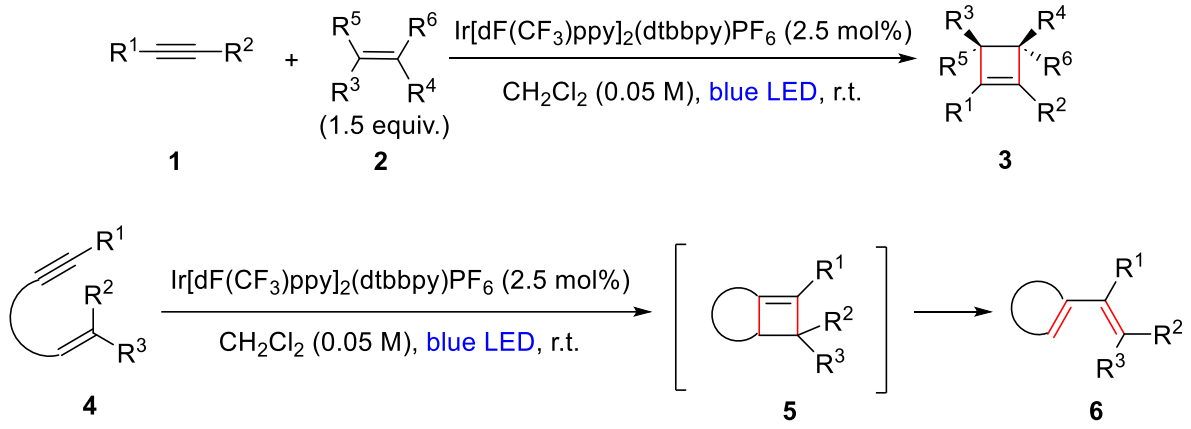


Figure 1-3. Photocatalysis – electron transfer (ET) and energy transfer (EnT).

In this work, two types of [2+2] cycloaddition were described depending on the substrate (Scheme 1-17). For intermolecular reaction, various cyclobutenes were formed from the alkyne and alkene using a 2.5 mol% Ir catalyst and blue LED. Under the same conditions, intramolecular reactions were also developed when the starting material was an enyne

This work



Scheme 1-17. Alkyne–Alkene [2 + 2] cycloaddition based on visible light photocatalysis.

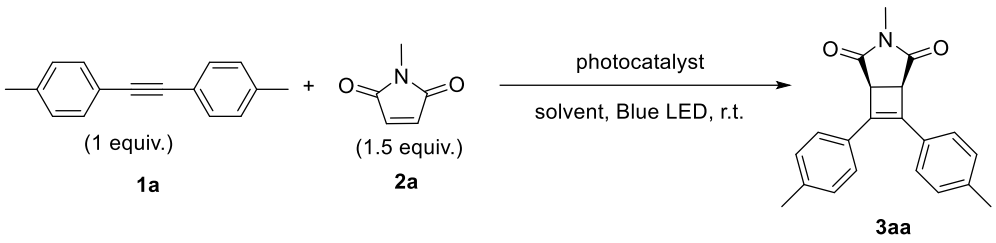
1.2. Optimization of reaction conditions

We started optimizing the alkyne-alkene [2+2] cycloaddtion using various photocatalysts. Initially, we tried organic dyes, but the reaction did not proceed (Table 1-1, entries 1-3). Unfortunately, we also did not get the desired product using $Ru(bpy)_3(PF_6)_2$, $Ir(ppy)_3$ and $Ir(ppy)_2(dtbbpy)PF_6$ (Table 1-1, entries 4-6). However, we found that several iridium-based photocatalysts were efficient in synthesizing the desired product cyclobutene (Table 1-1, entries 7-10). With $Ir[dF(CF)_3ppy]_2(dtbbpy)PF_6$ as the optimal photocatalyst, we optimized the amount of N-methyl maleimide and $Ir[dF(CF)_3ppy]_2(dtbbpy)PF_6$, solvents, and concentrations (Table 1-1, entries 11-16). We determined that using 1.5 equiv. of N-methyl maleimide with 2.5 mol% of $Ir[dF(CF)_3ppy]_2(dtbbpy)PF_6$ under 0.05 M of CH_2Cl_2 was the optimal condition for preparing the desired cyclobutene product (Table 1-1, entry 16). We also conducted control experiments to verify the necessity of the photocatalyst and light as an energy source (Table 1-1, entries 17-18). The reaction did not proceed if either one was missing.

Based on the catalyst screening, we tried to distinguish the two plausible reaction pathways, electron transfer (ET) and energy transfer (EnT) (Table 1-2). The reduction potential and triplet energy of N-methylmaleimide **2a** were calculated (-1.16V vs SCE and 55.9 kcal/mol). Compared to those of the catalysts, a clear correlation was observed between the yields and the triplet energies of catalysts. Entry 1 shows the highest triplet energy catalyst (60.8 kcal/mol), it turned out to be the most efficient for the cycloaddition reaction however, the reduction potential is not sufficient for the reduction of N-methylmaleimide. On the other hand, a trace conversion was observed in entry 6 condition, which has

a slightly higher reduction potential but lower triplet energy than that of N-methylmaleimide. These observations drive us to propose that energy transfer (EnT) process for the proposed mechanism (Figure 1-5 and Figure 1-6).

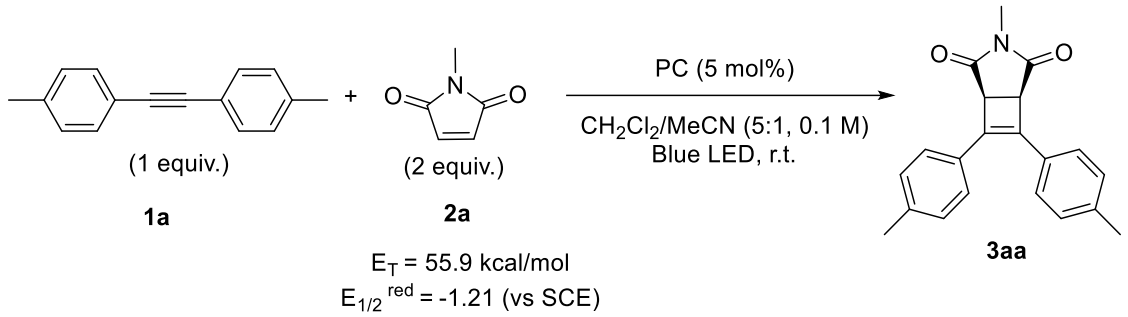
Table 1-1. Reaction Optimization table[a]



Entry	N-methyl maleimide (equiv.)	Photocatalyst (mol%)	Solvent	Conc. [M]	Yield (%)
1	2.0	Eosin Y (5)	CH_2Cl_2/MeCN (5:1)	0.1	N.R.
2	2.0	Rose Bengal (5)	CH_2Cl_2/MeCN (5:1)	0.1	N.R.
3	2.0	Acr-$Mes^+ClO_4^-$ (5)	CH_2Cl_2/MeCN (5:1)	0.1	N.R.
4	2.0	$Ru(bpy)_3(PF_6)_2$ (5)	CH_2Cl_2/MeCN (5:1)	0.1	N.R.
5	2.0	$Ir(ppy)_3$ (5)	CH_2Cl_2/MeCN (5:1)	0.1	N.R.
6	2.0	$Ir(ppy)_2(dtbbpy)PF_6$ (5)	CH_2Cl_2/MeCN (5:1)	0.1	Trace
7	2.0	$Ir(Fppy)_2(dtbbpy)PF_6$ (5)	CH_2Cl_2/MeCN (5:1)	0.1	35
8	2.0	$Ir(dFppy)_2(dtbbpy)PF_6$ (5)	CH_2Cl_2/MeCN (5:1)	0.1	62
9	2.0	$Ir(dFppy)_2pic$ (5)	CH_2Cl_2/MeCN (5:1)	0.1	74
10	2.0	$Ir[dF(CF)_3ppy]_2(dtbbpy)PF_6$ (5)	CH_2Cl_2/MeCN (5:1)	0.1	76
11	1.5	$Ir[dF(CF)_3ppy]_2(dtbbpy)PF_6$ (2.5)	CH_2Cl_2	0.1	74
12	1.5	$Ir[dF(CF)_3ppy]_2(dtbbpy)PF_6$ (2.5)	$CHCl_3$	0.1	73
13	1.5	$Ir[dF(CF)_3ppy]_2(dtbbpy)PF_6$ (2.5)	THF	0.1	15
14	1.5	$Ir[dF(CF)_3ppy]_2(dtbbpy)PF_6$ (2.5)	DMF	0.1	53
15	1.5	$Ir[dF(CF)_3ppy]_2(dtbbpy)PF_6$ (2.5)	Acetone	0.1	58
16	1.5	$Ir[dF(CF)_3ppy]_2(dtbbpy)PF_6$ (2.5)	CH_2Cl_2	0.05	83 (76[b])
17	1.5	-	CH_2Cl_2	0.05	Trace
18[c]	1.5	$Ir[dF(CF)_3ppy]_2(dtbbpy)PF_6$ (2.5)	CH_2Cl_2	0.05	N.R.

[a] Reactions were conducted on a 0.05 mmol scale under argon atmosphere. N.R. = no reaction.
[b] Isolated yield (0.1 mmol scale), reaction time : 4 h
[c] Reaction was conducted under dark condition

Table 1-2. Triplet Energies and Redox Potentials of Catalysts[a]



Entry	Photocatalyst	$E_{1/2}^{red}/E_{1/2}^{ox}$ (V)	E_T (kcal/mol)	Yield (%)
1	$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$	-0.89 / 1.21	60.8	76%
2	$Ir(dFppy)_2pic$	-1.23 / 1.40	60.5	74%
3	$Ir[dF(CF_3)ppy]_2(bpy)PF_6$	-0.97 / 0.97	60.4	74%
4	$Ir(dFppy)_2(dtbbpy)PF_6$	-0.93 / 1.14	55.4	62%
5	$Ir(Fppy)_2(dtbbpy)PF_6$	-1.04 / 1.07	53.0	35%
6	$Ir(ppy)_2(dtbbpy)PF_6$	-0.96 / 0.66	49.2	trace
7	$Ru(bpy)_3(PF_6)_2$	-0.81 / 0.77	46.5	N.R.
8	Rose Bengal	-0.68 / 0.99	40.9	N.R.

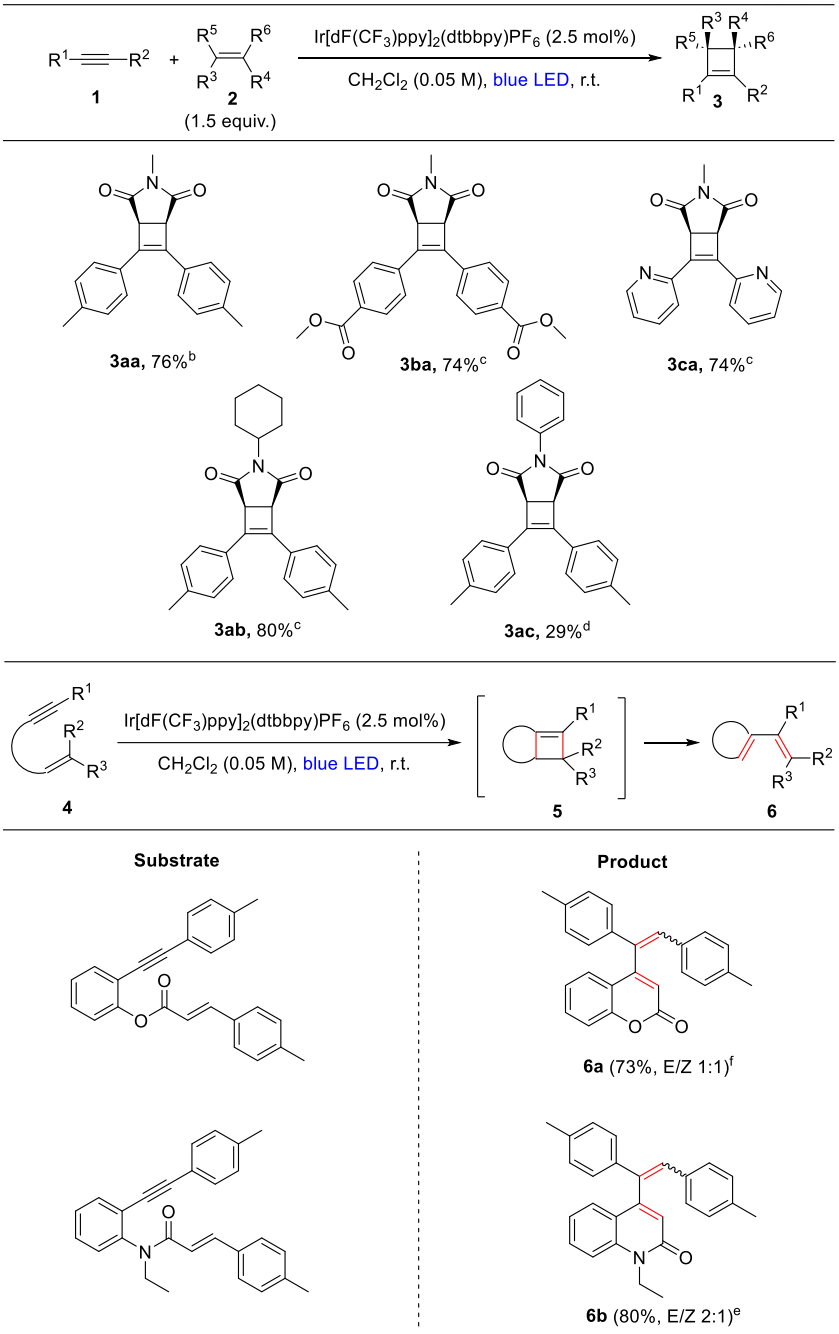
[a] Reactions were conducted on a 0.05 mmol scale under argon atmosphere. N.R. = no reaction.

1.3. Substrate scope

Within the optimized conditions, the scope was investigated. Reaction between the diarylalkynes **1** and N-methylmaleimide **2a** was examined. Both electron-rich and electron-deficinet alkynes were well tolerated to obtained desired cyclobutene products (**3aa, 3ba**). Also, heterocycle bearing alkyne **1c** gave the corresponding cyclobutene product in good yield (**3ca**). The reactivity of the alkene **2** were also investigated. Alkyl group protected maleimide turned out the be good substrate to synthesize corresponding cyclobutenes in excellent yields (**3ab**). However, the phenyl group substituted maleimide gave lower yield in the reaction (**3ac**).

For intramolecular cycloaddition, the enyne derivatives were investigated. The ester-tethered enyne **4a** was subjected to the reaction conditions and the coumarin **6a** was obtained in 73% yield. At first, we did not expect to have ring-opened products. We assumed that 1,3-diene products were formed by ring openings of cyclobutenes and the detailed mechanism was supported via DFT calculation (Figure 1-6). Amido-tethered enyne **4b** gave 2-quinolones in good to excellent yield (**6b**).

Table 1-3. Substrate scope of [2+2] cycloaddition[a]



[a] Reaction conditions : Reactions were performed with 0.1 mmol scale under irradiation of 12 W blue LED strip and Ar atmosphere; Isolated yields.
[b] Reaction time : 1-18 h.[c] 24-48 h.[d] 53 h-3d.[e] 2-18 h.[f] 24-48 h.

To find out the reason why the yield of the product was different, we performed DFT calculations on Mulliken spin density distributions and triplet energy of the substrates (Figure 1-4). Depending on the N-subtitution, the yield was dramatically different. N-phenyl maleimide gave lower yield compared to

N-cyclohexyl maleimide and N-methyl maleimide. Based on the Mulliken spin density the olefinic carbons, **2d** appears to have lower spin density than **2a** and **2c**.

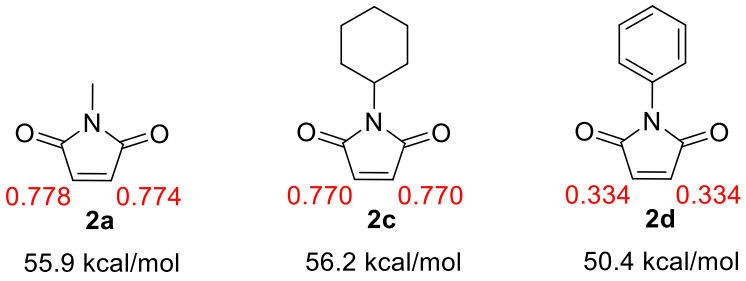
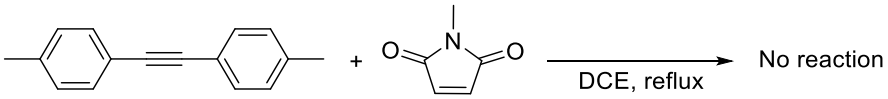


Figure 1-4. Mulliken spin densities (T1) and triplet-singlet energy gaps of selected substrates

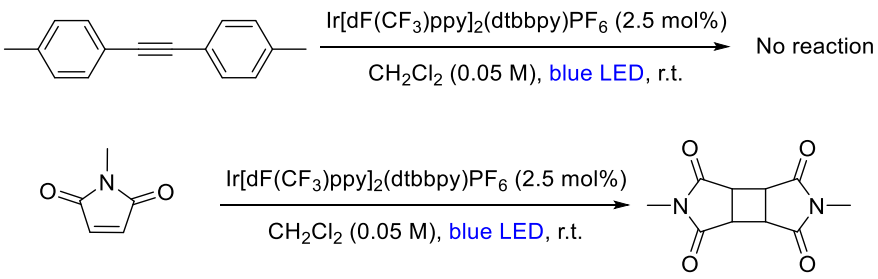
1.4. Mechanistic studies and proposed mechanism

To determine whether the described reaction is driven by photoreaction, we performed control experiments under thermal conditions (Scheme 1-18). Although alkyne and alkene [2+2] cycloaddition is a forbidden reaction in thermal conditions, a few previous works with reactive alkyne and alkene [2+2] cycloaddition have been reported.[20] When the alkyne and alkene were heated up to reflux in 1,2-dichloroethane solvent without an Ir photocatalyst and blue LED irradiation, the desired product cyclobutene did not form.



Scheme 1-18. Thermal condition of [2+2] cycloaddition of alkyne and alkyne.

We also performed photoreactions without reaction partners to determine which substrate is activated by the photocatalytic system (Scheme 1-19). While the reaction of the alkyne alone did not form any product, the reaction of N-methyl maleimide formed cyclobutene, which was a dimerized product. Based on these reaction results, we proposed the possibility that the alkene is excited to the triplet state in photocatalysis.



Scheme 1-19. Control experiments without reaction partner

For intermolecular [2+2] cycloaddition with the alkyne and alkene, the proposed mechanism is shown in Figure 1-4. Triplet energy transfer occurs from the Ir photocatalyst to the alkene under blue light irradiation. The triplet diradical intermediate undergoes radical addition onto the alkyne. The diradical intermediate affords cyclobutene after an intersystem crossing process.

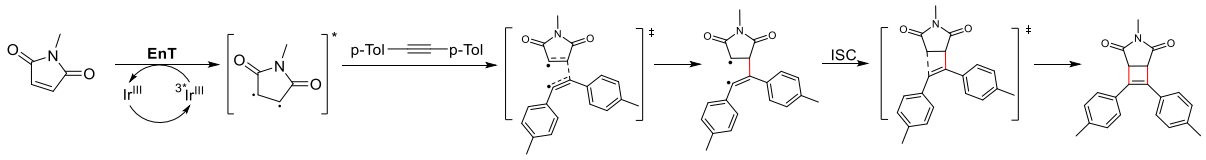
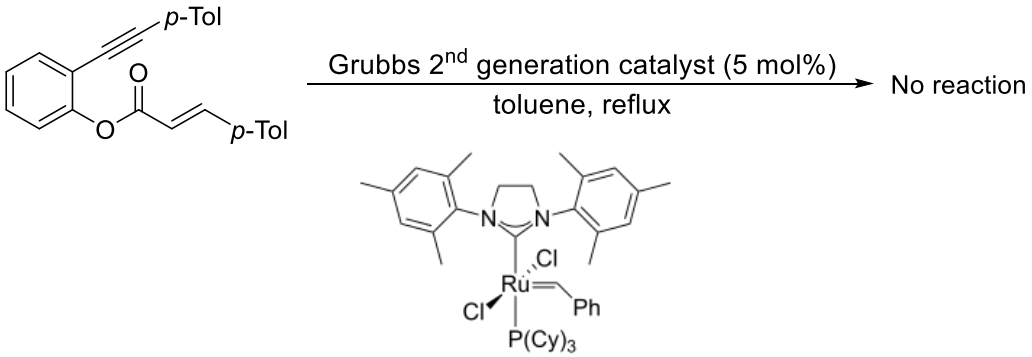


Figure 1-5. Proposed Mechanism – intermolecular [2+2] cycloaddition with alkyne and alkene.

We used ester substrate to test ring-closing enyne metathesis using a Ru-based Grubbs catalyst (Scheme 1-20). Unfortunately, the reaction did not yield the desired 1,3-diene. Under our optimized conditions, the corresponding starting material gave the desired product in 73%. Nonetheless, based on this result, our study gained an advantage in synthesizing highly substituted 1,3-diene through photochemistry.



Scheme 1-20. Control experiment – Ru catalyzed ring closing enyne methathesis.

For the intermolecular reaction, the enyne can be excited to its triplet state by the catalyst under visible light, and the intramolecular addition to the alkyne occurs to form a triplet diradical intermediate (Figure 1-5). It then transforms to cyclobutene after an intersystem crossing process. The cyclobutene can reach its triplet state through the photocatalyst, and the triplet diradical undergoes rearrangement to

afford a diradical intermediate, which can be transformed to a 1,3-diene after an intersystem crossing process.

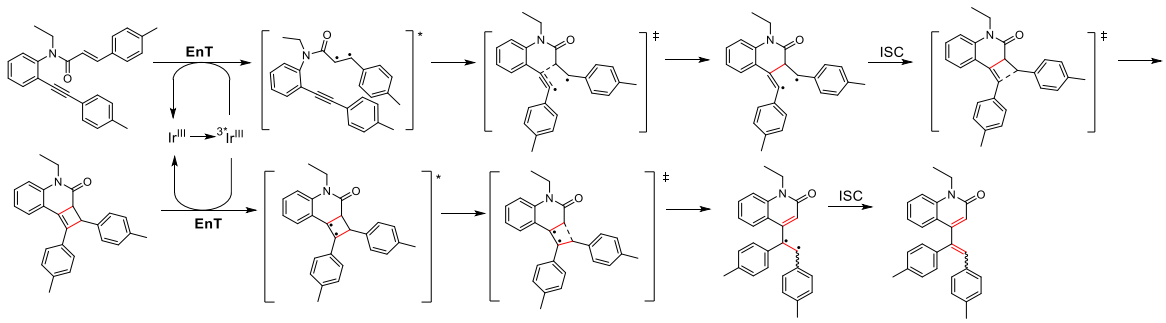


Figure 1-6. Proposed Mechanism – intramolecular [2+2] cycloaddition with enyne.

1.5. Conclusion

In this study, we described the intermolecular and intramolecular [2+2] cycloaddition through triplet energy transfer under visible light. In the intermolecular reactions, we successfully synthesized cyclobutene as the desired product. The wide range of substrate scope, including electron-deficient groups, performed smoothly to give the corresponding cyclobutene products. Furthermore, we demonstrated the intramolecular reaction with conjugated enynes, where ring-opening from cyclobutene as an intermediate occurred to afford conjugated dienes as corresponding products. Although the resulting conjugated dienes have been prepared using transition metal catalysis in previously reported methods, in this case, the resulting 1,3-diene product was formed with milder conditions under photocycloaddition. This development is meaningful because the 1,3-diene, which is the ring-opening product in the intramolecular reaction, is included in bioactive molecules. Overall, our study contributes to the expendation of efficient methods for the synthesis of valuable organic compounds using photochemistry.

1.6. Experimental data

1.6.1. General Procedures

General procedure (A)

In a flamed dried 4 mL vial, 2.5 mol% of photocatalyst Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6, alkyne (1.0 equiv.) and alkene (1.5 equiv.) were dissolved in CH_2Cl_2. The reaction solution was irradiated under 12 W blue

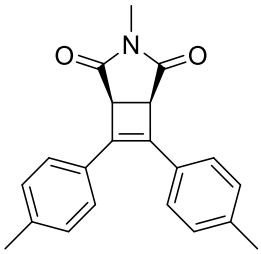
LED strip at room temperature under cooling fan. Monitoring via TLC method was used to determine alkyne consumption. After the reaction was completed, the reaction mixture was filtered, and solvent was eliminated under vacuum conditions. Flash column chromatography was used to purify the crude to obtain corresponding cyclobutene derivatives.

General procedure (B)

In a flamed dried 4 mL vial, conjugated enyne (0.05 mmol) and 2.5 mol% of photocatalyst $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ were dissolved in CH_2Cl_2. The reaction solution was irradiated under 12 W blue LED strip at room temperature under cooling fan. Monitoring via TLC method was used to determine alkyne consumption. After the reaction was completed, the reaction mixture was filtered, and solvent was eliminated under vacuum conditions. Flash column chromatography was used to purify the crude to obtain corresponding 1,3-diene derivatives.

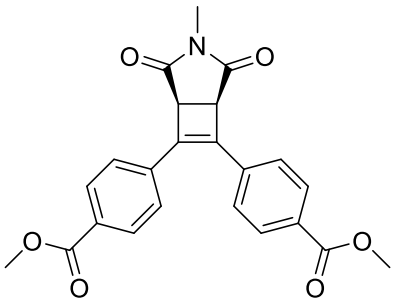
1.6.2. Characterization of products

3-methyl-6,7-di-*p*-tolyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (3aa)



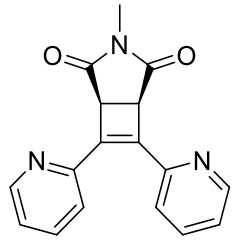
Prepared in accordance with the ***General Procedure A*** using di(*p*-tolyl)acetylene **1a** (0.1 mmol) and *N*-methylmaleimide **2a** (1.5 equiv.), 24 mg, 76% yield; white solid; m.p. 134 – 135 °C		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.64 (d, *J* = 8.2 Hz, 4H), 7.18 (d, *J* = 7.9 Hz, 4H), 4.06 (s, 2H), 2.97 (s, 3H), 2.37 (s, 6H)
^{13}C NMR	**100 MHz, $CDCl_3$**	175.2, 139.2, 138.3, 130.3, 129.3, 126.8, 44.9, 24.8, 21.4
HRMS *m/z*	**$[C_{21}H_{20}NO_2]^+$ ($[M+H]^+$)**	
	Calculated: 318.1489	observed: 318.1490

Dimethyl 4,4'-(3-methyl-2,4-dioxo-3-azabicyclo[3.2.0]hept-6-ene-6,7-diyl)dibenzoate (3ba)



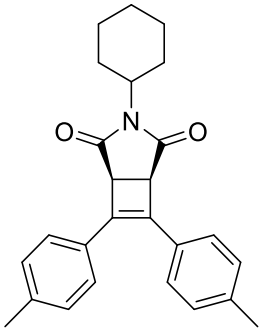
Prepared in accordance with the ***General Procedure A*** using dimethyl 4,4'-(ethyne-1,2-diyl)dibenzoate **1b** (0.1 mmol) and *N*-methylmaleimide **2a** (1.5 equiv.), 30 mg, 74% yield; white solid; m.p. 207 – 209 °C		
^{1}H NMR	**400 MHz, $CDCl_3$**	8.06 (d, *J* = 8.7 Hz, 4H), 7.80 (d, *J* = 8.7 Hz, 4H), 4.17 (s, 2H), 3.94 (s, 6H), 3.00 (s, 3H)
^{13}C NMR	**100 MHz, $CDCl_3$**	174.4, 166.5, 140.7, 136.6, 130.9, 130.2, 127.1, 52.4, 45.4, 25.2
HRMS *m/z*	**$[C_{23}H_{20}NO_6]^+$ ($[M+H]^+$)**	
	Calculated: 406.1285	observed: 406.1297

3-methyl-6,7-di(pyridin-2-yl)-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (**3ca**)



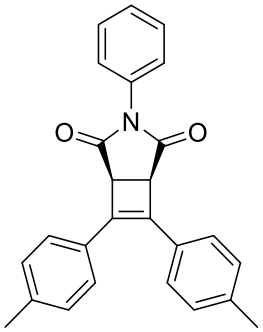
Prepared in accordance with the ***General Procedure A*** using 1,2-di(pyridin-2-yl)ethyne **1c** (0.1 mmol) and *N*-methylmaleimide **2a** (1.5 equiv.), 15 mg, 51% yield; pale yellow solid; m.p. 212 – 214 °C		
^{1}H NMR	**400 MHz, $CDCl_3$**	8.77 – 8.76 (m, 2H), 8.61 (d, *J* = 7.9 Hz, 2H), 7.80 (td, *J* = 7.8, 1.9 Hz, 2H), 7.29 – 7.26 (m, 2H), 4.33 (s, 2H), 2.97 (s, 3H)
^{13}C NMR	**100 MHz, $CDCl_3$**	174.6, 151.0, 149.7, 142.2, 136.6, 124.8, 123.7, 44.4, 25.1
HRMS *m/z*	**$[C_{17}H_{13}N_3NaO_2]^+$ ($[M+Na]^+$**	
	Calculated: 314.0900	observed: 314.0899

3-cyclohexyl-6,7-di-*p*-tolyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (**3ab**)



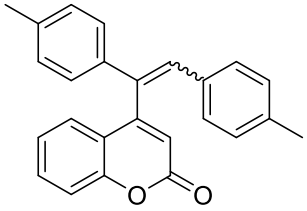
Prepared in accordance with the ***General Procedure A*** using di(*p*-tolyl)acetylene **1a** (0.1 mmol) and 1- cyclohexyl-1*H*-pyrrole-2,5-dione **2b**(1.5 equiv.), 31 mg, 80% yield; white solid; m.p. 178 – 180 °C		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.63 (d, *J* = 8.1 Hz, 4H), 7.17 (d, *J* = 8.0 Hz, 4H), 3.97 (s, 2H), 3.91 (tt, *J* = 12.3, 3.9 Hz, 1H), 2.36 (s, 6H), 2.15 – 2.00 (m, 2H), 1.85 – 1.75 (m, 2H), 1.68 – 1.56 (m, 2H), 1.36 – 1.11 (m, 4H)
^{13}C NMR	**100 MHz, $CDCl_3$**	175.5, 139.2, 138.8, 130.5, 129.4, 126.9, 51.6, 44.6, 28.7, 26.0, 25.2, 21.6
HRMS *m/z*	$[C_{26}H_{28}NO_2]^+$ ($[M+H]^+$)	
	Calculated: 386.2115	observed: 386.2115

3-phenyl-6,7-di-*p*-tolyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (**3ac**)



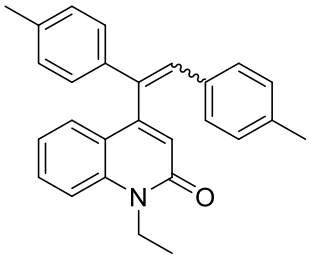
Prepared in accordance with the ***General Procedure A*** using di(*p*-tolyl)acetylene **1a** (0.1 mmol) and 1-phenyl- 1*H*-pyrrole-2,5-dione **2c**(1.5 equiv.), 11 mg, 29% yield; white solid; m.p. 185 – 187 °C		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.69 (d, *J* = 8.1 Hz, 4H), 7.44 – 7.40 (m, 2H), 7.36 – 7.32 (m, 1H), 7.27 – 7.24 (m, 2H), 7.19 (d, *J* = 7.9 Hz, 4H), 4.21 (s, 2H), 2.37 (s, 6H)
^{13}C NMR	**100 MHz, $CDCl_3$**	174.2, 139.5, 138.5, 132.1, 130.4, 129.5, 129.1, 128.6, 127.0, 126.7, 45.1, 21.6
HRMS *m/z*	$[C_{26}H_{22}NO_2]^+$ ($[M+H]^+$)	
	Calculated: 380.1645	observed: 380.1645

4-(1,2-di-*p*-tolylvinyl)-2*H*-chromen-2-one (**6a**)



Prepared in accordance with the ***General Procedure B*** using 2-(*p*-tolylethynyl)phenyl *(E)*-3-(*p*-tolyl)acrylate **4a** (0.1 mmol), 26 mg, 73% yield, (*E/Z* 1:1)		
***(E)*-6a :** pale yellow solid; m.p. 144 – 146 °C		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.53 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.45 (ddd, *J* = 8.7, 7.3, 1.6 Hz, 1H), 7.34 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.16 – 7.06 (m, 7H), 7.03 (d, *J* = 8.2 Hz, 2H), 6.83 (s, 1H), 6.41 (s, 1H), 2.33 (s, 3H), 2.32 (s, 3H)
^{13}C NMR	**100 MHz, $CDCl_3$**	161.2, 157.8, 154.2, 138.3, 138.2, 136.2, 135.0, 133.0, 132.8, 131.6, 129.8, 129.8, 129.4, 129.1, 127.3, 124.1, 119.2, 117.3, 115.7, 21.45, 21.45
HRMS *m/z*	$[C_{25}H_{21}O_2]^+$ ($[M+H]^+$)	
	Calculated: 353.1536	observed: 353.1536
***(Z)*-6a :** pale yellow solid; m.p. 76 – 77 °C		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.49 (t, *J* = 7.8 Hz, 1H), 7.47 – 7.36 (m, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.23 (s, 1H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.14 – 7.09 (m, 1H), 7.05 (d, *J* = 8.1 Hz, 2H), 6.98 (d, *J* = 8.2 Hz, 2H), 6.35 (s, 1H), 2.35 (s, 3H), 2.26 (s, 3H)
^{13}C NMR	**100 MHz, $CDCl_3$**	160.9, 155.5, 154.3, 138.4, 138.1, 137.2, 134.6, 133.0, 132.1, 130.9, 129.7, 129.4, 128.9, 127.1, 126.3, 124.7, 119.2, 117.4, 117.2, 21.32, 21.28
HRMS *m/z*	$[C_{25}H_{21}O_2]^+$ ($[M+H]^+$)	
	Calculated: 353.1536	observed: 353.1536

4-(1,2-di-*p*-tolylvinyl)-1-ethylquinolin-2(1*H*)-one (6b)



Prepared in accordance with the ***General Procedure B*** using *(E)*-*N*-ethyl-3-(*p*-tolyl)-*N*-(2-(*p*-tolylethynyl)phenyl)acrylamide **4b** (0.1 mmol), 30 mg, 80% yield, (*E/Z* 2:1)
(*E*)-6b : yellow solid; m.p. 168 – 169 °C

^{1}H NMR	**400 MHz, $CDCl_3$**	7.74 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.49 (ddd, *J* = 8.6, 7.1, 1.6 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.16 (d, *J* = 8.1 Hz, 2H), 7.10 – 6.99 (m, 7H), 6.74 (s, 1H), 6.73 (s, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.31 (s, 3H), 2.30 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H)
^{13}C NMR	**100 MHz, $CDCl_3$**	161.7, 152.8, 139.3, 137.6, 137.5, 137.4, 135.8, 133.5, 131.5, 130.3, 129.4, 129.4, 129.2, 128.9, 128.0, 121.7, 121.6, 120.7, 114.2, 37.3, 21.25, 21.25, 12.8
HRMS *m/z*	$[C_{27}H_{25}NNaO]^+$ ($[M+Na]^+$)	
	Calculated: 402.1828	observed: 402.1820
(*Z*)-6b : white solid; m.p. 147 – 149 °C		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.61 – 7.39 (m, 3H), 7.33 – 7.23 (m, 3H), 7.18 (s, 1H), 7.10 (d, *J* = 7.6 Hz, 2H), 7.05 (t, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 7.8 Hz, 2H), 6.90 (d, *J* = 7.7 Hz, 2H), 6.63 (s, 1H), 4.49 (dq, *J* = 14.1, 7.1 Hz, 1H), 4.36 (dq, *J* = 14.1, 7.1 Hz, 1H), 2.32 (s, 3H), 2.22 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H)
^{13}C NMR	**100 MHz, $CDCl_3$**	161.7, 149.8, 139.3, 138.0, 137.8, 137.3, 136.0, 133.3, 130.6, 129.9, 129.3, 129.0, 128.8, 127.8, 126.1, 122.6, 122.1, 120.6, 114.3, 37.3, 21.12, 21.10, 12.9
HRMS *m/z*	$[C_{27}H_{25}NNaO]^+$ ($[M+Na]^+$)	
	Calculated: 402.1828	observed: 402.1820

Chapter 2.

Electrochemical C(sp3)–H Functionalization of γ-Lactams Based on Hydrogen Atom Transfer

2.1. Introduction

2.1.1. Organic Synthesis via Electrochemistry

Electrochemical synthesis has emerged as a powerful tool to address typical issues, such as synthetic limitations in precious metals, difficulties in removing residual metals, and environmental impacts arising from reaction wastes. The use of electricity as a redox reagent to promote chemical reactions allows for tuning reactivity and selectivity more readily by simple adjusting electrical potential, along with the benefit of a reduced environmental footprint.

In recent years, organic electrosynthesis has experienced a considerable renaissance, increased its molecular synthesis with potential.[21] Looking back to the 19th century in the field of electro-organic synthesis, electrosynthesis gained significant momentum for sustainable organic synthesis based on a number of pioneering contributions. Electrons can be used as redox equivalents to achieve reaction selectivity and avoid the use of stoichiometric redox reagents and undesired byproduct generation. After the development of commercial electrochemical equipment, access of electrosynthesis became more user-friendly.

When comparing between direct and indirect electrolysis, direct electrolysis enables substrates to undergo electron transfer directly at the electrode surface. On the other hand, with indirect electrosynthesis, a redox mediator participates in the reaction, which can be more easily oxidized or reduced than the substrate and works as the electron transfer helper from the electrode surface to the substrate. Indirect electrolysis has several advantages. It can improve reaction efficiency and better selectivity by avoiding unwanted side reactions.

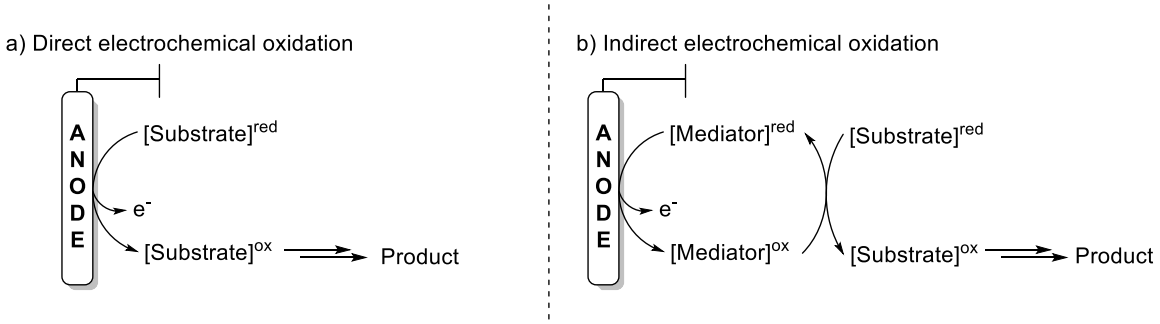


Figure 2-1. Direct and indirect electrochemical oxidation.

2.1.2. γ-Lactam

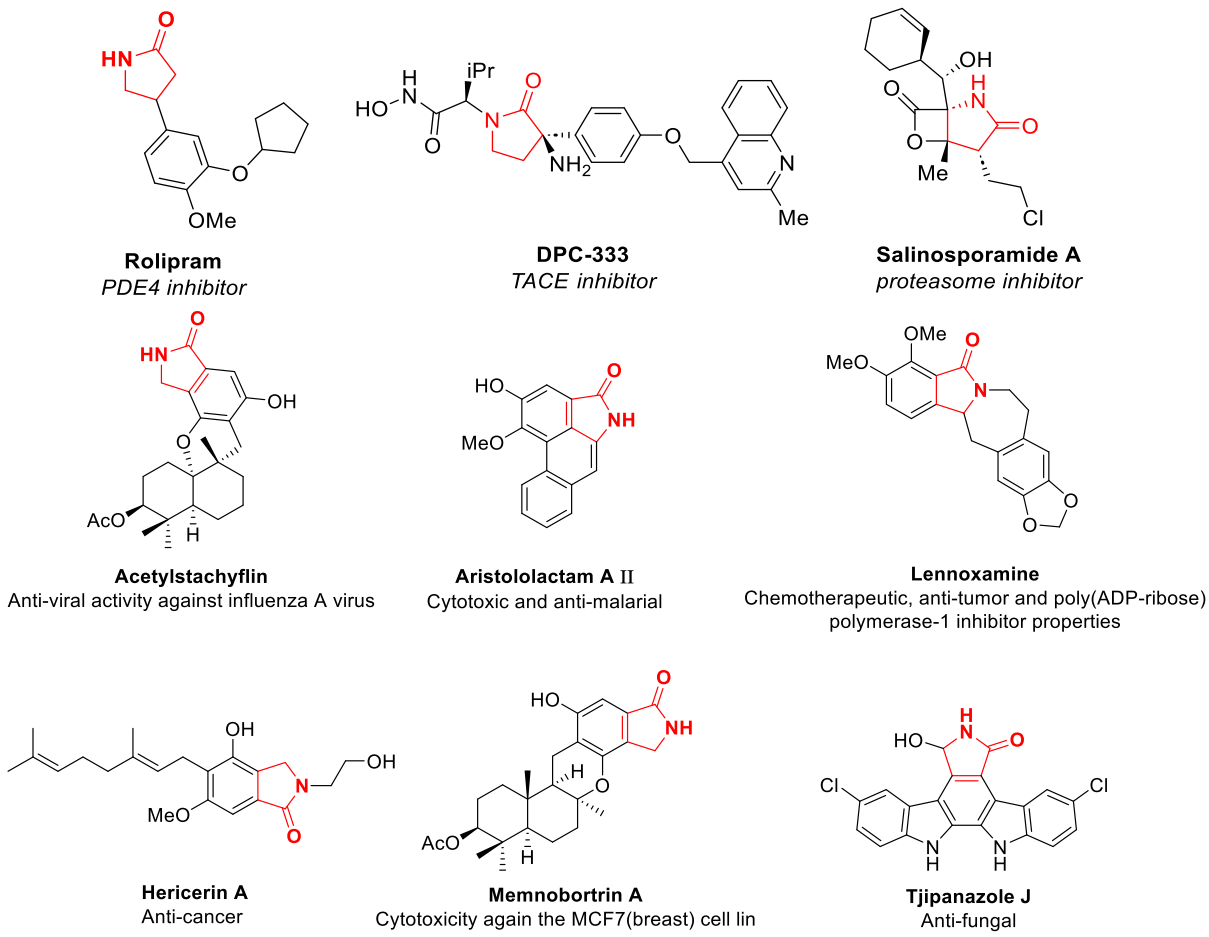


Figure 2-2. Biologically active compounds containing the γ-lactam core.

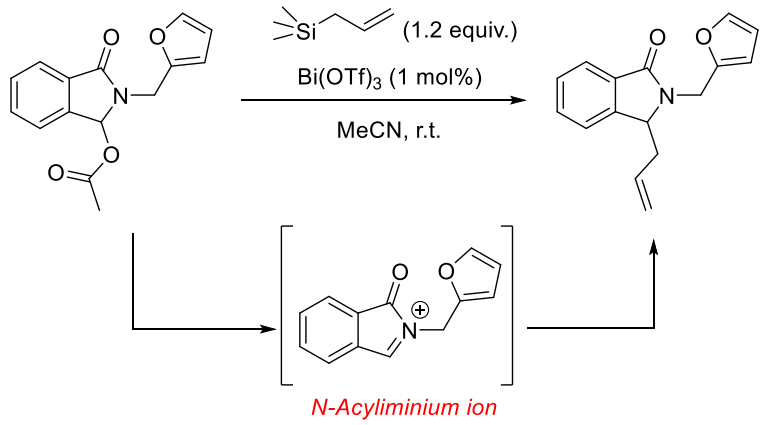
Lactams are cyclic amide organic compounds among them γ-lactams are consisted of a 5-membered atom ring. γ-Lactams shows various biological activities and pharmaceutical activities, including antibiotic, cytotoxic, antitumor, and anti-inflammatory. Figure 2-2 shows the biologically active compounds containing γ-lactams as compound core.[22]

For γ-lactam functionalization, typical synthesis approach is nucleophilic addition to N-acyliminium (NAI) intermediates formed by eliminating the leaving groups at the N-alpha position of the γ-lactam. To eliminate the leaving groups, Lewis acids, Bronsted acids, transition metal catalysts, and organocatalysts were employed. Amides or carbamates are oxidized under electrochemical reaction conditions at anode to generate NAIs, followed by trapped by the nucleophiles. NAIs are generally generated by direct two electron oxidation of the substrate (Shono type oxidation), anodic oxidation of electroauxiliary, azole-mediated HAT followed by anodic oxidation, and TEMPO mediated hydride transfer.

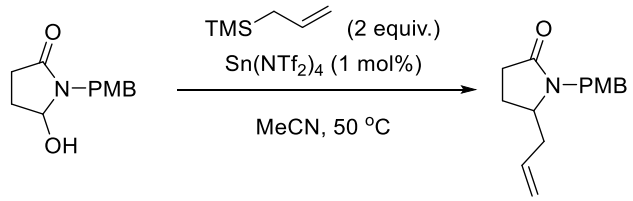
2.1.3. Previously reported γ-lactam functionalization

Bismuth(III) triflate, which is Lewis acid was found to support the generation of stable cyclic N-acyliminium (NAI) species in catalytic amounts (Scheme 2-1, (a)).[23] Compared to the results from the classical Lewis acids participated reactions, $Bi(OTf)_3$ was efficient for almost all of the α-acetoxy lactams. N-acyliminium ions are well known structure for electrophiles in α-amidoalkylation reactions. Othman et al. reported tin(IV) triflimidate catalyzed α-amidoalkylation reaction in 2010 (Scheme 2-1, (b)).[24] The reaction was conducted with simple NAI precursor hydroxy aminals with silicon-based derivatives which worked as nucelophiles. Because of the lower stabilizing effect of the lone pair of electrons on nitrogen, N,O-acetals are less favored to give iminium ions. In mild condition, low catalyst loadings were required to proceed the nucleophilic substitution reaction of hydroxy groups of unprotected hydroxy N,O-acetals. The scope of catalytic NAI chemistry is broaden as well as the field of application of the Lewis superacidic $Sn(NTf_2)_4$ catalsyt.

(a)

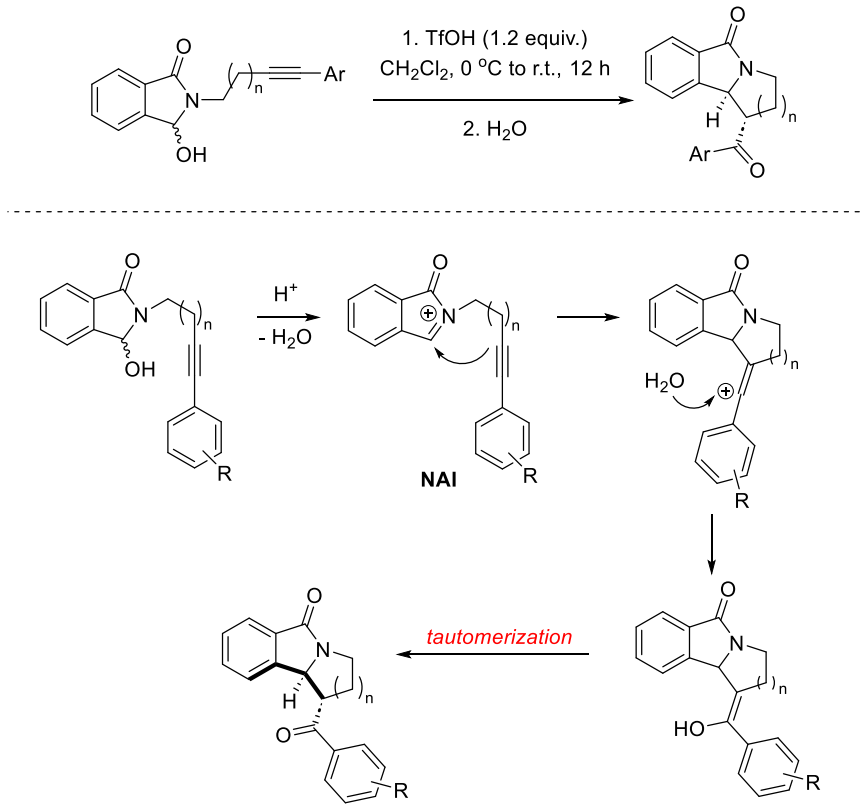


(b)



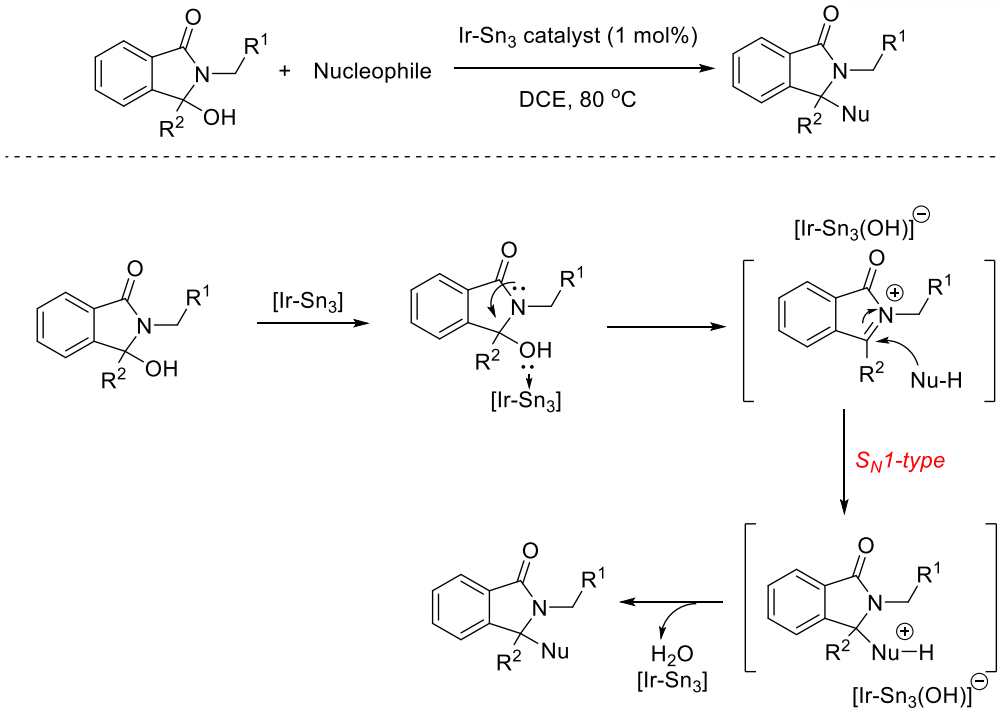
Scheme 2-1. Lewis acid-catalyzed γ-lactam functionalization

Das et al. reported synthesis of pyrroloisoindolone and pyridoisoindolone using aza-Prins cyclization of endocyclic NAIs (Scheme 2-2).[25] The Bronsted acid, trifluoromethanesulfonic acid (triflic acid) was used to produce desired products. First, triflic acid generates NAI from starting material then, the aza-Prins cyclization reaction forms carbocation. The carbocation is trapped by water during the work up process to generate enols. The enols give tricyclic azo-compounds after tautomerization.



Scheme 2-2. Brønsted acid-catalyzed γ-lactam functionalization.

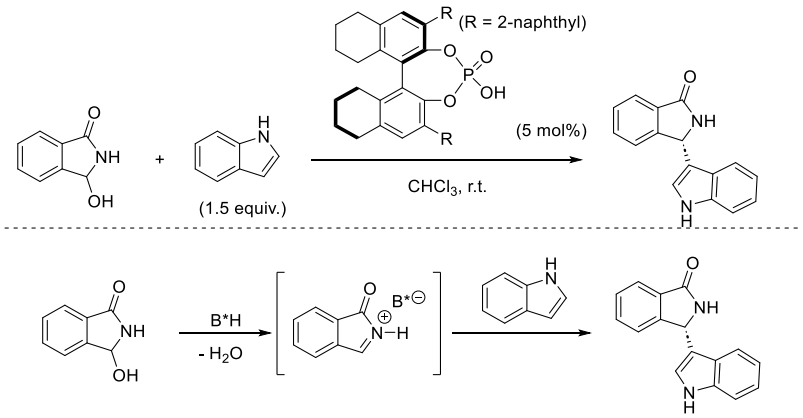
Maity et al. reported multimetallic complex catalytically promotes the nucleophilic substitution reaction of γ-hydroxylactam via NAIs (Scheme 2-3).[26] The catalyst performed as Lewis acid, which gives activation and elimination of the hydroxy group of the substrate. This process generates NAI and subsequently S_N1-type substitution step is afforded to leads to the alkylated product.



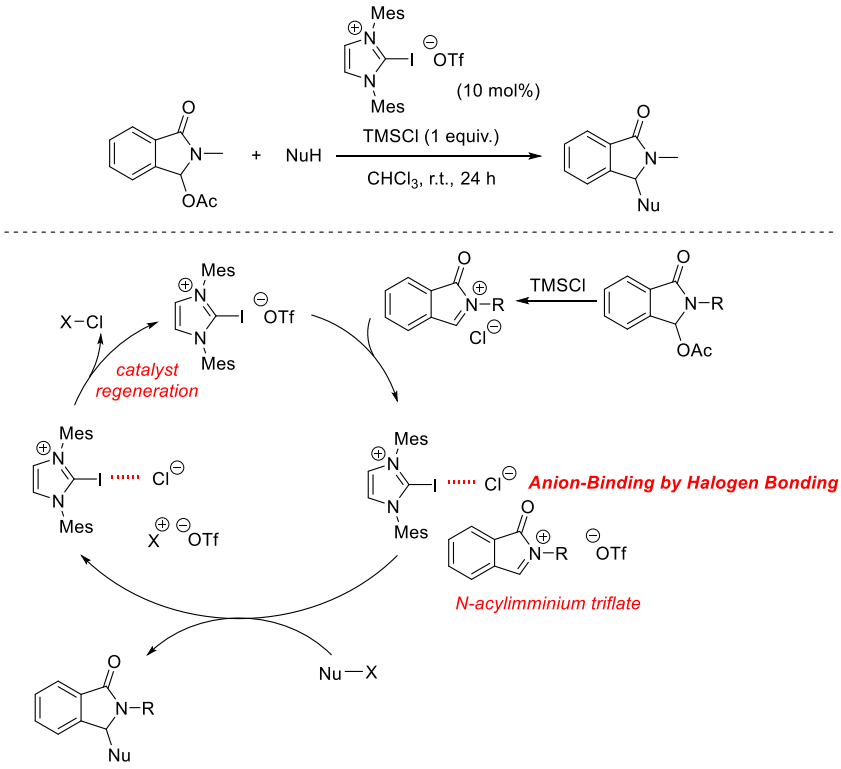
Scheme 2-3. Transition metal catalyzed γ-lactam functionalization.

In 2011, chiral phosphoric acid catalyzed asymmetric Friedel-Crafts alkylation of indole with γ-hydroxylactam was reported. Chrial phosphoric acids have been known to be essential organocatalysts for the asymmetric Friedel-Crafts alkylation of indoles with γ-hydroxylactams (Scheme 2-4, (a)).[27] The reaction with γ-hydroxylactam and chiral phosphoric acid leads to the generation of close counterion, in which the chiral phosphate anion creates a chiral atmosphere to control the enantioselectivity of the Friedel-Crafts reaction. Another organocatalytic addition reaction of carbon-based nucelophiles to NAI was reported in 2019 (Scheme 2-4, (b)).[28] A halogen-bond-catalyzed reaction of N,O-aminals with a wide range of nucleophiles obtained the corresponding products in good yield. During the reaction, in situ activating strategy with TMSCl and anion-binding by halogen bonding was used as a key strategy.

(a)



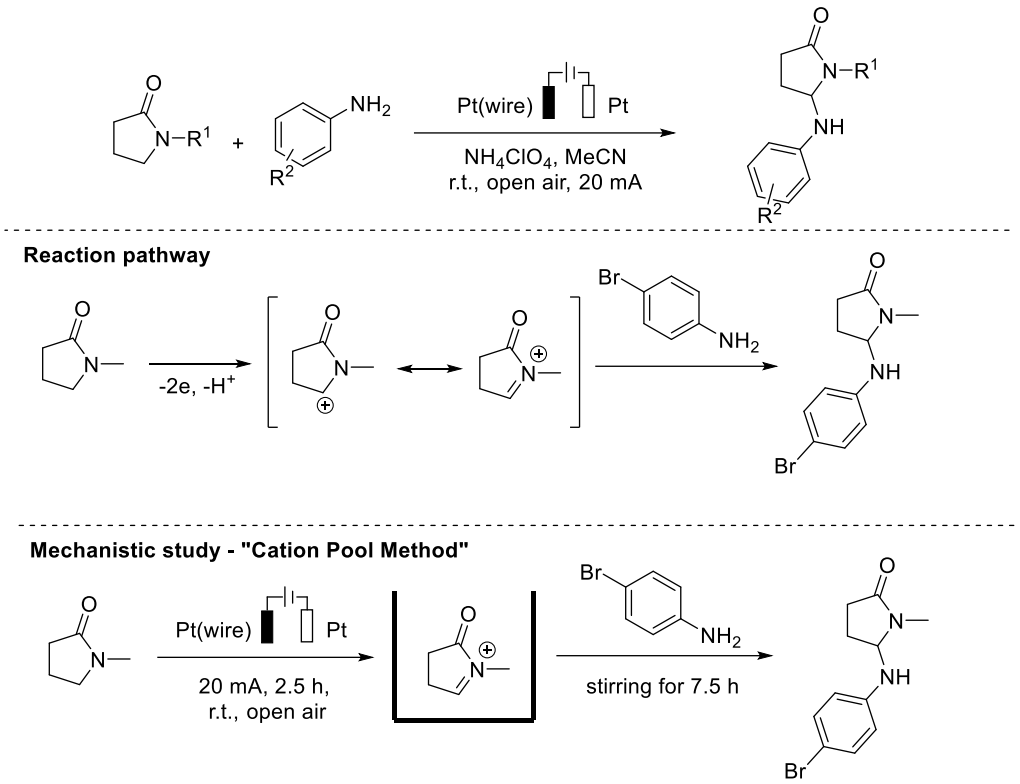
(b)



Scheme 2-4. Organocatalyzed γ-lactam functionalization.

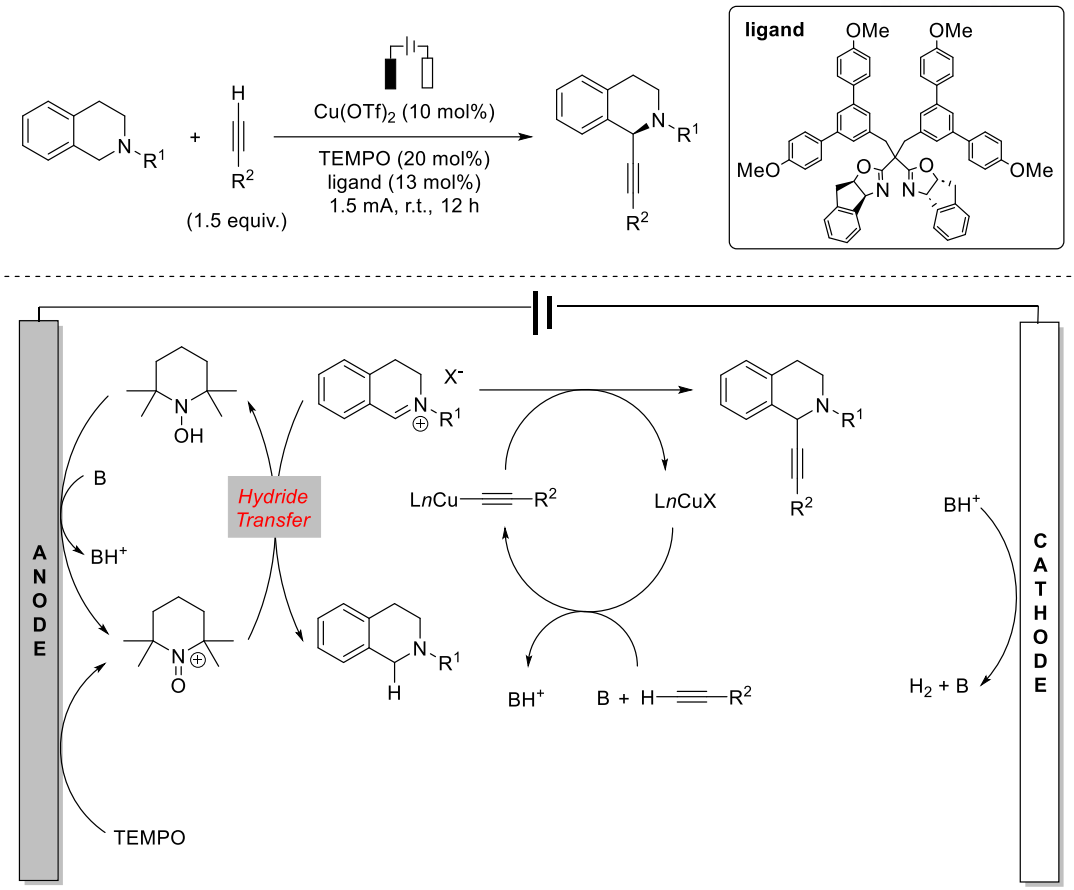
Gong et al. reported oxidative C-H/N-H coupling between γ-lactams and aniline under electrochemical condition (Scheme 2-5).[29] The reaction proceeded metal catalysts-free condition at room temperature to afford γ-substituted lactams. NAI generated from the γ-lactam directly trapped by nucleophile to form the corresponding products (Shono type oxidation). In this report, authors employed the "cation pool method" for control experiment. Under constant current condition (20 mA), the NMP went through electrochemical oxidation at room ambient temperature for 2 hours and 30 minutes. Then,

the given current was stopped, followed by the addition of aniline to the mixture. After the mixture was additionally stirred for 7 hours and 30 minutes, the excellent yield of desired product was obtained.



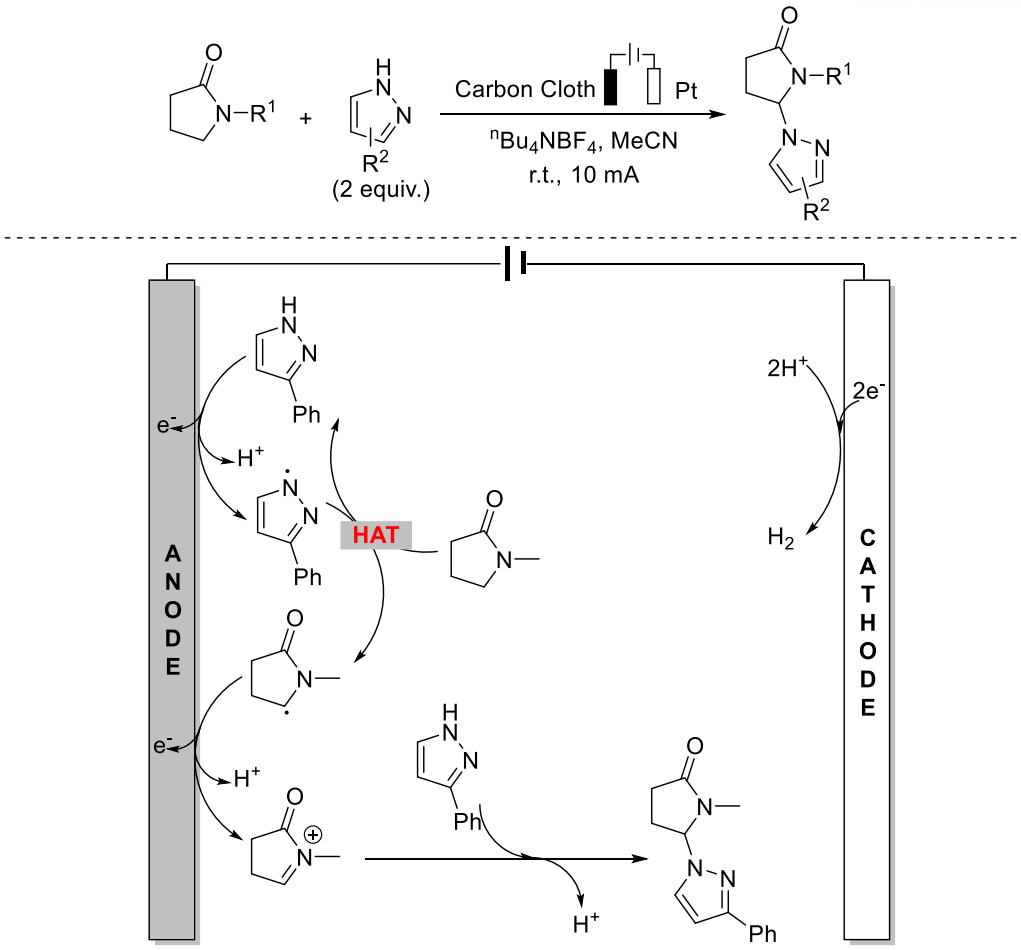
Scheme 2-5. Shono-type oxidation by Gong et al.

Gao et al. reported tertiary cyclic amines C(sp^3)-H alkynylation using Shono-type oxidation (Scheme 2-6).[30] TEMPO was used as a co-catalytic redox mediator, which oxidizing a lactam to iminium ion but also for diminishing the oxidation potential of the reaction. The work is introducing Cu/TEMPO co-catalyzed electrochemical oxidative cross-coupling between lactams and terminal alkynes using novel chiral ligand in an undivided cell to afford alkynylated tetrahydroisoquinolines.



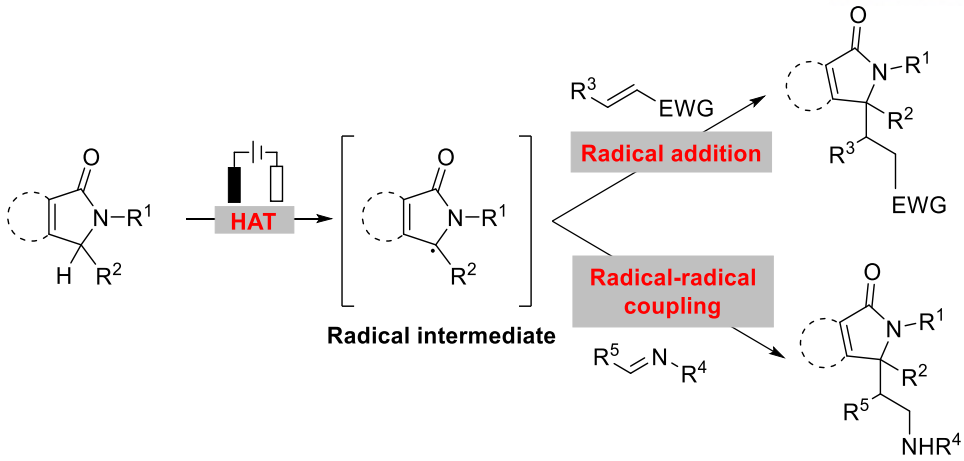
Scheme 2-6. Shono-type oxidation by Gao et al.

Lei group reported electrochemical oxidative C(sp^3)-H azolation of lactams under mild conditions (Scheme 2-7).[31] Various series of amides and lactams can be used in these methods. Additionally, by using the flow cell, gram scale product can be obtained in good conversion yield. Pyrazole is oxidized at anode, followed by HAT to form nitrogen radical intermediate. Generated N-radical intermediate and NMP undergo an intermolecular HAT to obtain N-alpha radical intermediate and pyrazole. N-alpha radical intermediate was oxidized on the anode and the iminium cation generated. It was trapped by pyrazole to give desired product.



Scheme 2-7. Azolation of γ-lactams via HAT and electrochemical oxidation.

In this work, the electrochemical C(sp^3)-H functionalization of γ-lactams based on Hydrogen Atom Transfer has been introduced. γ-Lactams, which have promising biologically active structure give radical intermediate in this method by HAT under electrochemical condition. Using $^nBu4NN_3$ as a HAT mediator which oxidized at anode involves N-alpha C(sp^3)-H functionalization. This process leads to form a new C-C bond formation with a coupling reaction between electron-deficient alkenes and radical intermediate. Beyond typical alkenes, N-sulfonyl imines were used for coupling partners to broaden reaction scopes.



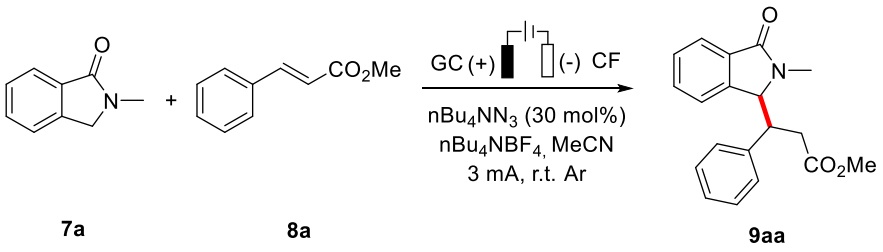
Scheme 2-8. Electrochemical C(sp3)–H functionalization of γ-lactams based on HAT

2.2. Optimization of reaction conditions

In the beginning, we started to optimize the reaction conditions using 2-methylisoindolin-1-one as the limiting reagent and methyl cinnamate as the coupling partner. The reaction was carried out at 3 mA in constant current mode, using nBu_4NN_3 as the HAT mediator, and $^nBu_4NBF_4$ as the electrolyte in MeCN solvent. Glassy carbon (GC) was used as the anode and carbon felt (CF) was used as the cathode in the undivided cell. The desired product was obtained with an 82% yield shown at entry 1 of Table 2-1. The reaction was conducted in much higher current of 6 mA or constant voltage mode of 2.5 V, and the yield of desired product decreased compared to the standard condition (Table 2-1, entries 2-3). Instead of nBu_4NBF_4, various electrolyte was tested for the reaction, but the reaction efficiency was not better than nBu_4NBF_4 (Table 2-1, entries 4-6). Entry 7 of Table 2-1 states when DMF was used as the solvent instead of MeCN, the desired product formed in lower yield. However, the electrolysis did not proceed when the reaction was conducted in DCM and MeOH solvent (Table 2-1, entries 8-9). To find out electrode combination efficiency, different anodes and cathodes were replaced with GC and CF. However, the reaction led to a lower yield comparing GC as the anode and CF as the cathode (Table 2-1, entries 10-12). Next, turned our attention to various HAT mediators and whether they can replace the nBu_4NN_3. 1,4-diazabicyclo[2.2.2]octane (DABCO), quinuclidine, methyl thioglycolate, and NaN_3 did not afford the better reaction efficiency toward nBu_4NN_3 (Table 2-1, entries 13-16). Even though those HAT mediators have capable bond dissociation energies (BDEs) for HAT reaction from 2—methylisoindolin-1-one, the reaction did not proceed well. Using a lower amount of $^nBu_4NN_3$, which is 5 mol% the reaction yield diminished because the conversion of 2-methylisoindolin-1-one to the product was reduced (Table 2-1, entry 17). Using 1 equivalent of $^nBu_4NN_3$ gives a similar yield to using

30 mol% conditions but using a catalytic amount of HAT mediator was enough (Table 2-1, entry 18). The reaction did not proceed when the HAT mediator $^{n}Bu_4NN_3$ or electricity was absent (Table 2-1, entries 19-20). The reaction efficiency is greatly diminished when the reaction was conducted under air conditions (Table 2-1, entry 21).

Table 2-1. Reaction Optimization table[a]



7a 8a 9aa

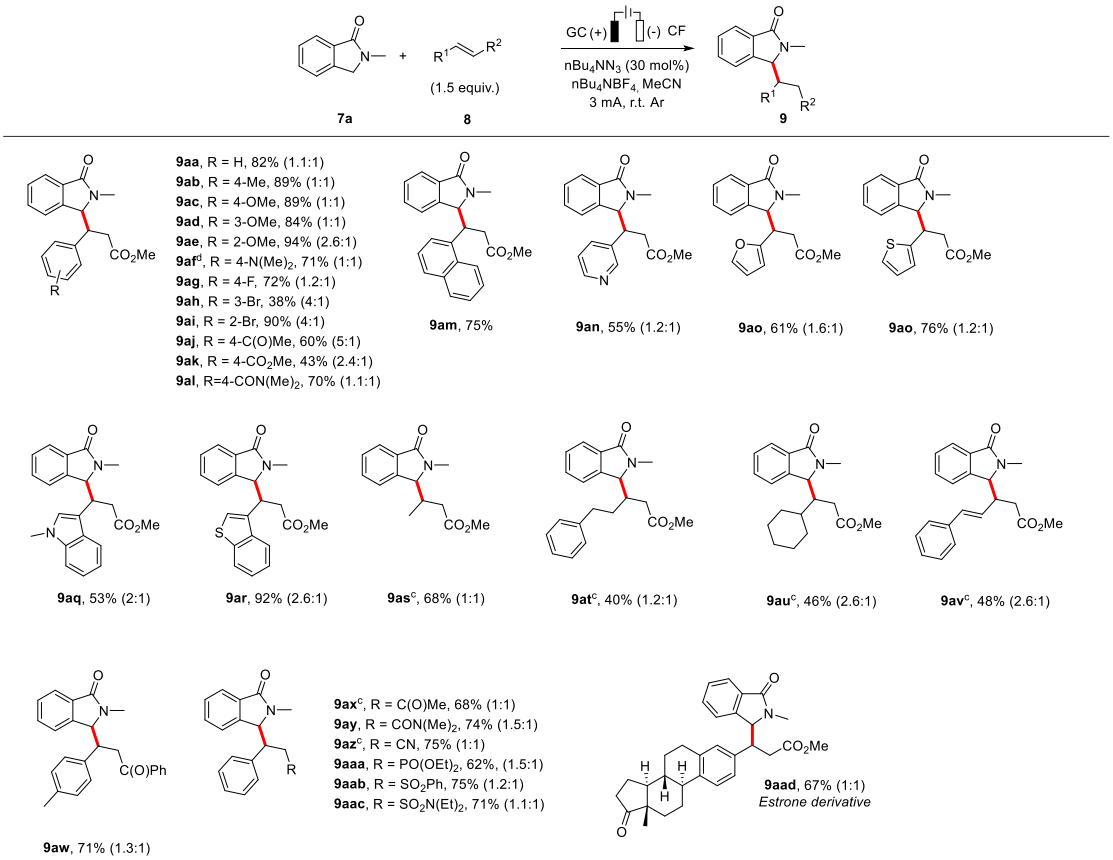
Entry	Variation from the standard conditions	Yield (%)
1	None	78 (82)[b]
2	6 mA	75
3	2.5 V	55
4	nBu_4NOAc instead of nBu_4NBF_4	35
5	nBu_4ClO_4 instead of nBu_4NBF_4	69
6	nBu_4NPF_6 instead of nBu_4NBF_4	76
7	DMF instead of MeCN	53
8	DCM instead of MeCN	N.R.
9	MeOH instead of MeCN	N.R.
10	C(+)|C(-) instead of GC(+)|CF(-)	59
11	GC(+)|C(-) instead of GC(+)|CF(-)	70
12	C(+)|CF(-) instead of GC(+)|CF(-)	69
13	DABCO instead of nBu_4NN_3	28
14	Quinuclidine instead of nBu_4NN_3	4
15	Methyl thioglycolate instead of nBu_4NN_3	N.R.
16	NaN_3 instead of nBu_4NN_3	Trace
17	$^{n}Bu_4NN_3$ (5 mol%)	45
18	$^{n}Bu_4NN_3$ (1 equiv.)	79
19	No $^{n}Bu_4NN_3$	N.R.
20	No electricity	N.R.
21	Under air	14

[a] Reaction conditions: Undivided cell, GC anode, CF cathode, 7a (0.1 mmol), 8a (0.15 mmol), $^{n}Bu_4NN_3$ (0.03 mmol), $^{n}Bu_4BF_4$ (0.1 M), dry MeCN (0.03 M). GC = glassy carbon, CF = carbon felt, N.R. = no reaction, DABCO =1,4-diazabicyclo[2.2.2]octane.
[b] Isolated yield

2.3. Substrate Scope

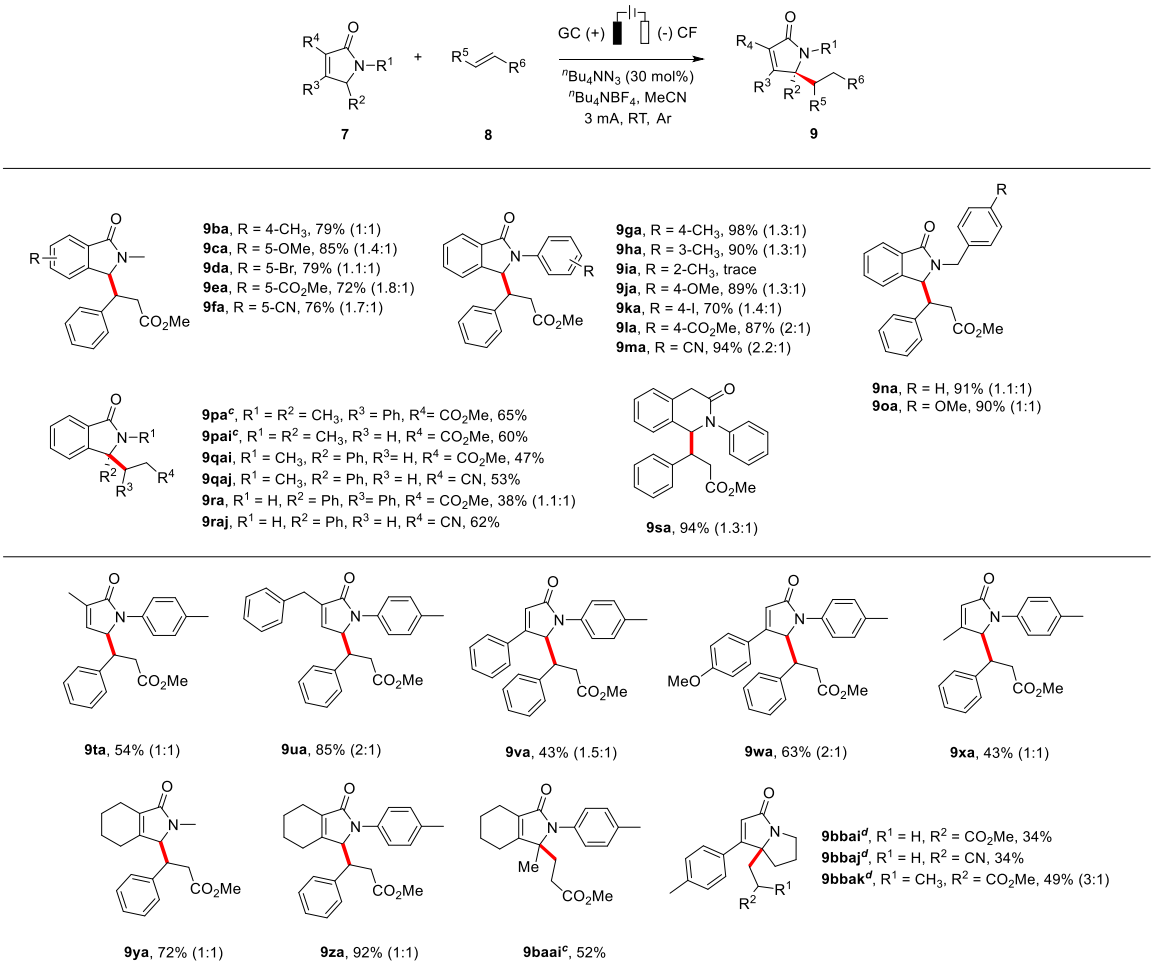
Within the optimized reaction, tried to examined the substrate scope of the reaction (Table 2-2). From electron-rich to deficient aryl group on alkenes were generated the corresponding products in moderate to excellent yield (**9aa-9al**). Additionally, not only naphthyl group substituted alkene, but also heteroatom containing alkenes also well tolerated to give desired products (**9am-9ar**). Alkyl group substituted alkenes also provided desired products in moderate yields (**9as-9au**). For 1,3-diene **8av** gave selective formation of beta substitution during the reaction. Furthermore, alkenes substituted with electron-withdrawing groups were tolerated in the reaction (**9aw-9aac**). The promising substrate which is estrone derivatives were synthesized in 67% yields (**9aad**).

Table 2-2. Substrate scope of alkene[a]



[a] Reaction conditions : Reactions were performed with 2-methylisoindolin-1-one **7a** (0.1 mmol) and alkene **8** (0.15 mmol) in dry MeCN (0.03 M) under Ar atmosphere. Isolated yield.
[b] The ratio in parenthesis is the diastereomeric ratio.
[c] 3.0 equivalent of alkene was used.

Table 2-3. Substrate scope of lactam[a]

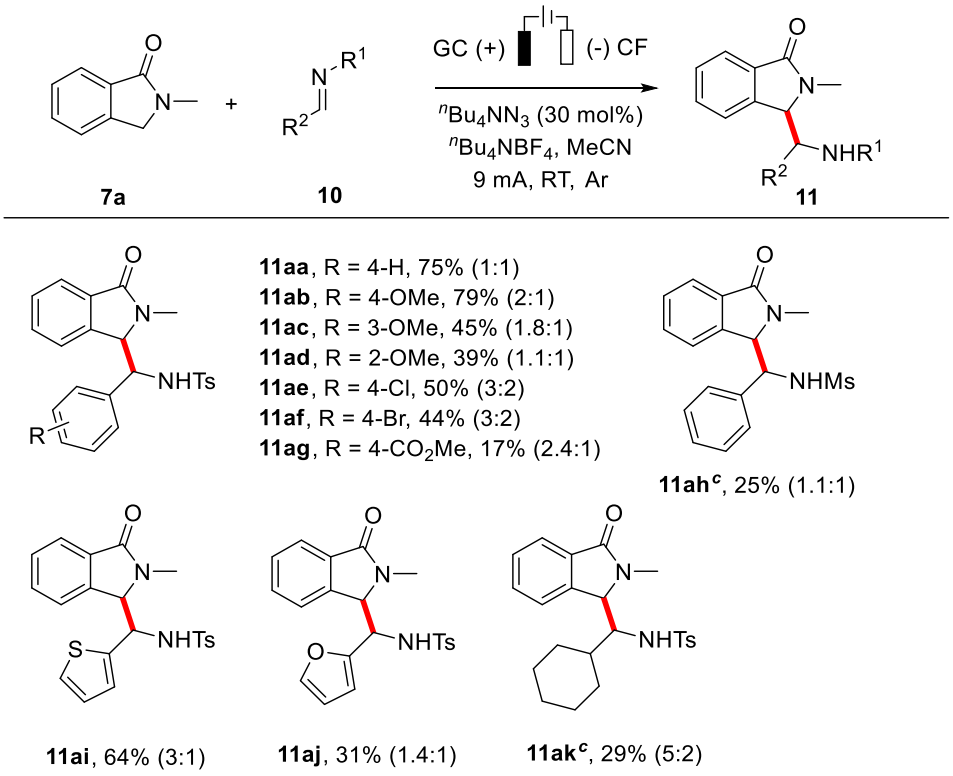


[a] Reaction conditions : Reactions were performed with lactam **7** (0.1 mmol) and alkene **8** (0.15 mmol) in dry MeCN (0.03 M) under Ar atmosphere. Isolated yield.
[b] The ratio in parenthesis is the diastereomeric ratio.
[c] 3.0 equivalent of alkene was used.
[d] Reactions were run under constant voltage mode (2.5 V)

Next, we found out the scope for various lactams (Table 2-3). No matter which functional groups were substituted-electron-donating and electron-withdrawing groups-various lactams proceeded well in the reaction (**9ba-9fa**). In good to excellent yields, N-aryl substituted lactams were also produced the corresponding products. Unfortunately, the methyl group substituted in ortho position did not gave the desired product during the reaction (**9ga-9ma**). N-benzyl substituted lactams were also selectively reacted in the reaction giving the N-α methylene position coupling products (**9na-9oa**). The sterically hindered substrate 3-methyl and phenyl substituted substrate were conducted in the reactions. For

methyl substituted lactam **7p** performed well with alkene and gave the corresponding products in moderate yield (**9pa, 9pai**). Instead, phenyl substituted lactam **7q** reacted only with methyl acrylate and acrylonitrile (**9qai, 9qaj**). Additionally, we tried phenyl group substituted N-H lactam **7r** in the reaction, and this lactam reacted with methyl cinnamate and acrylonitrile (**9ra, 9raj**). 2-phenyl-1,4-dihydroisoquinolin-3(2H)-one **7s** gave the desired products in excellent yield (**9sa**). Furthermore, wide range of α, β-unsaturated lactams were conducted in the reactions. Not only α, β-monosubstituted lactams, but also disubstituted lactams participated well in coupling reaction to generate the desired products (**9ta-9za**). Interestingly, the bicyclic lactams were also applicable in the reaction to form new C-C bonds in moderate yield (**3bbai-3bbak**).

Table 2-4. Substrate scope of imine[a]



[a] Reaction conditions : Reactions were performed with 2-methylisoindolin-1-one **7a** (0.4 mmol) and imine **10** (1.2 mmol) in dry MeCN (0.1 M) under Ar atmosphere. Isolated yield.
[b] The ratio in parenthesis is the diastereomeric ratio.
[c] Reaction were run under constant voltage mode (6 V).

To expand the substrate scope of the work, N-sulfonyl imines were attempted to reaction partners. The standard condition did not show the excellent yield (33%). The reaction was carried out at higher

concentration, higher current, and higher equivalent of reaction partner to improve the yield of the sulfonamide.

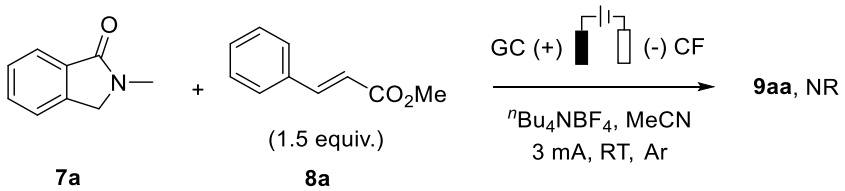
With the optimized condition in hand, radical-radical coupling mechanism reaction was attempted with various substituted N-sulfonyl imines (Table 2-4). The reaction with electron donating group substituted imines showed good to moderated yield regardless of the substituted position on aryl ring (**11ab-11ad**). Halide substituted imines were also well-tolerated in moderate yield (**11ae-11af**). Unfortunately, electron-deficient imine gave the low yield of the product (**11ag**). Furthermore, heteroaryl containing imines were used for the reactions and the corresponding product was obtained (**11ai-11aj**). Instead of tosyl group substituted imine, mesyl group substituted substrate **10h** also attempted for the reaction. Also the alkyl imine were attempted for the reaction, but in both cases the corresponding product were obtained in low yield (**11ah, 11ak**).

2.4. Mechanistic studies and proposed mechanism

To find out the reaction reagents' roles in the reaction conditions, several control experiments were proceeded. $^{n}Bu_4NN_3$ is used as a HAT mediator. The reaction that has been run without $^{n}Bu_4NN_3$; the desired product did not form (Scheme 2-9, (a)). There was no conversion of **7a** and confirmed that during the reaction HAT by the in-situ generated azido radical was needed.

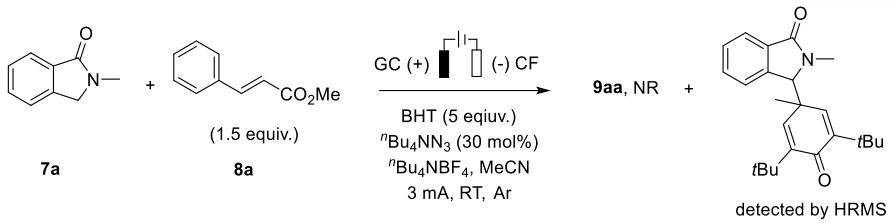
The reaction was carried out with well-known radical scavenger 2,6-Di-tert-butyl-4-methyl-phenol (BHT) (Scheme 2-9, (b)). The desired product did not obtain which demonstrated the reaction was completely inhibited. By HRMS, the adduct of **7a** and BHT was observed. Throughout the result of this experiment, we found out that **7a** radical intermediate is generated during the electrolysis.

(a)



7a **8a**

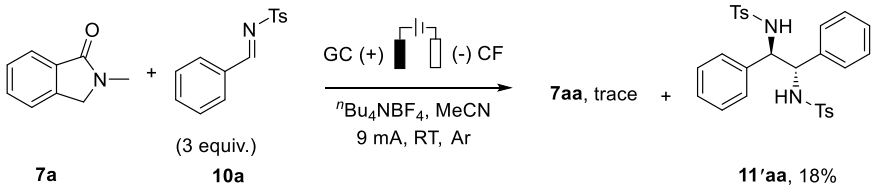
(b)



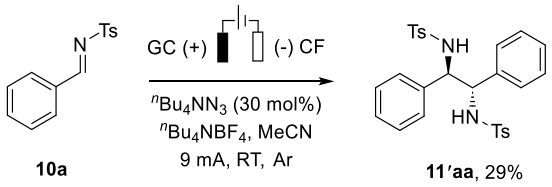
Scheme 2-9. Mechanistic studies – reaction with methyl cinnamate.

Control experiments also tried for the N-sulfonyl imines. The reaction without $^{n}Bu_4NN_3$, the reaction was inhibited to obtain desired product and additional imine dimer was observed (Scheme 2-10, (a)). The experiment performed without **7a**, 29% yield of imine dimer was observed. We confirmed that by reduction of imine at cathode, the radical can be formed in the reaction (Scheme 2-10, (b)). Scheme 2-10 (c) shows the reaction performed with radical scavenger BHT. The desired product **11aa** was obtained with 36% yield and **7a** and BHT adduct was observed by HRMS which can confirmed **7a** radical intermediate's presence in the reaction.

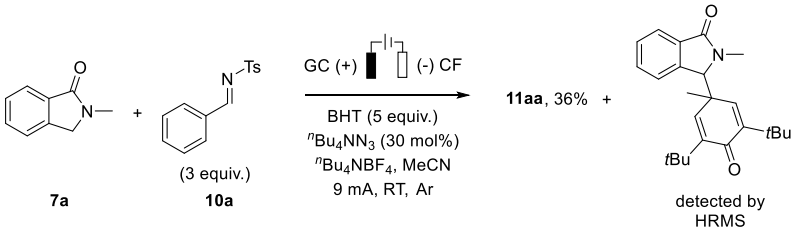
(a)



(b)



(c)



Scheme 2-10. Mechanistic studies – reaction with N-sulfonyl imine.

The mechanisms for the reactions are proposed in Figure 2-3 and Figure 2-4. Figure 2-3 shows the mechanism of 2-methylisoindolin-1-one **7a** with alkenes **8**. First, azide undergoes anode oxidation to form azido radical. This azido radical mediates HAT on **7a** to form radical intermediate **A**. Next,

reaction partner and radical intermediate **A** undergoes radical addition to form radical intermediate **B**, which generates desired product **9** via HAT.

The electrolysis reaction of 2-methylisoindolin-1-one **7a** reacting with imines **10** is shown in Figure 2-4. The radical intermediate **A** generated from HAT between azido radical and 2-methylisoinolin-1-one **7a** undergoes radical-radical coupling with radical-anion specie **C** which is generated from N-sulfonyl imine cathodic reduction. The desired product is produced by the protonation of anion intermediate **D.**

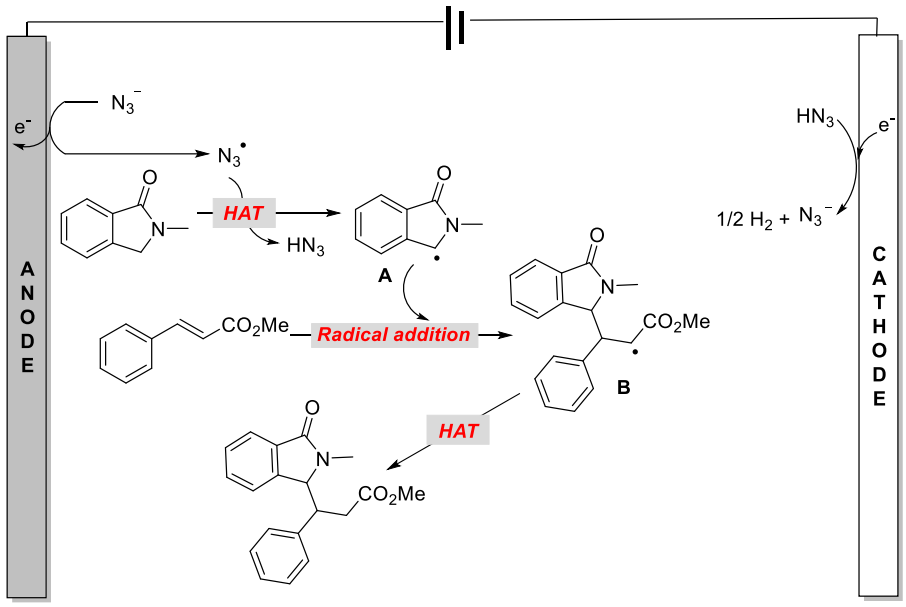


Figure 2-3. Proposed Mechanism - 2-methylisoindolin-1-one reacted with alkenes.

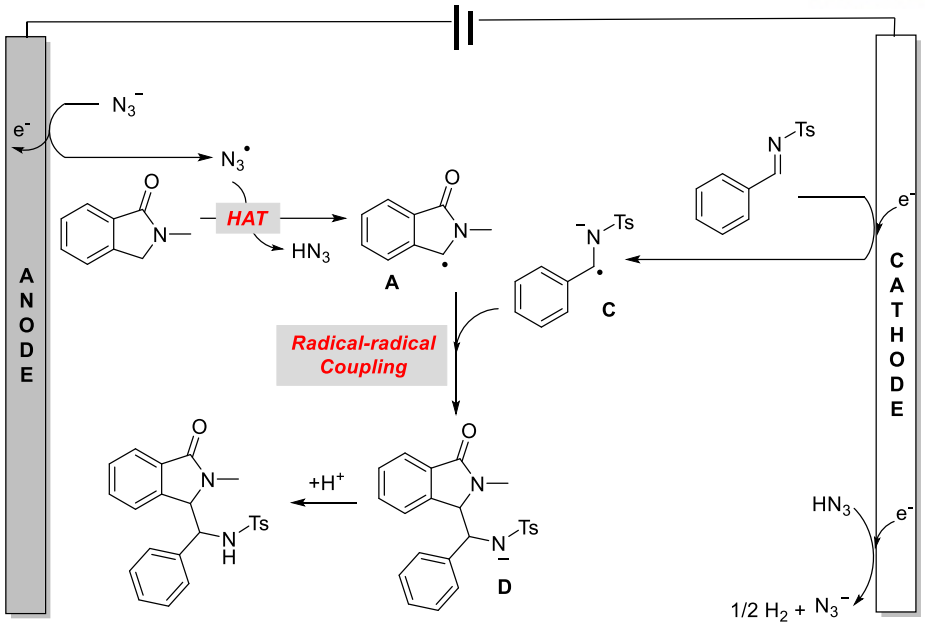


Figure 2-4. Proposed Mechanism - 2-methylisoindolin-1-one reacted with imines.

To support the proposed mechanisms, the density functional theory (DFT) calculation was performed. All DFT calculations were carried out using the B3LYP hybrid functional with Grimme′s D3 dispersion corrections. Geometry optimization was performed with the 6-31g(d,p) basis set for H, C, N, O atoms. Frequency calculations were performed for every optimized geometry with the same level of theory to obtain vibrational frequencies and thermochemical data at 298.15K. The SMD solvation model with the solvent of acetonitrile (ε=35.688) was used for all calculations. The transition states were identified by having one imaginary frequency, and IRC which stands for 'intrinsic reaction coordinate' calculations were conducted to connect transition states with corresponding intermediates. Each intermediate was verified as minima by having no imaginary frequency, and the geometries of intermediates with possibility of multiple conformations were optimized with several different starting geometries to find the lowest energy conformation. All calculations were performed using the Gaussian 09 software (Rev D.01).

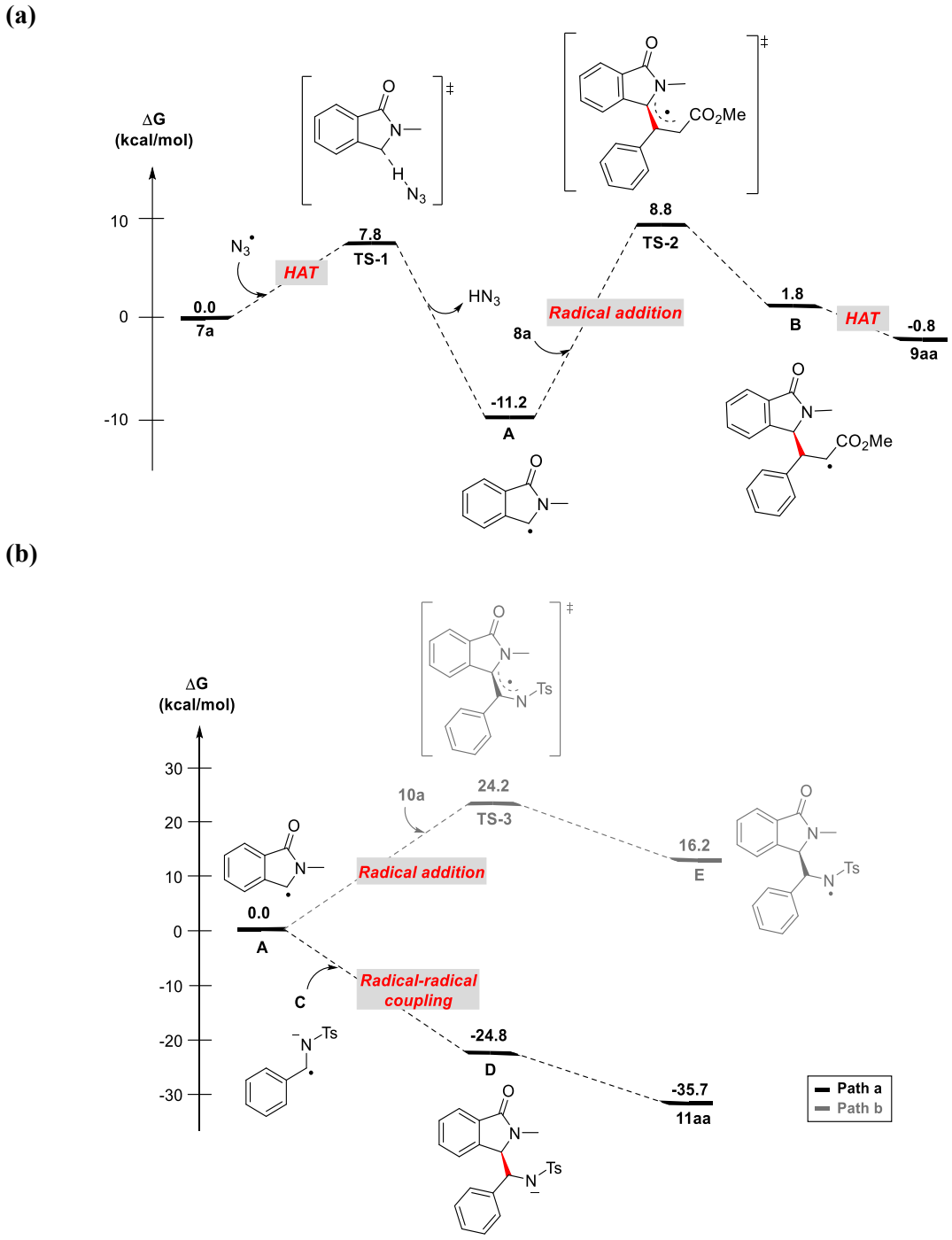


Figure 2-5. DFT calculation.

DFT calculation of this reaction is shown in Figure 2-5. Anodic oxidation of azide affords azido radical, which mediates HAT on **7a** to form **A**. Subsequent addition of **A** to **8a** provides **B** with $dG^{\ddagger}$ = 20 kcal/mol. **B** furnishes the coupling product **9aa** after the HAT (Figure 2-5, (a)). Throughout the

control experiments, the electrolysis with N-sulfonyl imines proceed by radical-radical coupling. Thus, radical species **A** initially formed by HAT undergoes coupling with radical anion **C** formed by cathodic reduction of **10a** (Figure 2-5, (b)). To confirm the mechanism, we performed DFT calculations, in which the barrierless coupling leads to highly exergonic reaction with dG = -24.8 kcal/mol. We also examined an alternative pathway involving radical addition of **A** to **10a**, which turned out to be unfavorable with $dG^{\ddagger}$ = 24.2 kcal/mol.

2.5. Conclusion

In conclusion, we developed γ-lactams C(sp^3)-H functionalization using hydrogen atom transfer based on electrochemistry. As a HAT mediator, $^{n}Bu_4NN_3$ was used only as a catalytic amount. Coupling reaction with various functional groups mediated alkenes and N-sulfonyl imines produced γ-lactams with a broad scope. Moreover, mechanistic studies, control experiments, and DFT calculations proceeded to support detailed reaction mechanisms.

2.6. Experimental data

2.6.1. General Procedures

General Procedure (C)

The reaction was carried out in an undivided cell. A 5 mL vial was charged with the lactam derivative **7** (0.1 mmol, 1.0 equiv.), alkene **8** (x equiv.), $^{n}Bu_4NN_3$ (0.3 M solution in MeCN) (0.1 ml, 30 mol%), MeCN (3.7 mL, 0.1 M $^{n}Bu_4NBF_4$) and a stir bar, and was closed with a cap attached with a glassy carbon anode and a carbon felt cathode. The solution was stirred at 900 rpm for 10 minutes at room temperature before current was turned on. The electrolysis was performed at a constant current of 3 mA. Upon full consumption of the lactam starting material as determined by thin-layer chromatography analysis, electrolysis was terminated, the solvent was eliminated under vacuum conditions. Flash column chromatography was used for product purification.

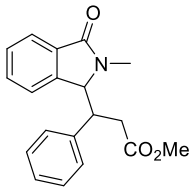
General Procedure (D)

The reaction was carried out in an undivided cell. A 5 mL vial was charged with the 2-methylisoindolin-1-one **7a** (0.4 mmol, 1.0 equiv.), aldimine **10** (3 equiv.), $^{n}Bu_4NN_3$ (0.3 M solution in

MeCN) (0.4 ml, 30 mol%), MeCN (3.6 mL, 0.1 M $^{n}Bu_4NBF_4$) and a stir bar, and was closed with a cap attached with a glassy carbon anode and a carbon felt cathode. The solution was stirred at 900 rpm for 10 minutes at room temperature before current was turned on. The electrolysis was performed at a constant current of 9 mA. Upon full consumption of the lactam starting material as determined by thin-layer chromatography analysis, electrolysis was terminated, the solvent was eliminated under vacuum conditions. Flash column chromatography was used for product purification.

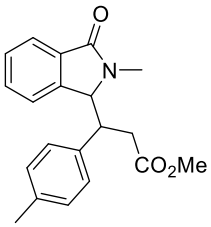
2.6.2. Characterization of products

methyl 3-(2-methyl-3-oxoisoindolin-1-yl)-3-phenylpropanoate (9aa)



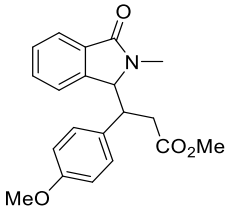
Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and methyl cinnamate **8a** (1.5 equiv.). 12.6 mg, 82% yield, 1 h, d.r. = 1.1:1, white solid, m.p. 117-120 ˚C		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.84 – 7.77 (m, 1.4H), 7.70 (d, J = 7.5 Hz, 1H), 7.61 (d, J = 7.4 Hz, 1H), 7.57 (dd, J = 7.3, 1.2 Hz, 1H), 7.47 – 7.37 (m, 5.4H), 7.37 – 7.30 (m, 3H), 7.29 (t, J = 1.5 Hz, 2H), 7.12 (dd, J = 3.9, 1.9 Hz, 3H), 6.90 – 6.84 (m, 2H), 6.56 (d, J = 7.6 Hz, 1.4H), 4.72 (d, J = 3.5 Hz, 1H), 4.68 (d, J = 3.7 Hz, 1.4H), 4.14 (dt, J = 9.5, 4.6 Hz, 1.4H), 4.05 – 3.96 (m, 1H), 3.63 (s, 3H), 3.57 (s, 4H), 3.26 (s, 4H), 3.03 (s, 3H), 2.93 (dd, J = 16.0, 8.8 Hz, 1H), 2.78 (dd, J = 16.0, 6.8 Hz, 1H), 2.30 (dd, J = 16.0, 9.9 Hz, 1.4H), 2.21 – 2.13 (m, 1.4H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.2, 172.1, 168.6, 143.0, 141.9, 138.3, 137.5, 133.1, 132.8, 131.1, 130.8, 128.8, 128.5, 128.5, 128.2, 128.1, 127.7, 127.5, 127.4, 123.6, 123.5, 123.3, 122.7, 66.4, 65.7, 52.0, 51.9, 43.1, 41.3, 34.9, 30.7, 28.8, 28.0
HRMS *m/z*	$C_{19}H_{20}NO_3^+$ ($[M+H]^+$)	
	Calculated: 310.1438	observed: 310.1439

methyl 3-(2-methyl-3-oxoisoindolin-1-yl)-3-(p-tolyl)propanoate (9ab)



Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and methyl (E)-3-(p-tolyl)acrylate **8b** (1.5 equiv.). 28.7 mg, 89% yield, 1 h, d.r. = 1:1, yellow oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.80 (d, J = 7.5 Hz, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.55 (td, J = 7.4, 1.1 Hz, 1H), 7.42 (dt, J = 12.6, 7.4 Hz, 2H), 7.32 (td, J = 7.5, 1.1 Hz, 1H), 7.21 (d, J = 7.9 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 6.92 (d, J = 7.8 Hz, 2H), 6.74 (d, J = 7.9 Hz, 2H), 6.60 (d, J = 7.6 Hz, 1H), 4.70 (d, J = 3.6 Hz, 1H), 4.66 (d, J = 3.8 Hz, 1H), 4.09 (dt, J = 9.5, 4.6 Hz, 1H), 3.97 (ddd, J = 9.2, 6.8, 3.5 Hz, 1H), 3.63 (s, 3H), 3.56 (s, 3H), 3.25 (s, 3H), 3.02 (s, 3H), 2.91 (dd, J = 16.0, 8.8 Hz, 1H), 2.76 (dd, J = 16.0, 6.8 Hz, 1H), 2.38 (s, 3H), 2.27 (dd, J = 16.0, 9.9 Hz, 1H), 2.21 (s, 3H), 2.16 (dd, J = 16.0, 5.3 Hz, 1H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.3, 172.1, 168.6, 168.5, 143.1, 142.0, 137.2, 137.0, 135.1, 134.4, 133.2, 132.9, 131.0, 130.8, 129.5, 129.0, 128.4, 128.4, 127.9, 127.6, 123.6, 123.5, 123.4, 122.7, 66.5, 65.8, 51.9, 51.9, 42.8, 40.9, 35.1, 30.7, 28.8, 27.9, 21.1, 20.9
HRMS *m/z*	$C_{20}H_{22}NO_3^+$ ($[M+H]^+$)	
	Calculated: 324.1594	observed: 324.1596

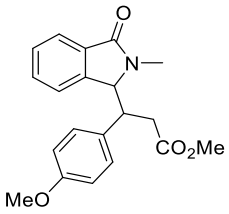
methyl 3-(4-methoxyphenyl)-3-(2-methyl-3-oxoisoindolin-1-yl)propanoate (9ac-1)



Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and methyl (E)-3-(4-methoxyphenyl)acrylate **8c** (1.5 equiv.). 15.1 mg, 44% yield (89% total yield), 1 h, clear oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.80 (d, J = 7.5 Hz, 1H), 7.41 (t, J = 7.4 Hz, 1H), 7.33 (t, J = 7.5 Hz, 1H), 7.18 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 8.7 Hz, 2H), 6.61 (d, J = 7.6 Hz, 1H), 4.64 (d, J = 3.8 Hz, 1H), 4.08 (dt, J = 9.6, 4.6 Hz, 1H), 3.84 (s, 3H), 3.57 (s, 3H), 3.25 (s, 3H), 2.21 (qd, J = 16.0, 7.6 Hz, 2H)

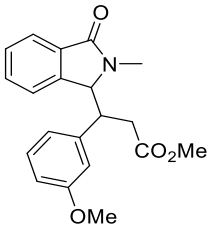
^{13}C NMR	**100 MHz, $CDCl_3$**	172.3, 168.6, 158.9, 142.0, 132.9, 130.8, 130.1, 129.1, 128.4, 123.5, 123.3, 114.2, 66.5, 55.3, 51.9, 40.6, 31.0, 28.0
HRMS *m/z*	$C_{20}H_{22}NO_4^+$ ([M+H]$^+$)	
	Calculated: 340.1543	observed: 340.1553

methyl 3-(4-methoxyphenyl)-3-(2-methyl-3-oxoisoindolin-1-yl)propanoate (9ac-2)



Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and methyl (E)-3-(4-methoxyphenyl)acrylate **8c** (1.5 equiv.). 15.1 mg, 45% yield (89% total yield), 1 h, clear oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.80 (d, J = 7.5 Hz, 1H), 7.41 (t, J = 7.4 Hz, 1H), 7.33 (t, J = 7.5 Hz, 1H), 7.18 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 8.7 Hz, 2H), 6.61 (d, J = 7.6 Hz, 1H), 4.64 (d, J = 3.8 Hz, 1H), 4.08 (dt, J = 9.6, 4.6 Hz, 1H), 3.84 (s, 3H), 3.57 (s, 3H), 3.25 (s, 3H), 2.21 (qd, J = 16.0, 7.6 Hz, 2H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.3, 168.6, 158.9, 142.0, 132.9, 130.8, 130.1, 129.1, 128.4, 123.5, 123.3, 114.2, 66.5, 55.3, 51.9, 40.6, 31.0, 28.0
HRMS *m/z*	$C_{20}H_{22}NO_4^+$ ([M+H]$^+$)	
	Calculated: 340.1543	observed: 340.1557

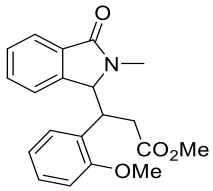
methyl 3-(3-methoxyphenyl)-3-(2-methyl-3-oxoisoindolin-1-yl)propanoate (9ad)



Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and methyl 3-(3-methoxyphenyl)acrylate **8d** (1.5 equiv.). 28.5 mg, 84% yield, 1 h, d.r. = 1:1, clear oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.81 (d, J = 7.5 Hz, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.57 (t, J = 7.4 Hz, 1H), 7.43 (dt, J = 14.8, 7.4 Hz, 2H), 7.33 (t, J = 7.8 Hz, 2H), 7.05 (t, J = 7.9 Hz, 1H), 6.87 (t, J = 7.0 Hz, 2H), 6.82 (s, 1H), 6.67 (d, J = 7.9 Hz, 1H), 6.62 (d, J = 7.6 Hz, 1H), 6.51 (d, J = 7.6

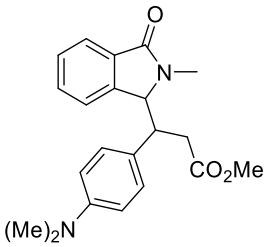
		Hz, 1H), 6.34 (s, 1H), 4.73 (d, J = 3.5 Hz, 1H), 4.69 (d, J = 3.7 Hz, 1H), 4.10 (dt, J = 9.4, 4.5 Hz, 1H), 3.98 (ddd, J = 9.5, 7.0, 3.3 Hz, 1H), 3.82 (s, 3H), 3.64 (s, 3H), 3.59 (s, 3H), 3.58 (s, 3H), 3.25 (s, 3H), 3.03 (s, 3H), 2.91 (dd, J = 16.1, 8.7 Hz, 1H), 2.76 (dd, J = 16.1, 6.8 Hz, 1H), 2.27 (dd, J = 16.1, 9.8 Hz, 1H), 2.16 (dd, J = 16.1, 5.2 Hz, 1H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.2, 172.0, 168.6, 168.5, 159.9, 159.3, 143.0, 141.9, 140.0, 139.2, 133.2, 132.9, 131.1, 130.8, 129.8, 129.3, 128.5, 128.5, 123.7, 123.5, 123.4, 122.7, 120.3, 114.3, 113.4, 112.9, 112.6, 66.4, 65.6, 55.3, 55.0, 52.0, 51.9, 43.1, 41.2, 35.1, 30.7, 28.8, 27.9
HRMS *m/z*	$C_{20}H_{22}NO_4^+$ ($[M+H]^+$)	
	Calculated: 340.1543	observed: 340.1558

methyl 3-(2-methoxyphenyl)-3-(2-methyl-3-oxoisoindolin-1-yl)propanoate (9ae)



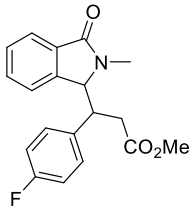
Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and methyl (E)-3-(2-methoxyphenyl)acrylate **8e** (1.5 equiv.). 31.9 mg, 94% yield, 1 h, d.r. = 2.6:1, yellow oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.82 (d, J = 7.5 Hz, 1H), 7.66 (d, J = 7.5 Hz, 0.45H), 7.58 (t, J = 7.4 Hz, 0.45H), 7.49 – 7.29 (m, 4H), 7.22 (t, J = 7.8 Hz, 1H), 7.10 (d, J = 7.2 Hz, 1H), 7.05 – 6.97 (m, 2H), 6.95 – 6.89 (m, 1H), 6.82 (t, J = 7.5 Hz, 0.45H), 6.66 (d, J = 7.6 Hz, 1H), 4.85 (d, J = 2.5 Hz, 0.45H), 4.78 (d, J = 3.2 Hz, 1H), 4.48 (m, 1H), 4.47 (m, 0.45H), 3.96 (s, 3H), 3.92 (s, 1H), 3.54 (s, 3H), 3.51 (s, 1H), 3.27 (s, 3H), 2.86 (s, 1H), 2.76 (dd, J = 16.1, 10.0 Hz, 0.45H), 2.30 (dd, J = 16.1, 5.8 Hz, 0.45H), 2.20 (dd, J = 15.8, 10.0 Hz, 1H), 2.09 (dd, J = 15.9, 5.5 Hz, 1H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.2, 172.0, 168.6, 168.5, 159.9, 159.3, 143.0, 141.9, 140.0, 139.2, 133.2, 132.9, 131.1, 130.8, 129.8, 129.3, 128.5, 128.5, 123.7, 123.5, 123.4, 122.7, 120.3, 114.3, 113.4, 112.9, 112.6, 66.4, 65.6, 55.3, 55.0, 52.0, 51.9, 43.1, 41.2, 35.1, 30.7, 28.8, 27.9
HRMS *m/z*	$C_{20}H_{22}NO_4^+$ ($[M+H]^+$)	
	Calculated: 340.1543	observed: 340.1559

methyl 3-(4-(dimethylamino)phenyl)-3-(2-methyl-3-oxoisoindolin-1-yl)propanoate (9af)



Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and methyl (E)-3-(4-(dimethylamino)phenyl)acrylate **8f** (3.0 equiv.). 25.0 mg, 71% yield, 3 h, d.r.=1:1, yellow solid; m.p. 137-145 ˚C		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.80 (d, *J* = 7.5 Hz, 1H), 7.72 (d, *J* = 7.4 Hz, 0.2H), 7.61 (d, *J* = 7.3 Hz, 0.2H), 7.55 (t, *J* = 7.5 Hz, 0.2H), 7.45 (d, *J* = 7.3 Hz, 0.2H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.13 (d, *J* = 8.6 Hz, 2H), 6.76 (d, *J* = 8.7 Hz, 2H), 6.71 (d, *J* = 8.6 Hz, 0.3H), 6.67 (d, *J* = 7.6 Hz, 1H), 6.47 (d, *J* = 8.7 Hz, 0.3H), 4.67 (d, *J* = 3.7 Hz, 0.2H), 4.63 (d, *J* = 3.8 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 0.2H), 4.04 (dt, *J* = 9.3, 4.5 Hz, 1H), 3.63 (s, 0.5H), 3.56 (s, 3H), 3.25 (s, 3H), 3.03 (s, 0.5H), 2.98 (s, 6H), 2.85 (s, 1H), 2.52 (dd, *J* = 16.1, 1.9 Hz, 0.2H), 2.35 (dd, *J* = 16.2, 10.6 Hz, 0.2H), 2.23 (dd, *J* = 15.9, 9.9 Hz, 1fH), 2.12 (dd, *J* = 15.8, 5.2 Hz, 1H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.5, 168.7, 149.8, 142.3, 132.9, 130.9, 130.7, 128.7, 128.3, 128.3, 125.5, 123.6, 123.6, 123.4, 122.7, 112.7, 112.2, 66.7, 65.9, 51.9, 51.8, 42.3, 40.5, 40.4, 40.3, 36.6, 35.3, 30.8, 28.8, 27.9, 25.6
HRMS *m/z*	$C_{21}H_{25}N_2O_3^+$ ($[M+H]^+$)	
	Calculated: 353.1860	observed: 353.1861

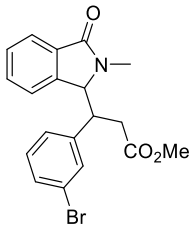
methyl 3-(4-fluorophenyl)-3-(2-methyl-3-oxoisoindolin-1-yl)propanoate (9ag)



Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and methyl (E)-3-(4-fluorophenyl)acrylate **8g** (1.5 equiv.). 23.6 mg, 72% yield, 1 h, d.r. = 1.2:1, colorless oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.81 (d, *J* = 7.5 Hz, 1H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.47 – 7.40 (m, 2H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.23 (dd, *J* = 8.5, 5.2 Hz, 2H), 7.10 (t, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 7.6 Hz, 4H), 6.60 (d, *J* = 7.6 Hz, 1H), 4.68 (d, *J* = 3.6 Hz, 1H), 4.64 (d, *J* = 3.7 Hz, 1H), 4.13 – 4.07 (m, 1H), 4.02 – 3.95 (m, 1H), 3.65 (s, 3H), 3.58 (s,

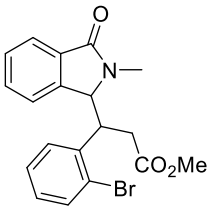
		3H), 3.26 (s, 3H), 3.07 (s, 3H), 2.90 (qd, *J* = 16.0, 7.8 Hz, 2H), 2.33 – 2.19 (m, 2H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.1, 171.8, 168.6, 168.3, 162.1 (d, *J* = 246.8 Hz), 161.9 (d, *J* = 246.4 Hz), 142.6, 141.8, 133.9, 133.9, 133.2, 132.9, 132.8, 132.8, 131.0 (d, *J* = 246.8 Hz), 129.7, 129.6, 129.3, 129.2, 128.6, 128.6, 123.8, 123.7, 123.1, 122.7, 115.8 (d, *J* = 21.4 Hz), 115.1 (d, *J* = 21.4 Hz), 66.3, 65.4, 52.0, 51.9, 42.3, 40.9, 35.6, 31.2, 28.6, 28.1
HRMS *m/z*	$C_{19}H_{19}FNO_3^+$ ($[M+H]^+$)	
	Calculated: 328.1343	observed: 328.1344

methyl 3-(3-bromophenyl)-3-(2-methyl-3-oxoisoindolin-1-yl)propanoate (9ah)



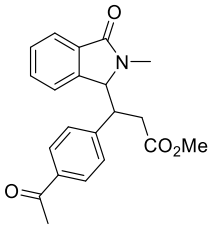
Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and methyl (E)-3-(3-bromophenyl)acrylate **8h** (1.5 equiv.). 14.8 mg, 38% yield, 1 h, d.r. = 4:1, yellow oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.82 (d, J = 7.5 Hz, 1H), 7.73 (d, J = 7.5 Hz, 0.25H), 7.59 (d, J = 6.3 Hz, 1H), 7.53 – 7.40 (m, 4H), 7.36 (t, J = 7.5 Hz, 1H), 7.30 (d, J = 7.8 Hz, 2H), 7.19 (d, J = 7.8 Hz, 1H), 7.04 – 6.94 (m, 1H), 6.78 (d, J = 7.8 Hz, 0.25H), 6.60 (d, J = 7.6 Hz, 1H), 4.70 (d, J = 3.6 Hz, 0.25H), 4.66 (d, J = 3.7 Hz, 1H), 4.10 (dt, J = 9.5, 4.7 Hz, 1H), 4.03 – 3.91 (m, 0.25H), 3.66 (s, 1H), 3.59 (s, 3H), 3.25 (s, 3H), 3.05 (s, 1H), 2.95 – 2.57 (m, 1H), 2.23 (qd, J = 16.2, 7.5 Hz, 2H)
^{13}C NMR	**100 MHz, $CDCl_3$**	171.9, 171.7, 168.5, 168.4, 142.5, 141.6, 140.8, 139.8, 133.1, 132.8, 131.5, 131.2, 131.0, 130.9, 130.8, 130.6, 130.3, 129.8, 128.8, 128.7, 126.6, 126.4, 123.8, 123.7, 123.1, 123.0, 122.6, 122.3, 66.1, 65.4, 52.1, 52.0, 42.8, 41.2, 35.0, 30.6, 28.8, 28.0
HRMS *m/z*	$C_{19}H_{19}BrNO_3^+$ ($[M+H]^+$)	
	Calculated: 388.0543	observed: 388.0544

methyl 3-(2-bromophenyl)-3-(2-methyl-3-oxoisoindolin-1-yl)propanoate (9ai)



Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and methyl 3-(2-bromophenyl)acrylate **8i** (1.5 equiv.). 34.9 mg, 90% yield, 1 h, d.r. = 4:1, yellow oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.84 (t, J = 7.7 Hz, 1H), 7.80 – 7.69 (m, 1H), 7.71 – 7.57 (m, 1H), 7.55 – 7.30 (m, 4H), 7.27 – 7.19 (m, 1H), 7.16 (td, J = 7.9, 1.7 Hz, 1H), 7.11 – 7.06 (m, 0.25H), 6.64 (d, J = 7.6 Hz, 1H), 4.95 (d, J = 2.4 Hz, 0.25H), 4.86 (d, J = 3.4 Hz, 1H), 4.52 (ddd, J = 9.4, 6.6, 3.5 Hz, 1H), 4.49 – 4.44 (m, 0.25H), 3.55 (s, 3H), 3.49 (s, 1H), 3.32 (s, 3H), 2.82 (s, 1H), 2.76 (dd, J = 16.3, 10.2 Hz, 0.25H), 2.26 – 2.22 (m, 0.25H), 2.20 (dd, J = 7.7, 2.6 Hz, 2H)
^{13}C NMR	**100 MHz, $CDCl_3$**	171.7, 171.6, 169.5, 168.5, 144.0, 141.8, 138.5, 137.3, 133.9, 133.9, 133.2, 132.6, 131.8, 130.7, 129.4, 129.1, 129.0, 128.7, 128.6, 128.1, 127.5, 127.5, 125.6, 125.3, 123.7, 123.6, 123.4, 122.5, 64.8, 62.8, 52.0, 51.9, 43.7, 40.4, 31.9, 30.6, 30.4, 27.6
HRMS *m/z*	$C_{19}H_{19}BrNO_3^+$ ($[M+H]^+$)	
	Calculated: 388.0543	observed: 388.0543

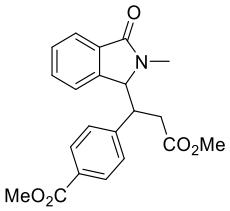
methyl 3-(4-acetylphenyl)-3-(2-methyl-3-oxoisoindolin-1-yl)propanoate (9aj)



Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and methyl (E)-3-(4-acetylphenyl)acrylate **8j** (1.5 equiv.). 21.1 mg, 60% yield, 1 h, d.r. = 5:1, colorless oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	8.00 (d, *J* = 8.0 Hz, 2H), 7.81 (d, *J* = 7.5 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 0.4H), 7.66 – 7.53 (m, 0.4H), 7.50 – 7.29 (m, 4.6H), 6.94 (d, *J* = 8.0 Hz, 0.2H), 6.57 (d, *J* = 7.6 Hz, 1H), 4.74 (d, *J* = 3.3 Hz, 0.2H), 4.70 (d, *J* = 3.4 Hz, 1H), 4.18 (dd, *J* = 9.3, 4.7 Hz, 1H), 4.09 (d, *J* = 9.4 Hz, 0.2H), 3.66 (s, 0.6H), 3.59 (s, 3H), 3.28 (s, 3H), 3.07 (s, 0.6H), 3.02 – 2.82 (m, 0.4H), 2.64 (s, 3H), 2.51 (s, 0.6H), 2.31 (qd, *J* = 16.3, 7.6 Hz, 2H)

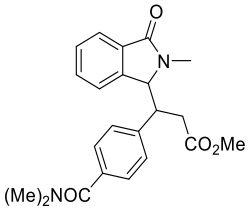
^{13}C NMR	**100 MHz, $CDCl_3$**	197.5, 171.9, 168.5, 143.8, 141.6, 136.4, 132.8, 131.2, 131.0, 128.8, 128.7, 128.4, 128.2, 128.0, 123.9, 123.8, 123.0, 122.6, 66.0, 65.4, 52.1, 52.0, 43.0, 41.7, 35.0, 30.8, 28.7, 28.1, 26.6, 26.5
HRMS *m/z*	$C_{21}H_{22}NO_4^+$ ([M+H]$^+$)	
	Calculated: 352.1543	observed: 352.1547

methyl 4-(3-methoxy-1-(2-methyl-3-oxoisoindolin-1-yl)-3-oxopropyl)benzoate (9ak)



Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and methyl (E)-4-(3-methoxy-3-oxoprop-1-en-1-yl)benzoate **8k** (3.0 equiv.). 15.8 mg, 43% yield, 1 h, d.r. = 2.4:1, yellow oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	8.08 (d, J = 8.1 Hz, 2H), 7.81 (d, J = 7.6 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.35 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 7.6 Hz, 1H), 4.69 (d, J = 3.7 Hz, 1H), 4.17 (dt, J = 9.7, 4.7 Hz, 1H), 3.94 (s, 3H), 3.57 (s, 3H), 3.26 (s, 3H), 2.37 – 2.20 (m, 2H)
^{13}C NMR	**100 MHz, $CDCl_3$**	171.9, 168.5, 166.6, 143.6, 141.6, 132.8, 131.0, 130.1, 129.5, 128.7, 128.2, 123.7, 123.1, 66.0, 52.2, 52.0, 41.6, 30.7, 28.1
HRMS *m/z*	$C_{21}H_{22}NO_5^+$ ([M+H]$^+$)	
	Calculated: 368.1492	observed: 368.1496

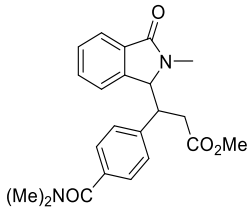
methyl 3-(4-(dimethylcarbamoyl)phenyl)-3-(2-methyl-3-oxoisoindolin-1-yl)propanoate (9al-1)



Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and methyl (E)-3-(4-(dimethylcarbamoyl)phenyl)acrylate **8l** (1.5 equiv.). 13.9 mg, 37% yield (70 % total yield), 1 h, d.r. = 1.1:1, yellow oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.80 (d, J = 7.5 Hz, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.42 (t, J = 7.5 Hz, 1H), 7.35 – 7.29 (m, 3H), 6.61 (d, J = 7.6 Hz, 1H), 4.68 (d, J = 3.6 Hz, 1H), 4.14 (dt, J = 9.5, 4.5 Hz, 1H), 3.58 (s, 3H), 3.26 (s, 3H), 3.13 (s, 3H), 3.01 (s, 3H),

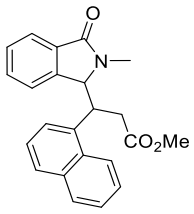
		2.31 (dd, J = 16.2, 9.8 Hz, 1H), 2.21 (dd, J = 16.2, 5.2 Hz, 1H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.0, 171.2, 168.7, 141.7, 140.1, 135.3, 132.7, 131.1, 128.7, 128.2, 127.7, 123.7, 123.2, 66.2, 52.0, 41.4, 30.7, 29.7, 28.1
HRMS *m/z*	$C_{22}H_{25}N_2O_4^+$ ($[M+H]^+$)	
	Calculated: 381.1809	observed: 381.1813

methyl 3-(4-(dimethylcarbamoyl)phenyl)-3-(2-methyl-3-oxoisoindolin-1-yl)propanoate (9al-2)



Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and methyl (E)-3-(4-(dimethylcarbamoyl)phenyl)acrylate **8l** (1.5 equiv.). 12.7 mg, 33% yield (70 % total yield), 1 h, d.r. = 1.1:1, yellow oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.67 (d, J = 7.6 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.43 (t, J = 7.4 Hz, 1H), 7.17 (d, J = 7.9 Hz, 2H), 6.88 (d, J = 7.9 Hz, 2H), 4.71 (d, J = 3.5 Hz, 1H), 4.06 – 4.00 (m, 1H), 3.64 (s, 3H), 3.06 (s, 3H), 3.04 (s, 3H), 2.94 (dd, J = 16.1, 8.8 Hz, 1H), 2.87 – 2.78 (m, 4H)
^{13}C NMR	**100 MHz, $CDCl_3$**	171.8, 171.0, 168.3, 142.7, 139.0, 135.3, 133.1, 131.2, 128.6, 127.8, 127.0, 123.7, 122.7, 65.5, 52.1, 42.8, 39.5, 35.0, 28.8
HRMS *m/z*	$C_{22}H_{25}N_2O_4^+$ ($[M+H]^+$)	
	Calculated: 381.1809	observed: 381.1813

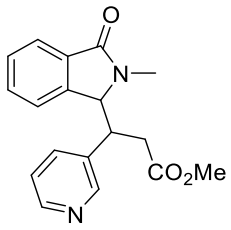
methyl 3-(2-methyl-3-oxoisoindolin-1-yl)-3-(naphthalen-1-yl)propanoate (9am)



Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and methyl (E)-3-(naphthalen-1-yl) **8m** (1.5 equiv.). 26.9 mg, 75% yield, 1 h, clear oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	8.30 (d, J = 8.6 Hz, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.84 (d, J = 7.5 Hz, 1H), 7.68 (ddd, J = 8.4, 6.8, 1.4 Hz, 1H), 7.60 – 7.49 (m, 2H), 7.41 (d, J = 7.5 Hz, 1H), 7.31 – 7.26 (m, 2H), 6.41 (d, J = 7.6 Hz,

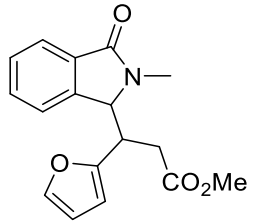
		1H), 4.97 (dt, J = 9.1, 5.1 Hz, 1H), 4.85 (d, J = 3.4 Hz, 1H), 3.54 (s, 3H), 3.45 (s, 3H), 2.42 – 2.27 (m, 3H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.2, 168.6, 141.9, 134.3, 133.8, 133.0, 131.4, 130.7, 129.6, 128.7, 128.5, 126.9, 126.0, 125.0, 124.9, 123.8, 123.6, 122.1, 63.9, 51.9, 36.6, 30.9, 27.8
HRMS *m/z*	$C_{23}H_{22}NO_3^+$ ($[M+H]^+$)	
	Calculated: 360.1594	observed: 360.1598

methyl 3-(2-methyl-3-oxoisoindolin-1-yl)-3-(pyridin-3-yl)propanoate (9an)



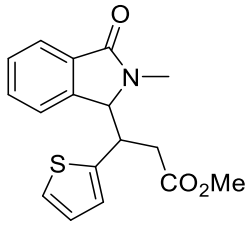
Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and methyl (E)-3-(pyridin-3-yl)acrylate **8n** (1.5 equiv.). 17 mg, 55% yield, 2 h, d.r.=1.2:1, yellow oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	8.56 (d, *J* = 16.5 Hz, 2H), 8.36 (t, *J* = 3.0 Hz, 1H), 8.15 (s, 1H), 7.80 (d, *J* = 7.5 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.60 (dt, *J* = 23.3, 8.0 Hz, 3H), 7.49 – 7.32 (m, 4H), 7.01 – 6.98 (m, 2H), 6.67 (d, *J* = 7.5 Hz, 1H), 4.72 (d, *J* = 3.6 Hz, 1H), 4.68 (d, *J* = 3.4 Hz, 1H), 4.14 (ddd, *J* = 9.2, 6.0, 3.8 Hz, 1H), 4.03 (td, *J* = 7.8, 3.7 Hz, 1H), 3.68 (s, 3H), 3.60 (s, 2.5H), 3.28 (s, 2.5H), 3.12 (s, 3H), 2.99 (d, *J* = 7.8 Hz, 2H), 2.42 – 2.36 (m, 1H), 2.36 – 2.31 (m, 1H)
^{13}C NMR	**100 MHz, $CDCl_3$**	171.7, 171.5, 168.5, 168.1, 149.8, 149.3, 149.0, 148.9, 142.1, 141.6, 135.6, 135.1, 133.8, 133.1, 132.7, 132.7, 131.3, 131.2, 128.9, 128.8, 124.0, 123.8, 123.5, 123.0, 122.8, 122.7, 65.9, 64.9, 52.2, 52.1, 40.7, 39.9, 35.4, 31.0, 28.5, 28.4
HRMS *m/z*	$C_{18}H_{19}N_2O_3^+$ ($[M+H]^+$)	
	Calculated: 311.1390	observed: 311.1393

methyl 3-(furan-2-yl)-3-(2-methyl-3-oxoisoindolin-1-yl)propanoate (9ao)



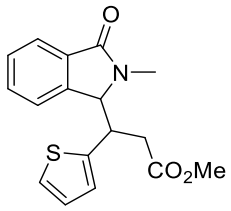
Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and methyl (E)-3-(furan-2-yl)acrylate **8o** (1.5 equiv.). 18.3 mg, 61% yield, 1 h, d.r. = 1.6:1, yellow oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.84 – 7.76 (m, 1.6H), 7.57 – 7.46 (m, 2.8H), 7.46 – 7.39 (m, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.30 (s, 0.6H), 6.51 (d, J = 7.5 Hz, 1H), 6.42 (dd, J = 3.4, 1.9 Hz, 1H), 6.24 (dd, J = 3.4, 1.9 Hz, 0.6H), 6.15 (d, J = 3.3 Hz, 1H), 5.95 (d, J = 3.3 Hz, 0.6H), 4.92 (d, J = 3.7 Hz, 1H), 4.89 (d, J = 2.8 Hz, 0.6H), 4.16 (dt, J = 9.1, 4.2 Hz, 1H), 4.09 (t, J = 4.4 Hz, 0.6H), 3.61 (s, 3H), 3.60 (s, 1.8H), 3.21 (s, 3H), 2.90 (s, 1.8H), 2.71 (dd, J = 16.2, 9.4 Hz, 0.6H), 2.29 (dd, J = 16.2, 5.1 Hz, 0.6H), 2.12 – 1.96(m, 2H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.0, 171.9, 168.8, 168.7, 152.9, 152.7, 142.7, 142.1, 141.7, 141.6, 132.9, 132.8, 131.4, 131.2, 128.6, 128.5, 123.6, 123.5, 122.9, 122.3, 110.7, 110.5, 107.3, 106.7, 64.0, 63.2, 52.0, 52.0, 37.8, 35.8, 31.8, 30.0, 28.4, 27.7
HRMS *m/z*	$C_{17}H_{18}NO_4^+$ ([M+H]$^+$)	
	Calculated: 300.1230	observed: 300.1230

methyl 3-(2-methyl-3-oxoisoindolin-1-yl)-3-(thiophen-2-yl)propanoate (9ap-1)



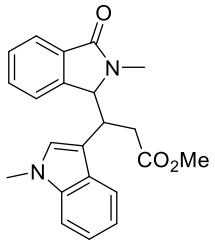
Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and methyl (E)-3-(thiophen-2-yl)acrylate **8p** (1.5 equiv.). 12.9 mg, 41% yield (76% total yield), 1 h, white solid, m.p. 102-105 ˚C		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.81 (d, J = 7.5 Hz, 1H), 7.43 (t, J = 7.4 Hz, 1H), 7.39 – 7.30 (m, 2H), 7.03 (dd, J = 5.1, 3.6 Hz, 1H), 6.88 (dd, J = 3.4, 1.3 Hz, 1H), 6.63 (d, J = 7.6 Hz, 1H), 4.78 (d, J = 3.6 Hz, 1H), 4.34 (dt, J = 9.1, 4.5 Hz, 1H), 3.63 (s, 3H), 3.25 (s, 3H), 2.33 – 2.17 (m, 2H)
^{13}C NMR	**100 MHz, $CDCl_3$**	171.9, 168.7, 142.3, 141.7, 132.8, 131.1, 128.7, 127.1, 125.0, 124.8, 123.5, 123.1, 66.4, 52.1, 37.7, 32.8, 28.1
HRMS *m/z*	$C_{17}H_{18}NO_3S^+$ ([M+H]$^+$)	
	Calculated: 316.1002	observed: 316.1002

methyl 3-(2-methyl-3-oxoisoindolin-1-yl)-3-(thiophen-2-yl)propanoate (9ap-2)



Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and methyl (E)-3-(thiophen-2-yl)acrylate **8p** (1.5 equiv.). 10.9 mg, 35% yield (76% total yield), 1 h, white solid, m.p. 135-137 ˚C		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.77 – 7.70 (m, 1H), 7.61 – 7.52 (m, 2H), 7.49 – 7.42 (m, 1H), 7.02 (dt, J = 5.0, 1.2 Hz, 1H), 6.75 (ddd, J = 6.2, 4.2, 1.8 Hz, 1H), 6.58 – 6.53 (m, 1H), 4.73 (d, J = 3.4 Hz, 1H), 4.35 – 4.27 (m, 1H), 3.69 (s, 3H), 3.10 (s, 3H), 3.02 – 2.81 (m, 2H)
^{13}C NMR	**100 MHz, $CDCl_3$**	171.6, 168.5, 142.2, 140.1, 133.4, 131.2, 128.7, 126.4, 125.3, 124.5, 123.7, 122.8, 65.3, 52.1, 38.7, 36.9, 28.2
HRMS *m/z*	$C_{17}H_{18}NO_3S^+$ ($[M+H]^+$)	
	Calculated: 316.1002	observed: 316.1005

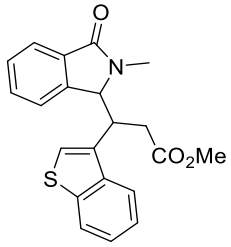
methyl 3-(1-methyl-1H-indol-3-yl)-3-(2-methyl-3-oxoisoindolin-1-yl)propanoate (9aq)



Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and methyl (E)-3-(1-methyl-1H-indol-3-yl)acrylate **8q** (1.5 equiv.). 19.2 mg, 53% yield, 1 h, d.r. = 2:1, yellow oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.82 (d, J = 7.5 Hz, 1.4H), 7.73 (d, J = 7.8 Hz, 1.4H), 7.65 – 7.60 (m, 0.8H), 7.51 (t, J = 7.5 Hz, 0.4H), 7.43 – 7.37 (m, 2H), 7.31 (q, J = 7.4 Hz, 2H), 7.25 – 7.17 (m, 1.8H), 7.11 (t, J = 7.4 Hz, 0.4H), 6.88 (s, 1H), 6.65 (d, J = 7.6 Hz, 1H), 6.24 (s, 0.4H), 4.97 – 4.93 (m, 1.4H), 4.42 (dt, J = 9.6, 4.8 Hz, 1.4H), 3.84 (s, 3H), 3.61 (s, 1.2H), 3.58 (s, 1.2H), 3.56 (s, 3H), 3.38 (s, 3H), 2.90 (s, 1.2H), 2.82 (dd, J = 15.5, 9.4 Hz, 0.4H), 2.58 (dd, J = 15.5, 5.9 Hz, 0.4H), 2.19 – 2.13 (m, 2H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.5, 172.4, 168.7, 143.8, 142.4, 137.6, 136.9, 133.0, 131.3, 130.6, 128.5, 128.3, 127.1, 126.8, 126.6, 126.0, 123.6, 123.5, 123.3, 122.7, 122.4, 121.9, 119.4, 119.2, 118.6, 118.4, 112.3, 111.9, 109.8, 109.6, 64.6, 63.9, 51.9, 35.5, 35.5, 33.6, 33.1, 32.8, 31.6, 29.7, 29.0, 27.9
HRMS *m/z*	$C_{22}H_{23}N_2O_3^+$ ($[M+H]^+$)	

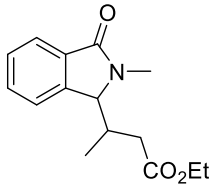
	Calculated: 363.1703	observed: 363.1705

methyl 3-(benzo[b]thiophen-3-yl)-3-(2-methyl-3-oxoisoindolin-1-yl)propanoate (9ar)



Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and methyl (E)-3-(benzo[b]thiophen-3-yl)acrylate **8r** (1.5 equiv.). 33.6 mg, 92% yield, 1 h, d.r. = 2.6:1, yellow oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	8.02 – 7.92 (m, 3H), 7.90 – 7.82 (m, 2H), 7.76 (d, J = 7.6 Hz, 0.45H), 7.65 (d, J = 1.2 Hz, 0.45H), 7.56 – 7.32 (m, 6H), 7.19 (d, J = 1.0 Hz, 1H), 6.79 (s, 0.45H), 6.60 (d, J = 7.6 Hz, 1H), 4.98 (d, J = 2.9 Hz, 0.45H), 4.86 (d, J = 3.4 Hz, 1H), 4.52 (tt, J = 6.4, 3.9 Hz, 2H), 4.48 – 4.43 (m, 0.45H), 3.57 (s, 3H), 3.55 (s, 1H), 3.40 (s, 3H), 2.88 (dd, J = 15.9, 9.7 Hz, 0.45H), 2.84 (s, 1H), 2.48 (dd, J = 15.9, 5.4 Hz, 0.45H), 2.33 – 2.19 (m, 2H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.0, 171.9, 169.0, 168.6, 143.5, 141.8, 140.9, 140.6, 137.9, 137.7, 133.8, 133.4, 133.1, 132.9, 131.7, 130.9, 128.9, 128.6, 125.0, 124.8, 124.6, 124.3, 123.8, 123.7, 123.5, 123.4, 123.4, 123.3, 122.9, 122.5, 121.2, 121.1, 64.2, 62.9, 52.0, 52.0, 37.8, 35.7, 33.9, 31.3, 29.6, 27.8
HRMS *m/z*	$C_{21}H_{20}NO_3S^+$ ($[M+H]^+$)	
	Calculated: 366.1158	observed: 366.1157

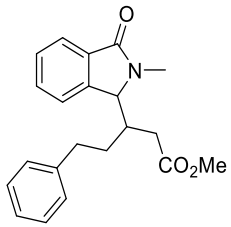
ethyl 3-(2-methyl-3-oxoisoindolin-1-yl)butanoate (9as)



Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and ethyl (E)-but-2-enoate **8s** (3.0 equiv.). 17.8 mg, 68% yield, 1 h, d.r. = 1:1, clear oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.85 (d, J = 7.3 Hz, 2H), 7.48 (td, J = 12.0, 10.4, 6.7 Hz, 6H), 4.45 (d, J = 3.1 Hz, 1H), 4.40 (d, J = 2.9 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 4.09 (q, J = 7.2 Hz, 2H), 3.14 (s, 6H), 2.90 – 2.77 (m, 2H), 2.58 (dd, J = 15.6, 6.7 Hz, 1H), 2.48 (dd, J = 15.6, 8.4 Hz, 1H), 2.00 (dd, J = 15.6,

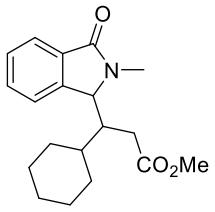
		4.7 Hz, 1H), 1.75 – 1.65 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H), 1.21 (t, J = 6.7 Hz, 6H), 0.58 (d, J = 6.8 Hz, 3H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.4, 172.1, 168.6, 168.5, 143.0, 142.5, 133.4, 133.0, 131.2, 131.0, 128.4, 128.3, 123.7, 122.8, 65.8, 64.9, 60.8, 60.6, 37.9, 35.5, 31.6, 31.3, 28.1, 27.8, 16.4, 14.2, 14.1, 13.2
HRMS *m/z*	$C_{15}H_{20}NO_3^+$ ($[M+H]^+$)	
	Calculated: 262.1438	observed: 262.1441

methyl 3-(2-methyl-3-oxoisoindolin-1-yl)-5-phenylpentanoate (9at)



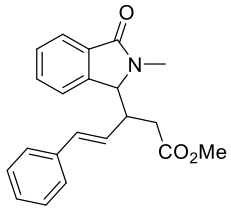
Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and methyl (E)-5-phenylpent-2-enoate **8t** (3.0 equiv.). 13.3 mg, 40% yield, 1 h, d.r.=1.2:1, yellow oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.84 (t, *J* = 7.5 Hz, 2H), 7.52 – 7.41 (m, 8H), 7.33 (t, *J* = 7.4 Hz, 3H), 7.24 – 7.16 (m, 6H), 7.07 (d, *J* = 7.5 Hz, 2H), 4.50 (d, *J* = 12.8 Hz, 2H), 3.72 (s, 3H), 3.61 (s, 4H), 3.06 (s, 3H), 2.97 (s, 3H), 2.80 (dt, *J* = 13.4, 6.8 Hz, 4H), 2.65 (d, *J* = 14.7 Hz, 2H), 2.59 (dd, *J* = 10.0, 6.4 Hz, 1H), 2.54 – 2.46 (m, 2H), 1.97 (q, *J* = 7.5 Hz, 3H), 1.84 (dd, *J* = 12.3, 6.7 Hz, 2H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.9, 172.8, 168.7, 168.6, 143.0, 142.7, 141.0, 140.9, 133.3, 133.2, 131.2, 131.2, 128.6, 128.5, 128.4, 128.3, 128.3, 126.3, 126.2, 123.8, 123.7, 122.7, 122.6, 63.9, 63.9, 51.9, 51.8, 35.9, 35.5, 35.4, 33.8, 33.8, 33.4, 33.2, 30.5, 27.9, 27.8
HRMS *m/z*	$C_{21}H_{24}NO_3^+$ ($[M+H]^+$)	
	Calculated: 338.1751	observed: 338.1748

methyl 3-cyclohexyl-3-(2-methyl-3-oxoisoindolin-1-yl)propanoate (9au)



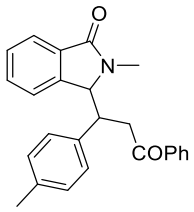
Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and methyl 3-cyclohexylacrylate **8u** (3.0 equiv.). 14.5 mg, 46% yield, 1 h, d.r.=2.6:1, yellow solid; m.p. 104-106 ˚C		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.87 – 7.82 (m, 1.5H), 7.53 – 7.42 (m, 4H), 7.38 (d, *J* = 7.3 Hz, 1H), 4.71 (d, *J* = 3.1 Hz, 1H), 4.62 (d, *J* = 2.6 Hz, 0.39H), 3.62 (s, 1.15H), 3.57 (s, 3H), 3.14 (s, 1.10H), 3.10 (s, 3H), 2.57 (ddd, *J* = 9.8, 6.7, 3.4 Hz, 1H), 2.40 (dd, *J* = 16.2, 5.8 Hz, 0.45H), 2.29 – 2.22 (m, 1H), 1.88 (d, *J* = 12.6 Hz, 1H), 1.83 – 1.53 (m, 10H), 1.41 – 0.94 (m, 9H)
^{13}C NMR	**100 MHz, $CDCl_3$**	173.6, 173.5, 168.7, 144.2, 142.7, 133.6, 132.8, 131.1, 128.4, 128.2, 123.7, 123.5, 122.9, 122.8, 62.6, 62.0, 51.8, 51.8, 42.7, 41.1, 40.0, 37.4, 32.5, 32.1, 31.9, 31.5, 31.5, 30.3, 28.6, 27.6, 26.4, 26.3, 26.2, 26.2, 26.1, 26.1
HRMS *m/z*	$C_{19}H_{26}NO_3^+$ ([M+H]$^+$)	
	Calculated: 316.1907	observed: 316.1909

methyl 3-(2-methyl-3-oxoisoindolin-1-yl)-5-phenylpent-4-enoate (9av)



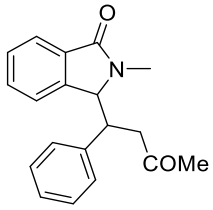
Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and methyl (2E,4E)-5-phenylpenta-2,4-dienoate **8v** (3.0 equiv.). 17.4 mg, 48% yield, 2 h, d.r. = 2.6:1, yellow oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.85 (d, *J* = 6.7 Hz, 2H), 7.58 – 7.50 (m, 3H), 7.48 (d, *J* = 3.0 Hz, 3H), 7.42 (d, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.30 (d, *J* = 7.4 Hz, 1H), 7.23 – 7.18 (m, 3H), 7.14 (d, *J* = 7.5 Hz, 2H), 6.62 (d, *J* = 16.0 Hz, 1H), 6.48 (d, *J* = 15.8 Hz, 1H), 6.33 (dd, *J* = 16.0, 7.1 Hz, 1H), 5.61 (dd, *J* = 15.8, 8.4 Hz, 1H), 4.59 (dd, *J* = 7.3, 3.3 Hz, 2H), 3.68 (s, 3H), 3.66 – 3.63 (m, 1H), 3.61 (s, 3H), 3.57 (d, *J* = 3.5 Hz, 1H), 3.20 (d, *J* = 6.6 Hz, 6H), 2.70 – 2.52 (m, 2H), 2.00 (qd, *J* = 15.6, 7.0 Hz, 2H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.3, 172.0, 168.6, 168.4, 142.4, 142.4, 136.5, 133.4, 133.1, 131.3, 131.2, 128.7, 128.6, 128.6, 128.5, 128.0, 127.7, 127.7, 126.3, 126.3, 126.0, 123.8, 123.8, 122.9, 122.6, 65.1, 64.9, 52.0, 51.9, 41.1, 39.8, 35.3, 32.3, 28.6, 27.8
HRMS *m/z*	$C_{21}H_{22}NO_3^+$ ([M+H]$^+$)	
	Calculated: 336.1594	observed: 336.1595

2-methyl-3-(3-oxo-3-phenyl-1-(p-tolyl)propyl)isoindolin-1-one (9aw)



Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and (E)-1-phenyl-3-(p-tolyl)prop-2-en-1-one **8w** (1.5 equiv.). 26.2 mg, 71% yield, 1 h, d.r. = 1.3:1, yellow solid, m.p. 105-110 ˚C		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.93 (d, J = 7.3 Hz, 2H), 7.83 (d, J = 7.5 Hz, 0.8H), 7.75 – 7.70 (m, 3H), 7.62 – 7.32 (m, 11H), 7.20 – 7.11 (m, 3H), 6.92 (d, J = 7.9 Hz, 2H), 6.81 (d, J = 8.1 Hz, 2H), 6.66 (d, J = 7.6 Hz, 0.8H), 4.84 (d, J = 3.4 Hz, 1H), 4.74 (d, J = 3.8 Hz, 0.8H), 4.40 (dt, J = 9.9, 4.0 Hz, 0.8H), 4.26 (ddd, J = 7.9, 6.3, 3.4 Hz, 1H), 3.63 (dd, J = 17.6, 8.0 Hz, 1H), 3.27 (m, 0.8H), 3.24 (s, 2.4H), 3.06 (m, 0.8H), 3.04 (s, 3H), 2.69 (dd, J = 17.7, 4.1 Hz, 1H), 2.35 (s, 2.4H), 2.21 (s, 3H)
^{13}C NMR	**100 MHz, $CDCl_3$**	197.7, 168.7, 143.5, 142.6, 137.0, 136.8, 136.7, 136.6, 135.6, 135.3, 133.4, 133.3, 133.2, 132.9, 131.1, 130.9, 129.5, 129.0, 128.7, 128.6, 128.4, 128.4, 128.0, 128.0, 127.9, 127.7, 123.7, 123.6, 123.5, 122.6, 66.5, 66.0, 41.5, 39.7, 38.3, 34.0, 29.0, 28.0, 21.0, 20.9
HRMS *m/z*	$C_{25}H_{24}NO_2^+$ ($[M+H]^+$)	
	Calculated: 370.1802	observed: 370.1809

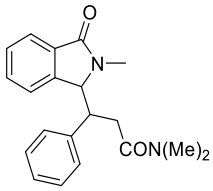
2-methyl-3-(3-oxo-1-phenylbutyl)isoindolin-1-one (9ax)



Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and methyl (E)-4-phenylbut-3-en-2-one **8x** (3.0 equiv.). 19.9 mg, 68% yield, 1 h, d.r.=1:1, yellow solid; m.p. 93-97 ˚C		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.83 (d, *J* = 7.5 Hz, 1H), 7.72 (d, *J* = 7.5 Hz, 0.5H), 7.56 (d, *J* = 3.3 Hz, 1H), 7.43 – 7.38 (m, 3H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.23 (d, *J* = 7.5 Hz, 2H), 7.14 – 7.12 (m, 1H), 6.91 – 6.86 (m, 1H), 6.55 (d, *J* = 7.6 Hz, 1H), 4.72 (d, *J* = 3.3 Hz, 0.3H), 4.66 (d, *J* = 3.8 Hz, 1H), 4.22 (dt, *J* = 8.8, 4.0 Hz, 1H), 4.12 – 4.02 (m, 0.3H), 3.22 (s, 3H), δ 3.11 (dd, *J* = 17.5, 8.6 Hz, 0.3H), 3.01 (s, 1H), 2.75 (dd,

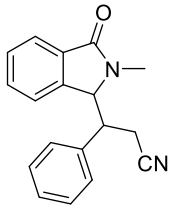
		J = 17.4, 5.7 Hz, 0.3H), 2.48 (dd, *J* = 17.6, 9.8 Hz, 1H), 2.17 (dd, *J* = 17.7, 4.3 Hz, 1H), 2.11 (s, 1H), 2.04 (s, 3H)
^{13}C NMR	**100 MHz, $CDCl_3$**	206.0, 168.6, 168.6, 143.3, 142.3, 138.6, 138.1, 133.1, 132.9, 131.1, 130.8, 128.8, 128.5, 128.3, 128.2, 127.8, 127.7, 127.5, 127.3, 123.7, 123.5, 123.4, 122.5, 66.4, 66.1, 43.3, 41.9, 40.0, 39.1, 30.6, 30.6, 29.0, 27.9
HRMS *m/z*	$C_{19}H_{20}NO_2^+$ ([M+H]$^+$)	
	Calculated: 294.1489	observed: 294.1490

N,N-dimethyl-3-(2-methyl-3-oxoisoindolin-1-yl)-3-phenylpropanamide (9ay)



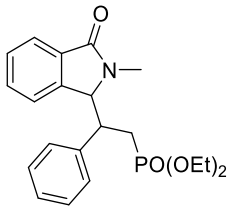
Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and N,N-dimethylcinnamamide **8y** (1.5 equiv.). 21.1 mg, 74% yield, 1 h, d.r. = 1.5:1, colorless oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.79 (d, *J* = 7.6 Hz, 0.6H), 7.69 (d, *J* = 7.5 Hz, 1H), 7.59 – 7.50 (m, 2H), 7.44 – 7.26 (m, 4.6H), 7.22 (d, *J* = 7.3 Hz, 1.2H), 7.11 – 7.06 (m, 3H), 6.84 – 6.80 (m, 2H), 6.62 (d, *J* = 7.6 Hz, 0.6H), 4.88 (d, *J* = 3.6 Hz, 1H), 4.72 (d, *J* = 3.8 Hz, 0.6H), 4.34 (dt, *J* = 8.8, 4.5 Hz, 0.6H), 4.15 (td, *J* = 7.2, 3.6 Hz, 1H), 3.25 (s, 2H), 3.05 (s, 3H), 2.99 (s, 3H), 2.91 (s, 3.5H), 2.87 (d, *J* = 8.7 Hz, 2.5H), 2.78 (d, *J* = 7.4 Hz, 1H), 2.76 (s, 2H), 2.33 (dd, *J* = 16.2, 8.7 Hz, 1H), 2.12 (dd, *J* = 16.3, 5.1 Hz, 1H)
^{13}C NMR	**100 MHz, $CDCl_3$**	170.4, 170.2, 168.6, 168.5, 143.5, 142.7, 139.4, 138.6, 133.3, 132.9, 130.9, 130.8, 128.7, 128.7, 128.3, 128.3, 128.2, 128.2, 128.1, 128.1, 127.8, 127.8, 127.2, 127.1, 123.6, 123.5, 123.4, 122.7, 66.6, 65.6, 42.8, 41.2, 37.2, 37.0, 35.6, 35.6, 33.6, 28.8, 28.7, 28.2
HRMS *m/z*	$C_{20}H_{23}N_2O_2^+$ ([M+H]$^+$)	
	Calculated: 323.1754	observed: 323.1752

3-(2-methyl-3-oxoisoindolin-1-yl)-3-phenylpropanenitrile (9az)



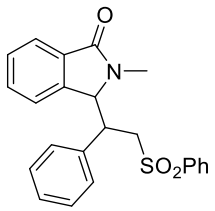
Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and cinnamonitrile **8z** (3.0 equiv.). 20.7 mg, 75% yield, 1 h, d.r. = 1:1, yellow solid, m.p. 78-84 °C		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.82 (d, J = 7.5 Hz, 1H), 7.76 (d, J = 7.5 Hz, 1H), 7.60 (t, J = 7.4 Hz, 1H), 7.56 – 7.38 (m, 6H), 7.33 (dd, J = 23.8, 7.5 Hz, 3H), 7.25 – 7.19 (m, 3H), 6.94 (dd, J = 6.3, 2.7 Hz, 2H), 6.57 (d, J = 7.6 Hz, 1H), 4.86 (d, J = 3.7 Hz, 1H), 4.75 (d, J = 3.9 Hz, 1H), 3.92 (dt, J = 9.8, 4.6 Hz, 1H), 3.79 (ddd, J = 8.7, 7.2, 3.7 Hz, 1H), 3.28 (s, 3H), 2.97 (s, 3H), 2.87 (dd, J = 17.1, 8.9 Hz, 1H), 2.69 (dd, J = 17.1, 7.2 Hz, 1H), 2.37 – 2.20 (m, 2H)
^{13}C NMR	**100 MHz, $CDCl_3$**	168.6, 168.3, 142.2, 140.6, 135.8, 132.9, 132.7, 131.6, 131.2, 129.2, 129.1, 129.1, 128.8, 128.4, 128.3, 128.0, 127.5, 124.1, 123.9, 123.4, 122.3, 117.9, 117.9, 110.0, 65.9, 65.3, 44.2, 42.0, 29.3, 28.1, 18.5, 14.7
HRMS *m/z*	$C_{18}H_{17}N_2O^+$ ([M+H]$^+$)	
	Calculated: 277.1335	observed: 277.1337

diethyl 2-(2-methyl-3-oxoisoindolin-1-yl)-2-phenylethyl)phosphonate (9aaa)



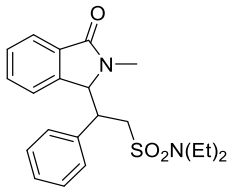
Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and diethyl (E)-styrylphosphonate **8aa** (1.5 equiv.). 24.0 mg, 62% yield, 1 h, d.r. = 1.5:1, clear oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.77 (d, J = 7.4 Hz, 1H), 7.65 (dd, J = 11.2, 7.6 Hz, 2H), 7.54 (t, J = 7.5 Hz, 1H), 7.45 – 7.34 (m, 4H), 7.29 (d, J = 10.5 Hz, 3H), 7.09 – 6.98 (m, 4H), 6.72 (t, J = 6.0 Hz, 3H), 4.80 (d, J = 3.9 Hz, 1H), 4.63 (t, J = 3.4 Hz, 0.8H), 4.04 – 3.66 (m, 10H), 3.28 (s, 2.3H), 3.11 (s, 3H), 2.45 – 2.36 (m, 2H), 1.78 (td, J = 16.3, 11.5 Hz, 0.8H), 1.58 (ddd, J = 21.2, 15.7, 2.7 Hz, 3H), 1.23 (t, J = 7.0 Hz, 5.5H), 1.13 (t, J = 7.1 Hz, 2.4H), 1.05 (t, J = 7.1 Hz, 3H)
^{13}C NMR	**100 MHz, $CDCl_3$**	168.6, 168.2, 142.7, 141.7, 137.6, 137.5, 137.0, 136.9, 133.4, 133.0, 130.9, 130.8, 129.5, 128.8, 128.5, 128.5, 128.0, 127.9, 127.6, 127.5, 123.7, 123.5, 123.5, 122.9, 67.2, 67.0, 66.0, 65.9, 61.9, 61.8, 61.7, 61.7, 61.6, 61.5, 61.5, 41.4, 41.4, 40.2, 40.2, 28.9, 28.4, 28.0, 27.5, 22.8, 21.4, 16.3, 16.3, 16.3, 16.2, 16.2, 16.2, 16.1, 16.1
HRMS *m/z*	$C_{21}H_{27}NO_4P^+$ ([M+H]$^+$)	
	Calculated: 388.1672	observed: 388.1671

2-methyl-3-(1-phenyl-2-(phenylsulfonyl)ethyl)isoindolin-1-one (9aab)



Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and (E)-(2-(phenylsulfonyl)vinyl)benzene **8ab** (1.5 equiv.). 29.4 mg, 75% yield, 1 h, d.r. = 1.2:1, clear oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.80 – 7.74 (m, 3H), 7.71 – 7.60 (m, 4H), 7.54 (dq, J = 13.3, 7.2 Hz, 3H), 7.46 – 7.31 (m, 7H), 7.25 (s, 2H), 7.14 – 7.10 (m, 2H), 7.02 (t, J = 7.3 Hz, 0.8H), 6.94 (t, J = 7.5 Hz, 2H), 6.72 (d, J = 7.6 Hz, 0.8H), 6.57 (d, J = 7.6 Hz, 2H), 4.99 (d, J = 3.7 Hz, 1H), 4.66 (d, J = 3.6 Hz, 0.8H), 4.17 (dt, J = 10.9, 2.9 Hz, 0.8H), 4.09 (td, J = 7.0, 3.8 Hz, 1H), 3.73 – 3.67 (m, 2H), 3.25 (dd, J = 14.9, 10.6 Hz, 0.8H), 3.20 (s, 2.4H), 3.09 (s, 3H), 2.84 (dd, J = 14.8, 2.3 Hz, 0.8H)
^{13}C NMR	**100 MHz, $CDCl_3$**	168.4, 168.2, 142.1, 141.2, 139.3, 139.2, 135.3, 134.8, 133.8, 133.7, 133.3, 132.7, 131.2, 131.1, 129.3, 129.1, 128.8, 128.8, 128.7, 128.5, 128.2, 128.0, 127.9, 127.9, 127.8, 127.8, 123.8, 123.8, 123.4, 122.7, 66.3, 65.0, 57.2, 52.5, 41.8, 40.6, 28.6, 27.9
HRMS *m/z*	$C_{23}H_{22}NO_3S^+$ ($[M+H]^+$)	
	Calculated: 392.1315	observed: 392.1317

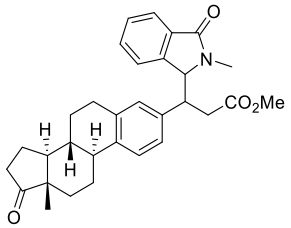
N,N-diethyl-2-(2-methyl-3-oxoisoindolin-1-yl)-2-phenylethane-1-sulfonamide (9aac)



Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and (E)-N,N-diethyl-3-phenylprop-2-ene-1-sulfonamide **8ac** (1.5 equiv.). 27.4 mg, 71% yield, 1 h, d.r. = 1.1:1, yellow oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.81 – 7.74 (m, 0.7H), 7.71 (d, J = 7.6 Hz, 1H), 7.66 (d, J = 7.5 Hz, 1H), 7.58 (t, J = 7.5 Hz, 1H), 7.49 – 7.30 (m, 5H), 7.27 – 7.24 (m, 1H), 7.16 – 7.01 (m, 3H), 6.83 (d, J = 7.3 Hz, 0.7H), 6.68 (dd, J = 7.5, 1.7 Hz, 2H), 5.06 (d, J = 3.8 Hz, 1H), 4.76 (d, J = 3.6 Hz, 0.7H), 4.17 (dt, J = 9.9, 3.4 Hz, 0.7H), 4.06 (td, J = 7.1, 3.9 Hz, 1H), 3.57 (dd, J = 14.2, 7.9 Hz, 1H), 3.46 (dd, J = 14.2, 6.3 Hz, 1H),

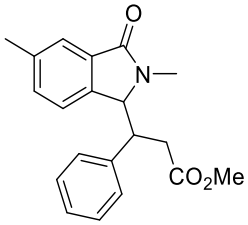
		3.35 (s, 2H), 3.23 (dt, J = 14.4, 7.2 Hz, 2H), 3.16 – 3.12 (m, 4.7H), 3.11 – 3.04 (m, 2.4H), 3.03 – 2.94 (m, 1.7H), 2.74 (dd, J = 14.5, 3.1 Hz, 0.7H), 1.16 (t, J = 7.1 Hz, 6H), 1.07 (t, J = 7.1 Hz, 4.2H)
^{13}C NMR	**100 MHz, $CDCl_3$**	168.5, 168.2, 142.4, 141.7, 136.3, 135.7, 133.4, 132.7, 131.0, 128.7, 128.7, 128.6, 128.5, 128.2, 128.0, 127.9, 127.9, 123.8, 123.7, 123.4, 123.0, 66.1, 64.5, 53.2, 48.4, 42.4, 42.2, 41.8, 41.6, 28.4, 28.4, 14.7, 14.6
HRMS *m/z*	$C_{21}H_{27}N_2O_3S^+$ ([M+H]$^+$)	
	Calculated: 387.1737	observed: 387.1737

Methyl 3-((8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl)-3-(2-methyl-3-oxoisoindolin-1-yl)propanoate (9aad)



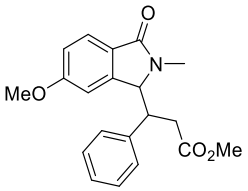
Prepared in accordance with the G***eneral Procedure (C)*** using 2-methylisoindolin-1-one **7a** (0.1 mmol) and methyl (E)-3-((8R,9S,13S,14S)-13-methyl 17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl)acrylate **8d** (1.5 equiv.). 32.5 mg, 67% yield, 1 h, d.r. = 1:1, colorless oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.82 (d, *J* = 7.5 Hz, 1H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.49 – 7.39 (m, 2H), 7.37 – 7.29 (m, 2H), 7.01 (t, *J* = 10.0 Hz, 3H), 6.71 – 6.52 (m, 3H), 4.71 (d, *J* = 3.6 Hz, 1H), 4.65 (d, *J* = 3.6 Hz, 1H), 4.10 – 4.03 (m, 1H), 3.94 (td, *J* = 7.7, 3.6 Hz, 1H), 3.66 (s, 3H), 3.58 (s, 3H), 3.26 (s, 3H), 3.03 (s, 3H), 2.96 – 2.84 (m, 3H), 2.81 – 2.60 (m, 3H), 2.53 – 2.44 (m, 2H), 2.36 – 1.89 (m, 15H), 1.71 – 1.39 (m, 15H), 0.95 (s, 3H), 0.89 (s, 3H)
^{13}C NMR	**100 MHz, $CDCl_3$**	220.7, 172.4, 172.2, 168.5, 168.5, 143.1, 142.0, 139.0, 138.8, 136.9, 136.2, 135.6, 134.9, 134.9, 133.3, 132.9, 131.0, 130.7, 129.0, 128.9, 128.5, 128.4, 125.7, 125.2, 125.1, 125.0, 123.6, 123.4, 122.8, 66.5, 65.6, 52.0, 51.9, 50.5, 50.5, 48.0, 47.9, 44.3, 44.1, 42.7, 40.7, 40.6, 38.1, 37.8, 35.8, 35.3, 31.5, 30.6, 29.5, 29.2, 28.7, 27.9, 26.5, 26.4, 25.7, 25.6, 25.5, 25.4, 21.6, 13.9, 13.8
HRMS *m/z*	$C_{31}H_{36}NO_4^+$ ([M+H]$^+$)	
	Calculated: 486.2639	observed: 486.2640

methyl 3-(2,5-dimethyl-3-oxoisoindolin-1-yl)-3-phenylpropanoate (9ba)



Prepared in accordance with the G***eneral Procedure (C)*** using 2,6-dimethylisoindolin-1-one **7b** (0.1 mmol) and methyl cinnamate **8a** (1.5 equiv.). 25.5 mg, 79% yield, 1 h, d.r. = 1:1, yellow oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.61 (s, 1H), 7.54 – 7.46 (m, 2H), 7.38 (dt, J = 21.8, 7.2 Hz, 4H), 7.28 (s, 2H), 7.12 (q, J = 6.0, 4.6 Hz, 4H), 6.91 – 6.85 (m, 2H), 6.43 (d, J = 7.8 Hz, 1H), 4.67 (d, J = 3.5 Hz, 1H), 4.63 (d, J = 3.7 Hz, 1H), 4.11 (dt, J = 9.5, 4.6 Hz, 1H), 3.98 (ddd, J = 9.8, 6.6, 3.5 Hz, 1H), 3.63 (s, 3H), 3.57 (s, 3H), 3.24 (s, 3H), 3.00 (s, 3H), 2.92 (dd, J = 16.1, 8.9 Hz, 1H), 2.76 (dd, J = 16.1, 6.7 Hz, 1H), 2.42 (s, 3H), 2.39 (s, 3H), 2.30 (dd, J = 16.1, 9.8 Hz, 1H), 2.17 (dd, J = 16.1, 5.3 Hz, 1H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.3, 172.1, 168.7, 168.7, 140.2, 139.1, 138.6, 138.6, 138.4, 137.7, 133.3, 133.0, 132.1, 131.8, 128.8, 128.3, 128.1, 127.8, 127.5, 127.3, 123.9, 123.8, 123.0, 122.4, 66.3, 65.6, 51.9, 51.9, 43.2, 41.3, 34.9, 30.6, 28.8, 27.9, 21.3, 21.3
HRMS *m/z*	$C_{20}H_{22}NO_3^+$ ($[M+H]^+$)	
	Calculated: 324.1594	observed: 324.1596

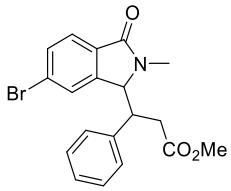
methyl 3-(6-methoxy-2-methyl-3-oxoisoindolin-1-yl)-3-phenylpropanoate (9ca)



Prepared in accordance with the G***eneral Procedure (C)*** using 5-methoxy-2-methylisoindolin-1-one **7c** (0.1 mmol) and methyl cinnamate **8a** (1.5 equiv.). 30.2 mg, 89% yield, 1 h, d.r. = 1.3:1, yellow oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.70 (d, J = 8.3 Hz, 1H), 7.63 (d, J = 8.4 Hz, 0.7H), 7.42 (t, J = 7.3 Hz, 2H), 7.33 (dd, J = 16.8, 7.3 Hz, 3H), 7.16 (dd, J = 5.1, 1.9 Hz, 2H), 7.07 (d, J = 2.1 Hz, 0.7H), 6.96 (dt, J = 6.0, 2.1 Hz, 2H), 6.92 (dd, J = 8.4, 2.3 Hz, 1H), 5.96 (d, J = 2.2 Hz, 1H), 4.65 (d, J = 3.6 Hz, 0.7H), 4.61 (d, J = 3.9 Hz, 1H), 4.13 (dt, J = 9.6, 4.7 Hz, 1H), 3.96 (ddd, J = 9.5, 6.5, 3.6 Hz, 0.7H), 3.90 (s, 2.2H), 3.64 (s, 3H), 3.62 (s, 2.2H), 3.58 (s, 3H), 3.23 (s, 3H), 2.95 (s, 2.2H), 2.94 – 2.87 (m, 0.7H), 2.70 (dd, J = 16.1, 6.5 Hz, 0.7H), 2.31 (dd, J = 16.1, 9.9 Hz, 1H), 2.20 (dd, J = 16.1, 5.2 Hz, 1H)

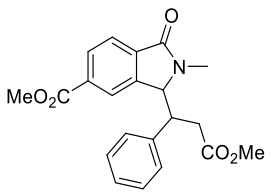
^{13}C NMR	**100 MHz, $CDCl_3$**	172.3, 172.1, 168.5, 168.5, 162.4, 161.9, 145.2, 144.1, 138.3, 137.9, 128.8, 128.3, 128.2, 127.7, 127.6, 127.4, 125.8, 125.4, 124.9, 124.7, 115.2, 114.3, 108.3, 108.1, 66.1, 65.7, 55.7, 55.3, 51.9, 51.9, 43.3, 41.2, 34.5, 30.4, 29.0, 27.9
HRMS *m/z*	$C_{20}H_{22}NO_4^+$ ($[M+H]^+$)	
	Calculated: 340.1543	observed: 340.1547

methyl 3-(6-bromo-2-methyl-3-oxoisoindolin-1-yl)-3-phenylpropanoate (9da)



Prepared in accordance with the G***eneral Procedure (C)*** using 5-bromo-2-methylisoindolin-1-one **7d** (0.1 mmol) and methyl cinnamate **8a** (1.5 equiv.), 31.0 mg, 79% yield, 20 min, d.r. = 1.1:1, yellow oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.93 (s, 1H), 7.82 (s, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.42 (ddd, *J* = 26.8, 19.8, 7.5 Hz, 6H), 7.24 (s, 1H), 7.16 – 7.12 (m, 3H), 6.85 (dd, *J* = 6.5, 2.9 Hz, 2H), 6.39 (d, *J* = 8.1 Hz, 1H), 4.68 (d, *J* = 3.6 Hz, 1H), 4.64 (d, *J* = 3.8 Hz, 1H), 4.13 (dt, *J* = 9.5, 4.7 Hz, 1H), 3.98 (td, *J* = 7.8, 3.5 Hz, 1H), 3.65 (s, 3H), 3.58 (s, 3H), 3.25 (s, 3H), 3.04 (s, 3H), 2.92 (dd, *J* = 16.1, 8.4 Hz, 1H), 2.78 (dd, *J* = 16.1, 7.2 Hz, 1H), 2.30 (dd, *J* = 16.0, 9.7 Hz, 1H), 2.17 (dd, *J* = 16.0, 5.5 Hz, 1H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.0, 171.9, 167.1, 167.0, 141.6, 140.5, 137.9, 137.1, 135.2, 134.9, 134.0, 133.8, 129.0, 128.4, 128.0, 127.8, 127.7, 127.6, 126.9, 126.7, 124.9, 124.3, 122.8, 122.7, 66.3, 65.4, 52.1, 52.0, 42.9, 41.1, 35.1, 30.6, 28.9, 28.1
HRMS *m/z*	$C_{19}H_{19}BrNO_3^+$ ($[M+H]^+$)	
	Calculated: 388.0543	observed: 388.0546

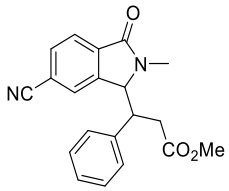
methyl 3-(3-methoxy-3-oxo-1-phenylpropyl)-2-methyl-1-oxoisoindoline-5-carboxylate (9ea)



Prepared in accordance with the G***eneral Procedure (C)*** using methyl 2-methyl-1-oxoisoindoline-5-carboxylate **7e** (0.1 mmol) and methyl cinnamate **8a** (1.5 equiv.). 26.5 mg, 72% yield, 1 h, d.r. = 1.8:1, yellow oil

^{1}H NMR	**400 MHz, $CDCl_3$**	8.46 (s, 1H), 8.34 (s, 0.5H), 8.26 (d, *J* = 7.9 Hz, 0.5H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 0.5H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.36 (d, *J* = 7.0 Hz, 1H), 7.27 (s, 2H), 7.11 (d, *J* = 4.8 Hz, 1.5H), 6.83 (d, *J* = 4.4 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 4.78 (d, *J* = 3.6 Hz, 0.5H), 4.74 (d, *J* = 3.8 Hz, 1H), 4.17 (dt, *J* = 9.6, 4.7 Hz, 1H), 4.02 (td, *J* = 7.8, 3.6 Hz, 0.5H), 3.94 (s, 1.5H), 3.93 (s, 3H), 3.66 (s, 1.5H), 3.58 (s, 3H), 3.28 (s, 3H), 3.08 (s, 1.5H), 2.97 (dd, *J* = 16.1, 8.3 Hz, 0.5H), 2.85 (dd, *J* = 16.1, 7.3 Hz, 0.5H), 2.30 (dd, *J* = 16.0, 9.5 Hz, 1H), 2.19 (dd, *J* = 16.0, 5.6 Hz, 1H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.0, 171.8, 167.6, 167.4, 166.2, 147.4, 146.4, 137.8, 136.9, 133.6, 133.4, 132.3, 132.1, 130.9, 130.9, 129.0, 128.4, 128.0, 127.8, 127.6, 127.6, 125.0, 124.8, 123.5, 122.9, 66.6, 65.7, 52.4, 52.1, 52.0, 42.8, 41.3, 35.2, 30.8, 28.8, 28.1
HRMS *m/z*	$C_{21}H_{22}NO_5^+$ ($[M+H]^+$)	
	Calculated: 368.1492	observed: 368.1497

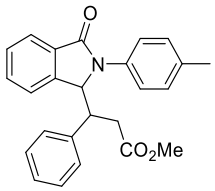
methyl 3-(6-cyano-2-methyl-3-oxoisoindolin-1-yl)-3-phenylpropanoate (9fa)



Prepared in accordance with the G***eneral Procedure (C)*** using 2-methyl-1-oxoisoindoline-5-carbonitrile **7f** (0.1 mmol) and methyl cinnamate **8a** (1.5 equiv.). 25.4 mg, 76% yield, 1 h, d.r. = 1.7:1, white solid, m.p. 129-134 ˚C		
^{1}H NMR	**400 MHz, $CDCl_3$**	8.06 (s, 1H), 7.93 (s, 1H), 7.83 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.60 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.43 (t, *J* = 7.3 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.24 (d, *J* = 7.1 Hz, 2H), 7.13 (d, *J* = 7.2 Hz, 3H), 6.80 (dd, *J* = 7.4, 2.0 Hz, 2H), 6.66 (d, *J* = 7.9 Hz, 1H), 4.82 – 4.79 (m, 1H), 4.78 (d, *J* = 3.9 Hz, 1H), 4.18 (dt, *J* = 9.6, 4.9 Hz, 1H), 4.02 (td, *J* = 7.8, 3.6 Hz, 1H), 3.69 – 3.66 (m, 3H), 3.60 (d, *J* = 1.2 Hz, 3H), 3.28 (d, *J* = 1.2 Hz, 3H), 3.11 – 3.08 (m, 3H), 2.97 (dd, *J* = 16.1, 8.0 Hz, 1H), 2.85 (dd, *J* = 16.1, 7.7 Hz, 1H), 2.31 (dd, *J* = 16.0, 9.4 Hz, 1H), 2.19 (dd, *J* = 15.9, 5.7 Hz, 1H)
^{13}C NMR	**100 MHz, $CDCl_3$**	171.7, 171.6, 166.4, 166.2, 147.2, 146.3, 137.4, 136.4, 134.4, 134.3, 134.2, 134.0, 129.1, 129.1, 128.5, 128.5, 128.0, 127.9, 127.8, 127.6, 127.5, 127.4, 124.4, 123.9, 117.9, 117.9, 112.9, 112.8, 66.6, 65.7, 52.2, 52.1, 42.7, 41.2, 35.2, 30.9, 28.8, 28.2
HRMS *m/z*	$C_{20}H_{19}N_2O_3^+$ ($[M+H]^+$)	

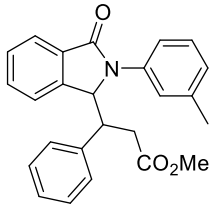
	Calculated: 335.1390	observed: 335.1392

methyl 3-(3-oxo-2-(p-tolyl)isoindolin-1-yl)-3-phenylpropanoate (9ga)



Prepared in accordance with the G***eneral Procedure (C)*** using 2-(p-tolyl)isoindolin-1-one **7g** (0.1 mmol) and methyl cinnamate **8a** (1.5 equiv.). 37.7 mg, 98% yield, 1 h, dr=1.3:1, yellow oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.88 (d, *J* = 7.4 Hz, 1H), 7.71 (dd, *J* = 15.9, 7.6 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.55 – 7.27 (m, 12H), 7.25 (s, 1H), 7.20 (d, *J* = 7.3 Hz, 2H), 7.04 (t, *J* = 7.3 Hz, 1H), 6.94 (t, *J* = 7.6 Hz, 2H), 6.76 (d, *J* = 7.4 Hz, 1H), 6.43 (d, *J* = 7.6 Hz, 2H), 5.56 (d, *J* = 3.8 Hz, 1H), 5.46 (d, *J* = 3.3 Hz, 1H), 3.99 – 3.87 (m, 2H), 3.71 (s, 3H), 3.48 (s, 2H), 3.11 (dd, *J* = 16.2, 8.9 Hz, 1H), 2.90 (dd, *J* = 16.2, 7.3 Hz, 1H), 2.42 (s, 2H), 2.40 (s, 3H), 2.31 (dd, *J* = 16.4, 5.1 Hz, 1H), 2.24 (dd, *J* = 16.4, 10.5 Hz, 1H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.1, 172.0, 167.1, 166.5, 142.0, 141.7, 138.3, 136.3, 136.0, 135.0, 134.4, 134.0, 133.5, 132.7, 131.4, 131.4, 130.1, 129.6, 128.7, 128.7, 128.2, 128.0, 127.7, 127.5, 127.3, 124.3, 124.2, 124.0, 123.4, 123.3, 123.1, 65.4, 62.9, 52.0, 51.7, 42.6, 41.6, 36.1, 30.8, 21.1, 21.0
HRMS *m/z*	$C_{25}H_{24}NO_3^+$ ([M+H]$^+$)	
	Calculated: 386.1756	observed: 386.1752

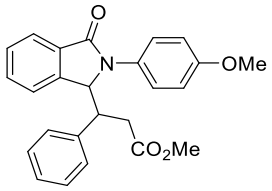
methyl 3-(3-oxo-2-(m-tolyl)isoindolin-1-yl)-3-phenylpropanoate (9ha)



Prepared in accordance with the G***eneral Procedure (C)*** using 2-(m-tolyl)isoindolin-1-one **7h** (0.1 mmol) and methyl cinnamate **8a** (1.5 equiv.). 34.7 mg, 90% yield, 1 h, d.r. = 1.3:1, clear oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.88 (d, J = 7.4 Hz, 0.7H), 7.74 (d, J = 7.5 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.62 (t, J = 7.4 Hz, 1H), 7.53 – 7.27 (m, 11H), 7.19 (d, J = 7.4 Hz, 1.8H), 7.13 (d, J = 5.4 Hz, 0.7H), 7.03 (t, J = 7.0 Hz, 2H), 6.94 (t, J = 7.5 Hz, 2H), 6.76 (d, J = 7.4 Hz, 0.7H), 6.45 (d, J = 7.5 Hz, 2H), 5.58 (d, J = 3.8 Hz, 1H), 5.49 (d, J = 3.4 Hz, 0.7H), 3.95 (dtd,

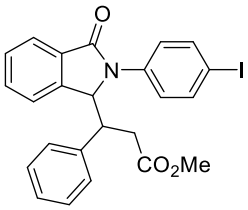
		J = 20.2, 8.4, 4.0 Hz, 1.8H), 3.69 (s, 3H), 3.48 (s, 2.3H), 3.06 (dd, J = 16.1, 8.7 Hz, 1H), 2.89 (dd, J = 16.2, 7.5 Hz, 1H), 2.46 (s, 2.3H), 2.39 (s, 3H), 2.36 – 2.19 (m, 1.8H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.0, 172.0, 167.1, 166.6, 142.0, 141.8, 139.3, 138.8, 138.2, 136.9, 136.6, 136.5, 133.4, 132.7, 131.5, 131.5, 129.2, 128.8, 128.8, 128.7, 128.7, 128.1, 128.0, 127.7, 127.5, 127.3, 127.1, 126.1, 124.8, 124.3, 124.2, 124.1, 123.4, 123.0, 121.0, 120.4, 65.3, 63.1, 52.0, 51.7, 42.8, 41.7, 35.9, 30.9, 21.7, 21.6
HRMS *m/z*	$C_{25}H_{24}NO_3^+$ ($[M+H]^+$)	
	Calculated: 386.1751	observed: 386.1754

methyl 3-(2-(4-methoxyphenyl)-3-oxoisoindolin-1-yl)-3-phenylpropanoate (9ja)



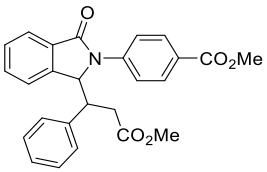
Prepared in accordance with the G***eneral Procedure (C)*** using 2-(4-methoxyphenyl)isoindolin-1-one **7j** (0.1 mmol) and methyl cinnamate **8a** (1.5 equiv.). 35.7 mg, 89% yield, 1 h, d.r. = 1.3:1, clear oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.87 (d, J = 7.4 Hz, 0.7H), 7.74 (d, J = 7.5 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.61 (t, J = 7.4 Hz, 1H), 7.55 – 7.26 (m, 9H), 7.19 (d, J = 7.4 Hz, 2H), 7.04 (dd, J = 11.7, 8.2 Hz, 3H), 7.00 – 6.90 (m, 4H), 6.77 (d, J = 7.5 Hz, 1H), 6.45 (d, J = 7.5 Hz, 2H), 5.52 (d, J = 3.9 Hz, 1H), 5.41 (d, J = 3.3 Hz, 1H), 3.98 – 3.88 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.69 (s, 3H), 3.48 (s, 2H), 3.07 (dd, J = 16.2, 8.7 Hz, 1H), 2.89 (dd, J = 16.3, 7.4 Hz, 1H), 2.35 – 2.20 (m, 2H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.0, 172.0, 167.1, 166.6, 142.0, 141.8, 139.3, 138.8, 138.2, 136.9, 136.6, 136.5, 133.4, 132.7, 131.5, 131.5, 129.2, 128.8, 128.8, 128.7, 128.7, 128.1, 128.0, 127.7, 127.5, 127.3, 127.1, 126.1, 124.8, 124.3, 124.2, 124.1, 123.4, 123.0, 121.0, 120.4, 65.3, 63.1, 52.0, 51.7, 42.8, 41.7, 35.9, 30.9, 21.7, 21.6
HRMS *m/z*	$C_{25}H_{24}NO_4^+$ ($[M+H]^+$)	
	Calculated: 402.1700	observed: 402.1703

methyl 3-(2-(4-iodophenyl)-3-oxoisoindolin-1-yl)-3-phenylpropanoate (9ka)



Prepared in accordance with the G***eneral Procedure (C)*** using 2-(4-iodophenyl)isoindolin-1-one **7k** (0.1 mmol) and methyl cinnamate **8a** (1.5 equiv.). 34.8 mg, 70% yield, 1 h, d.r. = 1.4:1, clear oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.88 – 7.80 (m, 2.5H), 7.80 – 7.61 (m, 6H), 7.53 – 7.28 (m, 10H), 7.18 (d, J = 7.5 Hz, 1.8H), 7.05 (t, J = 7.4 Hz, 1H), 6.94 (t, J = 7.5 Hz, 2H), 6.76 (d, J = 7.4 Hz, 0.8H), 6.39 (d, J = 7.6 Hz, 2H), 5.58 (d, J = 3.8 Hz, 1H), 5.48 (d, J = 3.3 Hz, 0.8H), 4.01 – 3.88 (m, 2H), 3.73 (s, 3H), 3.48 (s, 2.4H), 3.11 (dd, J = 16.5, 9.4 Hz, 1H), 2.88 (dd, J = 16.4, 6.8 Hz, 1H), 2.25 (d, J = 7.8 Hz, 1.7H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.0, 171.8, 167.0, 166.5, 141.7, 141.5, 138.5, 138.0, 137.9, 136.9, 136.6, 136.0, 133.1, 132.3, 131.8, 131.8, 128.9, 128.9, 128.8, 128.0, 128.0, 127.8, 127.7, 127.5, 125.4, 124.8, 124.4, 124.3, 123.5, 123.1, 90.3, 89.2, 64.8, 62.4, 52.1, 51.8, 42.4, 41.7, 35.7, 31.1
HRMS *m/z*	$C_{24}H_{21}INO_3^+$ ($[M+H]^+$)	
	Calculated: 498.0561	observed: 498.0560

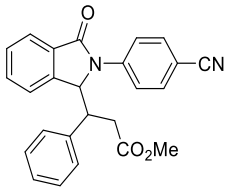
methyl 4-(1-(3-methoxy-3-oxo-1-phenylpropyl)-3-oxoisoindolin-2-yl)benzoate (9la)



Prepared in accordance with the G***eneral Procedure (C)*** using methyl 4-(1-oxoisoindolin-2-yl)benzoate **7l** (0.1 mmol) and methyl cinnamate **8a** (1.5 equiv.). 35.9 mg, 87% yield, 1 h, d.r. = 2:1, yellow oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	8.22 (d, *J* = 8.3 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 2H), 7.86 (dd, *J* = 21.8, 7.9 Hz, 1.5H), 7.79 – 7.68 (m, 4H), 7.67 (d, *J* = 7.3 Hz, 1H), 7.42 (ddd, *J* = 47.8, 16.5, 7.4 Hz, 3.5H), 7.20 (d, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 7.3 Hz, 1H), 6.92 (t, *J* = 7.5 Hz, 2H), 6.77 (d, *J* = 7.4 Hz, 0.5H), 6.34 (d, *J* = 7.6 Hz, 2H), 5.68 (d, *J* = 3.9 Hz, 1H), 5.60 (d, *J* = 3.4 Hz, 0.5H), 4.02 (q, *J* = 4.4, 3.5 Hz, 1H), 3.95 (s, 5H), 3.76 (s, 3H), 3.46 (s, 1H), 3.16 (dd, *J* = 16.5, 9.6 Hz, 1H), 2.89 (dd, *J* = 16.5, 6.6 Hz, 1H), 2.25 (d, *J* = 7.7 Hz, 1H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.0, 171.7, 167.1, 166.7, 166.6, 166.5, 141.7, 141.5, 141.4, 141.1, 137.9, 135.8, 133.0, 132.2, 132.0, 132.0, 130.9, 130.7, 129.0, 129.0, 128.8, 128.0, 128.0, 127.9, 127.8, 127.7, 127.5, 127.0, 126.2, 124.5, 124.4, 123.6,

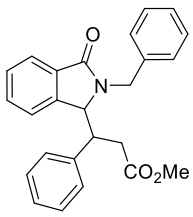
		123.1, 122.5, 121.9, 64.6, 62.3, 52.2, 52.1, 52.1, 51.8, 42.3, 41.7, 35.8, 31.2
HRMS *m/z*	$C_{26}H_{24}NO_5^+$ ([M+H]$^+$)	
	Calculated: 430.1649	observed: 430.1649

methyl 3-(2-(4-cyanophenyl)-3-oxoisoindolin-1-yl)-3-phenylpropanoate (9ma)



Prepared in accordance with the G***eneral Procedure (C)*** using 4-(1-oxoisoindolin-2-yl)benzonitrile **7m** (0.1 mmol) and methyl cinnamate **8a** (1.5 equiv.). 37.6 mg, 94% yield, 1 h, d.r. = 2.2:1, brown solid, m.p. 152-157 ˚C		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.87 (ddd, *J* = 22.6, 14.6, 8.3 Hz, 4H), 7.71 (ddd, *J* = 20.1, 12.9, 8.3 Hz, 5H), 7.50 (q, *J* = 9.7, 8.6 Hz, 2H), 7.38 (dd, *J* = 16.2, 7.1 Hz, 1H), 7.20 (d, *J* = 7.4 Hz, 0.8H), 7.06 (t, *J* = 7.4 Hz, 1H), 6.94 (t, *J* = 7.6 Hz, 2H), 6.75 (d, *J* = 7.4 Hz, 0.4H), 6.33 (d, *J* = 7.6 Hz, 2H), 5.68 (d, *J* = 3.8 Hz, 1H), 5.59 (d, *J* = 3.4 Hz, 0.4H), 4.17 – 3.99 (m, 0.4H), 3.95 (ddd, *J* = 10.1, 6.3, 3.8 Hz, 1H), 3.77 (s, 3H), 3.48 (s, 1.2H), 3.17 (dd, *J* = 16.8, 9.9 Hz, 1H), 2.88 (dd, *J* = 16.8, 6.2 Hz, 1H), 2.25 (dd, *J* = 13.1, 7.7 Hz, 0.8H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.2, 171.6, 167.2, 166.8, 141.6, 141.4, 141.4, 141.1, 137.7, 135.6, 133.4, 133.3, 133.2, 132.6, 132.4, 132.3, 131.9, 129.2, 129.2, 129.0, 127.9, 127.9, 127.9, 127.7, 124.7, 124.6, 123.7, 123.2, 122.8, 122.3, 118.8, 118.6, 108.6, 107.8, 64.4, 62.1, 52.3, 51.9, 42.2, 41.7, 35.4, 31.2
HRMS *m/z*	$C_{25}H_{21}N_2O_3^+$ ([M+H]$^+$)	
	Calculated: 397.1547	observed: 397.1548

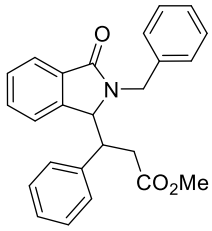
methyl 3-(2-benzyl-3-oxoisoindolin-1-yl)-3-phenylpropanoate (9na-1)



Prepared in accordance with the G***eneral Procedure (C)*** using 2-benzylisoindolin-1-one **7n** (0.1 mmol) and methyl cinnamate **8a** (1.5 equiv.). 16.4 mg, 43% yield (91% total yield), 1 h, d.r.=1.1:1, white solid; m.p. 111-114 ˚C

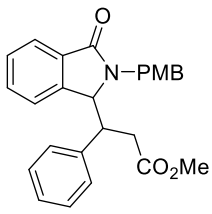
^{1}H NMR	**400 MHz, $CDCl_3$**	7.77 (d, *J* = 7.5 Hz, 1H), 7.63 – 7.52 (m, 2H), 7.50 – 7.41 (m, 1H), 7.22 (dd, *J* = 5.0, 1.8 Hz, 3H), 7.20 – 7.11 (m, 3H), 7.00 (dd, *J* = 6.6, 2.6 Hz, 2H), 6.92 – 6.85 (m, 2H), 5.39 (d, *J* = 15.0 Hz, 1H), 4.61 (d, *J* = 3.2 Hz, 1H), 4.03 (dd, *J* = 15.3, 3.8 Hz, 2H), 3.56 (s, 3H), 2.93 (dd, *J* = 15.9, 8.9 Hz, 1H), 2.68 (dd, *J* = 15.9, 6.8 Hz, 1H)
^{13}C NMR	**100 MHz, $CDCl_3$**	171.9, 168.6, 143.3, 137.6, 136.7, 132.8, 131.4, 128.6, 128.6, 128.3, 128.2, 127.8, 127.5, 127.4, 124.0, 122.9, 62.1, 51.9, 44.4, 42.8, 34.7
HRMS *m/z*	$C_{25}H_{24}NO_3^+$ ([M+H]$^+$)	
	Calculated: 352.1543	observed: 386.1743

methyl 3-(2-benzyl-3-oxoisoindolin-1-yl)-3-phenylpropanoate (9na-2)



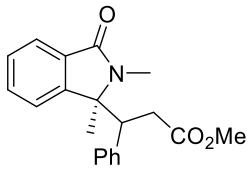
Prepared in accordance with the G***eneral Procedure (C)*** using 2-benzylisoindolin-1-one **7n** (0.1 mmol) and methyl cinnamate **8a** (1.5 equiv.). 18.6 mg, 48% yield (91% total yield), 1 h, d.r.=1.1:1, yellow oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.88 (d, J = 7.4 Hz, 1H), δ 7.46 – 7.38 (m, 5H), 7.37 – 7.27 (m, 5H)., 7.06 (d, J = 7.3 Hz, 2H), 6.43 (d, J = 7.7 Hz, 1H), 5.57 (d, J = 15.1 Hz, 1H), 4.56 (d, J = 3.6 Hz, 1H), 4.29 (d, J = 15.1 Hz, 1H), 4.17 (dt, J = 9.3, 4.5 Hz, 1H), 3.58 (s, 3H), 2.28 (dd, J = 16.1, 9.7 Hz, 1H), 2.17 (dd, J = 16.1, 5.2 Hz, 1H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.4, 168.5, 142.1, 138.4, 136.7, 132.6, 131.0, 129.0, 128.8, 128.5, 128.5, 127.9, 127.9, 127.5, 123.9, 123.5, 63.1, 52.0, 44.0, 40.3, 30.2
HRMS *m/z*	$C_{25}H_{24}NO_3^+$ ([M+H]$^+$)	
	Calculated: 386.1756	observed: 386.1745

methyl 3-(2-(4-methoxybenzyl)-3-oxoisoindolin-1-yl)-3-phenylpropanoate (9oa)



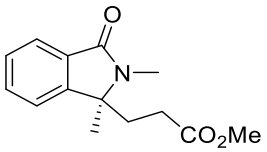
Prepared in accordance with the G***eneral Procedure (C)*** using 2-(4-methoxybenzyl)isoindolin-1-one **7o** (0.1 mmol) and methyl cinnamate **8a** (1.5 equiv.). 37.4 mg, 90% yield, 1 h, d.r. = 1:1, brown oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.87 (d, J = 7.5 Hz, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.61 – 7.52 (m, 2H), 7.48 – 7.40 (m, 2H), 7.37 – 7.28 (m, 6H), 7.19 – 7.15 (m, 3H), 7.08 (d, J = 7.3 Hz, 2H), 6.92 (dd, J = 8.5, 4.6 Hz, 6H), 6.75 (d, J = 8.6 Hz, 2H), 6.42 (d, J = 7.6 Hz, 1H), 5.50 (d, J = 15.0 Hz, 1H), 5.33 (d, J = 14.8 Hz, 1H), 4.60 (d, J = 3.2 Hz, 1H), 4.55 (d, J = 3.7 Hz, 1H), 4.23 (d, J = 15.0 Hz, 1H), 4.18 (dd, J = 9.5, 4.8 Hz, 1H), 4.02 (td, J = 6.4, 3.3 Hz, 1H), 3.97 (d, J = 14.9 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.58 (s, 3H), 3.57 (s, 3H), 2.92 (dd, J = 15.9, 8.9 Hz, 1H), 2.67 (dd, J = 16.0, 6.7 Hz, 1H), 2.27 (dd, J = 16.0, 9.8 Hz, 1H), 2.16 (dd, J = 16.0, 5.1 Hz, 1H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.3, 172.0, 168.5, 168.4, 159.3, 159.0, 143.4, 142.1, 138.5, 137.8, 132.9, 132.7, 131.3, 130.9, 129.8, 129.6, 128.9, 128.8, 128.8, 128.5, 128.5, 128.3, 127.9, 127.9, 127.5, 127.4, 124.0, 123.8, 123.4, 122.9, 114.3, 113.9, 63.0, 62.0, 55.3, 55.2, 51.9, 43.8, 43.4, 42.8, 40.3, 34.6, 30.2
HRMS *m/z*	$C_{26}H_{26}NO_4^+$ ($[M+H]^+$)	
	Calculated: 416.1856	observed: 416.1857

methyl 3-(1,2-dimethyl-3-oxoisoindolin-1-yl)-3-phenylpropanoate (9pa)



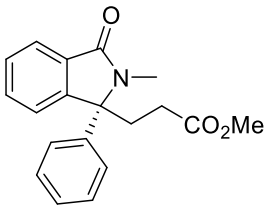
Prepared in accordance with the G***eneral Procedure (C)*** using 2,3-dimethylisoindolin-1-one **7p** (0.1 mmol) and methyl cinnamate 8**a** (3.0 equiv.). 21 mg, 65% yield, 1 h, yellow oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.87 – 7.83 (m, 1H), 7.49 – 7.40 (m, 2H), 7.35 (d, J = 7.1 Hz, 3H), 7.21 (dd, J = 7.5, 1.8 Hz, 2H), 6.92 (dd, J = 6.2, 1.7 Hz, 1H), 3.78 (dd, J = 10.2, 5.1 Hz, 1H), 3.45 (s, 3H), 3.12 (s, 3H), 2.25 – 2.09 (m, 2H), 1.39 (s, 3H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.1, 167.9, 146.8, 137.7, 132.3, 130.7, 129.9, 128.5, 128.1, 127.8, 123.5, 66.8, 51.7, 47.1, 33.8, 24.4, 23.2
HRMS *m/z*	$C_{20}H_{22}NO_3^+$ ($[M+H]^+$)	
	Calculated: 324.1594	observed: 324.1594

methyl 3-(1,2-dimethyl-3-oxoisoindolin-1-yl)propanoate (9pai)



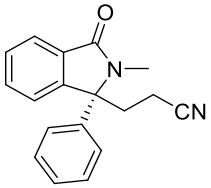
Prepared in accordance with the G***eneral Procedure (C)*** using 2,3-dimethylisoindolin-1-one 7**p** (0.1 mmol) and methyl acrylate **8ai** (3.0 equiv.). 14.8. mg, 60% yield, 1 h, clear oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.83 (d, J = 7.5 Hz, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.38 (d, J = 7.5 Hz, 1H), 3.54 (s, 3H), 2.98 (s, 3H), 2.36 – 2.21 (m, 2H), 1.78 (ddd, J = 16.1, 9.8, 6.0 Hz, 1H), 1.61 – 1.51 (m, 1H), 1.49 (s, 3H)
^{13}C NMR	**100 MHz, $CDCl_3$**	173.1, 167.7, 148.4, 131.9, 131.7, 128.3, 123.6, 120.8, 64.2, 51.7, 31.6, 28.1, 24.7, 23.9
HRMS *m/z*	$C_{14}H_{18}NO_3^+$ ($[M+H]^+$)	
	Calculated: 248.1281	observed: 248.1286

methyl 3-(2-methyl-3-oxo-1-phenylisoindolin-1-yl)propanoate (9qai)



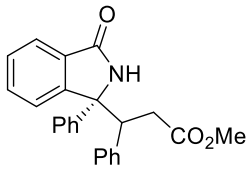
Prepared in accordance with the G***eneral Procedure (C)*** using 2-methyl-3-phenylisoindolin-1-one **7q** (0.1 mmol) and methyl acrylate **8ai** (1.5 equiv.). 14.7 mg, 47% yield, 1.5 h, colorless oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.89 (d, *J* = 6.6 Hz, 1H), 7.45 (p, *J* = 7.3, 6.8 Hz, 2H), 7.36 – 7.25 (m, 3H), 7.16 (dd, *J* = 21.2, 7.3 Hz, 3H), 3.59 (s, 3H), 2.92 (ddd, *J* = 15.8, 10.6, 5.3 Hz, 1H), 2.80 (s, 3H), 2.78 – 2.69 (m, 1H), 1.96 (ddd, *J* = 16.1, 10.7, 5.2 Hz, 1H), 1.66 (ddd, *J* = 16.2, 10.7, 5.2 Hz, 1H)
^{13}C NMR	**100 MHz, $CDCl_3$**	173.1, 168.7, 148.8, 139.4, 132.1, 131.6, 129.0, 128.4, 128.1, 126.1, 123.6, 121.9, 69.4, 51.8, 28.4, 27.9, 24.7
HRMS *m/z*	$C_{19}H_{20}NO_3^+$ ($[M+H]^+$)	
	Calculated: 310.1438	observed: 310.1436

3-(2-methyl-3-oxo-1-phenylisoindolin-1-yl)propanenitrile (9qaj)



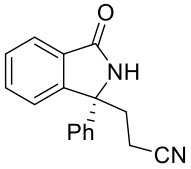
Prepared in accordance with the G***eneral Procedure (C)*** using 2-methyl-3-phenylisoindolin-1-one **7q** (0.1 mmol) and acrylonitrile **8aj** (1.5 equiv.). 14.7 mg, 53% yield, 1.5 h, white solid, m.p. 127-131 ˚C		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.91 (d, *J* = 6.6 Hz, 1H), 7.51 (t, *J* = 7.1 Hz, 2H), 7.38 – 7.31 (m, 3H), 7.14 (dd, *J* = 11.7, 7.2 Hz, 3H), 2.94 (ddd, *J* = 18.8, 9.5, 5.0 Hz, 1H), 2.81 (s, 3H), 2.80 – 2.75 (m, 1H), 1.96 (ddd, *J* = 16.5, 10.7, 5.3 Hz, 1H), 1.68 (ddd, *J* = 16.6, 10.7, 5.3 Hz, 1H)
^{13}C NMR	**100 MHz, $CDCl_3$**	168.5, 147.6, 138.4, 132.7, 131.3, 129.2, 129.0, 128.7, 128.5, 127.8, 125.8, 124.0, 121.8, 118.6, 68.9, 29.5, 24.8, 11.5
HRMS *m/z*	$C_{18}H_{17}N_2O^+$ ([M+H]$^+$)	
	Calculated: 277.1335	observed: 277.1334

methyl 3-(3-oxo-1-phenylisoindolin-1-yl)-3-phenylpropanoate (9ra)



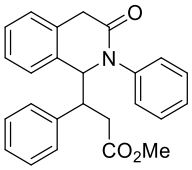
Prepared in accordance with the G***eneral Procedure (C)*** using 3-phenylisoindolin-1-one **7r** (0.1 mmol) and methyl cinnamate **8a** (1.5 equiv.). 14.1 mg, 38% yield, 1 h, d.r. = 1.1:1, white solid; m.p. 200–207 ˚C		
^{1}H NMR	**400 MHz, $CDCl_3$**	8.41 (s, 1H), 7.82 (d, J = 7.5 Hz, 0.9H), 7.76 (t, J = 7.6 Hz, 2.6H), 7.60 (t, J = 7.5 Hz, 0.9H), 7.53 (d, J = 7.8 Hz, 1H), 7.50 – 7.39 (m, 6.5H), 7.32 (t, J = 7.3 Hz, 1H), 7.29 – 7.24 (m, 2.7H), 7.20 (t, J = 7.3 Hz, 1.8H), 7.14 – 7.06 (m, 4.5H), 7.04 – 6.99 (m, 4.4H), 6.88 (s, 0.9H), 4.53 – 4.46 (m, 1.9 H), 3.46 (s, 3H), 3.38 (s, 2.7H), 2.99 (dd, J = 16.2, 11.4 Hz, 1H), 2.79 – 2.69 (m, 1.8H), 2.30 (dd, J = 16.1, 4.9 Hz, 1H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.2, 172.2, 171.4, 169.9, 149.9, 148.9, 140.7, 140.6, 138.0, 136.7, 132.5, 131.8, 131.0, 130.1, 129.6, 129.3, 129.3, 128.8, 128.7, 128.7, 128.6, 128.6, 128.3, 128.0, 127.9, 127.7, 127.5, 127.4, 127.1, 125.5, 125.4, 125.4, 124.3, 123.7, 123.6, 123.3, 122.9, 122.8, 70.5, 70.0, 51.7, 51.6, 49.2, 49.1, 36.0, 35.0
HRMS *m/z*	$C_{24}H_{22}NO_3^+$ ([M+H]$^+$)	
	Calculated: 372.1594	observed: 372.1592

3-(3-oxo-1-phenylisoindolin-1-yl)propanenitrile (9raj)



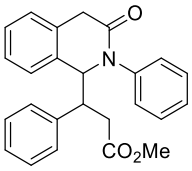
Prepared in accordance with the G***eneral Procedure (C)*** using 3-phenylisoindolin-1-one **7r** (0.1 mmol) and acrylonitrile **8aj** (1.5 equiv.). 16.3 mg, 62% yield, 1 h, white solid; m.p. 184-190 ˚C		
^{1}H NMR	**400 MHz, $CDCl_3$**	8.01 (s, 1H), 7.84 (d, J = 7.5 Hz, 1H), 7.58 (t, J = 7.5 Hz, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.48 – 7.43 (m, 2H), 7.41 – 7.35 (m, 3H), 7.32 (d, J = 7.1 Hz, 1H), 2.84 (ddd, J = 13.9, 10.8, 5.6 Hz, 1H), 2.70 (ddd, J = 14.0, 10.3, 5.5 Hz, 1H), 2.34 (ddd, J = 16.1, 10.3, 5.3 Hz, 1H), 2.07 (ddd, J = 16.6, 10.6, 5.3 Hz, 1H)
^{13}C NMR	**100 MHz, $CDCl_3$**	170.8, 149.1, 140.1, 133.0, 130.6, 130.5, 129.3, 129.0, 128.4, 125.1, 124.4, 122.3, 118.9, 66.1, 34.7, 29.7, 12.5
HRMS *m/z*	$C_{17}H_{15}N_2O^+$ ([M+H]$^+$)	
	Calculated: 263.1179	observed: 263.1180

methyl 3-(3-oxo-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-3-phenylpropanoate (9sa-1)



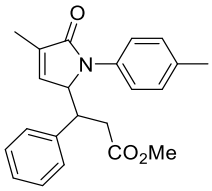
Prepared in accordance with the G***eneral Procedure (C)*** using 2-phenyl-1,4-dihydroisoquinolin-3(2H)-one **7s** (0.1 mmol) and methyl cinnamate **8a** (1.5 equiv.). 20.3 mg, 53% yield (94% total yield), 1 h, d.r.=1.3:1, yellow oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.52 (d, *J* = 7.6 Hz, 1H), 7.38 (dt, *J* = 15.8, 7.6 Hz, 3H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.25 – 7.16 (m, 4H), 7.05 (d, *J* = 7.5 Hz, 2H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 7.7 Hz, 2H), 4.15 (s, 1H), 3.91 (d, *J* = 15.4 Hz, 1H), 3.69 (s, 3H), 3.67 – 3.59 (m, 3H), 3.27 (d, *J* = 15.3 Hz, 1H), 2.94 (t, *J* = 11.1 Hz, 1H)
^{13}C NMR	**100 MHz, $CDCl_3$**	173.2, 169.0, 142.3, 139.0, 135.5, 132.0, 128.9, 128.5, 128.1, 128.0, 127.5, 126.9, 126.8, 125.4, 124.4, 52.7, 51.7, 51.3, 48.9, 37.3
HRMS *m/z*	$C_{25}H_{24}NO_3^+$ ([M+H]$^+$)	
	Calculated: 386.1756	observed: 386.1752

methyl 3-(3-oxo-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-3-phenylpropanoate (9sa-2)



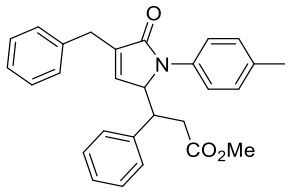
Prepared in accordance with the G***eneral Procedure (C)*** using 2-phenyl-1,4-dihydroisoquinolin-3(2H)-one **7s** (0.1 mmol) and methyl cinnamate **8a** (1.5 equiv.). 15.8 mg, 40% yield (94% total yield), 1 h, d.r.=1.3:1, yellow oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.37 (t, *J* = 7.6 Hz, 2H), 7.25 (dt, *J* = 7.5, 3.5 Hz, 5H), 7.20 – 7.13 (m, 4H), 6.99 (d, *J* = 5.1 Hz, 2H), 6.82 (d, *J* = 7.7 Hz, 2H), 4.04 (d, *J* = 15.4 Hz, 1H), 3.95 (s, 2H), 3.77 (d, *J* = 15.3 Hz, 1H), 3.58 (s, 3H), 3.08 (dd, *J* = 15.7, 6.3 Hz, 1H), 2.83 (dd, *J* = 15.6, 7.0 Hz, 1H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.1, 170.4, 142.4, 139.5, 133.1, 132.7, 128.9, 128.9, 128.5, 128.1, 127.5, 127.1, 127.1, 126.7, 125.5, 125.1, 53.8, 52.9, 51.8, 45.2, 38.0
HRMS *m/z*	$C_{25}H_{24}NO_3^+$ ([M+H]$^+$)	
	Calculated: 386.1756	observed: 386.1753

methyl-3-(4-methyl-5-oxo-1-(p-tolyl)-2,5-dihydro-1H-pyrrol-2-yl)-3-phenylpropanoate (9ta)



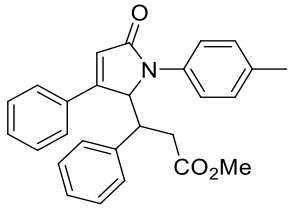
Prepared in accordance with the G***eneral Procedure (C)*** using 3-methyl-1-(p-tolyl)-1,5-dihydro-2H-pyrrol-2-one **7t** (0.1 mmol) and methyl cinnamate **8a** (1.5 equiv.). 18.9 mg, 54% yield, 1 h, d.r. = 1:1, clear oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.37 (dt, *J* = 16.7, 8.4 Hz, 6H), 7.25 (q, *J* = 7.3 Hz, 7H), 7.12 (d, *J* = 6.4 Hz, 3H), 6.82 (s, 1H), 6.71 (d, *J* = 6.0 Hz, 2H), 6.60 (s, 1H), 4.95 (s, 1H), 4.74 (s, 1H), 3.75 – 3.70 (m, 2H), 3.68 (s, 3H), 3.45 (s, 3H), 2.90 (dd, *J* = 16.3, 9.1 Hz, 1H), 2.79 (dd, *J* = 16.4, 6.5 Hz, 1H), 2.52 (dd, *J* = 16.3, 10.9 Hz, 1H), 2.38 (s, 6H), 2.35 – 2.30 (m, 1H), 1.96 (s, 3H), 1.77 (s, 3H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.0, 171.8, 170.5, 170.0, 139.1, 137.1, 137.0, 136.6, 136.6, 136.4, 136.1, 135.2, 134.4, 134.0, 129.9, 129.9, 129.5, 128.9, 128.3, 127.7, 127.4, 127.3, 122.7, 122.5, 65.1, 62.8, 51.9, 51.6, 41.5, 41.2, 36.1, 31.1, 21.0, 20.9, 11.4, 11.1
HRMS *m/z*	$C_{22}H_{24}NO_3^+$ ([M+H]$^+$)	
	Calculated: 350.1751	observed: 350.1754

methyl (3-(4-benzyl-5-oxo-1-(p-tolyl)-2,5-dihydro-1H-pyrrol-2-yl)-3-phenylpropanoate (9ua)



Prepared in accordance with the G***eneral Procedure (C)*** using 3-benzyl-1-(p-tolyl)-1,5-dihydro-2H-pyrrol-2-one **7u** (0.1 mmol) and methyl cinnamate **8a** (1.5 equiv.). 36.2 mg, 85% yield, 1 h, d.r. = 2:1, clear oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.42 – 7.38 (m, 3.3H), 7.35 – 7.26 (m, 7.4H), 7.22 (m, 3.2H), 7.17 – 7.09 (m, 4.3H), 7.05 – 7.01 (m, 2H), 6.66 – 6.62 (m, 2H), 6.53 (q, J = 1.6 Hz, 1H), 6.42 (q, J = 1.5 Hz, 0.5H), 4.95 (dq, J = 4.0, 2.0 Hz, 1H), 4.77 (dq, J = 3.9, 1.9 Hz, 0.5H), 3.70 (ddd, J = 9.9, 6.2, 4.1 Hz, 1.5H), 3.66 (s, 3H), 3.65 (s, 1H), 3.45 (s, 1.5H), 3.43 (s, 2H), 2.84 (dd, J = 16.5, 9.4 Hz, 1H), 2.74 (dd, J = 16.5, 6.2 Hz, 1H), 2.46 (dd, J = 16.2, 10.5 Hz, 0.5H), 2.41 – 2.31 (m, 5.8H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.0, 171.8, 169.7, 169.2, 141.2, 138.9, 138.1, 137.5, 136.8, 136.1, 135.3, 134.5, 134.3, 133.9, 129.9, 129.6, 129.0, 128.9, 128.8, 128.6, 128.5, 128.4, 127.7, 127.7, 127.4, 127.3, 126.5, 126.3, 122.8, 122.4, 65.2, 62.9, 51.9, 51.7, 41.5, 41.1, 35.9, 32.3, 32.1, 31.5, 21.0, 21.0
HRMS *m/z*	$C_{28}H_{28}NO_3^+$ ($[M+H]^+$)	
	Calculated: 426.2064	observed: 426.2064

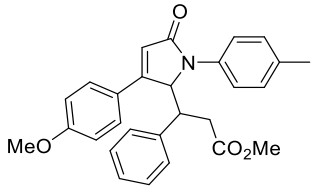
methyl 3-(5-oxo-3-phenyl-1-(p-tolyl)-2,5-dihydro-1H-pyrrol-2-yl)-3-phenylpropanoate (9va)



Prepared in accordance with the G***eneral Procedure (C)*** using 4-phenyl-1-(p-tolyl)-1,5-dihydro-2H-pyrrol-2-one **7v** (0.1 mmol) and methyl cinnamate **8a** (1.5 equiv.). 17.7 mg, 43% yield, 1 h, d.r. = 1.5:1, clear oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.50 (d, J = 3.6 Hz, 3H), 7.45 – 7.42 (m, 7H), 7.29 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.7 Hz, 1H), 7.19 – 7.15 (m, 2H), 7.14 – 7.07 (m, 4H), 6.70 – 6.63 (m, 3H), 6.12 (d, J = 4.5 Hz, 1.5H), 5.91 (d, J = 2.4 Hz, 1H), 5.81 (d, J = 2.8 Hz, 0.5H), 3.76 (qd, J = 8.3, 6.8, 2.4 Hz, 1.5H), 3.63 (d, J = 3.1 Hz, 4.5H), 2.62 (dd, J = 17.2, 9.3 Hz, 1.5H), 2.55

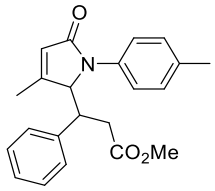
		(d, J = 7.1 Hz, 0.5H), 2.45 (d, J = 6.6 Hz, 1H), 2.41 (s, 1.5H), 2.36 (s, 3H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.6, 172.3, 169.9, 168.7, 159.0, 158.0, 137.1, 136.6, 135.6, 135.5, 134.6, 134.3, 133.5, 132.1, 130.1, 130.0, 129.8, 129.5, 129.1, 129.0, 129.0, 128.2, 128.1, 128.0, 127.9, 127.8, 127.4, 127.3, 127.3, 127.2, 125.3, 124.8, 123.8, 122.8, 122.1, 64.8, 64.3, 51.8, 51.7, 43.5, 42.2, 34.8, 34.0, 21.1, 20.9
HRMS *m/z*	$C_{27}H_{26}NO_3^+$ ([M+H]$^+$)	
	Calculated: 412.1907	observed: 412.1907

methyl 3-(3-(4-methoxyphenyl)-5-oxo-1-(p-tolyl)-2,5-dihydro-1H-pyrrol-2-yl)-3-phenylpropanoate (9wa)



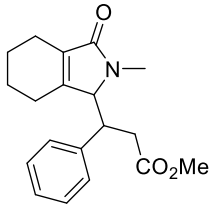
Prepared in accordance with the G***eneral Procedure (C)*** using 4-(4-methoxyphenyl)-1-(p-tolyl)-1,5-dihydro-2H-pyrrol-2-one **7w** (0.1 mmol), and methyl cinnamate **8a** (1.5 equiv.). 27.8 mg, 63% yield, 1 h, d.r. = 2:1, light brown oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.46 – 7.38 (m, 7H), 7.29 (s, 2H), 7.21 – 7.06 (m, 6H), 7.03 (d, *J* = 8.8 Hz, 1H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.70 – 6.65 (m, 3H), 6.05 – 6.03 (m, 0.4H), 6.02 – 6.00 (m, 1H), 5.88 – 5.86 (m, 1H), 5.77 – 5.72 (m, 0.4H), 3.91 (s, 1.4H), 3.88 (s, 3H), 3.80 – 3.72 (m, 2H), 3.63 (s, 3H), 3.63 (s, 1.4H), 2.69 – 2.56 (m, 2H), 2.45 (d, *J* = 6.4 Hz, 1H), 2.40 (s, 3H), 2.36 (s, 1.4H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.8, 172.4, 170.2, 169.0, 161.1, 161.0, 158.6, 157.7, 137.3, 136.6, 135.7, 135.4, 134.4, 134.4, 129.7, 129.5, 128.9, 128.8, 128.2, 128.0, 127.8, 127.7, 127.3, 127.1, 125.8, 124.7, 123.7, 122.9, 122.8, 120.0, 114.5, 114.4, 64.9, 64.1, 55.4, 55.4, 51.8, 51.7, 43.8, 42.4, 35.0, 33.9, 21.0, 20.9
HRMS *m/z*	$C_{28}H_{28}NO_4^+$ ([M+H]$^+$)	
	Calculated: 442.2013	observed: 442.2016

methyl-3-(3-methyl-5-oxo-1-(p-tolyl)-2,5-dihydro-1H-pyrrol-2-yl)-3-phenylpropanoate (9xa)



Prepared in accordance with the G***eneral Procedure (C)*** using 4-methyl-1-(p-tolyl)-1,5-dihydro-2H-pyrrol-2-one **7x** (0.1 mmol) and methyl cinnamate **8a** (1.5 equiv.). 15 mg, 43% yield, 1 h, d.r. = 1:1, clear oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.34 – 7.19 (m, 8H), 7.15 (d, *J* = 7.5 Hz, 2H), 7.11 – 7.02 (m, 6H), 6.79 (d, *J* = 7.1 Hz, 2H), 5.85 (s, 1H), 5.79 (s, 1H), 5.01 (s, 1H), 4.90 (s, 1H), 3.76 (q, *J* = 9.3, 7.6 Hz, 2H), 3.62 (s, 3H), 3.53 (s, 3H), 2.82 (dd, *J* = 16.2, 8.4 Hz, 1H), 2.72 (dd, *J* = 16.2, 7.3 Hz, 1H), 2.52 – 2.46 (m, 2H), 2.36 (s, 3H), 2.29 (s, 3H), 2.23 (s, 3H), 1.85 (s, 3H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.2, 172.1, 170.2, 169.6, 157.7, 156.5, 137.7, 137.7, 135.6, 134.6, 134.6, 134.1, 129.8, 129.3, 128.5, 128.0, 127.7, 127.5, 127.4, 126.9, 125.3, 124.4, 123.9, 123.4, 68.8, 68.7, 51.9, 51.7, 41.5, 33.4, 33.4, 29.7, 21.0, 20.9, 16.2, 15.8
HRMS *m/z*	$C_{22}H_{24}NO_3^+$ ($[M+H]^+$)	
	Calculated: 350.1751	observed: 350.1757

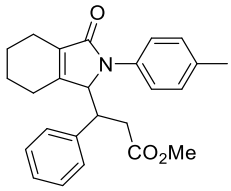
methyl 3-(2-methyl-3-oxo-2,3,4,5,6,7-hexahydro-1H-isoindol-1-yl)-3-phenylpropanoate (9ya)



Prepared in accordance with the G***eneral Procedure (C)*** using 2-methyl-2,3,4,5,6,7-hexahydro-1H-isoindol-1-one **7y** (0.1 mmol) and methyl cinnamate **8a** (1.5 equiv.). 22.6 mg, 72% yield, 1 h, d.r. = 1:1, white solid, m.p. 190-195 ˚C		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.30 (dd, J = 7.6, 6.0 Hz, 4H), 7.26 – 7.21 (m, 4H), 7.20 – 7.17 (m, 2H), 4.10 (p, J = 2.1 Hz, 1H), 4.04 (q, J = 2.4 Hz, 1H), 3.87 (ddd, J = 9.2, 5.2, 3.4 Hz, 1H), 3.77 (ddd, J = 8.9, 5.7, 2.6 Hz, 1H), 3.63 (s, 6H), 3.11 (s, 3H), 2.82 (dd, J = 16.3, 9.5 Hz, 1H), 2.69 (s, 3H), 2.68 – 2.61 (m, 1H), 2.47 (ddd, J = 16.0, 7.4, 5.5 Hz, 2H), 2.38 (td, J = 5.2, 2.6 Hz, 1H), 2.32 (dd, J = 5.4, 2.9 Hz, 1H), 2.20 – 2.06 (m, 4H), 1.96 – 1.87 (m, 1H), 1.86 – 1.59 (m, 7H), 1.46 (dddd, J = 22.5, 11.4, 5.6, 3.0 Hz, 2H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.5, 172.4, 172.1, 151.7, 151.5, 139.2, 138.3, 133.7, 133.4, 128.6, 128.5, 127.6, 127.4, 127.2, 127.2, 69.5,

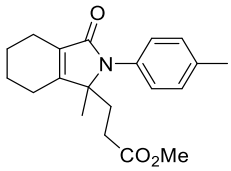
		69.2, 52.0, 51.9, 41.1, 40.7, 32.3, 32.2, 29.0, 28.2, 24.9, 24.4, 22.3, 22.2, 21.7, 21.7, 20.3
HRMS *m/z*	$C_{19}H_{24}NO_3^+$ ([M+H]$^+$)	
	Calculated: 314.1751	observed: 314.1750

methyl 3-(3-oxo-2-(p-tolyl)-2,3,4,5,6,7-hexahydro-1H-isoindol-1-yl)-3-phenylpropanoate (9za)



Prepared in accordance with the G***eneral Procedure (C)*** using 2-(p-tolyl)-2,3,4,5,6,7-hexahydro-1H-isoindol-1-one **7z** (0.1 mmol) and methyl cinnamate **8a** (1.5 equiv.). 35.8 mg, 92% yield, 1 h, d.r. = 1:1, clear oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.35 (s, 2H), 7.30 (t, J = 7.3 Hz, 3H), 7.25 – 7.15 (m, 6H), 7.14 – 7.07 (m, 5H), 6.82 – 6.77 (m, 2H), 4.92 (d, J = 2.7 Hz, 1H), 4.84 (d, J = 2.6 Hz, 1H), 3.74 (ddt, J = 9.4, 6.8, 3.6 Hz, 2H), 3.65 (s, 3H), 3.53 (s, 3H), 2.82 (d, J = 7.9 Hz, 2H), 2.60 – 2.39 (m, 4H), 2.37 (s, 3H), 2.33 (s, 3H), 2.16 – 2.09 (m, 4H), 1.89 – 1.60 (m, 7H), 1.60 – 1.47 (m, 3H)
^{13}C NMR	**100 MHz, $CDCl_3$**	172.3, 172.2, 170.3, 169.8, 152.2, 150.9, 138.2, 137.6, 135.2, 134.7, 134.5, 134.2, 134.1, 133.2, 129.8, 129.4, 128.4, 127.9, 127.7, 127.7, 127.2, 127.0, 123.6, 123.0, 67.2, 66.2, 51.9, 51.8, 41.6, 41.2, 34.4, 32.7, 25.7, 25.0, 22.5, 22.2, 21.7, 21.6, 21.0, 20.9, 20.3, 20.3
HRMS *m/z*	$C_{25}H_{28}NO_3^+$ ([M+H]$^+$)	
	Calculated: 390.2064	observed: 390.2065

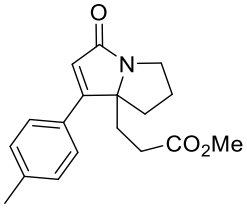
methyl 3-(1-methyl-3-oxo-2-(p-tolyl)-2,3,4,5,6,7-hexahydro-1H-isoindol-1-yl)propanoate (9baai)



Prepared in accordance with the G***eneral Procedure (C)*** using 3-methyl-2-(p-tolyl)-2,3,4,5,6,7-hexahydro-1H-isoindol-1-one **7ba** (0.1 mmol) and methyl acrylate **8ai** (3.0 equiv.). 17.1 mg, 52% yield, 4 h, yellow oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.22 (d, J = 8.1 Hz, 2H), 7.06 (d, J = 8.2 Hz, 2H), 3.66 (s, 3H), 2.36 (s, 3H), 2.31 – 2.12 (m, 5H), 2.02 – 1.89 (m, 3H), 1.82 – 1.65 (m, 4H), 1.26 (s, 3H)

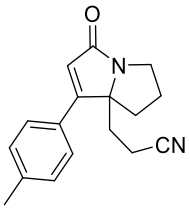
^{13}C NMR	**100 MHz, $CDCl_3$**	173.4, 171.3, 156.6, 137.4, 133.4, 131.7, 130.1, 128.5, 67.8, 51.8, 30.3, 28.4, 24.0, 22.3, 22.1, 21.8, 21.1, 20.2
HRMS *m/z*	$C_{20}H_{26}NO_3^+$ ($[M+H]^+$)	
	Calculated: 328.1907	observed: 328.1906

methyl 3-(5-oxo-7-(p-tolyl)-2,3-dihydro-1H-pyrrolizin-7a(5H)-yl)propanoate (9bbai)



Prepared in accordance with the G***eneral Procedure (C)*** using 1-(p-tolyl)-5,6,7,7a-tetrahydro-3H-pyrrolizin-3-one **7bb** (0.1 mmol) and methyl acrylate **8ai** (1.5 equiv.) at constant voltage mode (2.5 V). 10.2 mg, 34% yield, 1 h, white solid, m.p. 105-110 ˚C		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.38 (d, *J* = 7.8 Hz, 2H), 7.24 (d, *J* = 7.8 Hz, 2H), 6.17 (s, 1H), 3.67 (dt, *J* = 11.6, 8.6 Hz, 1H), 3.57 (s, 3H), 3.20 (ddd, *J* = 12.0, 9.2, 3.8 Hz, 1H), 2.49 – 2.41 (m, 1H), 2.39 (s, 3H), 2.36 (s, 1H), 2.30 – 2.18 (m, 2H), 2.13 (ddd, *J* = 15.2, 8.5, 5.9 Hz, 1H), 2.03 – 1.80 (m, 3H)
^{13}C NMR	**100 MHz, $CDCl_3$**	174.9, 173.5, 163.5, 140.6, 129.8, 128.6, 127.2, 120.8, 75.3, 51.6, 40.6, 35.0, 29.5, 28.4, 28.1, 21.4
HRMS *m/z*	$C_{18}H_{22}NO_3^+$ ($[M+H]^+$)	
	Calculated: 300.1594	observed: 300.1595

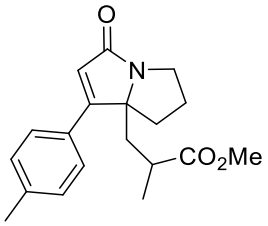
3-(5-oxo-7-(p-tolyl)-2,3-dihydro-1H-pyrrolizin-7a(5H)-yl)propanenitrile (9bbaj)



Prepared in accordance with the G***eneral Procedure (C)*** using 1-(p-tolyl)-5,6,7,7a-tetrahydro-3H-pyrrolizin-3-one **7bb** (0.1 mmol) and acrylonitrile **8aj** (2.5 equiv.) at constant voltage mode (2.5 V). 9.1 mg, 34% yield, 3 h, clear oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.37 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 6.4 Hz, 2H), 6.19 (s, 1H), 3.74 (dt, *J* = 11.5, 8.5 Hz, 1H), 3.25 (dt, *J* = 12.9, 6.5 Hz, 1H), 2.42 (s, 5H), 2.30 – 2.10 (m, 4H), 1.97 – 1.80 (m, 2H)
^{13}C NMR	**100 MHz, $CDCl_3$**	174.9, 162.6, 141.3, 130.1, 128.0, 127.2, 121.1, 119.1, 74.7, 41.0, 34.9, 30.6, 28.3, 21.4, 11.7
HRMS *m/z*	$C_{21}H_{22}NO_4^+$ ($[M+H]^+$)	

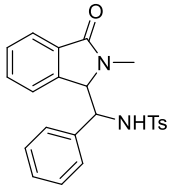
	Calculated: 267.1492	observed: 267.1491

methyl 2-methyl-3-(5-oxo-7-(p-tolyl)-2,3-dihydro-1H-pyrrolizin-7a(5H)-yl)propanoate (9bbak)



Prepared in accordance with the G***eneral Procedure (C)*** using 1-(p-tolyl)-5,6,7,7a-tetrahydro-3H-pyrrolizin-3-one **7bb** (0.1 mmol) and methyl methacrylate **8ak** (3.0 equiv.) at constant voltage mode (3.5 V). 15.3 mg, 49% yield, 3 h, d.r. = 3:1, clear oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.36 (d, *J* = 7.9 Hz, 3H), 7.22 (d, *J* = 8.0 Hz, 3H), 6.18 (s, 1H), 3.73 (q, *J* = 8.9 Hz, 1H), 3.63 (s, 1H), 3.55 (q, *J* = 8.8 Hz, 1H), 3.28 (s, 3H), 3.21 (ddd, *J* = 12.3, 8.4, 4.5 Hz, 0.3H), 2.39 (d, *J* = 6.0 Hz, 8H), 2.27 (q, *J* = 6.2 Hz, 1H), 2.20 (ddd, *J* = 12.3, 7.1, 2.6 Hz, 1H), 1.86 – 1.66 (m, 4H), 1.10 (d, *J* = 7.1 Hz, 3H), 0.90 (d, *J* = 7.1 Hz, 1H)
^{13}C NMR	**100 MHz, $CDCl_3$**	176.9, 176.2, 174.9, 174.9, 163.8, 163.6, 140.4, 140.4, 129.7, 129.5, 128.9, 128.8, 127.3, 127.2, 121.1, 120.7, 75.5, 51.8, 51.3, 40.5, 40.5, 38.7, 38.0, 35.6, 35.1, 34.7, 28.5, 28.3, 21.4, 21.4, 19.3, 18.8
HRMS *m/z*	$C_{19}H_{24}NO_3^+$ ($[M+H]^+$)	
	Calculated: 314.1751	observed: 314.1751

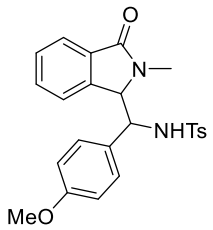
4-methyl-N-((2-methyl-3-oxoisoindolin-1-yl)(phenyl)methyl)benzenesulfonamide (11aa)



Prepared in accordance with the G***eneral Procedure (D)*** using 2-methylisoindolin-1-one **7a** (0.4 mmol) and N-benzylidene-4-methylbenzenesulfonamide **10a** (3.0 equiv.). 121.9 mg, 75% yield, 2 h, d.r. = 1:1, orange solid, m.p. 180-185 ˚C		
^{1}H NMR	**400 MHz, DMSO-*d_6***	8.45 (d, J = 8.9 Hz, 0.8H), 8.31 (s, 0.8H), 7.91 (d, J = 10.1 Hz, 1H), 7.65 (d, J = 7.4 Hz, 1H), 7.53 (td, J = 4.7, 4.1, 2.2 Hz, 2H), 7.50 – 7.39 (m, 7H), 7.35 – 7.31 (m, 1H), 7.21 (dd, J = 7.1, 2.7 Hz, 2H), 7.16 (dt, J = 7.5, 2.4 Hz, 4H), 7.11 (d, J = 8.5 Hz, 4H), 7.09 (s, 3H), 6.42 (d, J = 7.6 Hz, 1H), 5.17 (dd, J = 10.1, 4.1 Hz, 1H), 5.00 (dd, J = 9.0, 3.8 Hz, 0.8H), 4.89 (d, J = 3.9 Hz, 0.8H), 4.84 (d,

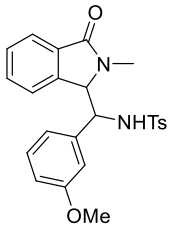
		J = 4.1 Hz, 1H), 3.10 (s, 3H), 2.75 (s, 2.4H), 2.28 (s, 2.5H), 2.24 (s, 3H)
^{13}C NMR	**100 MHz, DMSO-d_6**	167.9, 167.5, 142.7, 142.2, 142.1, 141.0, 138.5, 138.2, 137.2, 136.7, 133.3, 132.4, 130.9, 130.6, 129.1, 129.0, 128.4, 128.2, 127.8, 127.6, 127.2, 127.2, 127.1, 126.4, 126.3, 123.7, 123.7, 122.5, 122.1, 66.3, 65.6, 58.3, 56.8, 29.2, 27.6, 20.9, 20.8
HRMS *m/z*	$C_{23}H_{23}N_2O_3S^+$ ([M+H]$^+$)	
	Calculated: 407.1424	observed: 407.1423

N-((4-methoxyphenyl)(2-methyl-3-oxoisoindolin-1-yl)methyl)-4-methylbenzenesulfonamide (11ab)



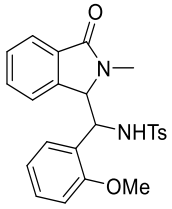
Prepared in accordance with the G***eneral Procedure (D)*** using 2-methylisoindolin-1-one **7a** (0.4 mmol) and N-(4-methoxybenzylidene)-4-methylbenzenesulfonamide **10b** (3.0 equiv.). 137.9 mg, 79% yield, 4 h, d.r. = 2:1, light yellow solid; m.p. 100-110 ˚C		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.77 (d, J = 7.5 Hz, 0.6H), 7.67 (dd, J = 6.1, 2.6 Hz, 1H), 7.57 (dd, J = 8.3, 4.3 Hz, 2.5H), 7.52 – 7.48 (m, 2.3H), 7.44 – 7.39 (m, 3H), 7.31 (td, J = 7.6, 1.2 Hz, 0.85H), 7.23 (d, J = 8.0 Hz, 1.2H), 7.12 (t, J = 8.7 Hz, 3.5H), 6.86 – 6.82 (m, 1.2H), 6.70 – 6.65 (m, 2.3H), 6.61 – 6.54 (m, 2.8H), 5.30 (d, J = 7.0 Hz, 1H), 5.05 (dd, J = 8.5, 3.5 Hz, 0.6H), 4.89 – 4.83 (m, 2.2H), 4.69 (d, J = 3.4 Hz, 0.6H), 4.47 (d, J = 8.4 Hz, 0.6H), 3.81 (s, 1.8H), 3.69 (s, 3H), 2.92 (s, 3H), 2.87 (s, 1.8H), 2.40 (s, 1.8H), 2.38 (s, 3H)
^{13}C NMR	**100 MHz, $CDCl_3$**	169.0, 168.3, 159.3, 159.3, 143.6, 143.4, 142.0, 139.7, 137.1, 136.8, 133.3, 132.8, 131.3, 131.1, 129.6, 129.5, 129.1, 128.6, 128.3, 128.0, 127.9, 127.1, 126.9, 123.8, 123.5, 123.5, 123.1, 114.0, 113.7, 66.1, 58.1, 56.2, 55.3, 55.2, 29.3, 27.9, 21.5, 21.5
HRMS *m/z*	$C_{24}H_{25}N_2O_4S^+$ ([M+H]$^+$)	
	Calculated: 437.1530	observed: 437.1525

N-((3-methoxyphenyl)(2-methyl-3-oxoisoindolin-1-yl)methyl)-4-methylbenzenesulfonamide (11ac)



Prepared in accordance with the G***eneral Procedure (D)*** using 2-methylisoindolin-1-one **7a** (0.4 mmol) and N-(3-methoxybenzylidene)-4-methylbenzenesulfonamide **10c** (3.0 equiv.). 78.6 mg, 45% yield, 4 h, d.r. = 1.8:1, white solid; m.p. 185-190 ˚C		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.73 – 7.69 (m, 1H), 7.58 – 7.54 (m, 1H), 7.48 (d, J = 8.3 Hz, 2H), 7.45 – 7.41 (m, 2H), 7.12 (d, J = 8.5 Hz, 2H), 7.04 (t, J = 8.1 Hz, 1H), 6.72 – 6.67 (m, 1H), 6.46 (d, J = 7.6 Hz, 1H), 6.30 (s, 1H), 5.17 (d, J = 6.8 Hz, 1H), 4.90 (m, 2H), 3.56 (s, 3H), 2.90 (s, 3H), 2.38 (s, 3H)
^{13}C NMR	**100 MHz, $CDCl_3$**	169.2, 159.5, 143.4, 142.1, 137.8, 136.8, 132.8, 131.5, 129.6, 129.5, 128.7, 126.9, 123.6, 123.0, 119.0, 114.0, 112.0, 66.3, 58.5, 55.1, 29.4, 21.5
HRMS *m/z*	$C_{24}H_{25}N_2O_4S^+([M+H]^+)$	
	Calculated: 437.1530	observed: 437.1529

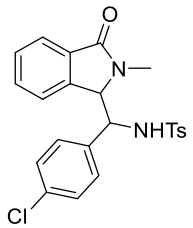
N-((2-methoxyphenyl)(2-methyl-3-oxoisoindolin-1-yl)methyl)-4-methylbenzenesulfonamide (11ad)



Prepared in accordance with the G***eneral Procedure (D)*** using 2-methylisoindolin-1-one **7a** (0.4 mmol) and (E)-N-(2-methoxybenzylidene)-4-methylbenzenesulfonamide **10d** (3.0 equiv.). 67.3 mg, 39% yield, 2 h, d.r. = 1.1:1, yellow solid, m.p. 210-215 ˚C		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.84 (d, *J* = 7.3 Hz, 1H), 7.71 (d, *J* = 7.0 Hz, 0.7H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.49 – 7.43 (m, 1H), 7.35 (dt, *J* = 8.5, 3.8 Hz, 4H), 7.19 (d, *J* = 7.6 Hz, 3H), 7.10 (d, *J* = 7.8 Hz, 1H), 7.02 (dd, *J* = 16.3, 7.6 Hz, 3H), 6.90 (d, *J* = 7.9 Hz, 2H), 6.85 (d, *J* = 6.6 Hz, 1H), 6.74 (dd, *J* = 14.2, 7.4 Hz, 2H), 5.44 – 5.36 (m, 0.7H), 5.24 (dd, *J* = 9.5, 3.6 Hz, 1H), 5.04 (dd, *J* = 8.8, 4.4 Hz, 0.7H), 4.88 (d, *J* = 4.3 Hz, 0.7H), 4.75 (d, *J* = 3.5 Hz, 1H), 4.49 – 4.42 (m, 1H), 3.90 (s, 3H), 3.76 (s, 2H), 2.98 (s, 2H), 2.74 (s, 3H), 2.38 (s, 3H), 2.33 (s, 2H)
^{13}C NMR	**100 MHz, $CDCl_3$**	169.5, 168.2, 155.9, 155.8, 143.3, 142.8, 142.7, 140.3, 137.0, 136.9, 133.5, 132.4, 131.0, 130.9, 129.4, 129.2, 129.2, 129.1, 128.9, 128.6, 128.2, 128.1, 127.0, 126.7,

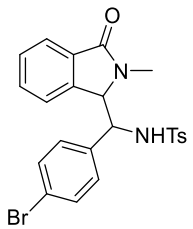
		125.1, 124.9, 123.8, 123.7, 123.2, 123.0, 120.6, 120.5, 110.4, 110.3, 65.1, 63.6, 56.1, 55.4, 55.3, 52.5, 30.3, 27.5, 21.4, 21.4
HRMS *m/z*	$C_{24}H_{25}N_2O_4S^+$ ($[M+H]^+$)	
	Calculated: 437.1530	observed: 437.1530

N-((4-chlorophenyl)(2-methyl-3-oxoisoindolin-1-yl)methyl)-4-methylbenzenesulfonamide (11ae)



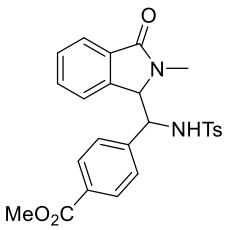
Prepared in accordance with the G***eneral Procedure (D)*** using 2-methylisoindolin-1-one **7a** (0.4 mmol) and N-(4-chlorobenzylidene)-4-methylbenzenesulfonamide **10e** (3.0 equiv.). 88.2 mg, 50% yield, 4 h, d.r. = 3:2, yellow oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.78 (d, J = 7.5 Hz, 1H), 7.67 (dd, J = 6.2, 1.9 Hz, 0.5H), 7.56 (d, J = 8.3 Hz, 2H), 7.49 – 7.39 (m, 3.7H), 7.34 – 7.29 (m, 3.2H), 7.24 (d, J = 8.0 Hz, 2.1H), 7.17 (d, J = 8.4 Hz, 2.1H), 7.09 (dd, J = 8.3, 6.7 Hz, 2.1H), 6.84 (d, J = 8.5 Hz, 1H), 6.51 (d, J = 8.1 Hz, 1H), 5.47 (d, J = 7.7 Hz, 0.5H), 5.07 (dd, J = 8.4, 3.5 Hz, 1H), 4.92 (dd, J = 7.7, 3.7 Hz, 0.5H), 4.84 (d, J = 3.7 Hz, 0.5H), 4.66 (d, J = 3.4 Hz, 1H), 4.50 (d, J = 8.4 Hz, 1H), 2.86 (s, 1.5H), 2.85 (s, 3H), 2.41 (s, 3H), 2.38 (s, 1.5H)
^{13}C NMR	**100 MHz, $CDCl_3$**	169.0, 168.0, 144.0, 143.7, 141.6, 139.0, 137.9, 136.8, 136.5, 135.2, 134.9, 134.2, 134.1, 133.3, 132.6, 131.6, 131.3, 129.8, 129.6, 129.5, 129.0, 128.9, 128.9, 128.7, 128.3, 128.2, 128.0, 127.1, 126.9, 125.3, 124.1, 123.7, 123.4, 122.7, 66.1, 65.8, 57.9, 55.8, 29.5, 27.6, 21.6, 21.5
HRMS *m/z*	$C_{23}H_{22}ClN_2O_3S^+$ ($[M+H]^+$)	
	Calculated: 441.1034	observed: 441.1034

N-((4-bromophenyl)(2-methyl-3-oxoisoindolin-1-yl)methyl)-4-methylbenzenesulfonamide (11af)



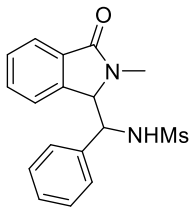
Prepared in accordance with the G***eneral Procedure (D)*** using 2-methylisoindolin-1-one **7a** (0.4 mmol) and (E)-N-(4-bromobenzylidene)-4-methylbenzenesulfonamide **10f** (3 equiv.). 121.9 mg, 44% yield, 4 h, d.r. = 3:2, orange solid, m.p. 120-125 ˚C		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.72 (t, *J* = 6.4 Hz, 1H), 7.64 (d, *J* = 6.5 Hz, 0.7H), 7.52 (d, *J* = 7.4 Hz, 1.7H), 7.45 – 7.37 (m, 6.4H), 7.29 (s, 1.7H), 7.21 (d, *J* = 7.8 Hz, 3.6H), 7.07 (d, *J* = 7.6 Hz, 3.6H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.53 (d, *J* = 7.6 Hz, 0.7H), 5.06 (d, *J* = 7.5 Hz, 0..7H), 4.92 (d, *J* = 7.9 Hz, 1H), 4.82 (s, 0.7H), 4.66 (s, 1H), 2.89 (s, 3H), 2.84 (s, 2H), 2.40 (s, 2H), 2.37 (s, 3H)
^{13}C NMR	**100 MHz, $CDCl_3$**	169.1, 168.1, 143.9, 143.5, 141.6, 139.2, 136.8, 135.6, 135.5, 133.2, 132.5, 131.7, 131.6, 131.5, 131.2, 131.1, 129.7, 129.6, 129.5, 129.3, 128.7, 128.6, 128.4, 127.0, 126.8, 126.8, 126.5, 124.0, 123.9, 123.5, 123.3, 122.8, 122.1, 122.1, 66.3, 65.7, 58.1, 56.1, 29.6, 27.7, 21.5, 21.5
HRMS *m/z*	$C_{23}H_{22}BrN_2O_3S^+$ ($[M+H]^+$)	
	Calculated: 485.0529	observed: 485.0530

methyl 4-((2-methyl-3-oxoisoindolin-1-yl)((4-methylphenyl)sulfonamido)methyl)benzoate (11ag)



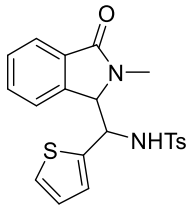
Prepared in accordance with the G***eneral Procedure (D)*** using 2-methylisoindolin-1-one **7a** (0.4 mmol), and methyl (E)-4-((tosylimino)methyl)benzoate **10g** (3.0 equiv.). 31.6 mg, 17% yield, 4 h, d.r. = 2.4:1, yellow solid, m.p. 195-200 ˚C		
^{1}H NMR	**400 MHz, $CDCl_3$**	8.01 (d, *J* = 7.8 Hz, 2H), 7.81 (t, *J* = 8.7 Hz, 2H), 7.67 (d, *J* = 7.1 Hz, 0.5H), 7.57 (d, *J* = 7.8 Hz, 2H), 7.46 – 7.40 (m, 4H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.11 – 7.03 (m, 2H), 6.40 (d, *J* = 7.7 Hz, 1H), 5.17 (dd, *J* = 8.5, 3.5 Hz, 1H), 5.07 – 4.99 (m, 0.5H), 4.87 (d, *J* = 3.4 Hz, 1H), 4.71 (d, *J* = 3.4 Hz, 1H), 4.60 – 4.45 (m, 1H), 3.95 (s, 3H), 3.88 (s, 1H), 2.86 (s, 3H), 2.81 (s, 1H), 2.39 (s, 3H), 2.36 (s, 1H)
^{13}C NMR	**100 MHz, $CDCl_3$**	169.1, 168.0, 168.0, 166.5, 143.9, 143.4, 141.8, 141.8, 141.6, 141.6, 139.0, 139.0, 136.8, 136.7, 133.2, 131.6, 131.2, 129.9, 129.9, 129.7, 129.6, 129.5, 129.4, 128.8, 127.0, 127.0, 126.8, 126.7, 124.0, 123.5, 123.3, 122.6, 66.5, 65.7, 58.3, 56.3, 52.3, 52.2, 29.6, 27.6, 21.5, 21.4
HRMS *m/z*	$C_{25}H_{25}N_2O_5S^+$ ($[M+H]^+$)	
	Calculated: 465.1479	observed: 465.1484

N-((2-methyl-3-oxoisoindolin-1-yl)(phenyl)methyl)methanesulfonamide (11ah)



Prepared in accordance with the G***eneral Procedure (D)*** using 2-methylisoindolin-1-one **7a** (0.4 mmol) and N-benzylidenemethanesulfonamide **10h** (3.0 equiv.) at constant voltage mode (6V). 33.1 mg, 25% yield, 4 h, d.r. = 1.1:1, light yellow solid; m.p. 195-200 ˚C		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.80 (d, J = 7.5 Hz, 1H), 7.73 (d, J = 7.5 Hz, 0.8H), 7.66 – 7.57 (m, 1.8H), 7.49 (m, 2.8H), 7.42 (m, 4H), 7.37 – 7.28 (m, 5.2H), 6.50 (d, J = 7.6 Hz, 1H), 5.95 (d, J = 9.4 Hz, 0.8H), 5.37 (dd, J = 9.7, 3.6 Hz, 1H), 5.23 (dd, J = 9.3, 3.3 Hz, 0.8H), 4.91 (d, J = 3.3 Hz, 0.8H), 4.77 (d, J = 3.6 Hz, 1H), 4.73 (d, J = 9.6 Hz, 1H), 3.33 (s, 3H), 2.80 (s, 2.4H), 2.71 (s, 3H), 2.47 (s, 2.4H)
^{13}C NMR	**100 MHz, $CDCl_3$**	169.4, 168.4, 142.5, 139.4, 137.4, 136.8, 133.5, 132.7, 131.7, 131.1, 129.2, 129.2, 129.0, 128.9, 128.6, 128.4, 126.7, 126.4, 123.8, 123.6, 123.5, 122.9, 67.1, 66.1, 58.8, 56.4, 42.4, 41.7, 29.9, 28.0
HRMS *m/z*	$C_{17}H_{19}N_2O_3S^+$ ($[M+H]^+$)	
	Calculated: 331.1111	observed: 331.1116

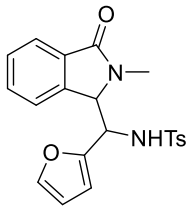
4-methyl-N-((2-methyl-3-oxoisoindolin-1-yl)(thiophen-2-yl)methyl)benzenesulfonamide (11ai)



Prepared in accordance with the G***eneral Procedure (D)*** using 2-methylisoindolin-1-one **7a** (0.4 mmol) and (E)-4-methyl-N-(thiophen-2-ylmethylene)benzenesulfonamide **10i** (3 equiv.). 121.9 mg, 64% yield, 4 h, d.r. = 3:1, orange solid, m.p. 90-95 ˚C		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.81 (d, *J* = 7.5 Hz, 0.7H), 7.76 – 7.72 (m, 1H), 7.71 – 7.68 (m, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.61 (d, *J* = 8.1 Hz, 1.7H), 7.51 – 7.48 (m, 1.7H), 7.45 (d, *J* = 7.5 Hz, 0.7H), 7.35 (t, *J* = 7.6 Hz, 0.7H), 7.29 (d, *J* = 8.0 Hz, 1.7H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 4.9 Hz, 1H), 6.97 (t, *J* = 4.4 Hz, 0.7H), 6.87 (d, *J* = 3.6 Hz, 0.7H), 6.68 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.64 (d, *J* = 7.6 Hz, 0.7H), 6.37 (d, *J* = 3.5 Hz, 0.7H), 5.35 – 5.29 (m, 0.7H), 5.21 (dd, *J* = 7.1, 4.2 Hz, 1H), 4.96 (d, *J* = 4.2 Hz, 1H), 4.88 (d, *J* = 7.1 Hz, 1H), 4.83 (d, *J* = 3.2 Hz, 0.7H), 4.31 (d, *J* = 8.8

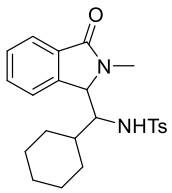
		Hz, 0.7H), 3.01 (s, 3H), 2.88 (s, 2H), 2.43 (s, 2H), 2.41 (s, 3H)
^{13}C NMR	**100 MHz, $CDCl_3$**	168.7, 168.3, 143.9, 143.8, 141.2, 140.4, 139.5, 137.9, 137.0, 136.4, 133.3, 133.3, 131.5, 131.4, 129.7, 129.7, 129.3, 129.0, 127.3, 127.1, 127.0, 126.6, 126.2, 125.9, 125.7, 125.6, 123.9, 123.6, 123.3, 122.9, 66.1, 65.4, 54.4, 53.7, 28.4, 28.0, 21.5, 21.5
HRMS *m/z*	$C_{21}H_{21}N_2O_3S_2^+$ ([M+H]$^+$)	
	Calculated: 413.0988	observed: 413.0989

N-(furan-2-yl(2-methyl-3-oxoisoindolin-1-yl)methyl)-4-methylbenzenesulfonamide (11aj)



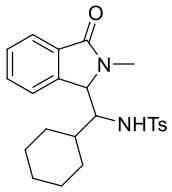
Prepared in accordance with the G***eneral Procedure (D)*** using 2-methylisoindolin-1-one **7a** (0.4 mmol) and N-(furan-2-ylmethylene)-4-methylbenzenesulfonamide **10j** (3.0 equiv.). 49.2 mg, 31% yield, 4 h, d.r. = 1.4:1, brown solid; m.p. 165-170 ˚C		
^{1}H NMR	**400 MHz, DMSO-*d*$_6$**	8.43 (d, J = 9.1 Hz, 0.6H), 7.85 (d, J = 9.8 Hz, 1H), 7.68 (d, J = 7.0 Hz, 1H), 7.61 – 7.55 (m, 3.6H), 7.47 (m, 6.5H), 7.26 (d, J = 7.9 Hz, 2H), 7.21 (d, J = 7.8 Hz, 1.2H), 6.52 (d, J = 7.4 Hz, 1H), 6.28 (s, 1H), 6.21 (s, 0.6H), 5.90 (s, 1H), 5.83 (s, 0.6H), 5.13 (ddd, J = 13.7, 9.5, 3.8 Hz, 1.7H), 4.94 (dd, J = 11.7, 3.7 Hz, 1.7H), 3.08 (s, 3H), 2.76 (s, 1.8H), 2.32 (s, 4.8H)
^{13}C NMR	**100 MHz, DMSO-*d*$_6$**	168.4, 168.1, 151.1, 150.7, 143.0, 142.9, 142.9, 142.7, 142.7, 141.3, 138.8, 138.6, 133.7, 132.9, 131.5, 131.4, 129.7, 129.7, 128.9, 128.8, 126.9, 126.8, 124.0, 123.8, 123.0, 122.6, 111.0, 110.9, 108.8, 108.4, 64.7, 63.9, 53.2, 52.0, 28.8, 28.0, 21.4
HRMS *m/z*	$C_{21}H_{21}N_2O_4S^+$ ([M+H]$^+$)	
	Calculated: 397.1217	observed: 397.1219

N-(cyclohexyl(2-methyl-3-oxoisoindolin-1-yl)methyl)-4-methylbenzenesulfonamide (11ak-1)



Prepared in accordance with the G***eneral Procedure (D)*** using 2-methylisoindolin-1-one **7a** (0.4 mmol) and (E)-N-(cyclohexylmethylene)-4-methylbenzenesulfonamide **10k** (3 equiv.) at constant voltage mode (6V). 34.2 mg, 20% yield, (29% total yield), 2 h, yellow solid, m.p. 120-125 ˚C		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.73 (dd, J = 6.5, 1.6 Hz, 1H), 7.65 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 7.1 Hz, 1H), 7.47 – 7.38 (m, 2H), 7.24 (d, J = 8.1 Hz, 2H), 4.93 (d, J = 8.5 Hz, 1H), 4.68 (d, J = 3.5 Hz, 1H), 3.70 (ddd, J = 8.5, 5.3, 3.6 Hz, 1H), 3.12 (s, 3H), 2.41 (s, 3H), 1.58 – 1.43 (m, 3H), 1.31 – 1.21 (m, 2H), 1.07 – 0.78 (m, 5H), 0.61 (q, J = 12.0 Hz, 1H)
^{13}C NMR	**100 MHz, $CDCl_3$**	169.0, 143.6, 143.0, 137.3, 132.5, 131.4, 129.7, 128.5, 126.9, 123.7, 123.0, 63.8, 58.9, 37.6, 31.2, 29.0, 28.5, 26.0, 25.7, 25.7, 21.6
HRMS *m/z*	$C_{23}H_{29}N_2O_3S^+$ ($[M+H]^+$)	
	Calculated: 413.1893	observed: 413.1897

N-(cyclohexyl(2-methyl-3-oxoisoindolin-1-yl)methyl)-4-methylbenzenesulfonamide (11ak-2)



Prepared in accordance with the G***eneral Procedure (D)*** using 2-methylisoindolin-1-one **7a** (0.4 mmol) and N-(cyclohexylmethylene)-4-methylbenzenesulfonamide **10k** (3 equiv.) at constant voltage mode (6V). 4 mg, 9% yield, (29% total yield), 2 h, yellow solid, m.p. 190-195 ˚C		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.77 (dt, J = 7.1, 0.9 Hz, 1H), 7.55 – 7.46 (m, 4H), 7.37 (dd, J = 7.4, 1.1 Hz, 1H), 7.27 (d, J = 0.9 Hz, 1H), 7.25 (s, 1H), 4.59 (d, J = 1.7 Hz, 1H), 3.81 – 3.72 (m, 2H), 2.82 (s, 3H), 2.43 (s, 3H), 2.01 (d, J = 12.7 Hz, 1H), 1.90 (d, J = 12.4 Hz, 1H), 1.85 – 1.78 (m, 2H), 1.73 – 1.64 (m, 2H), 1.35 – 1.08 (m, 6H)
^{13}C NMR	**100 MHz, $CDCl_3$**	167.9, 143.4, 140.9, 138.1, 133.8, 131.4, 129.7, 129.0, 126.4, 124.1, 122.4, 63.0, 58.9, 40.4, 31.1, 30.4, 27.9, 26.0, 25.9, 25.9, 21.6
HRMS *m/z*	$C_{23}H_{29}N_2O_3S^+$ ($[M+H]^+$)	
	Calculated: 413.1893	observed: 413.1895

Chapter 3.

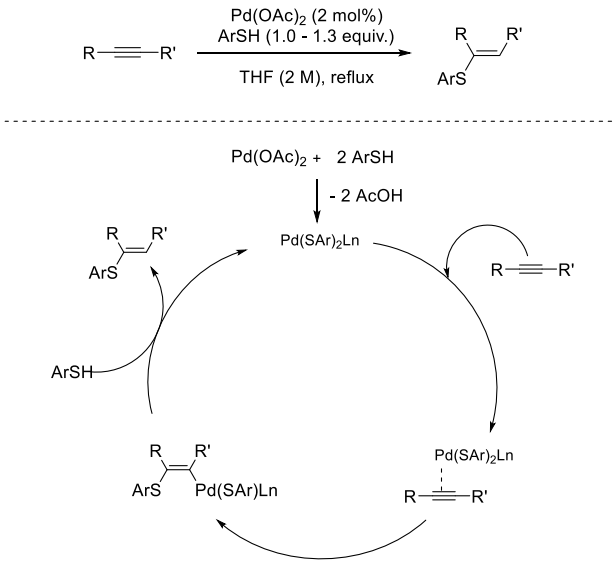
Synthesis of Dithioacetals via Gold-Catalyzed Hydrothiolation of Vinyl Sulfides

3.1. Introduction

3.1.1. Transition metal-catalyzed hydrothiolation

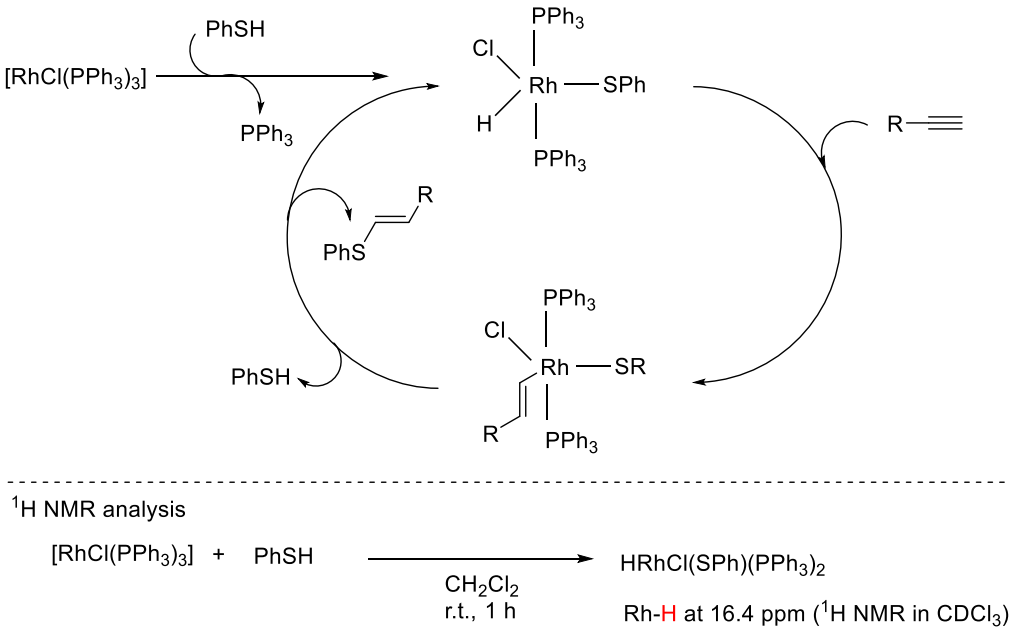
To produce sulfur-containing organic frameworks, using transition metal-catalyzed hydrothiolation of unsaturated C-C bonds in olefin, alkyne and allene moiety is an interesting method. Including synthetic chemistry, medicinal chemistry, and functional material science the sulfur derivatives have wide application. Because of the potentials of the organosulfur derivatives that can poison the transition metal catalysts, the hydrothiolation methods on transition metal catalyzed addition are scarce. Compared to development of transition metal-catalyzed hydrothiolation of alkynes and allenes, the hydrothiolation of olefins has been less underdeveloped because of their reactivity compared to alkynes and allenes. The hydrothiolation of olefin containing heteroatoms are challenges, this drives the motivation of the development of transition metal catalyzed hydrothiolation of heteroatom containing olefins.

In 1991, Kuniyasu et al. reported the first example of transition-metal catalyzed addition of aromatic thiols to acetylenes. By using $Pd(OAc)_2$, the reaction successfully afforded the Markovnikov adducts. The proposed mechanism is included in scheme 3-1.[32] First, the ligand exchange of the AcO ligand with the ArS group occurs in presence of acetylene to give AcOH and an active catalyst complex. Next, the coordination of acetylene to the Pd complex is followed. The Markovnikov adduct is obtained by syn-thiopalladation to acetylene to form cis-vinylpalladium and finally trapping the vinyl group by aryl thiol or AcOH with the regeneration of the catalyst.



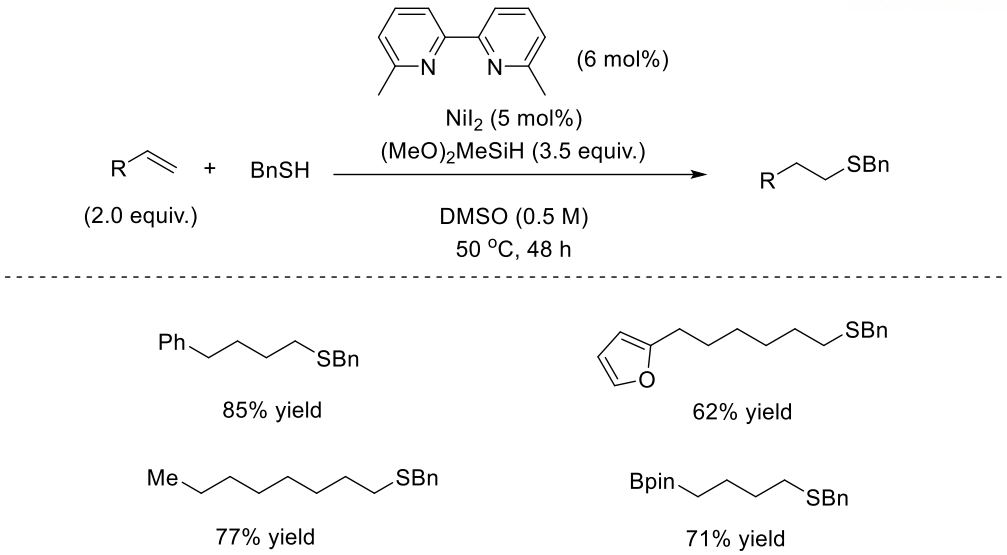
Scheme 3-1. Pd-catalyzed hydrothiolation.

Ogawa's group studied the mechanism for Rh catalyzed hydrothiolation. The reaction pathway for Wilkinson's catalyst is show on Scheme 3-2.[33] Also, NMR studies for mechanism were described. Based on the ^{1}H NMR in $CDCl_3$, the chemical shift for hydride (Rh-H) at 16.4 ppm was disappeared and new double peak appeared at 5.1 ppm. They have developed a selective anti-Markovnikov addition of benzenethiol to alkynes. An excess amount of benzenethiol was used for giving the vinyl sulfide with anti-Markonikov selectivity.



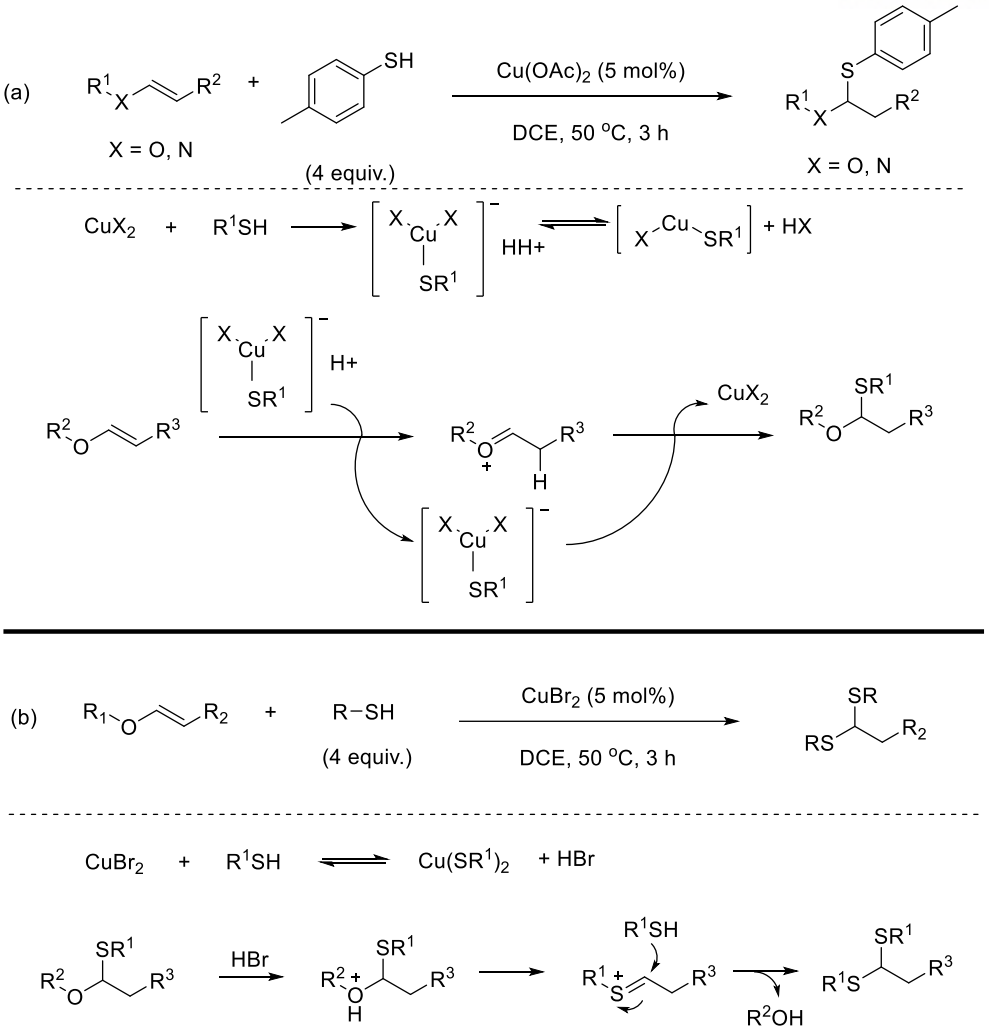
Scheme 3-2. Rh(Wilkinson's catalyst)-catalyzed hydrothiolation.

By using Ni catalyst, anti-Markovnikov hydrothiolation on alkene has been reported (Scheme 3-3).[34] A series of terminal alkenes were used for effective hydrothiolation under mild reaction condition. As a single isomer in a good to excellent yield, the linear form of desired thioether was made.



Scheme 3-3. Ni-catalyzed hydrothiolation.

Xi et al. described synthesis of Cu-catalyzed Markovnikov hydrothiolation products and thioacetals (Scheme 3-4).[35] By simply switching copper catalysts, they developed efficient methods for both Markovnikov-type products and thioacetals from same starting alkene materials and thiols. For Markovnikov-type hydrothiolation product, a copper thiolate intermediate is generated in situ. After protonation on alkene gives an oxonium ion intermediate and then the thiolation is followed to generated final product. If $CuBr_2$ is used for the catalyst instead of $Cu(OAc)_2$, a thionium ion intermediate is generated because of the HBr generation from the reaction with thiol. The reaction of thionium ion intermediate with thiol generates desired thioacetal product by releasing an alcohol as a byproduct. The difference of these reaction is coming from the reaction with thiol. In the reaction, the cause of $Cu(OAc)_2$ as catalyst, it generates more weaker acetic acid than the reaction of $CuBr_2$, which cannot facilitate the hydrothiolation.

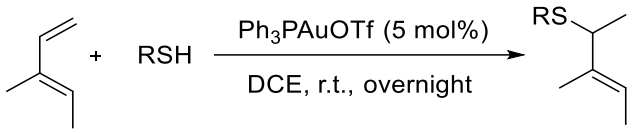


Scheme 3-4. Cu-catalyzed hydrothiolation.

3.1.2. Gold catalyzed hydrothiolation

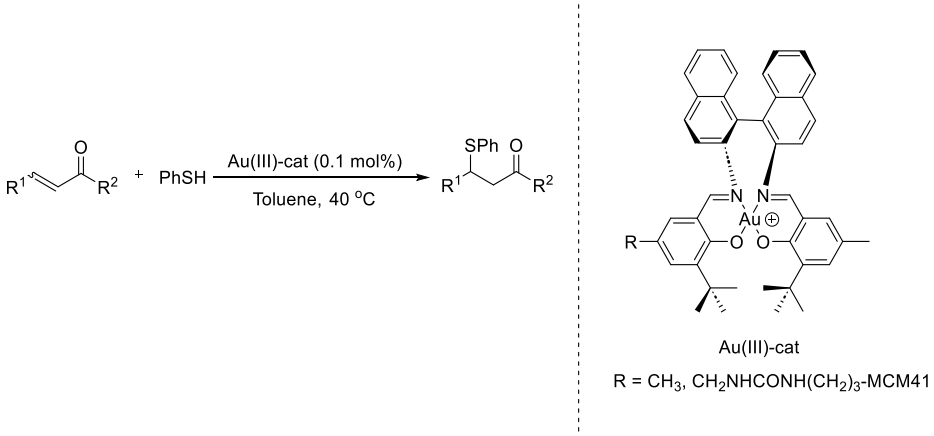
Because of gold catalysis's carbophilic nature toward π-bonds, the synthetic community gain much attention in the last decade. To the hydrothiolation of unsaturated bonds such as alkynes, allenes, and olefins, gold catalysis has a significant contribution.

He and co-workers reported gold-catalyzed hydrothiolation of conjugated olefins in mild conditions (Scheme 3-5).[36] Thiol additions to conjugated olefins were catalyzed by Au(I) catalyst. Various thiols which substituted by either electron-donating or electron-withdrawing group tolerated for the reaction system.



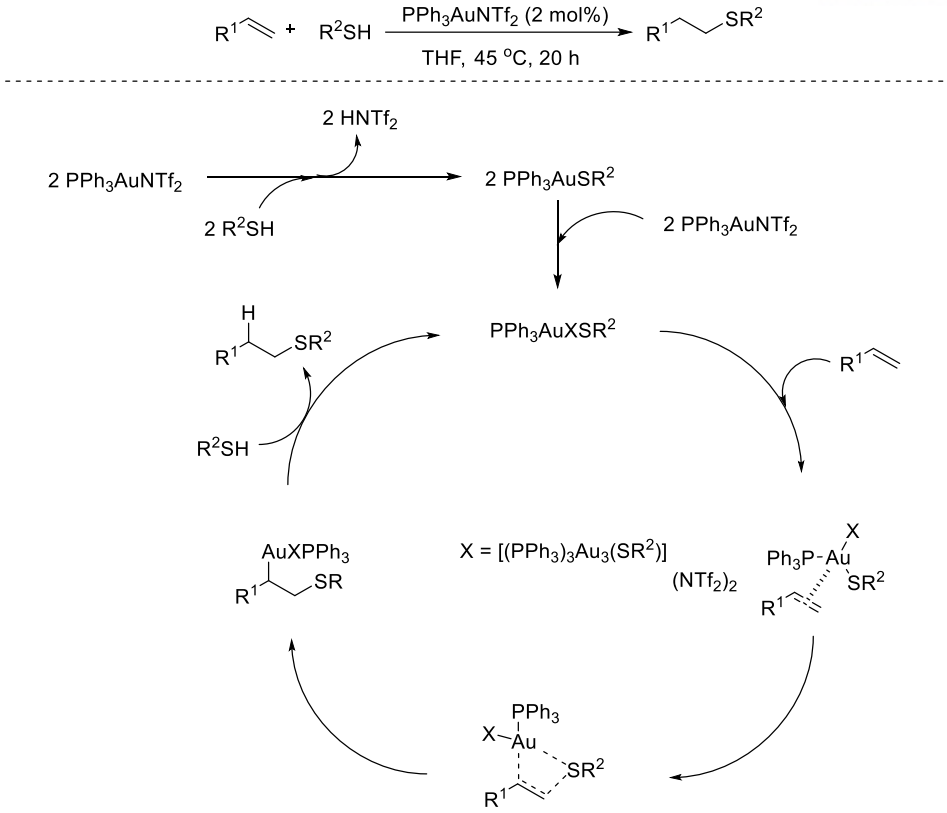
Scheme 3-5. Gold(I)-Mediated Hydrothiolation of Conjugated Olefins.

Sánchez and co-workers described the hydrothiolation of activated olefins by gold catalyst (Scheme 3-6).[37] They reported gold catalyzed hydrothiolation of alkynes and electron-deficient olefins having high anti-Markovnikov selectivity. The gold complexes are well-defined soluble and heterogenized in the reaction, furthermore, heterogenized catalysts could be recycled in several successive runs by simple filtration without loss of efficiency, representing a green methodology for preparing vinyl and alkyl sulfides.



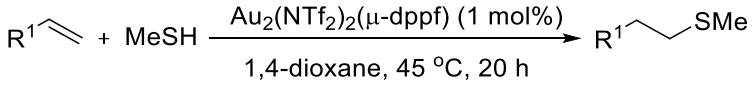
Scheme 3-6. Gold-catalyzed hydrothiolation of activated olefins

In 2016, a novel gold-catalyzed hydrothiolation of unactivated alkenes was reported by Ogawa group, which proceeds effectively to give the anti-Markovnikov-selective adducts as products (Scheme 3-7).[38] Conventional transition-metal-catalyzed reactions of organo-sulfur compounds to unactivated alkenes are difficult. However, this research reveal that the highly cationic gold catalyst enables selective hydrothiolation of unactivated alkenes to afford the desired anti-Markovnikov adduct.



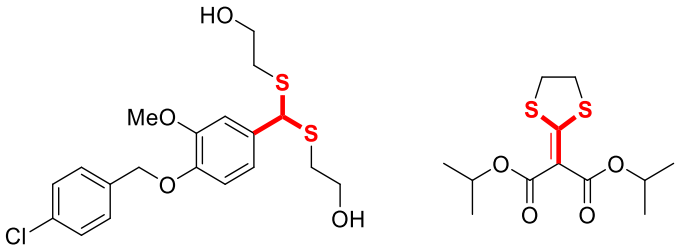
Scheme 3-7. Gold-catalyzed hydrothiolation by Ogawa group

A protocol for the Au-promoted anti-Markovnikov hydrothiolation of olefins using ex situ generated methanethiol was reported by Kristensen at el. (Scheme 3-8).[39] The use of S-methylisothiourea hemisulfate salt as a solid precursor for methanethiol generation ensures a safe and reliable deliverance of a stoichiometric amount of this thiol.



Scheme 3-8. Gold-promoted anti-Markovnikov hydrothiolation of olefin

3.1.3. Preparation of Dithioacetals



Xiangcaoliusuobingmi
Good anti-CMV/PVY activity

Isoprothiolane

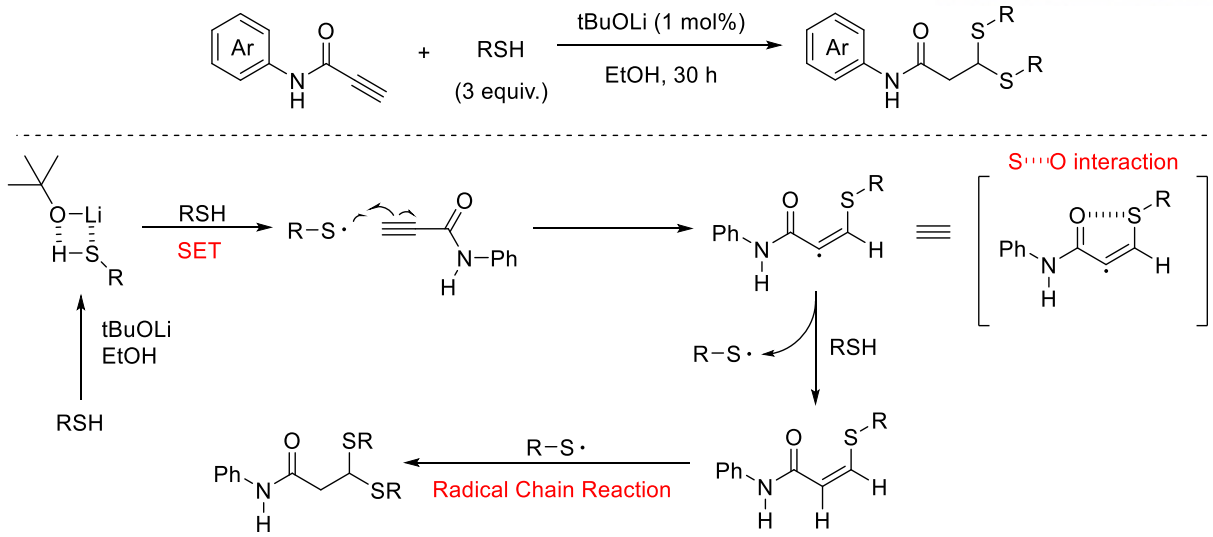
Figure 3-1. Biologically active compounds containing the dithioacetals

In umpolung chemistry dithioacetals are key intermediates. While synthetic routes for dithioacetal preparation mainly employ carbonyl compounds as substrates, transition metal-catalyzed hydrothiolation of alkynes with thiols represents an attractive alternative strategy. The utility of dithioacetals includes not only umpolung intermediates, but anti-germicidal properties including antiviral, antibacterial, antifungal, and activators for plant resistance induction (Figure 3-1).[40]

3.1.3.1. Dithioacetal preparation using terminal alkyne and thiols

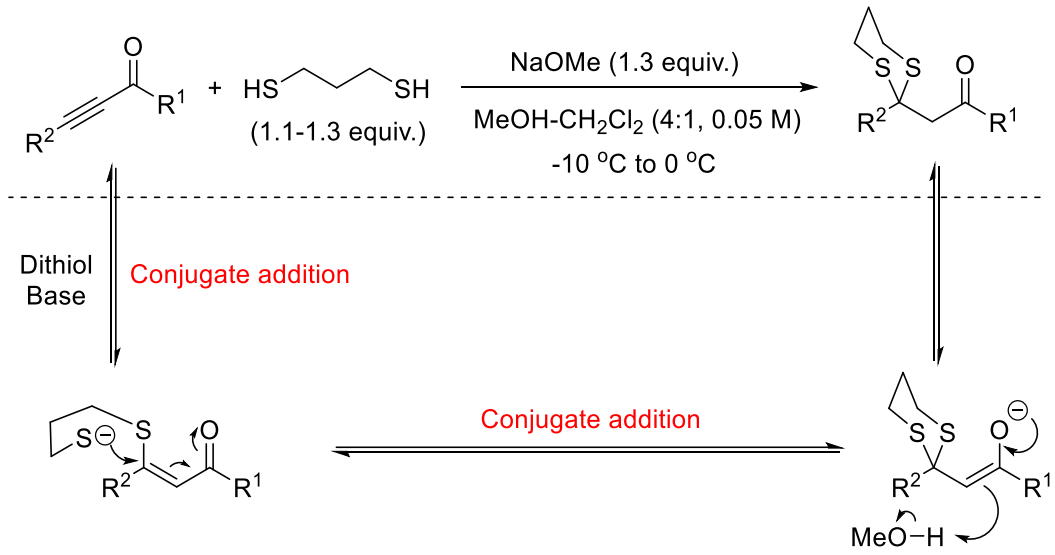
Considerable efforts have been made to access dithioacetals from alkynes based on transition metal catalysis or using a base-catalyzed crosslinking reaction. The fact that the contemporary methods lead to the formation of symmetrically substituted dithioacetals prompted us to develop the synthesis of unsymmetrical dithioacetals by hydrothiolation of vinyl sulfides based on gold catalysis.

Pramanik and coworkers reported the selective addition of aliphatic thiols to terminal alkynes using lithium tert-butoxide in ethanol as a solvent (scheme 3-9).[41] The reaction proceeded through the generation of thiyl radical, and the amide group in limiting reagent could help in the activation of the alkyne, which made to thioacetalization through the generation of a (Z)-selective anti-Markovnikov vinyl sulfide. The selectivity was controlled by an intramolecular sulfur atom and oxygen interaction which was formed during the formation of vinyl sulfides.



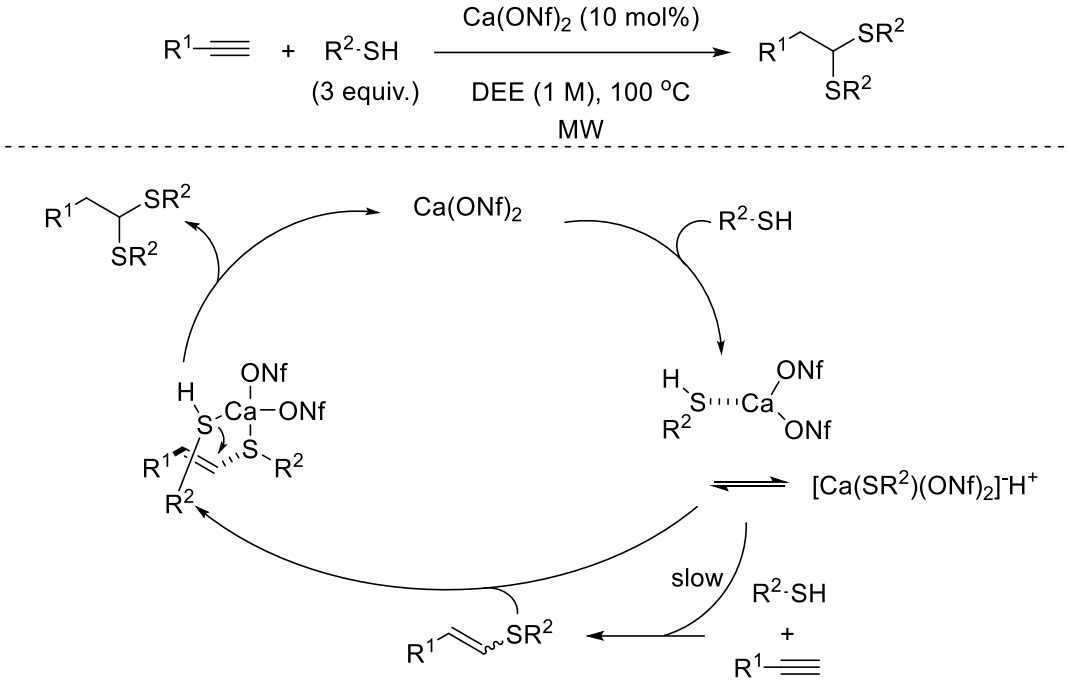
Scheme 3-9. Dithioacetal synthesis using tBuOLi

In 2003, an efficient method for the conjugate addition of dithiols to propargylic ketones was reported (scheme 3-10).[42] By the double conjugate addition process, β-keto 1,3-dithianes can be formed as the desired products. For the substrate scopes, the research group did not limit the scope in propargylic ketones but also reported esters and aldehydes containing compounds.



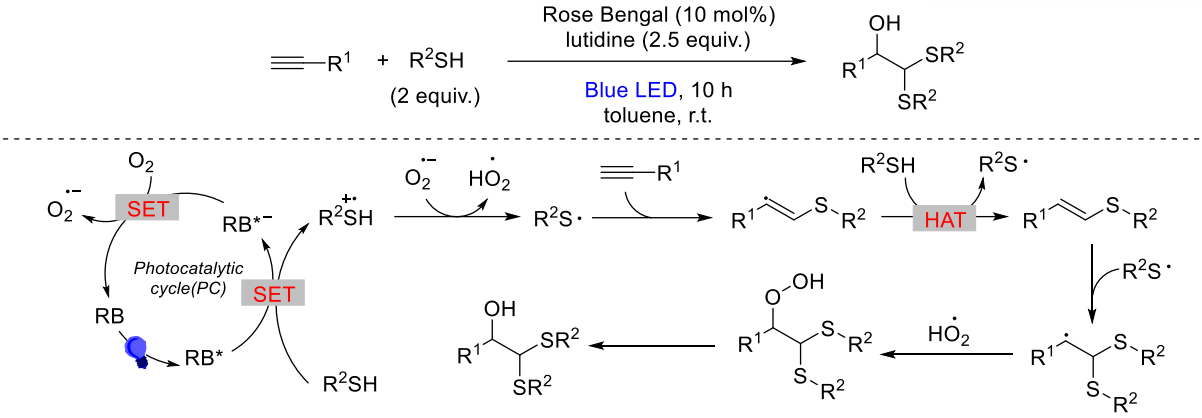
Scheme 3-10. β-keto 1,3-dithianes preparation using dithiol

Kobayashi group reported bis-hydrothiolation of alkynes providing anti-Markovnikov dithioacetals (Scheme 3-11).[43] By synthesizing Lewis-acidic catalyst which is $Ca(ONf)_2$, the reaction achieved the highly selective and wide substrate scope as results. In mechanism, the transition states for $Ca(ONf)_2$, thiol and vinyl sulfide, the catalyst interacts with the S atoms for the thiol and the vinyl sulfide. Coordination of the thiol to Calcium atom might increase its nucleophilicity as well as the acidity of the SH proton, and the nucleophilic addition of the thiol occurs from the same side of the coordinated calcium.



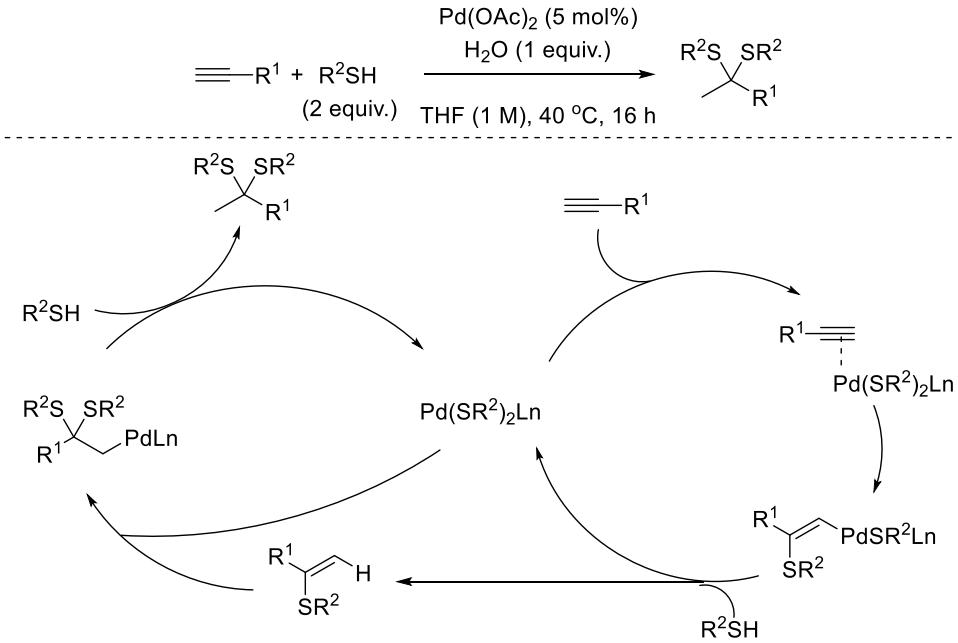
Scheme 3-11. Dithioacetal synthesis using calcium catalyst

Manhas et al. reported visible light mediated strategy for the synthesizing the β-hydroxydithioacetals using thiophenol and terminal alkynes (Scheme 3-12).[44] The reaction can be performed in aerobic condition. The reaction proceeds well both aromatic and aliphatic alkynes. By using radical scavenger TEMPO and superoxide radical scavenger benzoquinone, the reaction process was completely inhibited of forming desired product.



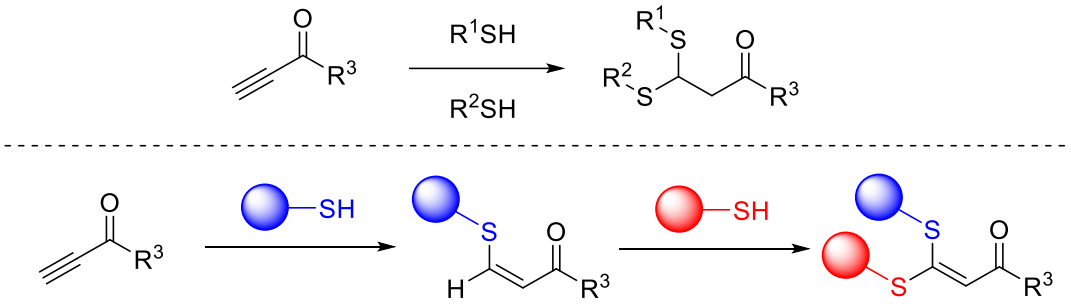
Scheme 3-12. Dithioacetal synthesis using photoredox chemistry

Ogawa group reported double hydrothiolation of terminal acetylenes with thiols catalyzed by $Pd(OAc)_2$ (Scheme 3-13).[45] By using 2 equivalents of thiols in the presence of Pd catalyst and H_2O, caused regioselective double hydrothiolation of terminal acetylenes. As a result, corresponding dithioketals in moderate yields.



Scheme 3-13. Dithioacetal synthesis using palladium catalyst

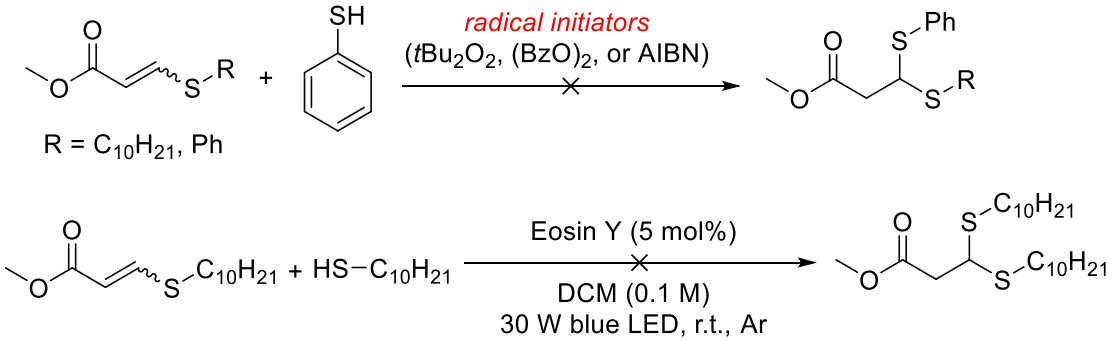
Herck and coworkers reported covalent adaptable networks mediated preparation of thiol-yne using simple activated alkynes (Scheme 3-14).[46] By using a various series of activated alkynes have been synthesized and produced dynamic thioacetal linkages.



Scheme 3-14. Dithioacetal synthesis using covalent adaptable networks

3.1.3.2. Initial attempts to approach the dithioacetals

Before designing unsymmetrical dithioacetals synthesis, we explored the radical addition of thiyl radicals to vinyl sulfides by employing radical initiators including $^{t}Bu_2O_2$, $(BzO)_2$, or AIBN, all of which failed to give the corresponding products (Scheme 3-15).[47] Also, we tried a visible light irradiation reaction. Bhat et al. reported visible light-mediated hydrothiolation of terminal alkynes. Instead of alkynes, we attempted vinyl sulfide. Unfortunately, the result turned out to be unsuccessful.[48]



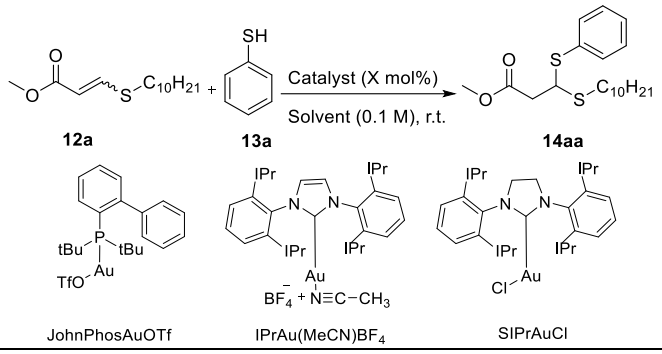
Scheme 3-15. Initial trials to synthesize dithioacetals.

3.2. Optimization of reaction conditions

Methyl 3-(decylthio)acrylate **12a** and benzenethiol **13a** as substrates, we began the screening of the reaction conditions. The various silver catalysts failed to give the addition product in presence of **12a** and **13a** in DCE solvent at room temperature (Table 3-1, entries 1-2). Based on these results, we tried several gold catalysts to run the reactions. Various gold catalysts having different ligands were screened. (Table 3-1, entries 3-9). The gold catalyst with JohnPhos ligand and PPh_3AuNTf_2 gave the desired product. Furthermore, comparing the results of catalyst loadings, only 1 mol% was sufficient to

give the addition product (Table 3-1, entries 9-12). It is not clear why low catalyst loading give better yield than the higher catalyst loading entries, but during the reactions, some unidentified spots were observed. With solvent screening, the chlorinated solvents were appropriate to give the product, and DCE turned to be better yield than DCM (Table 3-1, entries 12-15). Without the catalyst, the reaction did not proceed (Table 3-1, entry 16).

Table 3-1. Optimization of synthesis of dithioacetal



Entry[a]	Cat (X mol%)	Solvent	% Yield of 3aa[b]
1	AgOTf (5 mol%)	DCE	-
2	$AgNTf_2$ (5 mol%)	DCE	-
3	JohnPhosAuOTf (5 mol%)[c]	DCE	79
4	$IPrAu(MeCN)BF_4$ (5 mol%)[d]	DCE	-
5	SIPrAuCl (5 mol%)[e]	DCE	-
6	$NaAuCl_4$ (5 mol%)	DCE	-
7	$AuCl_3$ (5 mol%)	DCE	-
8	PPh_3AuCl (5 mol%)	DCE	-
9	PPh_3AuNTf_2 (5 mol%)	DCE	82
10	PPh_3AuNTf_2 (10 mol%)	DCE	69
11	PPh_3AuNTf_2 (2 mol%)	DCE	88
12	PPh_3AuNTf_2 (1 mol%)	DCE	93
13	PPh_3AuNTf_2 (1 mol%)	DCM	85
14	PPh_3AuNTf_2 (1 mol%)	Toluene	-
15	PPh_3AuNTf_2 (1 mol%)	THF	-
16	-	DCE	-

[a] **12a** (0.2 mmol), **13a** (1.5 equiv., 0.3 mmol), solvent (2 mL), All the reactions were carried out closed reaction tubes at room temperature. [b] Yields are for isolated products.

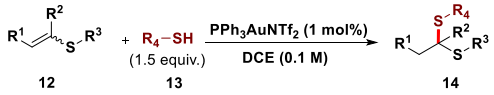
[c] in situ generated from 5 mol% JohnPhosAuCl and 5 mol% AgOTf.

[d] $IPrAu(MeCN)BF_4$: 1,3-Bis(2,6-di-i-propylphenyl)imidazol-2-ylidene(acetonitrile)gold(I) tetrafluoroborate.

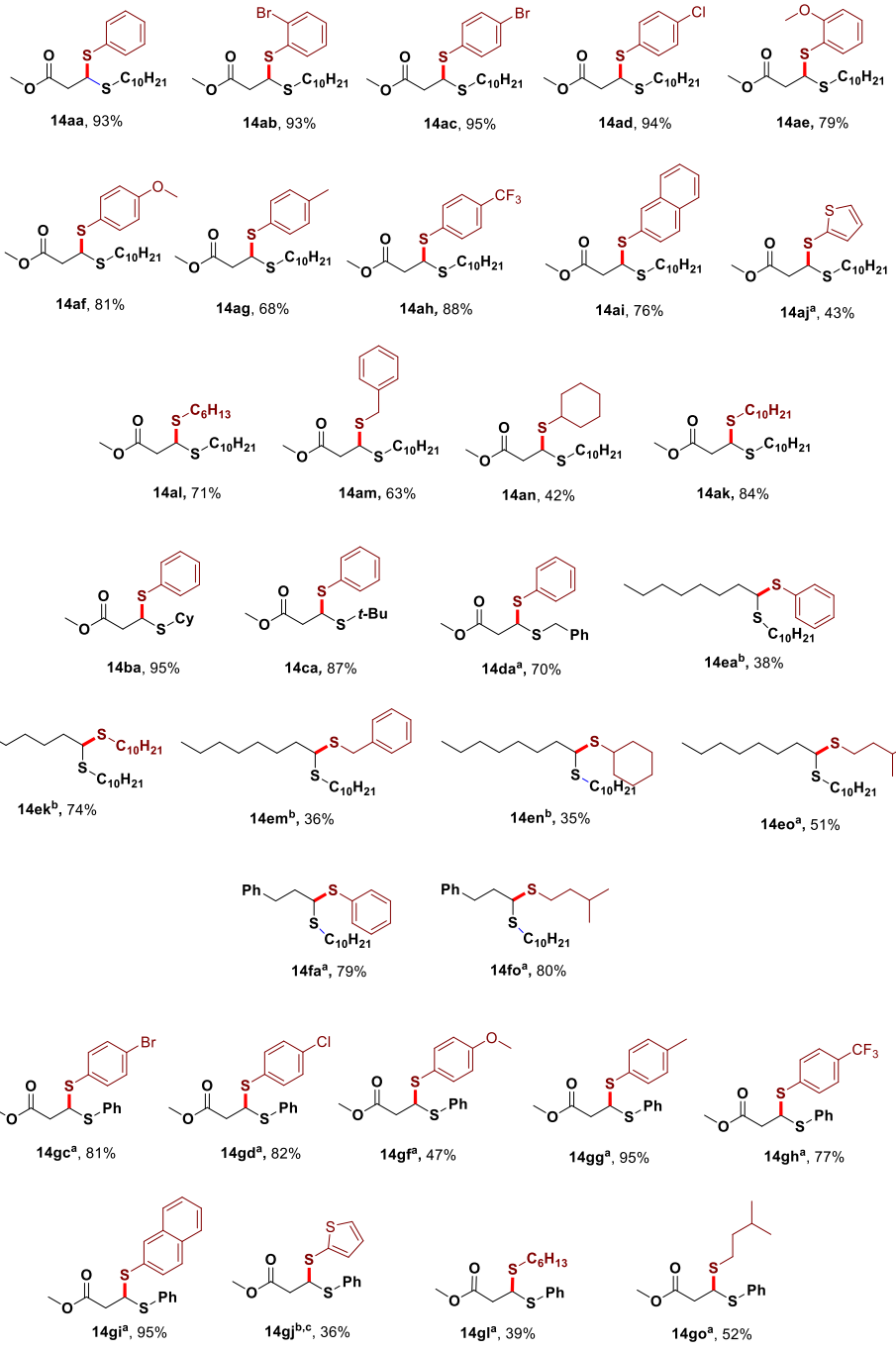
[e] SIPrAuCl: Chloro{1,3-bis[2,6-di-i-propylphenyl]-4,5-dihydroimidazol-2-ylidene}gold(I)

3.3. Substrate scope

Table 3-2. Substrate scope of Dithioacetals



12 13 14

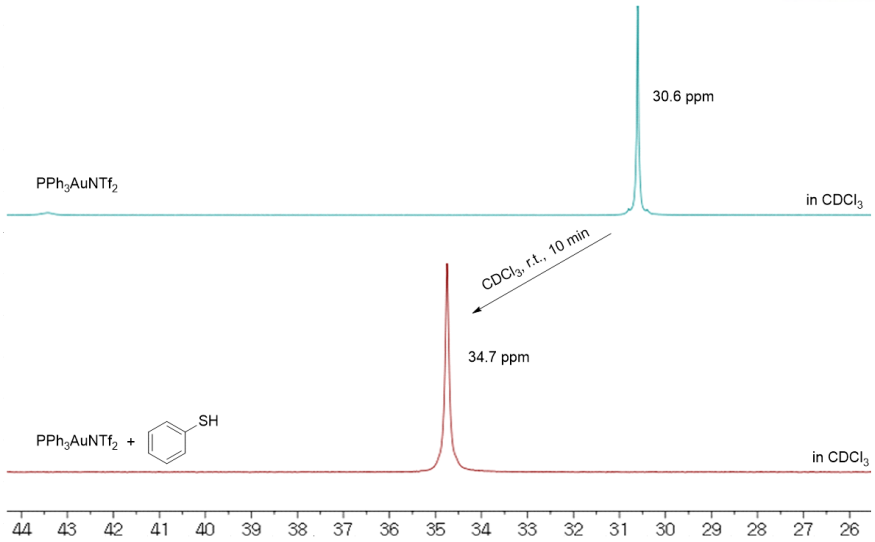


Reaction performed with **12** (0.2 mmol), **13** (0.3 mmol), PPh_3AuNTf_2 (1 mol%), DCE (0.1 M) under N_2 at room temperature.
[a] 50 °C.
[b] 90 °C(reflux).
[c] NMR yield

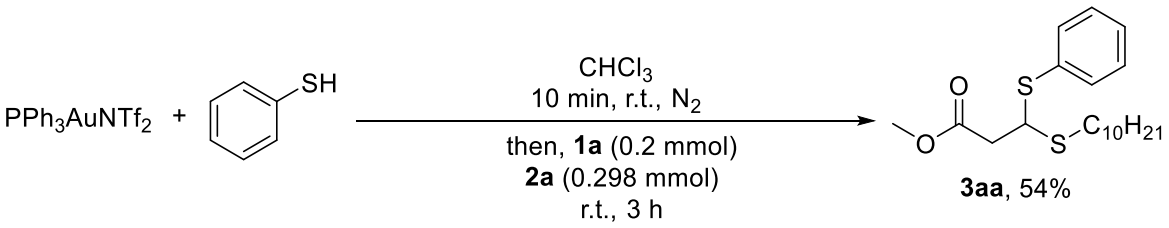
With optimized conditions in hand, began to test the various aryl thiol reactivity. First, the reactivity of conjugated alkyl vinyl sulfide **12a** was examined. Thiols which containing halide groups proceeded smoothly in the reaction and gave corresponding thioacetals in excellent yield (**14ab-14ad**). Additionally, both of electron rich thiols and electron poor thiols gave the corresponding desired products in good to excellent yields (**14ae-14ah**). Naphtahlene-2-thiol **13i** was reacted well with **12a** to afford **14ai**. When thiophene-2-thiol **13j** was used as an addition partner, the product **14aj** was obtained in moderate yield comparing to other thiols. Not only $-C_{10}H_{21}$ substituted vinyl sulfide, but also cyclohexyl-, t-Bu-, benzyl substituted vinyl sulfide was tested to find out their reactivity toward benzenethiol **13a**. Even sterically hindered alkyl substituents gave excellent yields (**14ba, 14ca, 14da**). Not limited to aryl thiols, next we examined aliphatic thiols as reaction partners. Primary thiols afford good yields with **12a** (**14ak-14am**). More hindered thiol cyclohexylthiol **13n** afforded corresponding product in moderate yield. Also, not only the ester-conjugated vinyl sulfide **12a**, but also the alkyl substituted vinyl sulfides **12e** and **12f** was participated to the reaction as starting materials. They also provide hydrothiolated product in moderate to good yields (**14ea, 14ek, 14em, 14en, 14eo, 14fa, 14fo**). Next, an aryl vinyl sulfide **12g** reactivity was examined. The results turned out that both aryl and alkyl thiol was sufficient for reaction partners, giving moderated to excellent yield for corresponding products (**14gc – 14go**).

3.4. Mechanistic studies and proposed mechanism

^{31}P NMR experiment was performed to find out whether gold catalyst complex I is generating in-situ while running the reactions (Scheme 3-16). The ^{31}P NMR spectrum shows the peak at 30.6 ppm when only PPh_3AuNTf_2 was taken in $CDCl_3$, without the benzenethiol. However, the peak that showed in 30.6 ppm was disappeared and showed new peak at 34.7 ppm with the benzenethiol and PPh_3AuNTf_2 in $CDCl_3$. These results support the formation of new gold complex, which generates in-situ. Furthermore, a stepwise reaction was performed (Scheme 3-17). Using catalytic amounts of gold catalyst and thiol in $CHCl_3$, 1a was added after the preformation of gold-thiol catalyst complex. The desired product was obtained in 54% yield after 3 h. This indicates that the hydrothiolation reaction proceeds after the gold catalyst complex is generated in-situ.



Scheme 3-16. ^{31}P NMR studies.



Scheme 3-17. Stepwise reaction.

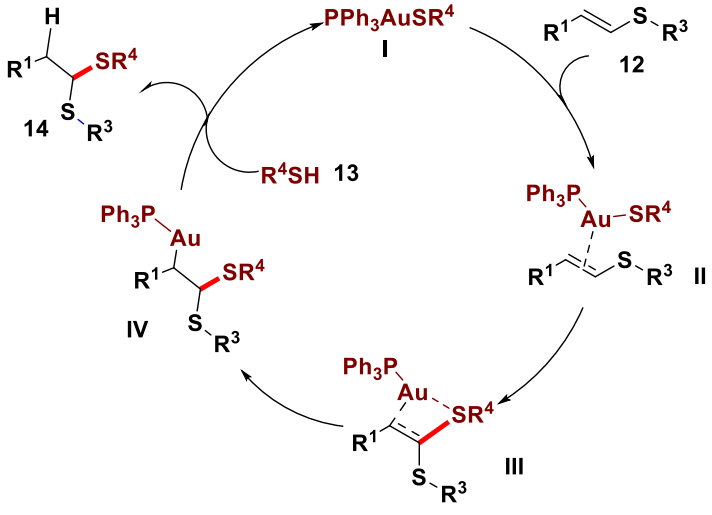


Figure 3-18. Proposed mechanism.

A plausible mechanistic pathway for the thioacetal formation is shown in Scheme 3-18. Based on the NMR experiments above and the previously literature report,[38] it is proposed that the in-situ generated gold catalyst complex **I** is involved in the activation of the vinyl sulfide **12**. Subsequently, the thiolate ligated on the catalyst undergoes migration to form intermediate **IV**. Finally, protodemetallation provides desired product of thioacetal **14** with the regeneration of catalyst **I**.

3.5. Conclusion

In conclusion, the synthesis of symmetrically and unsymmetrically substituted dithioacetal using low amount of gold catalyst under mild conditions have developed. Both aryl and alkyl thiols having electron donating and electron withdrawing functional groups were sufficient to give broad substrate scopes. Not only the thiols, but also aryl and aliphatic containing vinyl sulfides gave good reaction results.

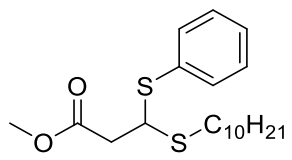
3.6. Experimental data

3.6.1. General Procedures

General Procedure (E) : To an oven-dried reaction tube, a magnetic stirrer bar was equipped. Then, PPh_3AuNTf_2 (1 mol%) was put into the tube and degassed with N_2. DCE (0.1 M, 2 mL) was added followed by the addition of thiol **13** (1.5 equiv., 0.3 mmol) and vinyl sulfide **12** (0.2 mmol). The reaction mixture was monitored via TLC until alkene was consumed. When the reaction was completed, the reaction mixture was filtered. Solvent was eliminated under vacuum conditions. Flash column chromatography was used for the purification of the reaction mixture to obtain corresponding dithioacetal derivatives **14**.

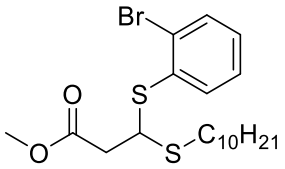
3.6.2. Characterization of products

Methyl 3-(decylthio)-3-(phenylthio)propanoate (14aa)



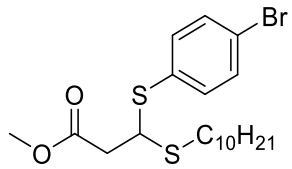
Prepared in accordance with the G***eneral Procedure (E)*** using methyl 3-(decylthio)acrylate **12a** and benzenethiol **13a** at r.t., 2 h, 93% yield; Colorless oil			
^{1}H NMR		**400 MHz, $CDCl_3$**	7.50 (d, J = 6.9 Hz, 2H), 7.38 – 7.30 (m, 3H), 4.50 (t, J = 7.5 Hz, 1H), 3.69 (s, 3H), 2.88 – 2.66 (m, 4H), 1.67 – 1.56 (m, 2H), 1.42 – 1.23 (m, 14H), 0.88 (t, J = 6.6 Hz, 3H)
^{13}C NMR		**100 MHz, $CDCl_3$**	170.5, 133.7, 133.0, 128.9, 128.2, 51.9, 50.3, 41.4, 31.9, 31.7, 29.5, 29.5, 29.3, 29.2, 29.1, 28.9, 22.7, 14.1
HRMS ***m/z***	**ESI**	$C_{20}H_{32}NaO_2S_2^+$ ([M+Na]$^+$)	
		Calculated: 391.1736	observed: 391.1737

Methyl 3-((2-bromophenyl)thio)-3-(decylthio)propanoate (14ab)



Prepared in accordance with the G***eneral Procedure (E)*** using methyl 3-(decylthio)acrylate **12a** and 2-bromobenzenethiol **13b** at r.t., 2 h, 93% yield			
^{1}H NMR		**400 MHz, $CDCl_3$**	7.60 (d, J = 7.9 Hz, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.34 – 7.25 (m, 1H), 7.14 (t, J = 7.6 Hz, 1H), 4.68 (dd, J = 9.0, 5.6 Hz, 1H), 3.67 (s, 3H), 2.90 (dd, J = 16.0, 5.6 Hz, 1H), 2.86 – 2.77 (m, 2H), 2.77 – 2.67 (m, 1H), 1.61 (dd, J = 13.4, 5.8 Hz, 2H), 1.42 – 1.23 (m, 14H), 0.88 (t, J = 6.7 Hz, 3H)
^{13}C NMR		**100 MHz, $CDCl_3$**	170.4, 135.3, 133.6, 133.4, 129.0, 127.9, 127.2, 52.0, 49.1, 41.3, 31.9, 31.7, 29.5, 29.5, 29.3, 29.2, 29.1, 28.8, 22.7, 14.1
HRMS ***m/z***	**ESI**	$C_{20}H_{31}BrNaO_2S_2^+$ ([M+Na]$^+$)	
		Calculated: 469.0841	observed: 469.0845

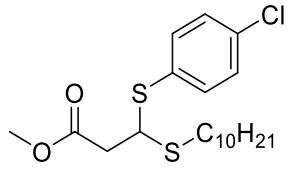
Methyl 3-((4-bromophenyl)thio)-3-(decylthio)propanoate (14ac)



Prepared in accordance with the G***eneral Procedure (E)*** using methyl 3-(decylthio)acrylate **12a** and 4-bromobenzenethiol **13c** at r.t., 2 h, 95% yield; Colorless oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	7.45 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 4.47 (t, J = 7.4 Hz, 1H), 3.69 (s, 3H), 2.85 – 2.71 (m, 3H),

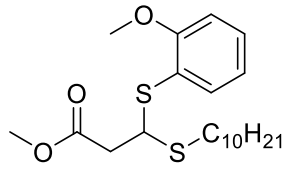
			2.72 – 2.63 (m, 1H), 1.66 – 1.53 (m, 2H), 1.40 – 1.26 (m, 14H), 0.88 (t, J = 6.7 Hz, 3H)
^{13}C NMR		**100 MHz, $CDCl_3$**	170.3, 135.2, 132.0, 131.9, 122.7, 52.0, 50.4, 41.2, 31.8, 31.6, 29.5, 29.5, 29.3, 29.1, 29.0, 28.8, 22.6, 14.1
HRMS ***m/z***	**ESI**	$C_{20}H_{31}BrNaO_2S_2^+$ ([M+Na]$^+$)	
		Calculated: 469.0841	observed: 469.0845

Methyl 3-((4-chlorophenyl)thio)-3-(decylthio)propanoate (14ad)



Prepared in accordance with the G***eneral Procedure (E)*** using methyl 3-(decylthio)acrylate **12a** and 4-chlorobenzenethiol **13d** at r.t., 2 h, 94% yield; Colorless oil			
^{1}H NMR		**400 MHz, $CDCl_3$**	7.43 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 4.46 (t, J = 7.4 Hz, 1H), 3.69 (s, 3H), 2.82 – 2.72 (m, 3H), 2.71 – 2.63 (m, 1H), 1.59 (p, J = 7.5, 7.1 Hz, 2H), 1.40 – 1.25 (m, 14H), 0.88 (t, J = 6.7 Hz, 3H)
^{13}C NMR		**100 MHz, $CDCl_3$**	170.3, 135.1, 134.6, 131.2, 129.1, 52.0, 50.6, 41.2, 31.8, 31.6, 29.5, 29.5, 29.3, 29.1, 29.0, 28.8, 22.6, 14.1
HRMS ***m/z***	**ESI**	$C_{20}H_{31}ClNaO_2S_2^+$ ([M+Na]$^+$)	
		Calculated: 425.1346	observed: 425.1344

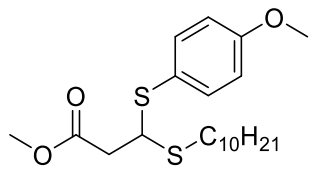
Methyl 3-(decylthio)-3-((2-methoxyphenyl)thio)propanoate (14ae)



Prepared in accordance with the G***eneral Procedure (E)*** using methyl 3-(decylthio)acrylate **12a** and 2-methoxybenzenethiol **13e** at r.t., 2 h, 79% yield; Colorless oil			
^{1}H NMR		**400 MHz, $CDCl_3$**	7.46 – 7.42 (m, 1H), 7.32 – 7.25 (m, 1H), 6.94 – 6.87 (m, 2H), 4.67 (dd, J = 9.1, 5.6 Hz, 1H), 3.89 (s, 3H), 3.64 (s, 3H), 2.88 – 2.80 (m, 2H), 2.76 – 2.66 (m, 2H), 1.66 – 1.57 (m, 2H), 1.41 – 1.24 (m, 14H), 0.88 (t, J = 6.8 Hz, 3H)
^{13}C NMR		**100 MHz, $CDCl_3$**	170.7, 159.1, 134.9, 129.8, 121.5, 120.9, 110.9, 55.7, 51.8, 47.9, 41.5, 31.9, 31.5, 29.5, 29.5, 29.3, 29.2, 29.2, 28.9, 22.6, 14.1
HRMS	**ESI**	$C_{21}H_{34}NaO_3S_2^+$ ([M+Na]$^+$)	

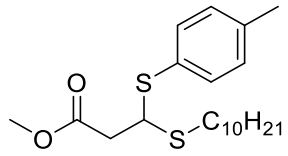
m/z		Calculated: 421.1842	observed: 421.1842

Methyl 3-(decylthio)-3-((4-methoxyphenyl)thio)propanoate (14af)



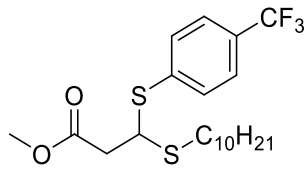
Prepared in accordance with the G***eneral Procedure (E)*** using methyl 3-(decylthio)acrylate **12a** and 4-methoxybenzenethiol **13f** at r.t., 2 h, 81% yield; Colorless oil			
^{1}H NMR		**400 MHz, $CDCl_3$**	7.45 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 4.35 (t, J = 7.5 Hz, 1H), 3.81 (s, 3H), 3.69 (s, 3H), 2.84 – 2.74 (m, 2H), 2.71 – 2.64 (m, 2H), 1.60 (ddt, J = 14.9, 9.4, 3.6 Hz, 2H), 1.44 – 1.22 (m, 14H), 0.88 (t, J = 6.7 Hz, 3H)
^{13}C NMR		**100 MHz, $CDCl_3$**	170.6, 160.2, 136.9, 122.7, 114.4, 55.3, 51.9, 51.1, 41.2, 31.9, 31.6, 29.5, 29.5, 29.3, 29.2, 29.1, 28.9, 22.6, 14.1
HRMS	**ESI**	$C_{21}H_{34}NaO_3S_2^+$ ($[M+Na]^+$)	
m/z		Calculated: 421.1842	observed: 421.1842

Methyl 3-(decylthio)-3-(p-tolylthio)propanoate (14ag)



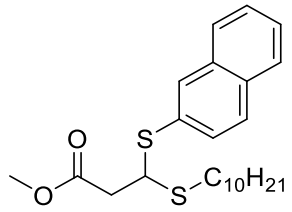
Prepared in accordance with the G***eneral Procedure (E)*** using methyl 3-(decylthio)acrylate **12a** and 4-methylbenzenethiol **13g** at r.t., 2 h, 68% yield; Colorless oil			
^{1}H NMR		**400 MHz, $CDCl_3$**	7.39 (d, J = 7.5 Hz, 2H), 7.15 (d, J = 7.7 Hz, 2H), 4.43 (t, J = 7.3 Hz, 1H), 3.69 (s, 3H), 2.85 – 2.76 (m, 2H), 2.74 – 2.64 (m, 2H), 2.35 (s, 3H), 1.66 – 1.58 (m, 2H), 1.38 – 1.26 (m, 14H), 0.88 (t, J = 6.5 Hz, 3H)
^{13}C NMR		**100 MHz, $CDCl_3$**	170.6, 138.6, 134.4, 129.7, 129.0, 51.9, 50.6, 41.3, 31.9, 31.6, 29.5, 29.5, 29.3, 29.2, 29.1, 28.9, 22.7, 21.2, 14.1
HRMS	**ESI**	$C_{21}H_{34}NaO_2S_2^+$ ($[M+Na]^+$)	
m/z		Calculated: 405.1892	observed: 405.1892

Methyl 3-(decylthio)-3-((4-(trifluoromethyl)phenyl)thio)propanoate (14ah)



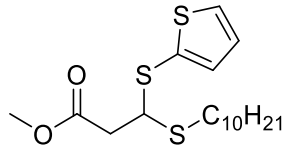
Prepared in accordance with the G***eneral Procedure (E)*** using methyl 3-(decylthio)acrylate **12a** and 4-(trifluoromethyl)benzenethiol **13h** at r.t., 2 h, 88% yield; Colorless oil			
^{1}H NMR		**400 MHz, $CDCl_3$**	7.57 (s, 4H), 4.62 (dd, J = 7.9, 6.8 Hz, 1H), 3.70 (s, 3H), 2.91 – 2.77 (m, 2H), 2.81 – 2.72 (m, 1H), 2.73 – 2.63 (m, 1H), 1.60 (dt, J = 14.8, 6.8 Hz, 2H), 1.44 – 1.24 (m, 14H), 0.88 (t, J = 6.8 Hz, 3H)
^{13}C NMR		**100 MHz, $CDCl_3$**	170.2, 138.7, 131.9, 129.54 (q, J = 32.7 Hz), 125.71 (q, J = 3.7 Hz), 123.91 (q, J = 272.2 Hz), 52.0, 49.6, 41.3, 31.9, 31.7, 29.5, 29.5, 29.3, 29.1, 29.0, 28.8, 22.6, 14.1
HRMS *m/z*	**ESI**	$C_{21}H_{31}F_3NaO_2S_2^+$ ([M+Na]$^+$)	
		Calculated: 459.1610	observed: 459.1608

Methyl 3-(decylthio)-3-(naphthalen-2-ylthio)propanoate (14ai)



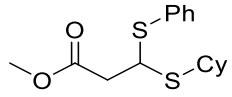
Prepared in accordance with the G***eneral Procedure (E)*** using methyl 3-(decylthio)acrylate **12a** and naphthalene-2-thiol **13i** at r.t., 2 h, 76% yield; Colorless oil			
^{1}H NMR		**400 MHz, $CDCl_3$**	7.98 (s, 1H), 7.86 – 7.75 (m, 3H), 7.59 – 7.53 (m, 1H), 7.49 (dt, J = 9.4, 4.8 Hz, 2H), 4.61 (dd, J = 8.2, 6.6 Hz, 1H), 3.67 (s, 3H), 3.03 – 2.59 (m, 4H), 1.61 (p, J = 8.1 Hz, 2H), 1.43 – 1.22 (m, 14H), 0.88 (t, J = 6.8 Hz, 3H)
^{13}C NMR		**100 MHz, $CDCl_3$**	170.6, 133.5, 132.7, 130.6, 130.4, 128.5, 127.7, 127.7, 126.6, 126.6, 52.0, 50.3, 41.5, 31.9, 31.8, 29.5, 29.5, 29.3, 29.2, 28.9, 22.7, 14.1
HRMS *m/z*	**ESI**	$C_{24}H_{34}NaO_2S_2^+$ ([M+Na]$^+$)	
		Calculated: 441.1892	observed: 441.1893

Methyl 3-(decylthio)-3-(thiophen-2-ylthio)propanoate (14aj)



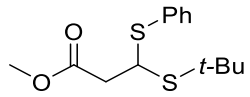
Prepared in accordance with the G***eneral Procedure (E)*** using methyl 3-(decylthio)acrylate **12a** and thiophene-2-thiol **13j** at 50 °C, overnight, 43% yield; Colorless oil			
^{1}H NMR		**400 MHz, $CDCl_3$**	7.45 (d, J = 5.3 Hz, 1H), 7.24 – 7.18 (m, 1H), 7.08 – 7.00 (m, 1H), 4.32 (t, J = 7.1 Hz, 1H), 3.71 (s, 3H), 2.83 (td, J = 13.9, 12.2, 7.0 Hz, 2H), 2.69 (dd, J = 14.9, 7.7 Hz, 2H), 1.63 (dt, J = 13.8, 6.8 Hz, 2H), 1.46 – 1.23 (m, 14H), 0.88 (t, J = 6.0 Hz, 3H)
^{13}C NMR		**100 MHz, $CDCl_3$**	170.4, 136.7, 131.3, 129.9, 127.6, 52.3, 52.0, 40.9, 31.9, 31.9, 29.5, 29.5, 29.3, 29.2, 29.0, 28.9, 22.7, 14.1
HRMS *m/z*	**ESI**	$C_{18}H_{30}NaO_2S_3^+$ ([M+Na]$^+$)	
		Calculated: 397.1300	observed: 397.1302

Methyl 3-(cyclohexylthio)-3-(phenylthio)propanoate (14ba)



Prepared in accordance with the G***eneral Procedure (E)*** using methyl 3-(cyclohexylthio)acrylate **1b** and benzenethiol **2a** at r.t., 4 h, 95% yield; Colorless oil			
^{1}H NMR		**400 MHz, $CDCl_3$**	7.50 (d, J = 6.8 Hz, 2H), 7.33 (d, J = 6.3 Hz, 3H), 4.57 (t, J = 7.3 Hz, 1H), 3.68 (s, 3H), 3.00 (td, J = 10.1, 4.6 Hz, 1H), 2.83 (dd, J = 15.8, 6.3 Hz, 1H), 2.70 (dd, J = 15.8, 8.4 Hz, 1H), 2.11 – 1.90 (m, 2H), 1.80 – 1.69 (m, 2H), 1.67 – 1.49 (m, 1H), 1.42 – 1.32 (m, 3H), 1.30 – 1.22 (m, 2H)
^{13}C NMR		**100 MHz, $CDCl_3$**	170.6, 133.6, 133.2, 129.0, 128.2, 51.9, 48.6, 44.2, 41.6, 33.6, 33.1, 26.0, 25.8, 25.7
HRMS *m/z*	**ESI**	$C_{16}H_{22}NaO_2S_2^+$ ([M+Na]$^+$)	
		Calculated: 333.0953	observed: 333.0957

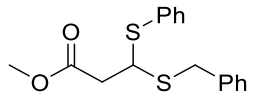
Methyl 3-(tert-butylthio)-3-(phenylthio)propanoate (14ca)



Prepared in accordance with the G***eneral Procedure (E)*** using methyl 3-(tert-butylthio)acrylate **12c** and benzenethiol **13a** at r.t., 3 h, 87% yield; Colorless oil			
^{1}H NMR		**400 MHz, $CDCl_3$**	7.50 (d, J = 7.5 Hz, 2H), 7.38 – 7.27 (m, 3H), 4.54 (dd, J = 9.1, 5.5 Hz, 1H), 3.67 (s, 3H), 2.85 (dd, J = 16.2, 5.2 Hz, 1H), 2.71 (dd, J = 15.4, 9.2 Hz, 1H), 1.40 (s, 9H)
^{13}C NMR		**100 MHz, $CDCl_3$**	170.7, 134.3, 133.0, 129.0, 128.0, 51.8, 46.6, 45.0, 42.8, 31.1
HRMS	**ESI**	$C_{14}H_{20}NaO_2S_2^+$ ([M+Na]$^+$)	

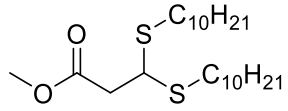
m/z		Calculated: 307.0797	observed: 307.0794

Methyl 3-(benzylthio)-3-(phenylthio)propanoate (14da)



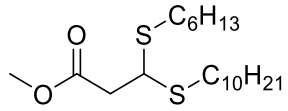
Prepared in accordance with the G***eneral Procedure (E)*** using methyl 3-(benzylthio)acrylate **12d** and benzenethiol **13a** at 50 °C, 2 h, 70% yield, Colorless oil			
^{1}H NMR		**400 MHz, $CDCl_3$**	7.44 (dd, J = 6.3, 2.8 Hz, 3H), 7.31 (dd, J = 6.0, 2.9 Hz, 11H), 7.29 – 7.23 (m, 3H), 4.34 (t, J = 7.4 Hz, 1H), 4.05 – 3.84 (m, 2H), 3.62 (s, 4H), 2.78 (dd, J = 15.8, 7.0 Hz, 1H), 2.69 (dd, J = 15.9, 7.9 Hz, 1H)
^{13}C NMR		**100 MHz, $CDCl_3$**	170.2, 137.2, 133.7, 132.6, 129.1, 129.0, 128.6, 128.3, 127.3, 51.9, 49.4, 41.1, 36.0
HRMS ***m/z***	**ESI**	$C_{17}H_{18}NaO_2S_2^+$ ([M+Na]$^+$)	
		Calculated: 341.0640	observed: 341.0636

Methyl 3,3-bis(decylthio)propanoate (14ak)



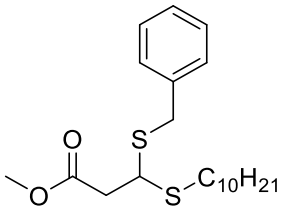
Prepared in accordance with the G***eneral Procedure (E)*** using methyl 3-(decylthio)acrylate **12a** and decane-1-thiol **13k** at r.t., 2 h, 84% yield; Colorless oil			
^{1}H NMR		**400 MHz, $CDCl_3$**	4.21 (t, J = 7.6 Hz, 1H), 3.72 (s, 3H), 2.81 (d, J = 7.6 Hz, 2H), 2.72 – 2.63 (m, 2H), 2.62 – 2.54 (m, 2H), 1.58 (q, J = 9.1, 8.0 Hz, 4H), 1.41 – 1.24 (m, 28H), 0.88 (t, J = 6.7 Hz, 6H)
^{13}C NMR		**100 MHz, $CDCl_3$**	170.6, 51.9, 47.1, 41.7, 31.9, 30.4, 29.5, 29.5, 29.3, 29.2, 29.2, 29.0, 22.7, 14.1
HRMS ***m/z***	**ESI**	$C_{24}H_{48}NaO_2S_2^+$ ([M+Na]$^+$)	
		Calculated: 455.2988	observed: 455.2981

Methyl 3-(cyclohexylthio)-3-(decylthio)propanoate (14al)



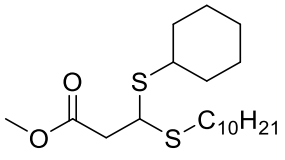
Prepared in accordance with the G***eneral Procedure (E)*** using methyl 3-(decylthio)acrylate **12a** and hexane-1-thiol **13l** at r.t., 6 h, 71% yield; Colorless oil			
^{1}H NMR		**400 MHz, $CDCl_3$**	4.21 (t, J = 7.6 Hz, 1H), 3.72 (s, 3H), 2.81 (d, J = 7.6 Hz, 2H), 2.68 (dt, J = 14.2, 7.4 Hz, 2H), 2.62 – 2.54 (m, 2H), 1.59 (p, J = 7.2 Hz, 4H), 1.43 – 1.26 (m, 20H), 0.92 – 0.86 (m, 6H)
^{13}C NMR		**100 MHz, $CDCl_3$**	170.6, 51.9, 47.1, 41.7, 31.9, 31.4, 30.4, 29.5, 29.5, 29.3, 29.2, 29.2, 28.9, 28.6, 22.6, 22.5, 14.1, 14.0
HRMS ***m/z***	**ESI**	$C_{20}H_{40}NaO_2S_2^+$ ([M+Na]$^+$)	
		Calculated: 399.2362	observed: 399.2400

Methyl 3-(benzylthio)-3-(decylthio)propanoate (14am)



Prepared in accordance with the G***eneral Procedure (E)*** using methyl 3-(decylthio)acrylate **12a** and phenylmethanethiol **13m** at r.t., 4 h, 63% yield; Colorless oil			
^{1}H NMR		**400 MHz, $CDCl_3$**	7.38 – 7.27 (m, 4H), 7.28 – 7.19 (m, 1H), 4.09 (t, J = 7.6 Hz, 1H), 3.93 – 3.76 (m, 2H), 3.68 (s, 3H), 2.77 (d, J = 7.6 Hz, 2H), 2.62 (dt, J = 12.5, 7.4 Hz, 1H), 2.53 (dt, J = 12.4, 7.5 Hz, 1H), 1.53 (p, J = 7.3 Hz, 2H), 1.39 – 1.24 (m, 14H), 0.88 (t, J = 6.8 Hz, 3H)
^{13}C NMR		**100 MHz, $CDCl_3$**	170.4, 137.7, 129.0, 128.5, 127.1, 51.9, 46.6, 41.5, 35.1, 31.9, 30.3, 29.6, 29.5, 29.3, 29.2, 29.2, 29.0, 22.7, 14.1
HRMS ***m/z***	**ESI**	$C_{21}H_{34}NaO_2S_2^+$ ([M+Na]$^+$)	
		Calculated: 405.1892	observed: 405.1897

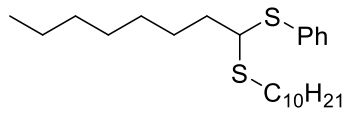
Methyl 3-(cyclohexylthio)-3-(decylthio)propanoate (14an)



Prepared in accordance with the G***eneral Procedure (E)*** using methyl 3-(decylthio)acrylate **12a** and cyclohexanethiol **13n** at r.t., 3 h, 42% yield; Colorless oil		
^{1}H NMR	**400 MHz, $CDCl_3$**	4.27 (t, J = 7.5 Hz, 1H), 3.72 (s, 3H), 2.88 (tt, J = 10.0, 3.9 Hz, 1H), 2.81 (d, J = 7.6 Hz, 2H), 2.71 – 2.56 (m, 2H), 1.97 (ddd, J = 20.2, 9.9, 4.7 Hz, 2H), 1.75 (dt, J =

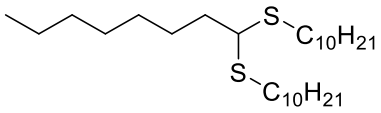
			9.5, 4.5 Hz, 2H), 1.59 (p, J = 7.6, 7.1 Hz, 3H), 1.44 – 1.20 (m, 19H), 0.88 (t, J = 6.6 Hz, 3H)
^{13}C NMR		**100 MHz, $CDCl_3$**	170.7, 51.9, 45.6, 43.4, 42.2, 33.8, 33.5, 31.9, 30.2, 29.5, 29.5, 29.3, 29.3, 29.2, 28.9, 26.1, 25.8, 25.7, 22.7, 14.1
HRMS ***m/z***	**ESI**	$C_{20}H_{38}NaO_2S_2^+$ ([M+Na]$^+$)	
		Calculated: 397.2205	observed: 397.2202

Decyl(1-(phenylthio)octyl)sulfane (14ea)



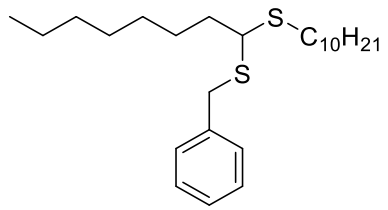
Prepared in accordance with the G***eneral Procedure (E)*** using decyl(oct-1-en-1-yl)sulfane **12e** and benzenethiol **13a** at reflux, 10 h, 38% yield; Colorless oil			
^{1}H NMR		**400 MHz, $CDCl_3$**	7.50 – 7.42 (m, 2H), 7.35 – 7.23 (m, 3H), 4.08 (t, J = 6.7 Hz, 1H), 2.76 (dt, J = 12.5, 7.3 Hz, 1H), 2.65 (dt, J = 12.5, 7.5 Hz, 1H), 1.90 – 1.69 (m, 2H), 1.63 – 1.52 (m, 4H), 1.41 – 1.24 (m, 22H), 0.92 – 0.83 (m, 6H)
^{13}C NMR		**100 MHz, $CDCl_3$**	134.6, 132.9, 128.8, 127.5, 55.4, 36.0, 31.9, 31.7, 31.3, 29.6, 29.5, 29.3, 29.2, 29.1, 29.1, 29.0, 27.1, 22.7, 22.6, 14.1, 14.1
HRMS ***m/z***	**ESI**	$C_{24}H_{42}NaS_2^+$ ([M+Na]$^+$)	
		Calculated: 417.2620	observed: 417.2623

Octane-1,1-diylbis(decylsulfane) (14ek)



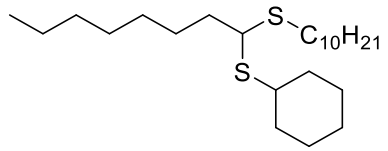
Prepared in accordance with the G***eneral Procedure (E)*** using decyl(oct-1-en-1-yl)sulfane **12e** and decane-1-thiol **13k** at reflux, 20 h, 74% yield; Colorless oil			
^{1}H NMR		**400 MHz, $CDCl_3$**	3.73 (t, J = 7.0 Hz, 1H), 2.65 (dt, J = 14.5, 7.4 Hz, 2H), 2.54 (dt, J = 12.4, 7.4 Hz, 2H), 1.77 (q, J = 7.3 Hz, 2H), 1.55 (dp, J = 15.3, 7.6, 7.2 Hz, 6H), 1.43 – 1.22 (m, 36H), 0.88 (t, J = 6.8 Hz, 9H)
^{13}C NMR		**100 MHz, $CDCl_3$**	52.0, 36.1, 31.9, 31.8, 30.0, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 29.1, 29.1, 27.5, 22.7, 22.6, 14.1, 14.1
HRMS ***m/z***	**ESI**	$C_{28}H_{58}NaS_2^+$ ([M+Na]$^+$)	
		Calculated: 481.3872	observed: 481.3873

Benzyl(1-(decylthio)octyl)sulfane (14em)



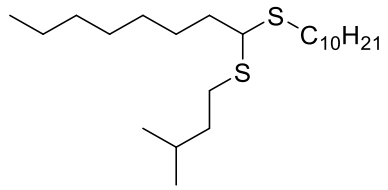
Prepared in accordance with the G***eneral Procedure (E)*** using decyl(oct-1-en-1-yl)sulfane **12e** and phenylmethanethiol **13m** at reflux, 1 h, 36% yield; Colorless oil			
^{1}H NMR		**400 MHz, $CDCl_3$**	7.35 – 7.20 (m, 5H), 3.91 – 3.73 (m, 2H), 3.58 (t, J = 7.0 Hz, 1H), 2.65 – 2.47 (m, 2H), 1.75 (q, J = 7.4 Hz, 2H), 1.54 (dd, J = 14.3, 6.8 Hz, 2H), 1.45 (td, J = 6.9, 3.9 Hz, 2H), 1.36 (dd, J = 8.4, 5.2 Hz, 2H), 1.31 – 1.23 (m, 20H), 0.88 (td, J = 6.8, 4.2 Hz, 6H)
^{13}C NMR		**100 MHz, $CDCl_3$**	138.3, 129.0, 128.4, 126.9, 51.2, 35.8, 34.8, 31.9, 31.8, 29.8, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 29.1, 29.0, 27.3, 22.7, 22.6, 14.1, 14.1
HRMS ***m/z***	**ESI**	$C_{25}H_{44}NaS_2^+$ ([M+Na]$^+$)	
		Calculated: 431.2777	observed: 431.2771

Cyclohexyl(1-(decylthio)octyl)sulfane (14en)



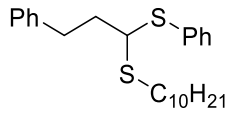
Prepared in accordance with the G***eneral Procedure (E)*** using decyl(oct-1-en-1-yl)sulfane **12e** and cyclohexanethiol **13n** at reflux, 20 h, 35% yield; Colorless oil			
^{1}H NMR		**400 MHz, $CDCl_3$**	3.81 (t, J = 6.9 Hz, 1H), 2.88 (tt, J = 9.9, 3.9 Hz, 1H), 2.64 (dt, J = 12.4, 7.4 Hz, 1H), 2.56 (dt, J = 12.4, 7.4 Hz, 1H), 1.96 (ddd, J = 21.6, 10.0, 4.7 Hz, 2H), 1.83 – 1.73 (m, 3H), 1.63 – 1.48 (m, 5H), 1.44 – 1.22 (m, 28H), 0.88 (t, J = 6.6 Hz, 6H)
^{13}C NMR		**100 MHz, $CDCl_3$**	50.4, 42.9, 36.6, 34.1, 33.7, 31.9, 31.8, 29.8, 29.6, 29.5, 29.5, 29.3, 29.3, 29.2, 29.1, 29.0, 27.4, 26.1, 25.9, 25.8, 22.7, 22.6, 14.1, 14.1
HRMS ***m/z***	**ESI**	$C_{24}H_{48}NaS_2^+$ ([M+Na]$^+$)	
		Calculated: 423.3090	observed: 423.3092

Decyl(1-(isopentylthio)octyl)sulfane (14eo)



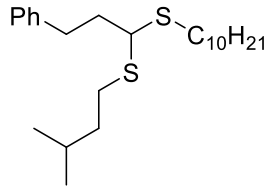
Prepared in accordance with the G***eneral Procedure (E)*** using decyl(oct-1-en-1-yl)sulfane **12e** and 3-methylbutane-1-thiol **13o** at 50 °C, 1 h, 51% yield; Colorless oil			
^{1}H NMR		**400 MHz, $CDCl_3$**	3.74 (t, J = 7.0 Hz, 1H), 2.72 – 2.59 (m, 2H), 2.56 (dq, J = 12.4, 7.4 Hz, 2H), 1.78 (q, J = 7.9, 7.2 Hz, 2H), 1.69 (dt, J = 13.3, 6.7 Hz, 1H), 1.60 – 1.51 (m, 3H), 1.50 – 1.44 (m, 3H), 1.42 – 1.24 (m, 22H), 0.91 (d, J = 6.6 Hz, 6H), 0.90 – 0.86 (m, 6H)
^{13}C NMR		**100 MHz, $CDCl_3$**	52.0, 38.4, 36.1, 36.1, 31.9, 31.8, 30.0, 29.5, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 28.0, 27.5, 27.5, 22.7, 22.6, 22.3, 22.2, 14.1, 14.1
HRMS *m/z*	**EI**	$C_{23}H_{48}S^{2+}$ ([M]$^{+}$)	
		Calculated: 388.3197	observed: 388.3200

Decyl(3-phenyl-1-(phenylthio)propyl)sulfane (14fa)



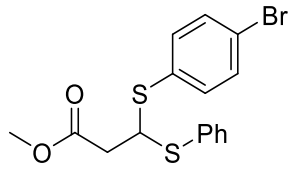
Prepared in accordance with the G***eneral Procedure (E)*** using decyl(3-phenylprop-1-en-1-yl)sulfane **12f** and benzenethiol **13a** at 50 °C, 2 h, 79% yield; Colorless oil			
^{1}H NMR		**400 MHz, $CDCl_3$**	7.39 (dd, J = 7.5, 1.8 Hz, 2H), 7.31 – 7.24 (m, 5H), 7.19 (d, J = 7.2 Hz, 1H), 7.14 (d, J = 7.1 Hz, 2H), 4.03 (dd, J = 7.6, 5.9 Hz, 1H), 2.97 – 2.79 (m, 2H), 2.75 (dt, J = 12.7, 7.3 Hz, 1H), 2.65 (dt, J = 12.4, 7.6 Hz, 1H), 2.22 – 1.99 (m, 2H), 1.63 – 1.49 (m, 2H), 1.42 – 1.24 (m, 14H), 0.88 (t, J = 6.7 Hz, 3H)
^{13}C NMR		**100 MHz, $CDCl_3$**	140.9, 134.2, 132.7, 128.8, 128.5, 128.3, 127.5, 126.0, 54.0, 37.3, 33.0, 31.9, 31.3, 29.5, 29.5, 29.3, 29.3, 29.2, 28.9, 22.7, 14.1
HRMS *m/z*	**ESI**	$C_{25}H_{36}NaS_2^{+}$ ([M+Na]$^{+}$)	
		Calculated: 423.2151	observed: 423.2153

Decyl(1-(isopentylthio)-3-phenylpropyl)sulfane (14fo)



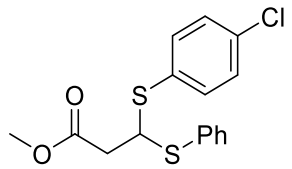
Prepared in accordance with the G***eneral Procedure (E)*** using decyl(3-phenylprop-1-en-1-yl)sulfane **12f** and 3-methylbutane-1-thiol **13o** at 50 °C, 1 h, 80% yield; Colorless oil			
^{1}H NMR		**400 MHz, $CDCl_3$**	7.32 – 7.14 (m, 5H), 3.69 (t, J = 7.0 Hz, 1H), 2.85 (t, J = 7.6 Hz, 2H), 2.65 (dtd, J = 14.5, 7.6, 2.5 Hz, 2H), 2.55 (dq, J = 12.5, 7.5 Hz, 2H), 2.09 (q, J = 7.4 Hz, 2H), 1.67 (dt, J = 13.3, 6.7 Hz, 1H), 1.54 (q, J = 8.4 Hz, 2H), 1.44 (q, J = 7.4 Hz, 2H), 1.39 – 1.24 (m, 14H), 0.91 – 0.86 (m, 9H)
^{13}C NMR		**100 MHz, $CDCl_3$**	141.2, 128.5, 128.4, 126.0, 51.0, 38.4, 37.7, 33.5, 31.9, 30.1, 29.6, 29.5, 29.4, 29.3, 29.3, 29.1, 28.1, 27.6, 22.7, 22.4, 22.3, 14.1
HRMS *m/z*	**EI**	$C_{24}H_{42}S_2^+$ ([M]$^+$)	
		Calculated: 394.2728	observed: 394.2730

Methyl 3-((4-bromophenyl)thio)-3-(phenylthio)propanoate (14gc)



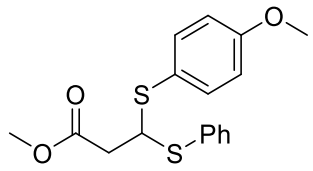
Prepared in accordance with the G***eneral Procedure (E)*** using methyl 3-(phenylthio)acrylate **12g** and 4-bromobenzenethiol **13c** at 50 °C, 4 h, 81% yield; Colorless oil			
^{1}H NMR		**400 MHz, $CDCl_3$**	7.46 (dd, J = 12.7, 6.8 Hz, 4H), 7.38 – 7.31 (m, 5H), 4.77 (t, J = 7.3 Hz, 1H), 3.70 (s, 3H), 2.80 (dd, J = 7.0, 4.5 Hz, 2H)
^{13}C NMR		**100 MHz, $CDCl_3$**	170.3, 135.0, 133.5, 132.7, 132.2, 132.1, 129.1, 128.4, 122.8, 53.6, 52.1, 40.9
HRMS *m/z*	**ESI**	$C_{16}H_{15}BrNaO_2S_2^+$ ([M+Na]$^+$)	
		Calculated: 404.9589	observed: 404.9587

Methyl 3-((4-chlorophenyl)thio)-3-(phenylthio)propanoate (14gd)



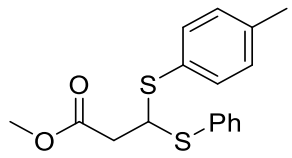
Prepared in accordance with the G***eneral Procedure (E)*** using methyl 3-(phenylthio)acrylate **12g** and 4-chlorobenzenethiol **13d** at 50 °C, 3 h, 82% yield; Colorless oil			
^{1}H NMR		**400 MHz, $CDCl_3$**	7.47 (dd, J = 6.4, 2.9 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.33 – 7.26 (m, 5H), 4.77 (t, J = 7.4 Hz, 1H), 3.69 (s, 3H), 2.80 (dd, J = 7.4, 4.4 Hz, 2H)
^{13}C NMR		**100 MHz, $CDCl_3$**	170.3, 134.9, 134.6, 133.5, 132.8, 131.3, 129.2, 129.1, 128.4, 53.7, 52.1, 40.9
HRMS *m/z*	**ESI**	$C_{16}H_{15}ClNaO_2S_2^+$ ([M+Na]$^+$)	
		Calculated: 361.0094	observed: 361.0097

Methyl 3-((4-methoxyphenyl)thio)-3-(phenylthio)propanoate (14gf)



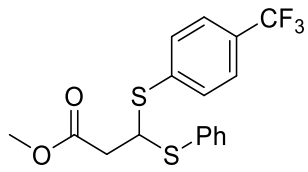
Prepared in accordance with the G***eneral Procedure (E)*** using methyl 3-(phenylthio)acrylate **12g** and 4-methoxybenzenethiol **13f** at 50 °C, 5 h, 47% yield; Colorless oil			
^{1}H NMR		**400 MHz, $CDCl_3$**	7.47 (dd, J = 12.4, 7.8 Hz, 4H), 7.37 – 7.27 (m, 3H), 6.87 (d, J = 8.0 Hz, 2H), 4.67 (t, J = 7.4 Hz, 1H), 3.82 (s, 3H), 3.70 (s, 3H), 2.77 (d, J = 7.4 Hz, 2H)
^{13}C NMR		**100 MHz, $CDCl_3$**	170.5, 160.3, 136.8, 133.4, 133.0, 129.0, 128.0, 122.7, 114.5, 55.3, 54.2, 52.0, 40.9
HRMS *m/z*	**ESI**	$C_{17}H_{18}NaO_3S_2^+$ ([M+Na]$^+$)	
		Calculated: 357.0590	observed: 357.0587

Methyl 3-(phenylthio)-3-(p-tolylthio)propanoate (14gg)



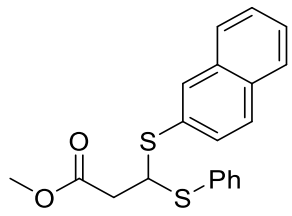
Prepared in accordance with the G***eneral Procedure (E)*** using methyl 3-(phenylthio)acrylate **12g** and 4-methylbenzenethiol **13g** at 50 °C, 5 h, 95% yield; Colorless oil			
^{1}H NMR		**400 MHz, $CDCl_3$**	7.49 (d, J = 5.5 Hz, 1H), 7.39 (d, J = 7.7 Hz, 3H), 7.32 (d, J = 5.6 Hz, 2H), 7.14 (d, J = 7.5 Hz, 3H), 4.71 (dt, J = 24.7, 7.3 Hz, 1H), 3.69 (s, 3H), 2.78 (dd, J = 10.7, 7.7 Hz, 2H), 2.35 (s, 3H)
^{13}C NMR		**100 MHz, $CDCl_3$**	170.5, 138.5, 134.2, 134.0, 133.4, 133.3, 129.8, 129.0, 128.1, 53.7, 51.9, 41.0, 21.2
HRMS *m/z*	**ESI**	$C_{17}H_{18}NaO_2S_2^+$ ([M+Na]$^+$)	
		Calculated: 341.0640	observed: 341.0639

Methyl 3-(phenylthio)-3-((4-(trifluoromethyl)phenyl)thio)propanoate (14gh)



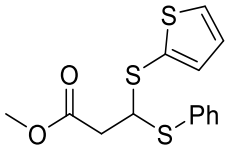
Prepared in accordance with the G***eneral Procedure (E)*** using methyl 3-(phenylthio)acrylate **12g** and 4-(trifluoromethyl)benzenethiol **13h** at 50 °C, 5 h, 77% yield; Colorless oil			
^{1}H NMR		**400 MHz, $CDCl_3$**	7.54 (s, 4H), 7.50 – 7.46 (m, 2H), 7.34 – 7.31 (m, 3H), 4.90 (t, J = 7.4 Hz, 1H), 3.71 (s, 3H), 2.85 (t, J = 7.4 Hz, 2H)
^{13}C NMR		**100 MHz, $CDCl_3$**	170.2, 138.6, 133.8, 132.2, 131.7, 129.56 (q, J = 32.6 Hz), 129.1, 128.7, 125.77 (q, J = 3.7 Hz), 123.88 (q, J = 272.2 Hz), 52.8, 52.1, 40.8
HRMS *m/z*	**ESI**	$C_{17}H_{15}F_3NaO_2S_2^+$ ([M+Na]$^+$)	
		Calculated: 395.0358	observed: 395.0358

Methyl 3-(naphthalen-2-ylthio)-3-(phenylthio)propanoate (14gi)



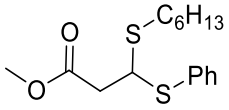
Prepared in accordance with the G***eneral Procedure (E)*** using methyl 3-(phenylthio)acrylate **12g** and naphthalene-2-thiol **13i** at 50 °C, 5 h, 95% yield; Colorless oil			
^{1}H NMR		**400 MHz, $CDCl_3$**	7.96 (s, 1H), 7.78 (dq, J = 14.5, 6.9, 5.4 Hz, 4H), 7.58 – 7.47 (m, 6H), 7.32 (d, J = 4.7 Hz, 1H), 4.96 (dt, J = 43.3, 7.4 Hz, 1H), 3.69 (s, 3H), 2.88 (dd, J = 18.0, 7.3 Hz, 2H)
^{13}C NMR		**100 MHz, $CDCl_3$**	170.5, 133.6, 133.4, 132.8, 132.6, 130.3, 130.2, 129.0, 128.6, 128.3, 127.7, 126.6, 126.6, 53.4, 52.0, 41.1
HRMS *m/z*	**ESI**	$C_{20}H_{18}NaO_2S_2^+$ ([M+Na]$^+$)	
		Calculated: 377.0640	observed: 377.0638

Methyl 3-(phenylthio)-3-(thiophen-2-ylthio)propanoate (14gj)



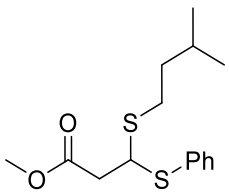
Prepared in accordance with the G***eneral Procedure (E)*** using methyl 3-(phenylthio)acrylate **12g** and thiophene-2-thiol **13j** at reflux, 8 h, 36% yield; Colorless oil			
There were inseparable mixture, the yield was obtained by NMR yield			
^{1}H NMR		**400 MHz, $CDCl_3$**	7.51 – 7.43 (m, 3H), 7.38 – 7.30 (m, 3H), 7.20 (d, J = 3.4 Hz, 1H), 7.04 (t, J = 4.6 Hz, 1H), 4.63 (t, J = 7.1 Hz, 1H), 3.71 (s, 3H), 2.82 (q, J = 8.7, 8.1 Hz, 2H)
^{13}C NMR		**100 MHz, $CDCl_3$**	170.3, 136.8, 133.4, 133.3, 131.5, 129.1, 129.0, 128.3, 127.7, 55.3, 52.1, 40.6
HRMS *m/z*	**ESI**	$C_{14}H_{14}NaO_2S_3^+$ ([M+Na]$^+$)	
		Calculated: 333.0048	observed: 333.0047

Methyl 3-(hexylthio)-3-(phenylthio)propanoate (14gl)



Prepared in accordance with the G***eneral Procedure (E)*** using methyl 3-(phenylthio)acrylate **12g** and hexane-1-thiol **13l** at 50 °C, 6 h, 39% yield; Colorless oil			
^{1}H NMR		**400 MHz, $CDCl_3$**	7.55 – 7.46 (m, 2H), 7.39 – 7.28 (m, 3H), 4.50 (dd, J = 8.1, 6.8 Hz, 1H), 3.69 (s, 3H), 2.89 – 2.76 (m, 2H), 2.80 – 2.65 (m, 2H), 1.61 (dd, J = 10.6, 3.4 Hz, 2H), 1.42 – 1.26 (m, 6H), 0.89 (t, J = 6.8 Hz, 3H)
^{13}C NMR		**100 MHz, $CDCl_3$**	170.6, 133.7, 133.0, 128.9, 128.2, 52.0, 50.3, 41.4, 31.7, 31.3, 29.1, 28.5, 22.5, 14.0
HRMS *m/z*	**ESI**	$C_{16}H_{24}NaO_2S_2^+$ ([M+Na]$^+$)	
		Calculated: 335.1110	observed: 335.1114

Methyl 3-(isopentylthio)-3-(phenylthio)propanoate (14go)



Prepared in accordance with the G***eneral Procedure (E)*** using methyl 3-(phenylthio)acrylate **12g** and 3-methylbutane-1-thiol **13o** at 50 °C, 6 h, 52% yield; Colorless oil

^{1}H NMR		**400 MHz, $CDCl_3$**	7.51 – 7.48 (m, 2H), 7.36 – 7.30 (m, 3H), 4.51 (dd, J = 8.2, 6.7 Hz, 1H), 3.69 (s, 3H), 2.88 – 2.66 (m, 4H), 1.66 (dt, J = 13.3, 6.7 Hz, 1H), 1.49 (q, J = 7.5 Hz, 2H), 0.91 (dd, J = 6.6, 3.5 Hz, 6H)
^{13}C NMR		**100 MHz, $CDCl_3$**	170.5, 133.7, 133.0, 129.0, 128.2, 52.0, 50.3, 41.4, 38.0, 29.7, 27.4, 22.3, 22.2
HRMS ***m/z***	**ESI**	$C_{15}H_{22}NaO_2S_2^+$ ($[M+Na]^+$)	
		Calculated: 321.0953	observed: 321.0958

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