C-H Functionalization/Annulation of Arenes and Atroposelective Allylation of 1-Arylisoquinoline *N*-Oxides

A Thesis Submitted

in Partial Fulfilment of the Requirements

for the Degree of

Doctor of Philosophy in Chemistry

By

Sharajit Saha

Roll No. 206122114

Department of Chemistry
Indian Institute of Technology Guwahati
Guwahati 781039
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Dedicated To

My Parents

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati, India under the supervision of Prof. Tharmalingam Punniyamurthy.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

Guwahati
January 2026

Sharajit Saha

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

CERTIFICATE

This is to certify that Mr. Sharajit Saha has been working under my supervision since March 2021. I am forwarding his thesis entitled "*C-H Functionalization/Annulation of Arenes and Atroposelective Allylation of 1-Arylisoquinoline N-Oxides*" being submitted for the Ph.D. degree of this institute. I certify that he has fulfilled all the requirements according to the rules of this institute, and regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

Guwahati
January 2026

Prof. Tharmalingam Punniyamurthy
Supervisor

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"Alone we can do so little; together we can do so much." – Helen Keller. This thesis stands as a testament to the collective support, guidance, and encouragement I have received throughout my academic journey. Each step of this journey was made lighter and brighter by those who walked beside me-thank you all.

Sharajit Saha

List of Abbreviations

Ar	aryl
Ac	acetyl
AIBN	azobisisobutyronitrile
AcOH	acetic acid
Ac-*L*-Ile-OH	*N*-acetyl-*L*-isoleucine
Å	angstrom (10^{-10} m)
Ac-*L*-Leu-OH	*N*-acetyl-*L*-leucine
Ac-*L*-Phe-OH	*N*-acetyl-*L*-phenylalanine
Ac-*L*-Ala-OH	*N*-acetyl-*L*-alanine
Ac-*L*-Val-OH	*N*-acetyl-*L*-valine
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BQ	1,4-benzoquinone
CCDC	Cambridge crystallographic data center
CMD	concerted metalation deprotonation
Cp*	1,2,3,4,5-pentamethylcyclopentadiene
Cy	cyclohexyl
p-cymene	4-isopropyltoluene
DMC	dimethyl carbonate
DABCO	4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromenthane
DMA	*N,N*-dimethylacetamide
DG	directing group
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
DIPEA	diisopropylethylamine
equiv	equivalent

Et	ethyl
EtOAc	ethyl acetate
ESI	electrospray ionization
EWG	electron withdrawing group
FT-IR	Fourier transform infrared spectroscopy
FG	functional group
GC	gas chromatography
g	gram
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HRMS	high-resolution mass spectrometry
Hz	hertz
^{i}Pr	isopropyl
LG	leaving group
Me	methyl
MHz	megahertz
mp	melting point
mg	milligram
mL	millilitre
MPAA	monoprotected amino acids
MS	molecular sieves
MW	microwave
m/z	mass to charge ratio
nm	nanometer
NIS	*N*-Iodosuccinimide
NMR	nuclear magnetic resonance
ORTEP	oak ridge thermal ellipsoid plot
Piv	pivaloyl
py	pyridyl
Ph	phenyl
R_f	retention factor
rt	room temperature

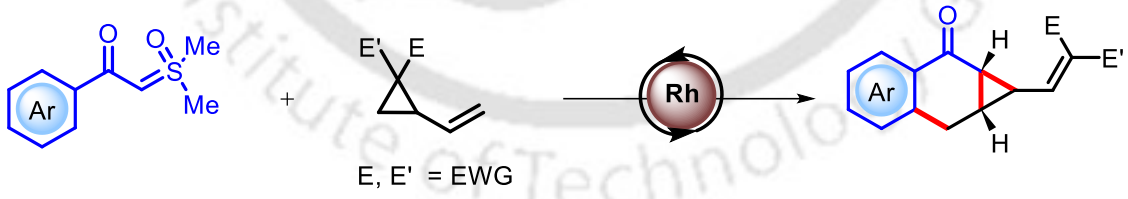
^{t}AmOH	*tert*-amyl alcohol
^{t}BuOH	*tert*-butyl alcohol
TCE	2,2,2-trichloroethanol
THF	tetrahydrofuran
Tf	trifluoromethanesulfonyl
TFE	2,2,2-trifluoroethanol
TLC	thin layer chromatography
TM	transition metal
TMS	trimethylsilyl
VCP	vinylcyclopropane
μm	micrometre
μL	microlitre

Abstract

The thesis is divided into four chapters. The first chapter presents a Rh-catalyzed cascade C-H activation/annulation strategy of sulfoxonium ylides with vinyl cyclopropanes (VCPs) to access cyclopropane fused *α*-tetralones. The second chapter explores a Co-catalyzed C-H allylation of sulfoxonium ylides with 3-membered vinyl strained rings. The third chapter demonstrates a Ru-catalyzed redox-neutral coupling of *N*-chlorobenzamides with unsymmetrical alkynes in water. The fourth chapter focuses on a Pd-catalyzed atroposelective allylation of 1-arylisoquinoline *N*-oxides with *trans*-3-alkenoates, enabling the simultaneous construction of axial and central chirality.

Chapter 1. Rh-Catalyzed C-H Annulation of Benzoyl Sulfoxonium Ylides with VCPs

Recent progress in C–H functionalization has underscored the importance of traceless or weakly coordinating directing groups (DGs) that streamline the synthesis of complex molecules *via* step- and atom-economical sequences. In this context, benzoyl sulfoxonium ylides have emerged as a traceless DG, enabling diverse C–H activation processes and facilitating efficient assembly of aryl-fused carbo-/heterocyclic motifs. Although their reactivity has been studied in C–H activation and annulation reactions with unsaturated partners but their potential in ring opening/annulation involving strained ring systems remains largely underdeveloped.



Org. Lett. **2023**, *19*, 3352.

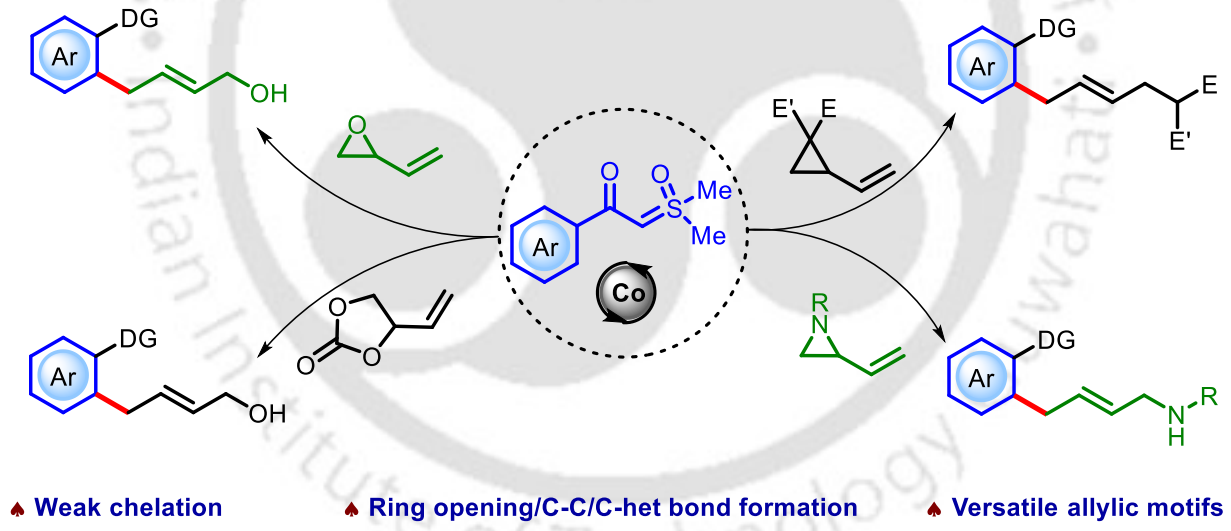
Scheme 1. Rh-Catalyzed C–H Annulation of Sulfoxonium Ylides with Vinyl Cyclopropanes

Addressing this gap, we have developed a Rh-catalyzed cascade strategy that leverages benzoyl sulfoxonium ylides in a weak traceless DG-assisted C–H activation, ring scission and annulation

sequence with vinyl cyclopropanes (VCPs) (Scheme 1). This method offers a concise route to CP-fused α-tetralone frameworks, featuring excellent step economy, substrate scope and synthetic utility in constructing structurally diverse carbocyclic architectures.

Chapter 2. Co-Catalyzed C-H Allylation of Benzoyl Sulfoxonium Ylides with Vinyl Strained Rings

Weak chelation-assisted C–H functionalization represents a transformative strategy for streamlining molecular assembly through direct C–H bond activation. Benzoyl sulfoxonium ylides have emerged as uniquely versatile substrates, leveraging their stability, low toxicity and dual role as DGs and coupling partners. While Rh-catalyzed C–H activation/annulation protocols using these ylides and unsaturated partners are well established, the development of C–H allylation with earth-abundant Co-catalyzed variants remains a significant challenge due to competitive C(aryl)–H/C(olefinic)–H selectivity and sulfur–catalyst compatibility.



Chem. Commun. **2023**, *59*, 14173.

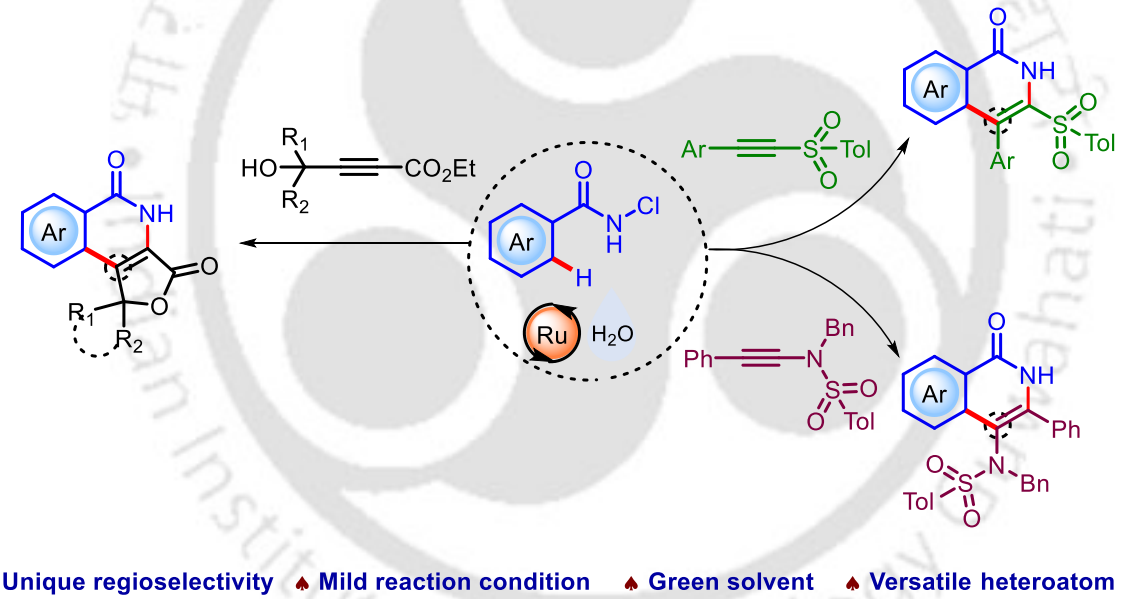
Scheme 2. C–H Allylation of Benzoyl Sulfoxonium Ylide with Vinyl Strained Rings

To address this challenge, a Co-catalyzed weak chelation-assisted C–H allylation of sulfoxonium ylides with strained vinyl ring systems such as VCPs, 2-vinyloxirane, 2-vinylaziridine and 4-vinyl-1,3-dioxolan-2-one has been developed (Scheme 2). The reaction proceeds *via* sequential C–H and C–C/C–het bond activation, offering a step- and atom-economical route to produce allylated

frameworks. The method highlights the potential of sulfoxonium ylides as weak chelation assisted DGs in sustainable C–H activation chemistry.

Chapter 3. Ru-Catalyzed C-H Annulation of *N*-Chlorobenzamides with Unsymmetrical Alkynes

Directed C–H functionalization has become a cornerstone strategy for site-selective C–C and C–het bond formation from simple arenes. Benzamide auxiliaries have proven particularly effective, enabling annulation with unsaturated partners to access isoquinolones and related nitrogen heterocycles prevalent in natural products and bioactive molecules. While *N*-chlorobenzamides have emerged as innovative oxidizing DGs that integrate coordination and internal oxidation to bypass external oxidants. While their coupling with unsymmetrical alkynes in sustainable media remains underexplored.



J. Org. Chem. **2024**, *89,* 16850.

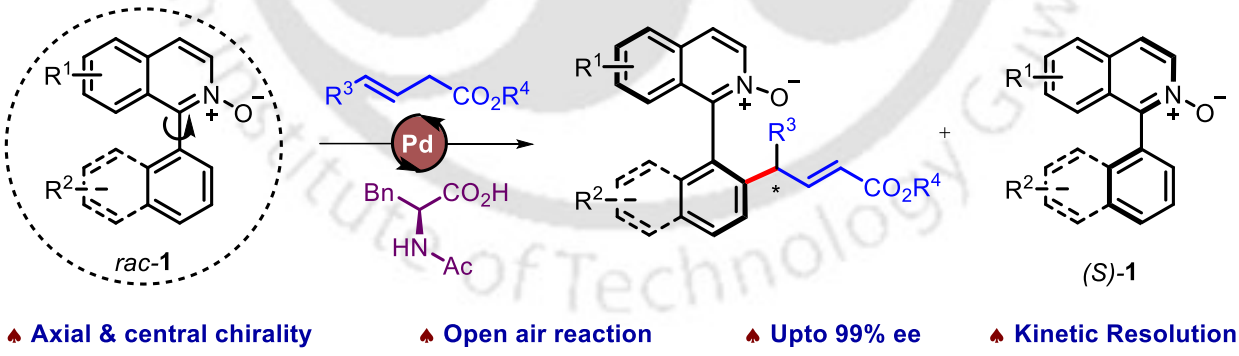
Scheme 3. Ru-Catalyzed C–H Annulation of *N*-Chlorobenzamides with Unsymmetrical Alkynes

To address this gap, a Ru-catalyzed C–H activation/annulation of *N*-chlorobenzamides with heteroatom-functionalized unsymmetrical alkynes such as 4-hydroxy-2-alkynoates, alkynyl sulfones and sulfonyl-based ynamides has been developed in water under oxidant-free conditions. The reaction delivers regioselective furanone-fused isoquinolones *via* cascade C–H activation,

annulation, lactonization and synthesis of isoquinolone with versatile heteroatom handler offering substrate scope, operational simplicity and enhanced sustainability.

Chapter 4. Atroposelective C-H Allylation: Enabling Concurrent Axial and Central Chirality

Axially chiral binaphthyl frameworks represent privileged motifs in natural product synthesis and asymmetric catalysis, yet enantioselective C–H functionalization of biaryl rings remains challenging due to racemization risks at elevated temperatures. Recent advances emphasize chiral-ligand-assisted asymmetric construction of C-stereogenic molecules, but concurrent generation of axial and central chirality using prochiral partners often yields uncontrollable stereoisomers. Among biaryl motifs, axially chiral 1-arylisoquinoline *N*-oxides serve as versatile ligands and organocatalysts, though their atroposelective C–H allylation with substituted internal olefins like *trans*-3-alkenoates remains unexplored. This approach faces key hurdles: preferential styrenyl selectivity and formation of stereoisomer mixtures rather than single diastereomers. To address these limitations, a Pd-catalyzed, weakly DG-assisted atroposelective C–H allylation of 1-arylisoquinoline *N*-oxides with *trans*-3-alkenoates *via* kinetic resolution has been developed using *N*-Ac-*L*-Phe-OH as chiral ligand. This protocol enables concurrent axial and central chirality with excellent enantio-/diastereoselectivity.



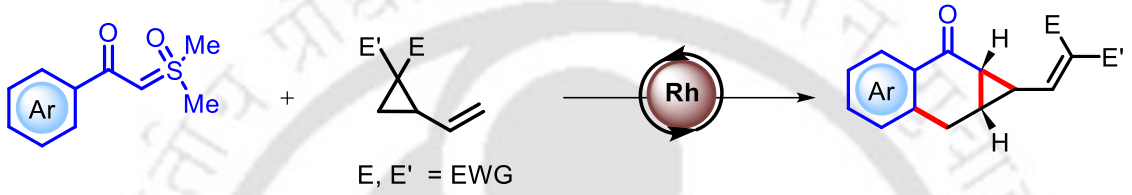
(Manuscript under preparation)

Scheme 4. Atroposelective C–H Allylation of 1-Arylisoquinoline *N*-oxides with *trans*-3-Alkenoates

Contents

Chapter 1

Rh-Catalyzed C-H Annulation of Benzoyl Sulfoxonium Ylides with VCPs



♠ **Traceless DG** ♠ **Ring opening/annulation** ♠ **Step economy** ♠ **DMSO as a byproduct**

Org. Lett. **2023**, *19*, 3352.

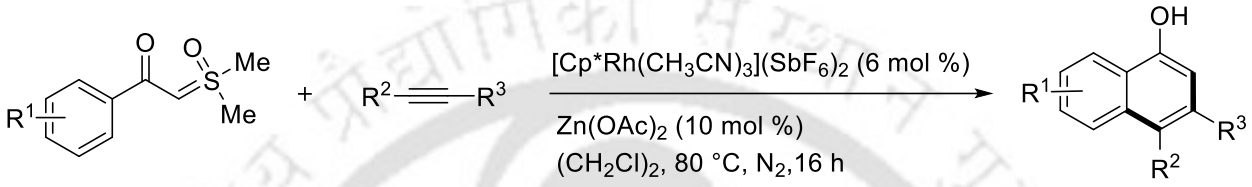
Rh-Catalyzed C–H Annulation of Benzoyl Sulfoxonium Ylides with VCPs

Transition-metal-catalyzed C–H activation is emerged as a cornerstone in modern synthesis, enabling the selective assembly of diverse molecular scaffolds directly from simple and readily available feedstock substrates.[1] In particular, the development of strategies that forge aryl-fused carbo- and heterocyclic architectures in a step- and atom-economical manner remains highly desirable due to their prevalence in natural products, bioactive molecules and functional materials.[2] Against this backdrop, benzoyl sulfoxonium ylides have emerged as robust carbene surrogates in C–H activation chemistry, combining operational safety, thermal stability and low toxicity with broad compatibility under Rh-catalysis.[3] These ylides efficiently participate as traceless, bifunctional DGs or carbene synthons in a range of annulative C–H functionalization processes, enabling the rapid construction of polycyclic frameworks through C–C and C–heteroatom bond formation in a single operation. Despite these advances, the integration of vinyl strained rings as coupling partners in sulfoxonium-ylide-driven C–H activation remains underdeveloped. Vinyl cyclopropanes (VCPs) are particularly attractive in this regard, as their substantial ring strain (~28 kcal·mol^{-1})[5d] promotes facile C–C bond cleavage under transition-metal catalysis, thereby enabling ring-opening and annulation.[5] Directed-group (DG)-assisted ring scission/functionalization of VCPs therefore provide a valuable strategy for constructing complex carbocyclic architectures, yet examples that merging VCP ring opening with annulation *via* traceless DG-assisted C–H/C–C activation are exceedingly rare. Such tandem C–H activation/ring scission/annulation sequences are intrinsically step- and atom-economical and are well suited for rapidly accessing libraries of structurally diverse carbocycles from simple precursors. Among the possible targets, *α*-tetralone motifs are widely embedded in bioactive compounds and functional molecules, but their preparation often relies on multistep routes from prefunctionalized starting materials.[6] Thus, designing of one-pot C–H activation strategy that harnesses benzoyl sulfoxonium ylides and VCPs to deliver cyclopropane-fused *α*-tetralones would therefore constitute a distinct entry to these privileged scaffolds.

1.1 Literature

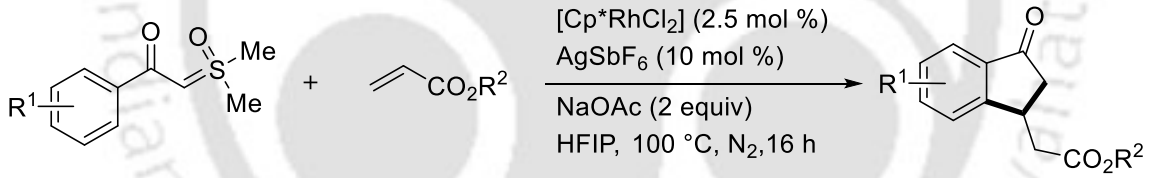
1.1.1 Sulfoxonium Ylide Directed C–H Functionalization and Annulation

Li and co-workers developed a Rh-catalyzed C–H activation/annulation of benzoyl sulfoxonium ylides with internal alkynes to access 3,4-substituted 1-naphthols (Scheme 1).[3b] The redox-neutral protocol features substrate scope, provides moderate to high yields and tolerates various functional groups.



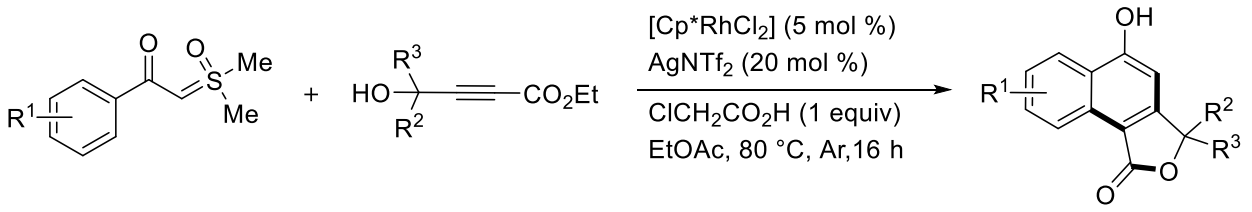
Scheme 1. Rh-Catalyzed C-H Annulation of Sulfoxonium Ylides with Internal Alkynes

Chatani and co-workers developed Rh-catalyzed reaction of benzoyl sulfoxonium ylides with alkenes (Scheme 2).[3e] The method provides substituted indanones *via* [4 + 1]-cycloaddition under mild conditions with substrate scope and high yields, tolerating various functional groups.



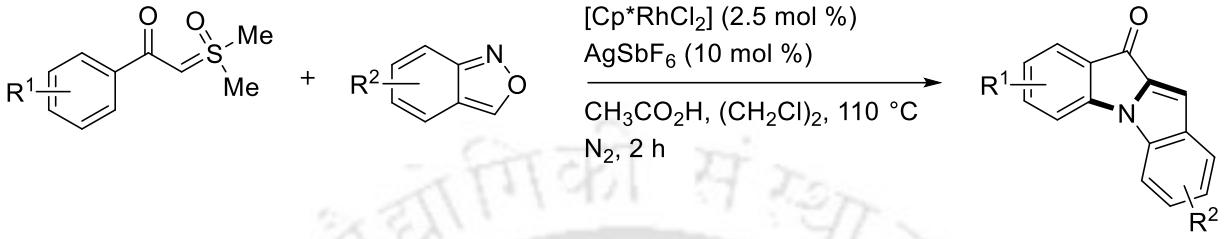
Scheme 2. Rh-Catalyzed Annulation of Sulfoxonium Ylides with Activated Alkenes

Prabhu group developed a Rh-catalyzed domino C–H activation/annulation followed by lactonization of sulfoxonium ylides with 4-hydroxy-2-alkynoates to produce furanone-fused 1-naphthols (Scheme 3).[3d] The protocol shows substrate scope, gram-scale viability and utility in synthesizing bromo lactones for photochromic materials.



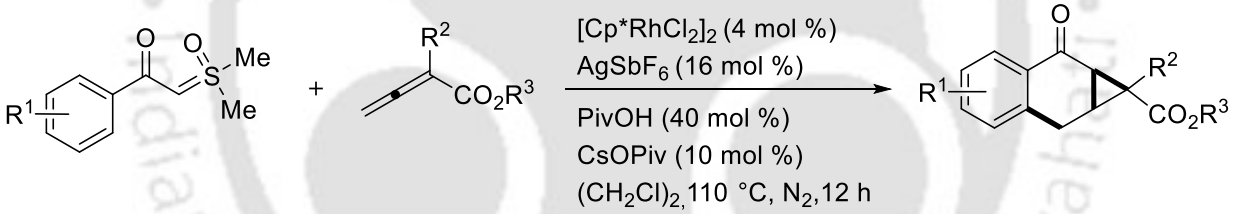
Scheme 3. Rh-Catalyzed Annulation of Sulfoxonium Ylides with 4-Hydroxy-2-alkynoates

Cheng and co-workers developed a methodology for the synthesis of indole and indolone rings with sulfoxonium ylides using anthranil under Rh-catalysis. The transformation was carried out by *ortho*-amination in benzoyl sulfoxonium ylides using anthranils as coupling partner *via* the insertion of N-H to carbene precursors (Scheme 4).[3c]



Scheme 4. Rh-Catalyzed C–H Activation/Annulation of Sulfoxonium Ylides with Anthranils

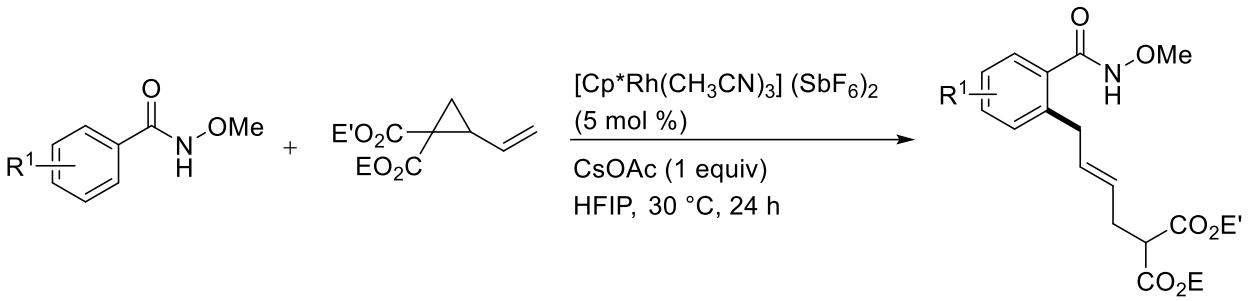
Yu and co-workers developed a Rh-catalyzed annulative coupling of sulfoxonium ylides with allenoates *via* C–H activation/cyclopropanation cascade to synthesize 2H-cyclopropa[*b*]-naphthalen-2-ones. The protocol exhibits substrate scope, gram-scale synthesis and versatile derivatizations to oxime esters, hydrazones and fused heterocycles. (Scheme 5).[3e]



Scheme 5. Rh-Catalyzed C–H Activation/Annulation of Sulfoxonium Ylides with Allenoates

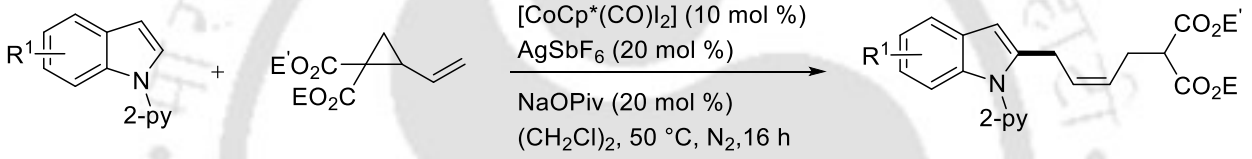
1.1.2 VCPs in C–H Functionalization

Wang and co-workers developed a Rh-catalyzed sequential C–H/C-C activation of *N*-methoxybenzamides with VCPs to afford C–H allylation. The robust protocol features substrate scope and derivatizations to isoquinolinones and amino alcohols and DFT computations (Scheme 6).[7]



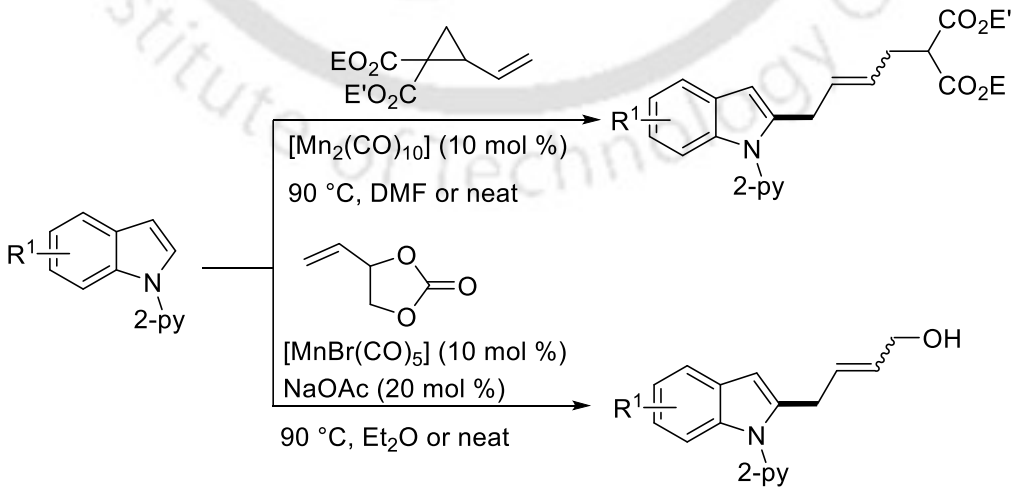
Scheme 6. Rh-Catalyzed C–H Allylation of *N*-methoxybenzamides with VCPs

Ackermann and co-workers developed Co-catalyzed C–H/C-C activation of indoles with VCPs, delivering *Z*-selective allyl arenes (>11:1 *Z*/*E*). The reaction operates at room temperature with substrate scope, functional group tolerance and selectivity contrasting rhodium catalysis (Scheme 7).[9]



Scheme 7. Co-Catalyzed C–H Allylation of Indoles with Vinyl Cyclopropanes

Glorius group developed a Mn-catalyzed sequential C–H/C-C and C-O bond activation of indoles/arenes with VCPs and vinyl-1,3-dioxolan-2-ones to produce allylic alcohols (Scheme 8).[8] The sustainable protocol operates solvent-free condition with substrate scope, formation of both C-C and C-O bonds and functional group tolerance.

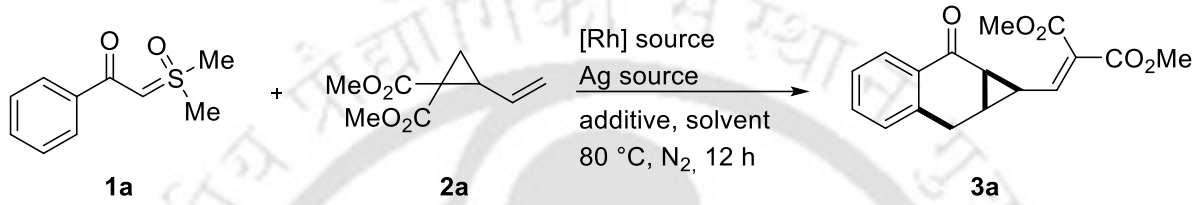


Scheme 8. C–H Allylation of Indoles with Vinyl Strained Rings

1.2 Present Study

We report here an expeditious Rh-catalyzed traceless DG-assisted tandem C–H activation/ring scission/annulation using VCPs as coupling partner to accomplish cyclopropane fused *α*-tetralones. One-pot C-C bond formation, use of traceless DG, synthesis of cyclopropane fused tetralones and functional group tolerance are the important practical features.

Table 1. Optimization of Reaction Conditions[a]



1a **2a** **3a**

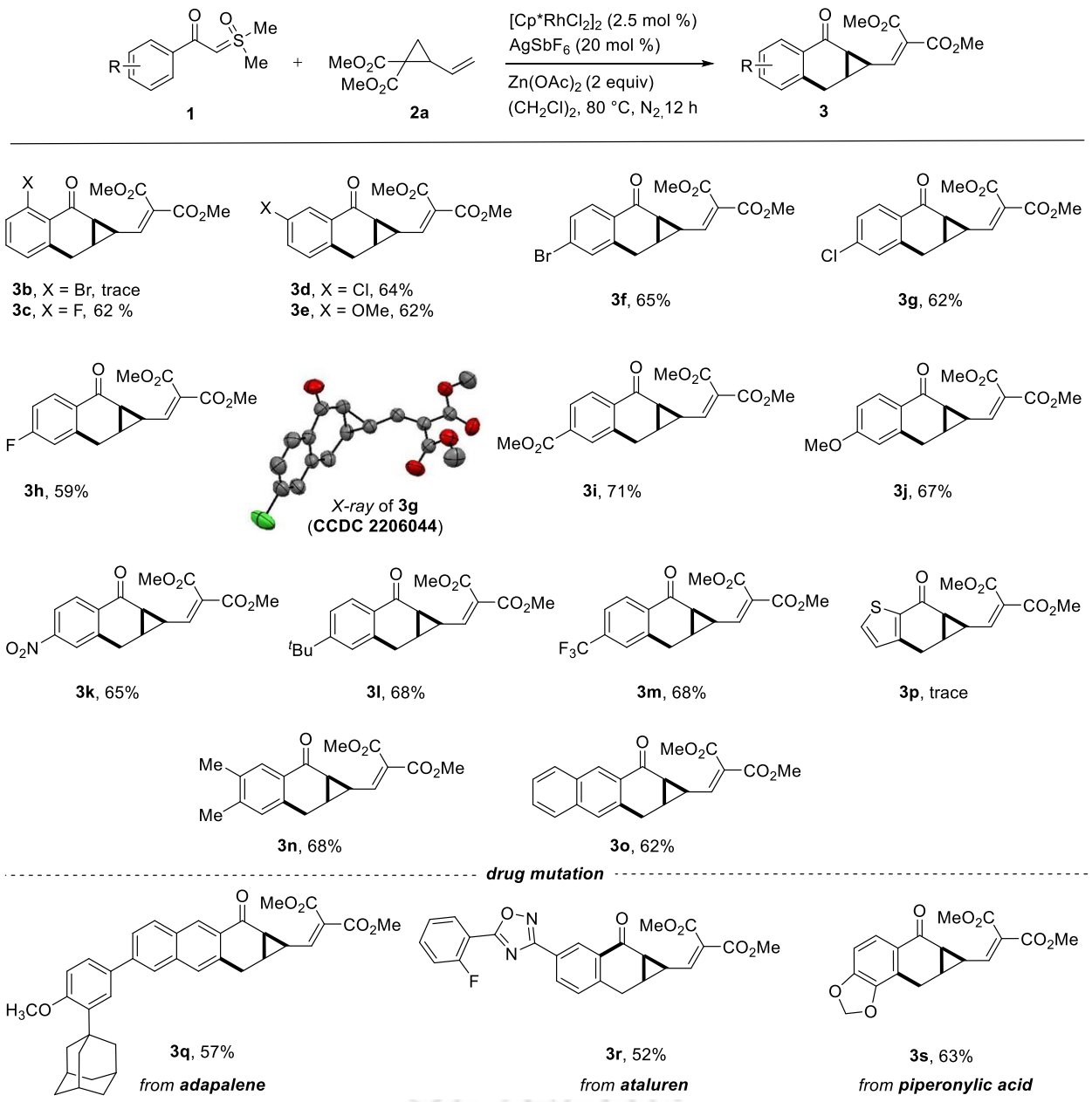
Entry	[Rh] source	Ag source	Additive	Solvent	Yield (%)[b]
1	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Cu(OAc)_2$	$(CH_2Cl)_2$	35
2	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Cu(OAc)_2{\cdot}H_2O$	$(CH_2Cl)_2$	28
3	$[Cp^*RhCl_2]_2$	$AgSbF_6$	Ag_2O	$(CH_2Cl)_2$	30
4	**$[Cp^*RhCl_2]_2$**	**$AgSbF_6$**	**$Zn(OAc)_2$**	**$(CH_2Cl)_2$**	**72**
5	$[Cp^*RhCl_2]_2$	$AgSbF_6$	Cu_2O	$(CH_2Cl)_2$	22
6	$[Cp^*RhCl_2]_2$	$AgSbF_6$	AgOAc	$(CH_2Cl)_2$	39
7	$[Cp^*RhCl_2]_2$	$AgSbF_6$	CsOAc	$(CH_2Cl)_2$	27
8	$[Cp^*RhCl_2]_2$	$AgSbF_6$	CsOPiv	$(CH_2Cl)_2$	30
9	$[Cp^*RhCl_2]_2$	$AgSbF_6$	Cs_2CO_3	$(CH_2Cl)_2$	24
10	$[Cp^*RhCl_2]_2$	$AgSbF_6$	NaOAc	$(CH_2Cl)_2$	trace
11	$[Cp^*RhCl_2]_2$	$AgSbF_6$	CH_3CO_2H	$(CH_2Cl)_2$	n.d.
12	$[Cp^*RhCl_2]_2$	$AgSbF_6$	PivOH	$(CH_2Cl)_2$	25
13	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$AdCO_2H$	$(CH_2Cl)_2$	33
14	$[Cp^*RhCl_2]_2$	$AgSbF_6$	-	$(CH_2Cl)_2$	trace
15	$[Cp^*RhCl_2]_2$	$AgBF_4$	$Zn(OAc)_2$	$(CH_2Cl)_2$	trace
16	$[Cp^*RhCl_2]_2$	$AgNTf_2$	$Zn(OAc)_2$	$CH_2Cl)_2$	trace

17	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Zn(OAc)_2$	TFE	n.d.
18	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Zn(OAc)_2$	CH_3CN	n.d.
19	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Zn(OAc)_2$	toluene	n.d.
20	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Zn(OAc)_2$	1,4-dioxane	trace
21	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Zn(OAc)_2$	THF	trace
22[c]	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Zn(OAc)_2$	$(CH_2Cl)_2$	42
23	$[Cp^*RhCl_2]_2$	-	$Zn(OAc)_2$	$(CH_2Cl)_2$	n.d.
24[d]	$Rh_2(OAc)_4$	$AgSbF_6$	$Zn(OAc)_2$	$(CH_2Cl)_2$	n.d.
25[e]	$[Cp^*Rh(CH_3CN)_3](SbF_6)_2$	-	$Zn(OAc)_2$	$(CH_2Cl)_2$	55
26[f]	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Zn(OAc)_2$	$(CH_2Cl)_2$	71
27[g]	-	$AgSbF_6$	$Zn(OAc)_2$	$(CH_2Cl)_2$	n.d.
28[h]	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Zn(OAc)_2$	$(CH_2Cl)_2$	61
29[i]	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Zn(OAc)_2$	$(CH_2Cl)_2$	59
30[j]	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Zn(OAc)_2$	$(CH_2Cl)_2$	52
31[k]	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Zn(OAc)_2$	$(CH_2Cl)_2$	trace
32[l]	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Zn(OAc)_2$	$(CH_2Cl)_2$	17

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), Ag source (0.05 mmol), additive (0.2 mmol), solvent (1 mL), 80 °C, 12 h, N_2 atmosphere. [b]Isolated yield. [c]Using 0.12 mmol of **2a**. [d]Using 2.5 mol % $Rh_2(OAc)_4$. [e]Using 5 mol % $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$. [f]Using 5 mol % $[Cp^*RhCl_2]_2$. [g]Without $[Cp^*RhCl_2]_2$. [h]Using 60 °C. [i]Using 100 °C. [j]Using 120 °C. [k]Room temperature. [l]Using air. n.d. = not detected.

Initially, we optimized the reaction conditions using **1a** and **2a** as the representative substrates with Ag source, additives, solvents and Rh salts (Table 1). Gratifyingly, treatment of **1a** with **2a** in the presence of $[RhCpCl_2]_2$ (2.5 mol %), $AgSbF_6$ (20 mol %) and $Cu(OAc)_2$ (2 equiv) in CH_2Cl_2 at 80 °C for 12 h under N_2 afforded **3a** in 35% yield. Among the additives evaluated, $Zn(OAc)_2$ delivered the best outcome, presumably owing to its strong coordination with the two oxygen

Table 2. Substrate Scope of Sulfoxonium Ylides[a,b]



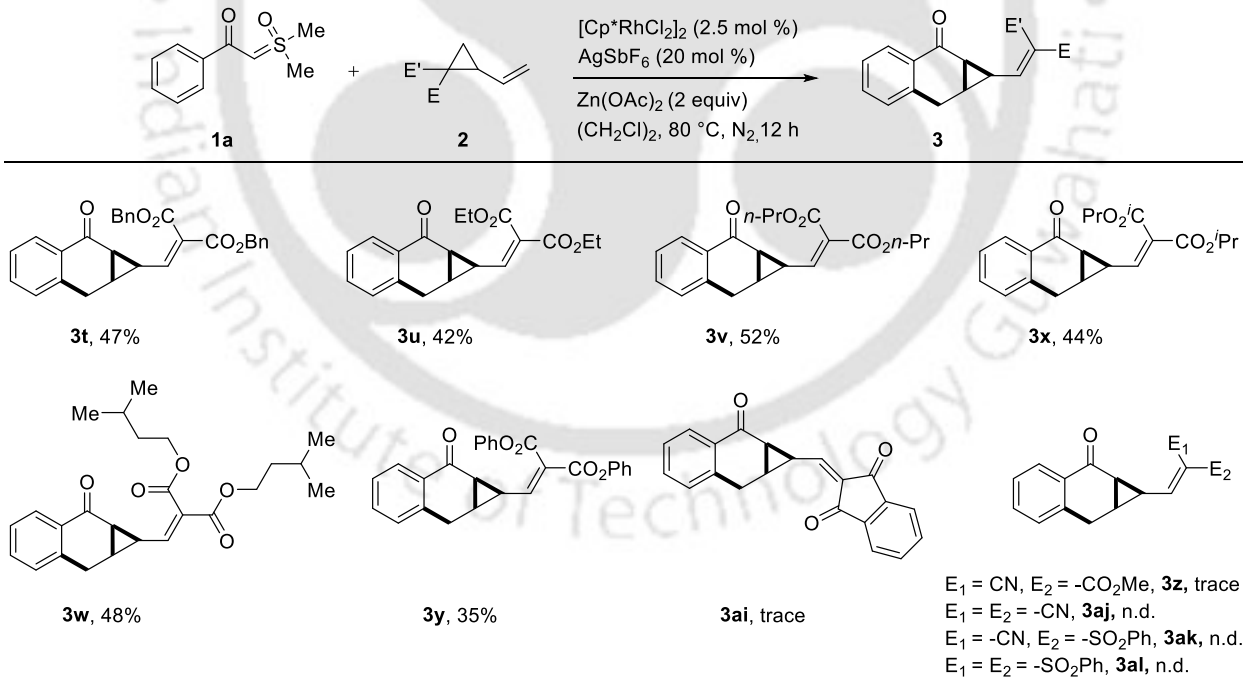
[a]Reaction conditions: **1b-s** (0.1 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (20 mol %), $Zn(OAc)_2$ (0.2 mmol), $(CH_2Cl)_2$ (1 mL), 80 °C, 12 h, N_2. [b]Isolated yield.

atoms of the sulfoxonium ylide,[12] thereby promoting the C–H activation. Moreover, omission of both the Ag source and additive led to a significant decrease in the yield of **3a**. In a set of Ag source investigated from $AgSbF_6$ to $AgBF_4$ and $AgNTf_2$ former yielded the best result. $(CH_2Cl)_2$ emerged as the solvent of choice, whereas TFE, CH_3CN, toluene, 1,4-dioxane and THF led to

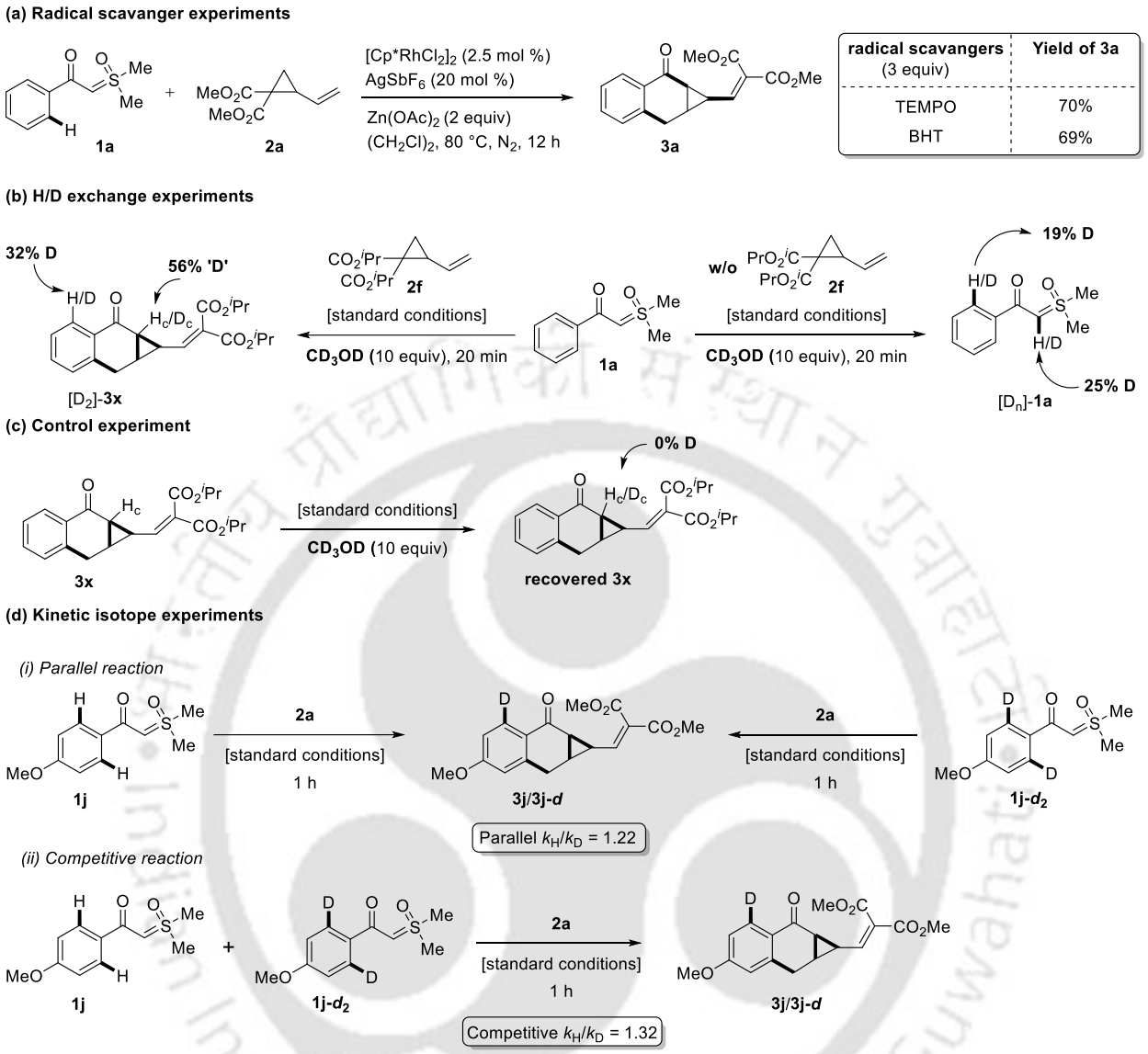
diminished yields. Among the catalysts examined, $[Cp^*RhCl_2]_2$ outperformed $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ and $Rh_2(OAc)_4$. The optimal reaction temperature was 80 °C, while conducting the reaction under air resulted decrease in yield.

Having optimized the reaction conditions, the scope of the procedures was investigated using substituted sulfoxonium ylides **1b-s** with VCP **2a** as a standard substrate (Table 2). Substrates bearing 2-bromo **1b** produced **3b** in trace amount, presumably due to steric encumbrance proximal to the reactive center, whereas 2-fluoro analogue **1c** was well tolerated to deliver **3c** in 62% yield. Further, substrates bearing 3-chloro **1d** and 3-methoxy **1e** groups furnished **3d** and **3e** in 64% and 62% yields, respectively. Likewise, 4-substituted aryl rings bearing bromo **1f**, chloro **1g**, fluoro **1h**, ester **1i**, methoxy **1j**, nitro **1k**, *tert*-butyl **1l** and trifluoromethyl **1m** groups afforded the annulated products **3f-m** in moderate to good yields (59-71%). Furthermore, ylides bearing 3,4-dimethyl **1n** and phenyl **1o** substituents furnished the corresponding products **3n** and **3o** in 68% and 62% yields respectively. These outcomes demonstrate that both electron-donating and electron

Table 3. Substrate Scope of VCPs[a,b]



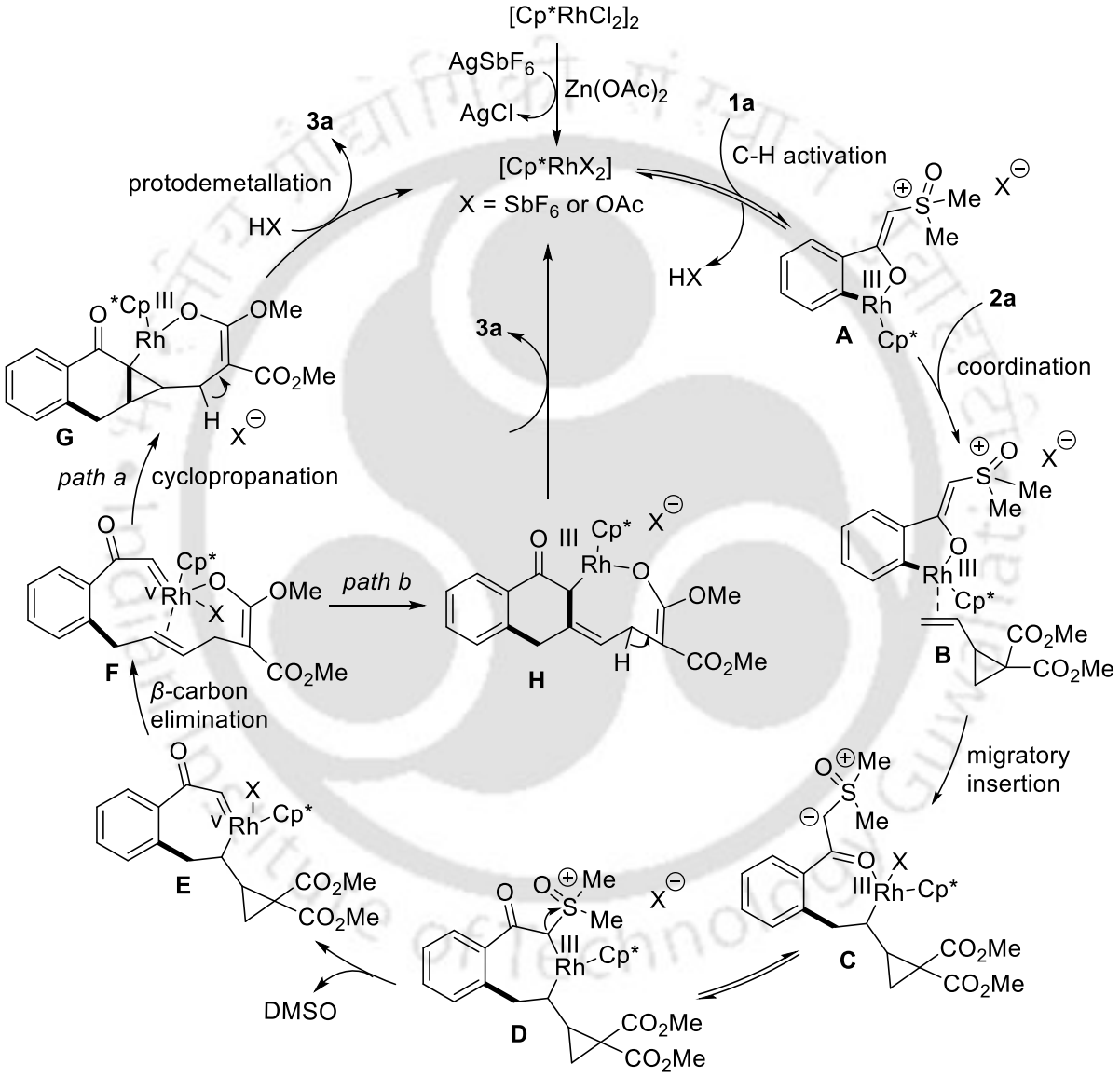
[a]Reaction conditions: **1a** (0.1 mmol), **2b-l** (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (20 mol %), $Zn(OAc)_2$ (0.2 mmol), $(CH_2Cl)_2$ (1 mL), 80 °C, 12 h, N_2. n.d. = not detected. [b]Isolated yield.



Scheme 9. Preliminary Mechanistic Investigation

-withdrawing substituents on the aryl ring of the ylides were well tolerated under the standard reaction conditions. Structural assignment of **3g** was unequivocally confirmed by single crystal *X*-ray diffraction (CCDC 2206044). However, the heteroaryl substrate 2-thiophenyl **1p** derivative afforded **3p** in trace amount, which may be attributed to heteroatom coordination with the catalyst. In contrast, ylides derived from adapalene **1q**, ataluren **1r** and piperonylic acid **1s** underwent smooth coupling to furnish **3q-s** in 52-63% yields, highlighting the applicability of this protocol for late-stage functionalization of bioactive scaffolds. The substrate scope was further expanded by diversifying **2b-l** using sulfoxonium ylide **1a** as standard substrate (Table 3). VCPs bearing

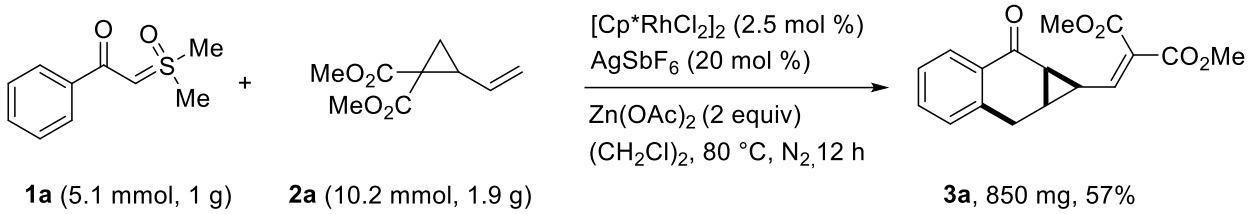
benzyl **2b**, ethyl **2c**, *n*-propyl **2d**, isoamyl **2e,** isopropyl **2f** and phenyl **2g** substituents furnished **3t-y** in 35-52% yields. However, cyano-ester bearing VCP **2h** and indandione VCP **2i** yielded the trace amounts of **3z** and **3ai** respectively. While, dicyano **2j**, phenylsulfonyl-cyano **2k** and diphenylsulfonyl **2l** substituted VCPs remained unreactive, likely due to coordination of the cyano group to the catalyst or steric congestion from the phenylsulfonyl substituents.



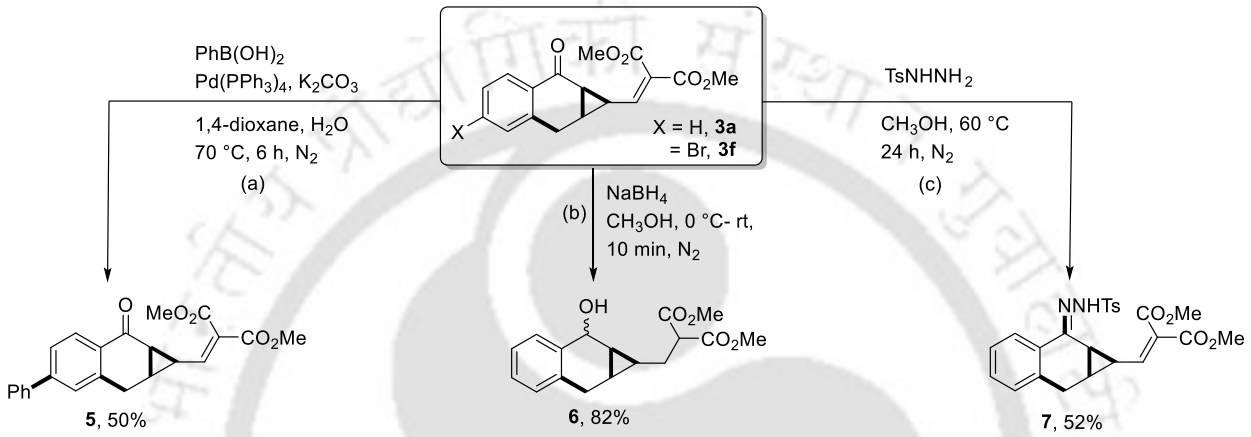
Scheme 10. Plausible Reaction Pathway

To gain mechanistic insight, the reaction of **1a** and **2a** was conducted separately in the presence of the radical scavengers 2,2,6,6- tetramethylpiperidine 1-oxyl (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) (Scheme 9). The reaction yields were unaffected, indicating that a radical pathway is unlikely to operate. The H/D exchange experiments were performed using CD_3OD as a co-solvent revealed 19% and 32% deuterium incorporation at the *ortho* position of the benzoyl ring of sulfoxonium ylide in the absence and presence of **2f** respectively suggested that the C–H activation step is reversible. Additionally, **1a** exhibited 25% deuterium incorporation at the *α*-position of the carbonyl group in absence of **2f**. Further, the reaction of **1a** with **2f** was conducted in presence of CD_3OD and [D_2]-**3x** was obtained with 56% deuterium incorporation at the cyclopropane fusion site. Control experiment confirmed that this incorporation did not originate from H/D exchange after product formation. These findings are consistent with the generation of a Rh–alkyl intermediate in which the Rh center resides at the cyclopropane junction during the catalytic cycle (Scheme 10). Moreover, kinetic isotope effect studies using **1j** and **1j-*d*$_2$** with **2a** under standard conditions for 1 h gave k_H/k_D=1.22 for parallel and k_H/k_D=1.32 for competitive experiments which indicates C–H bond cleavage might not be involved in the rate determining step.[13]

Based on the experimental observations and previous reports,[10,11] a plausible reaction pathway is proposed (Scheme 10). The catalytic cycle is initiated through the coordination of the carbonyl moiety of sulfoxonium ylide **1a** to the active Rh(III) catalyst, which subsequently may undergo a concerted metalation-deprotonation process to form the five-membered rhodacyclic intermediate **A**.[14] Coordination of the VCP **2a** to the Rh center generates complex **B** which undergo migratory insertion to furnish intermediate **C**. An intramolecular rearrangement of **C** leads to **D**, which subsequently undergoes internal oxidation to form the Rh-bound *α*-oxo carbene species **E,** accompanied by the extrusion of DMSO.[3c] The ensuing *β*-carbon elimination and C–C bond cleavage yield intermediate **F**. This species may undergo intramolecular cyclopropanation to afford the fused intermediate **G** (*path a*) which may undergo proto-demetallation to furnish **3a**. Alternatively, **F** can participate in a migratory insertion followed by a [4+2]-annulation to deliver **H** (*path b*). Subsequently, an intramolecular nucleophilic attack by the *α*-carbon on the adjacent carbon atom may produce **3a**, concomitantly regenerating the catalytically active Rh(III) species, thereby completing the catalytic cycle.



Scheme 11. Scale-up Synthesis



[a]Reaction conditions: (a) **3f** (0.1 mmol), $PhB(OH)_2$ (0.1 mmol), $Pd(PPh_3)_4$ (10 mol %), K_2CO_3 (0.2 mmol), 1,4-dioxane (2 mL), 70 °C, 6 h, N_2 (b) **3a** (0.2 mmol), $NaBH_4$ (0.4 mmol), MeOH (2 mL), rt, 10 mins. (c) **3a** (0.2 mmol), $TsNHNH_2$ (0.3 mmol), MeOH (2 mL), 60 °C, 24 h, N_2.

Scheme 12. Post-Synthetic Transformations

To demonstrate the synthetic utility of the protocol, a gram-scale reaction was performed using **1a** (5.1 mmol) and **2a** (10.2 mmol) as standard substrates to afford **3a** in 57% yield. (Scheme 11). Furthermore, the synthetic versatility of the product was illustrated through several downstream transformations (Scheme 12). For instance, treatment of **3f** with phenylboronic acid under Pd catalysis furnished **5** in 50% yield, while $NaBH_4$ reduction of **3a** gave **6** in 82% yield as a 4:1 diastereomeric mixture. In addition, **3a** was converted to **7** in 52% yield, demonstrating its potential as a valuable synthetic intermediate.[15]

In summary, a Rh-catalyzed cascade C–H activation/ring opening/annulation of benzoyl sulfoxonium ylides with VCPs has been developed to access cyclopropane-fused α-tetralones under mild conditions. The cooperative interplay of strain-release coupling and sequential C–C

bond formation with C–H activation provides a practical platform for the construction of fused carbocycles and late-stage diversification of drug-like scaffolds.

1.3 Experimental Section

General Information. $[Cp^*RhCl_2]_2$ (97%), $AgSbF_6$ (98%), $Cu(OAc)_2$ (98%), $Cu(OAc)_2 \cdot H_2O$ (>98%), Ag_2O (99%), $Zn(OAc)_2$ (>98%), Cu_2O (≥99.99%), AgOAc (≥99.99%), CsOAc (98%), CsOPiv (>98%), Cs_2CO_3 (>98%), NaOAc (>98%), CH_3COOH (>98%), PivOH (>98%), AdCOOH (>98%), trifluoroethanol (TFE) and carboxylic acids of Aldrich and TCI chemicals and used as received. Acetonitrile (CH_3CN), toluene, 1,4-dioxane, tetrahydrofuran (THF) and 1,2-dichloroethane $(CH_2Cl)_2$ were dried prior as per the standard procedure. Silica gel-G/GF254 plates (Merck) were used for TLC analysis with a mixture of hexane and ethyl acetate as the eluent. Column chromatography was carried out using Rankem silica gel (60-120 mesh). Bruker Avance III 400, 500 and 600 MHz NMR spectrometers were used to record (^1H, ^{13}C and ^{19}F) spectra using $CDCl_3$ and DMSO-d_6 as the solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) and spin-spin coupling constant (*J*) are reported in parts per million and hertz (Hz), respectively, and to describe peak patterns following abbreviations were used when appropriate: s = singlet, d = doublet, t = triplet and m = multiplet. Melting point of the products was measured on Büchi melting point apparatus, MPB-540. Open capillary tubes were used for the measurements and are uncorrected. Mestre nova software was used throughout the spectral analysis. Q-Tof ESI-MS instrument (model HAB273) was used for recording HRMS data. Infrared spectra were recorded on Perkin Elmer FT-IR instrument. Single crystal X-ray data were collected on a Bruker SMART APEX equipped with a CCD area detector using Mo/-Kα radiation and the structure was solved by direct method using SHELXL-16 (Göttingen, Germany).

General Procedure for the Preparation of Sulfoxonium Ylides 1.

Step-I: To a stirred solution of a carboxylic acid (5 mmol) and DMF (2 drops) in CH_2Cl_2 (15 mL), $(COCl)_2$ (6.5 mmol, 0.56 mL) was added dropwise. The reaction was allowed to stir at room temperature for 12 h. Evaporation of the reaction mixture gave a residue which was dissolved in THF (10 mL). The resulting solution was used as acid chloride solution in subsequent reactions.
Step-II: To a stirred solution of potassium *tert*-butoxide (6.9 mmol, 774 mg) in dry THF (10 mL), trimethylsulfoxonium iodide (6.9 mmol, 1.5 g) was added and the reaction was allowed to reflux

for 3 h. The reaction mixture was cooled to 0 °C and the solution of the acid chloride (obtained by **step-I**) was added dropwise to it. Then, the reaction was allowed to stir at room temperature for additional 3 h. After completion, 10 mL of water was added to the reaction mixture and the organic part was extracted with ethyl acetate (3 x 25 mL). The combined organic layer was washed with brine (10 mL) and water (5 mL). Drying (Na_2SO_40 and evaporation of the solvent gave a residue that was purified on silica gel column chromatography (ethyl acetate/methanol = 9:1) to afford sulfoxonium ylides **1a-s**.

General Procedure for the Preparation of VCPs 2.

Synthesis of 2a. To a round bottom flask was containing dry MeOH (10 mL) portion wise Na metal (10.3 mmol, 250 mg) was added at room temperature and the solution was allowed to stir till all the sodium metal gets dissolved. The resulting solution was then added dropwise to a stirred solution of (*E*)-1,4-dibromobut-2-ene (4.7 mmol, 1 g) and dimethyl malonate (5.1 mmol, 0.59 mL) in dry MeOH (5 mL) at room temperature under N_2 atmosphere. The reaction was allowed to stir for 16 h. After completion of the reaction, water (20 mL) was added to quench the reaction. Then, the reaction mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic part was washed with brine (10 mL) and water (5 mL), dried over Na_2SO_4, and evaporated to afford a residue which was purified using silica gel column chromatography (hexane/ethyl acetate = 9:1) to afford VCP **2a**.

Synthesis of 2b, 2d-e and 2i. To a stirred solution of the corresponding malonate (2.1 mmol) and (*E*)-1,4-dibromobut-2-ene (2.3 mmol, 492 mg) in dry EtOH (7 mL) was added potassium carbonate (4.2 mmol, 580 mg). The reaction mixture was then heated to reflux for 16 h. The reaction mixture was cooled to room temperature and passed through a short pad of celite. The organic part was washed with saturated aq. NH_4Cl (20 mL), extracted with ethyl acetate (3 x 15 mL) and dried over Na_2SO_4. Then all the volatiles were removed under reduced pressure to get a residue which was purified using silica gel column chromatography (hexane/ethyl acetate = 8:2) to afford VCPs **2b** and **2d-e** and **2g**.

Synthesis of 2c, 2f-h and 2j-l. To a stirred solution of the corresponding malonate (2.3 mmol) and (*E*)-1,4-dibromobut-2-ene (2.3 mmol, 492 mg) in dry THF (12 mL) was added cesium carbonate (5.8 mmol, 1.9 g). The reaction mixture was stirred at 60 °C for 48 h. After completion, the reaction

mixture was diluted with ethyl acetate (10 mL) and filtered through a short celite pad. The filtrate was washed with saturated aq. $NaHCO_3$ (5 mL) and water (5 mL). Drying (Na_2SO_4) and evaporation of the solvent under reduced pressure gave the residue, which was purified using silica gel column chromatography (hexane/ethyl acetate = 8:2) to afford VCPs **2c** and **2f-l.**

General Procedure of Rh-Catalyzed Annulation of Sulfoxonium Ylide 3. Sulfoxonium ylide **1** (0.2 mmol), VCP **2** (0.4 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %, 0.005 mmol, 3 mg), $AgSbF_6$ (20 mol %, 0.04 mmol, 12 mg) and $Zn(OAc)_2$ (0.4 mmol, 66 mg) were stirred in $(CH_2Cl)_2$ (5 mL) at 80 °C in an oil bath for 12 h. After completion (monitored by TLC), the reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and filtered through a short celite pad. Evaporation of the solvent gave a residue, which was purified using silica gel chromatography (hexane: ethyl acetate =7:3) to afford the annulated tetralones.

Scale-up Synthesis of 3a. 2-(Dimethyl(oxo)-l6-sulfaneylidene)-1-phenylethan-1-one **1a** (5.1 mmol, 1 g), 1-dimethyl 2-vinylcyclopropane-1,1-dicarboxylate **2a** (10.2 mmol, 1.9 g), $[Cp^*RhCl_2]_2$ (2.5 mol %, 0.25 mmol, 79 mg), $AgSbF_6$ (20 mol %, 2 mmol, 350 mg) and $Zn(OAc)_2$ (10.2 mmol, 1.8 g) were stirred in $(CH_2Cl)_2$ (60 mL) at 80 °C for 12 h. After completion, the reaction mixture was cooled to room temperature and was diluted with ethyl acetate (20 mL) and filtered through a celite pad. Evaporation of the solvent provided residue, which was purified using silica gel chromatography (hexane: ethyl acetate =7:3) to afford the annulated tetralones **3a** in 57% (850 mg) yield.

Post-Synthetic Modifications

Synthesis of 5. Compound **3f** (0.1 mmol, 50 mg), phenylboronic acid (0.1 mmol, 18 mg), $(PdPPh_3)_4$ (10 mol %, 12 mg), K_2CO_3 (0.2 mmol, 22 mg) and H_2O (0.1 mL) were stirred in 1,4-dioxane (2 mL) at 70 °C for 6 h under N_2 atmosphere. After completion (monitored by TLC), the reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL), washed with water (5 mL) and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified using silica gel chromatography (hexane/ethyl acetate = 8:2) to afford **5** in 50% (34 mg) yield.

Synthesis of 6. To a stirred solution of **3a** (0.2 mmol, 60 mg) in MeOH (2 mL) was added $NaBH_4$ (0.4 mmol, 15 mg) at 0 °C under N_2 atmosphere and the reaction was allowed to stir for 10 minutes

at room temperature. After completion (monitored by TLC), all the volatiles were evaporated using rotary evaporator. The resulting residue was purified using silica gel chromatography (hexane/ethyl acetate = 7:3) to afford **6** in 82% (41 mg) yield.

Synthesis of 7. Compound **3a** (0.2 mmol, 60 mg) and $TsNHNH_2$ (0.3 mmol, 45 mg) were stirred in MeOH (2 mL) at 60 °C for 24 h under N_2 atmosphere. After completion (monitored by TLC), the reaction mixture was cooled to ambient temperature. Then all the volatiles were evaporated under reduced pressure and the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 8:2) to afford **7** in 52% (41 mg) yield.

Mechanistic Investigation

H/D Exchange Experiment of 1a with CD_3OD in Absence of 2f. To a stirred solution of 2-(dimethyl(oxo)-l6-sulfaneylidene)-1-phenylethan-1-one **1a** (0.2 mmol, 50 mg), $[Cp^*RhCl_2]_2$ (2.5 mol%, 0.005 mmol, 3 mg), $AgSbF_6$ (20 mol %, 0.04 mmol, 14 mg) and $Zn(OAc)_2$ (0.4 mmol, 73 mg) in $(CH_2Cl)_2$ (5 mL), CD_3OD (2 mmol, 0.05 mL) was added and stirred at 80 °C in an oil bath for 20 minutes under N_2 atmosphere. The resulting reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and passed through a short pad of celite. **1a** was recovered using silica gel chromatography (ethyl acetate: methanol=9:1) to afford $[D_n]$-**1a**. The deuterium incorporation was observed as 19% at C2-H, 25% at the H of α-carbon of carbonyl group of $[D_n]$-**1a** based on 600 MHz ^{1}H NMR.

H/D Exchange Experiment of 1a with CD_3OD in Presence of 2f. To a stirred solution of 2-(dimethyl(oxo)-l6-sulfaneylidene)-1-phenylethan-1-one **1a** (0.2 mmol, 50 mg), diisopropyl 2-vinylcyclopropane-1,1-dicarboxylate **2f** (0.4 mmol, 94 mg), $[Cp^*RhCl_2]_2$ (2.5 mol%, 0.005 mmol, 3 mg), $AgSbF_6$ (20 mol %, 0.04 mmol, 14 mg) and $Zn(OAc)_2$ (0.4 mmol, 73 mg) in $(CH_2Cl)_2$ (5 mL), CD_3OD (2 mmol, 0.05 mL) was added and stirred at 80 °C in an oil bath for 12 h under N_2 atmosphere. The resulting reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and filtered through a short pad of celite. Evaporation of the filtrate gave a residue, which was purified using silica gel chromatography (hexane: ethyl acetate =7:3) to afford $[D_2]$-**3x**. The deuterium incorporation was calculated in H_c of $[D_2]$-**3x** from 400 MHz ^{1}H NMR spectrum.

Preparation of 2-(Dimethyl(oxo)-l6-sulfaneylidene)-1-(4-methoxyphenyl-2,6-d2)ethan-1-one 1j-*d*$_2$.

Step-I: In a round bottom flask 4-methoxybenzoic acid (0.50 mmol, 76 mg), [Ru(O_2CAd)$_2$(p-cymene)] (5 mol %, 14.9 mg) and D_2O (10 mmol, 180 µL) in 1,4-dioxane (1 mL) were allowed to stir at 100 °C for 16 h under N_2 atmosphere. After cooling to room temperature, the residue was diluted with CH_2Cl_2 (8 mL) and filtered through a short pad of celite. Evaporation of the solvent gave a residue that was purified using silica gel column chromatography (hexane/ethyl acetate/acetic acid= 8:1:0.1) to afford [D]-**1j**.

Step-II: To a stirred solution of [D]-**1j** (0.6 mmol, 100 mg) and DMF (1 drop) in CH_2Cl_2 (2 mL), $(COCl)_2$ (0.8 mmol, 0.07 mL) was added dropwise. The reaction mixture was allowed to stir at room temperature for 12 h. Then the solvent was evaporated under reduced pressure and the residue having [D]-**1j** acid chloride was used in the subsequent step.

Step-III: To a stirred solution of potassium *tert*-butoxide (2.4 mmol, 266 mg) in dry THF (4 mL), trimethylsulfoxonium iodide (2.4 mmol, 522 mg) was added at room temperature. The reaction was allowed to reflux for 3 h. The reaction mixture was then cooled to 0 °C, followed by the slow addition of the solution of the [D]-**1j** acid chloride obtained by the above procedure (**Step II**). The reaction was allowed to warm to room temperature and stirred for 3 h. After completion, the reaction mixture was concentrated using rotary evaporator and water (10 mL) was added to the residue and extracted with ethyl acetate (3 x 10 mL) and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified using silica gel chromatography (ethyl acetate/methanol = 9:1) to afford **1j-*d*$_2$** with 93% deuteriation.

Control Experiments. To a stirred solution of **3x** (0.25 mmol, 50 mg), $Zn(OAc)_2$ (0.5 mmol, 90 mg), $AgSbF_6$ (0.05 mmol, 17 mg), [Cp*$RhCl_2$]$_2$ (2.5 mol %, 0.025 mmol, 3.8 mg) in $(CH_2Cl)_2$ (5 mL), CD_3OD (2.5 mmol, 0.1 mL) was added and the stirring continued at 80 °C for 12 h under N_2 atmosphere. The resulting reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and passed through a short pad of celite. The purification was performed as described in the general procedure and **3x** was recovered in 72% yield with no deuteration at the junction of the cyclopropane ring.

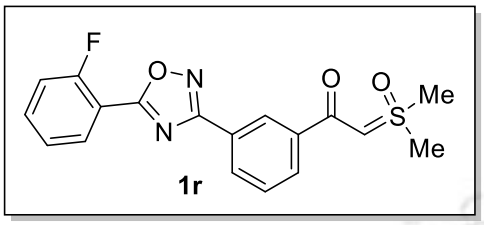
Kinetic Isotope Effect Experiments

Parallel Reactions. Two round bottom flasks were charged with $[Cp^*RhCl_2]_2$ (3 mg, 2.5 mol %), $Zn(OAc)_2$ (80 mg, 0.5 mmol.), 2-(dimethyl(oxo)-l6-sulfaneylidene)-1-(4 methoxyphenyl)ethan-1-one (**1j** or **1j-*d*$_2$** , 0.2 mmol), dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**2a**, 0.22 mmol) and $(CH_2Cl)_2$ (5 mL) for 1 h at standard reaction conditions. The reaction was cooled to room temperature, diluted with ethyl acetate (10 mL) and filtered through a short pad of celite. The solvent was removed under vacuum and purification was performed as described in the general procedure to afford **3j** and **3j-*d*** (20% yield in total). The KIE value was determined to be k_H/k_D = 1.22 on the basis of ^{1}H NMR analysis.

Competitive Reactions. A mixture of 2-(dimethyl(oxo)-l6-sulfaneylidene)-1-(4 methoxyphenyl)ethan-1-one **1j** (0.25 mmol, 32 mg) and 2-(dimethyl(oxo)-l6 sulfaneylidene)-1-(4-methoxyphenyl-2,6-d2)ethan-1-one **1j-*d*$_2$** (0.25 mmol, 34 mg) [93% D] was reacted with dimethyl 2-vinylcyclopropane-1,1-dicarboxylate **2a** (0.5 mmol, 92 mg), $Zn(OAc)_2$ (80 mg, 0.5 mmol) in $(CH_2Cl)_2$ (5 mL) for 1 h at standard reaction conditions. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and passed through a short pad of celite. Then the solvent was removed under vacuum and the purification was performed as described in the general procedure to afford mixture of **3j/3j-*d*** and k_H/k_D = 1.32, based on 500 MHz ^{1}H NMR.

1.4 Characterization data

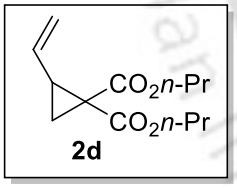
Characterization Data of Newly Synthesized Sulfoxonium Ylides



1r

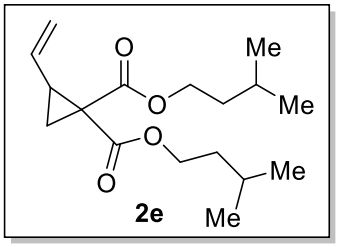
2-(Dimethyl(oxo)-l6-sulfaneylidene)-1-(3-(5-(2-fluoro-phenyl)-1,2,4-oxadiazol-3-yl)phenyl)ethan-1-one 1r. Analytical TLC on silica gel, 1:9 methanol/ethyl acetate R_f = 0.28; brown solid; mp 167-168 °C; yield 68% (200 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.25-8.22 (m, 2H), 8.00 (d, *J* = 8 Hz, 1H), 7.61-7.53 (m, 2H), 7.36-7.26 (m, 2H), 5.12 (s, 1H), 3.55 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.4, 173.0 ($J_{C\text{-}F}$ = 4.2 Hz), 168.6, 161.9 ($J_{C\text{-}F}$ = 259.0 Hz), 139.8, 134.8 ($J_{C\text{-}F}$ = 8.6 Hz), 131.1, 129.8, 129.5, 129.1, 126.8, 126.0, 124.8 ($J_{C\text{-}F}$ = 3.7 Hz), 117.4 ($J_{C\text{-}F}$ = 20.7 Hz), 113.0 ($J_{C\text{-}F}$ = 11.2 Hz), 69.2, 42.6; ^{19}F NMR (377 MHz, $CDCl_3$) δ -108.25; FT-IR (KBr) 3017, 1621, 1552, 1382, 1223, 1178, 745 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{18}H_{16}FN_2O_3S$: 359.0860; Found 359.0862.

Characterization Data of Newly Synthesized Vinyl cyclopropanes



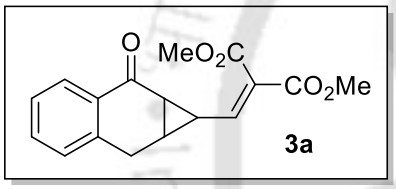
2d

Dipropyl 2-vinylcyclopropane-1,1-dicarboxylate 2d. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.28; colorless liquid; yield 42% (50 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.46-5.39 (m, 1H), 5.30-5.26 (m, 1H), 5.13-5.11 (m, 1H), 4.14-4.03 (m, 4H), 2.57 (q, *J* = 8.5 Hz, 1H), 1.69-1.63 (m, 5H), 1.55-1.53 (m, 1H), 0.93 (t, *J* = 7.5 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 167.7, 133.4, 118.6, 67.3, 67.2, 36.2, 31.3, 22.1, 22.0, 20.6, 10.5, 10.4; FT-IR (neat) 2969, 1721, 1318, 1267, 1195, 1127, 914 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{13}H_{21}O_4$: 241.1434; Found 241.1437.

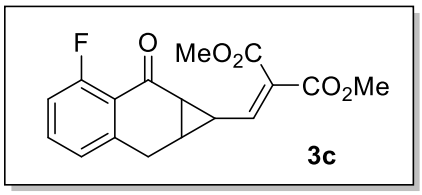


Diisopentyl 2-vinylcyclopropane-1,1-dicarboxylate 2e. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.31; colorless liquid; yield 48% (50 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.46-5.39 (m, 1H), 5.30-5.26 (m, 1H), 5.13-5.11 (m, 1H), 4.21-4.10 (m, 4H), 2.56 (q, *J* = 8.0 Hz, 1H), 1.72-1.66 (m, 3H), 1.59-1.58 (m, 1H), 1.54-1.50 (m, 4H), 0.92-0.90 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 167.6, 133.3, 118.5, 70.3, 64.4, 64.2, 37.4, 37.3, 36.1, 31.2, 26.0, 25.0, 24.9, 22.5, 22.4, 20.5; FT-IR (neat) 2958, 1723, 1317, 1268, 1196, 1127, 913 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{29}O_4$: 297.2060; Found 297.2061.

Characterization Data of the Products

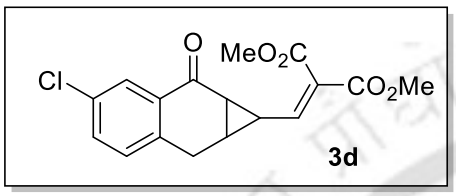


Dimethyl-2-((2-oxo-1a,2,7,7a-tetrahydro-1H-cyclopropa[b]-naphthalen-1-yl)methylene)malonate 3a. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.28; brown liquid; yield 72% (55 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 6.55 (d, *J* = 10.5 Hz, 1H), 3.77 (s, 3H), 3.67 (s, 3H), 3.42-3.37 (m, 1H), 3.35-3.32 (m, 1H), 2.47-2.41 (m, 2H), 2.23-2.20 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.7, 165.3, 164.4, 151.3, 138.3, 133.8, 130.8, 129.1, 127.5, 127.4, 126.8, 52.6, 52.3, 35.3, 27.1, 26.8, 23.8; FT-IR (neat) 2954, 1724, 1671, 1437, 1342, 1288, 1255, 1154 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}O_5$: 301.1071; Found 301.1071.

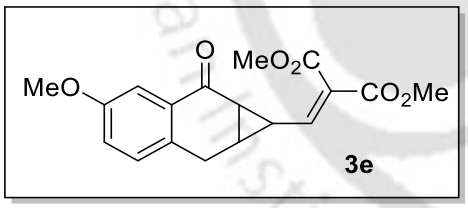


Dimethyl 2-((3-fluoro-2-oxo-1a,2,7,7a-tetrahydro-1H-cyclopropa[b]naphthalen-1-yl)methylene)malonate 3c. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.25; brown solid; mp 90-91 °C; yield 62% (45 mg); ^{1}H NMR (500 MHz,

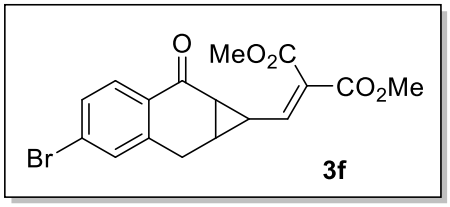
$CDCl_3$) δ 7.45-7.41 (m, 1H), 7.03-6.98 (m, 2H), 6.51 (d, J = 10.5 Hz, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 3.35 (s, 2H), 2.51-2.43 (m, 2H), 2.22-2.19 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.6, 165.2, 164.3, 162.2 (J_{C-F} = 261.6 Hz), 150.6, 140.5, 134.6 (J_{C-F} = 9.9 Hz), 127.0, 124.7 (J_{C-F} = 3.7 Hz), 119.9 (J_{C-F} = 7.8 Hz), 115.9 (J_{C-F} = 21.4 Hz), 52.6 (J_{C-F} = 38.4 Hz), 36.5, 27.6, 26.8, 23.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ -113.54; FT-IR (KBr) 2954, 1721, 1677, 1612, 1437, 1252, 1224 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{17}H_{15}FO_5Na$: 341.0796; Found 341.0794.



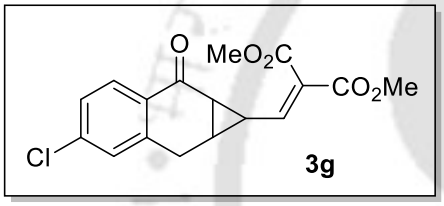
Dimethyl 2-((4-chloro-2-oxo-1a,2,7,7a-tetrahydro-1H-cyclopropa[b]naphthalen-1-yl)methylene)malonate 3d. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.26; brown sticky liquid; yield 64% (45 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 8.5 Hz, 1H), 6.52 (d, J = 10.0 Hz, 1H), 3.77 (s, 3H), 3.70 (s, 3H), 3.34-3.33 (s, 2H), 2.47-2.42 (m, 2H), 2.25-2.21 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.4, 165.2, 164.4, 150.8, 136.6, 133.8, 133.7, 132.0, 130.6, 127.2, 127.1, 52.6, 52.4, 34.9, 26.67, 26.60, 23.7; FT-IR (neat) 2953, 1722, 1674, 1436, 1253, 1154, 1069 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{17}H_{15}ClO_5Na$: 357.0500; Found 357.0513.



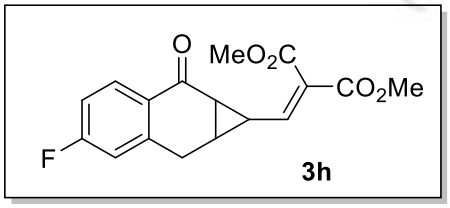
Dimethyl 2-((4-methoxy-2-oxo-1a,2,7,7a-tetrahydro-1H-cyclopropa[b]naphthalen-1-yl)methylene)malonate 3e. Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.27; yellow sticky liquid; yield 62% (45 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 8.0 Hz, 1H), 7.30-7.27 (m, 1H), 7.03 (d, J = 8.5 Hz, 1H), 6.53-6.51 (m, 1H), 3.85 (s, 3H), 3.77 (s, 3H), 3.69 (s, 3H), 3.57-3.53 (m, 1H), 3.00-2.95 (m, 1H), 2.44-2.39 (m, 2H), 2.25-2.22 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.8, 165.4, 164.4, 156.9, 151.7, 131.6, 127.7, 127.6, 126.6, 119.0, 114.6, 55.7, 52.6, 52.3, 35.1, 26.7, 24.3, 20.8; FT-IR (neat) 2953, 1722, 1673, 1438, 1345, 1283, 1257, 1159, 1067 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{18}H_{18}O_6Na$: 353.0996; Found 353.0997.



Dimethyl-2-((5-bromo-2-oxo-1a,2,7,7a-tetrahydro-1H-cyclopropa[b]naphthalen-1-yl)methylene)malonate 3f. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.29; brown sticky liquid; yield 65% (44 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.38 (s, 1H), 6.51-6.50 (m, 1H), 3.77 (s, 3H), 3.70 (s, 3H), 3.39-3.36 (m, 1H), 3.32-3.29 (m, 1H), 2.46-2.44 (m, 2H), 2.22-2.19 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.7, 165.2, 164.4, 150.9, 140.1, 132.0, 131.0, 129.6, 129.1, 128.9, 127.1, 52.6, 52.4, 35.0, 26.8, 26.6, 23.6; FT-IR (neat) 2953, 1733, 1575, 1670, 1437, 1171, 1122 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{17}H_{15}BrO_5Na$: 400.9995; Found 400.9997.

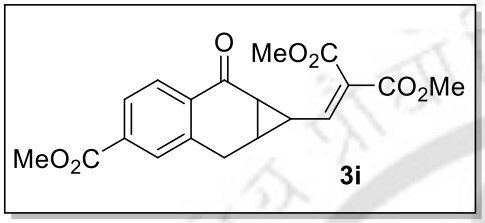


Dimethyl 2-((5-chloro-2-oxo-1a,2,7,7a-tetrahydro-1H-cyclopropa[b]naphthalen-1-yl)methylene)malonate 3g. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.25; brown solid; mp 149-150 °C; yield 62% (45 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.5 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.20 (s, 1H), 6.52 (d, *J* = 11.0 Hz, 1H), 3.77 (s, 3H), 3.70 (s, 3H), 3.40-3.35 (m, 1H), 3.32-3.29 (m, 1H), 2.46-2.42 (m, 2H), 2.23-2.19 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.5, 165.2, 164.4, 150.9, 140.2, 140.0, 129.2, 129.1, 129.0, 128.1, 127.0, 52.6, 52.4, 35.0, 26.9, 26.6, 23.6; FT-IR (KBr) 2952, 1726, 1674, 1593, 1437, 1255 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{17}H_{15}ClO_5Na$: 357.0500; Found 357.0503.

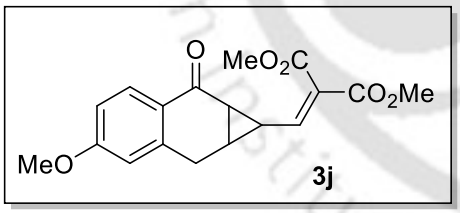


Dimethyl-2-((5-fluoro-2-oxo-1a,2,7,7a-tetrahydro-1H-cyclopropa[b]naphthalen-1-yl)methylene)malonate 3h. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.24; brown sticky liquid; yield 59% (42 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96-7.93 (m, 1H), 7.04-7.00 (m, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.52 (d, *J* = 10.5 Hz, 1H), 3.77 (s,

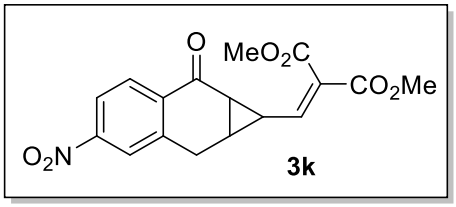
3H), 3.70 (s, 3H), 3.42-3.37 (m, 1H), 3.34-3.31 (m, 1H), 2.45-2.42 (m, 2H), 2.22-2.19 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.2, 167.1 (J_{C-F} = 253.8 Hz), 165.2, 164.4, 151.0, 141.4 (J_{C-F} = 9.0 Hz), 130.5 (J_{C-F} = 9.6 Hz), 127.3 (J_{C-F} = 2.7 Hz), 127.0, 115.6 (J_{C-F} = 21.8 Hz), 115.4 (J_{C-F} = 21.9 Hz), 52.6 (J_{C-F} = 27.9 Hz), 34.9, 27.3, 26.7, 23.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ -104.09; FT-IR (neat) 2955, 1722, 1674, 1610, 1436, 1344, 1256, 1232, 1070, 1042 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{16}FO_5$: 319.0976; Found 319.0987.



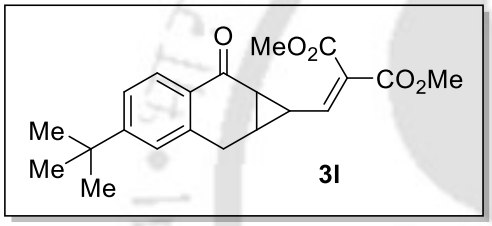
Dimethyl 2-((5-(methoxycarbonyl)-2-oxo-1a,2,7,7a-tetrahydro-1H-cyclopropa[b]naphthalen-1-yl)methylene)malonate 3i. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.22; yellow solid; mp 154-155 °C; yield 71% (50 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (s, 2H), 7.89 (s, 1H), 6.53 (d, *J* = 10.8 Hz, 1H), 3.93 (s, 3H), 3.76 (s, 3H), 3.67 (s, 3H), 3.41 (s, 2H), 2.50-2.48 (m, 1H), 2.46-2.43 (m, 1H), 2.27-2.24 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.1, 166.2, 165.1, 164.3, 150.7, 138.4, 134.5, 134.0, 130.5, 128.3, 127.6, 127.1, 52.6, 52.4, 35.4, 27.1, 26.6, 23.8; FT-IR (KBr) 2955, 1722, 1676, 1437, 1282, 1253 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{19}H_{18}O_7Na$: 381.0945; Found 381.0948.



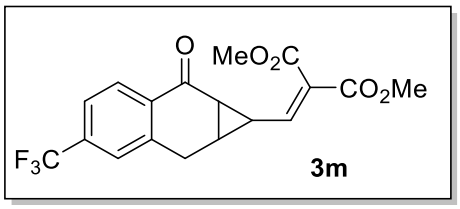
Dimethyl 2-((5-methoxy-2-oxo-1a,2,7,7a-tetrahydro-1H-cyclopropa[b]naphthalen-1-yl)methylene)malonate 3j. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.28; yellow solid; mp 120-121 °C; yield 67% (49 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 10.2 Hz, 1H), 6.64 (s, 1H), 6.53 (d, *J* = 10.8 Hz, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 3.69 (s, 3H), 3.38-3.34 (m, 1H), 3.30-3.27 (m, 1H), 2.40-2.37 (m, 2H), 2.18-2.15 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.5, 165.4, 164.4, 164.0, 151.7, 140.7, 129.7, 126.6, 124.0, 113.9, 113.1, 55.5, 52.5, 52.3, 34.8, 27.4, 27.0, 23.7; FT-IR (KBr) 2953, 1724, 1663, 1599, 1341, 1260, 1069 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{18}H_{18}O_6Na$: 353.0996; Found 353.0993.



Dimethyl 2-((5-nitro-2-oxo-1a,2,7,7a-tetrahydro-1H-cyclopropa[b]naphthalen-1-yl)methylene)malonate 3k. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.25; brown solid; mp 150-151 °C; yield 65% (47 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17-8.15 (m, 1H), 8.10-8.07 (m, 2H), 6.53 (d, *J* = 10.5 Hz, 1H), 3.78 (s, 3H), 3.69 (s, 3H), 3.50-3.49 (m, 2H), 2.56-2.50 (m, 2H), 2.33-2.29 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.0, 165.1, 164.3, 150.8, 150.1, 139.8, 135.3, 129.1, 127.5, 124.3, 122.4, 52.7, 52.5, 35.2, 27.3, 26.4, 23.7 ; FT-IR (KBr) 2954, 1723, 1679, 1528, 1436, 1341, 1255 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{17}H_{15}NO_7Na$: 368.0741; Found 368.0741.

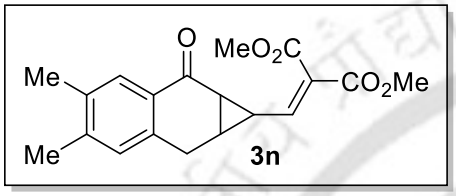


Dimethyl 2-((5-(*tert*-butyl)-2-oxo-1a,2,7,7a-tetrahydro-1H-cyclopropa[b]naphthalen-1-yl)methylene)malonate 3l. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.27; colorless solid; mp 146-147 °C; yield 68% (48 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.5 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.16 (s, 1H), 6.54-6.52 (m, 1H), 3.77 (s, 3H), 3.68 (s, 3H), 3.40-3.36 (m, 1H), 3.33-3.29 (m, 1H), 2.44-2.40 (m, 2H), 2.21-2.17 (m, 1H), 1.31 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.5, 165.4, 164.4, 157.6, 151.8, 138.2, 128.2, 127.2, 126.4, 125.8, 124.9, 52.6, 52.4, 35.2, 35.1, 31.1, 27.2, 26.8, 23.9; FT-IR (KBr) 2958, 1725, 1671, 1606, 1436, 1257 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{21}H_{24}O_5Na$: 379.1516; Found 379.1520.

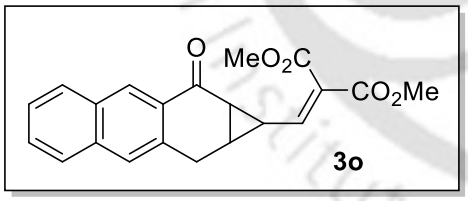


Dimethyl 2-((2-oxo-5-(trifluoromethyl)-1a,2,7,7a-tetrahydro-1H-cyclopropa[b]naphthalen-1-yl)methylene)malonate 3m. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.25; brown solid; mp 105-106 °C; yield 64% (44 mg); ^{1}H NMR

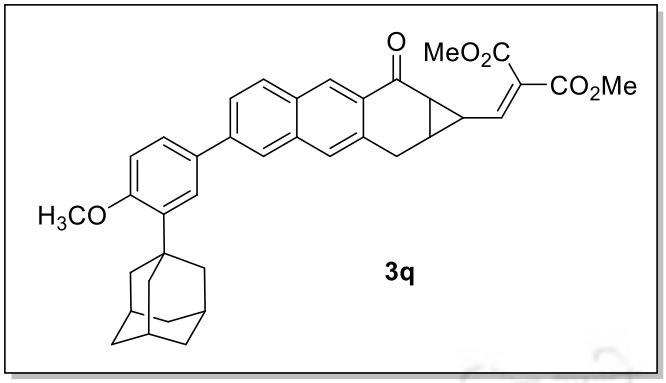
(500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.48 (s, 1H), 6.53 (d, *J* = 10.5 Hz, 1H), 3.77 (s, 3H), 3.69 (s, 3H), 3.44-3.43 (m, 2H), 2.52-2.46 (m, 2H), 2.29-2.25 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.6, 165.2, 164.3, 150.7, 138.9, 135.1 (J_{C-F} = 32.4 Hz), 133.3, 128.2, 127.1, 126.2 (J_{C-F} = 3.8 Hz), 124.4 (J_{C-F} = 3.6 Hz), 122.6 (J_{C-F} = 261.6 Hz), 52.7, 52.5, 35.1, 27.1, 26.4, 23.7; ^{19}F NMR (565 MHz, $CDCl_3$) δ -121.87; FT-IR (KBr) 2956, 1727, 1680, 1435, 1329, 1257, 1169, 1131 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{18}H_{15}F_3O_5Na$: 391.0764; Found 391.0761.



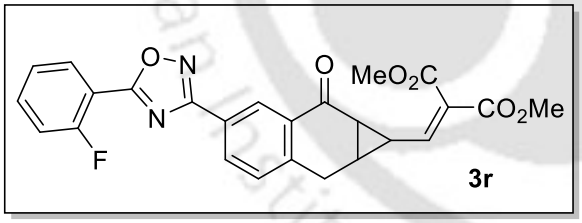
Dimethyl-2-((4,5-dimethyl-2-oxo-1a,2,7,7a-tetrahydro-1H-cyclopropa[b]naphthalen-1-yl)methylene)malonate 3n. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.26; brown sticky liquid; yield 68% (50 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (s, 1H), 6.94 (s, 1H), 6.53-6.51 (m, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 3.33-3.28 (m, 1H), 3.26-3.22 (m, 1H), 2.41-2.39 (m, 2H), 2.27-2.26 (m, 6H), 2.18-2.15 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.8, 165.4, 164.5, 151.8, 143.7, 136.1, 135.9, 130.1, 128.5, 128.0, 126.5, 52.5, 52.3, 35.3, 27.0, 26.5, 23.9, 20.1, 19.4; FT-IR (neat) 2955, 1724, 1667, 1611, 1437, 1258, 1216 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{21}O_5$: 329.1384; Found 329.1392.



Dimethyl 2-((2-oxo-1a,2,9,9a-tetrahydro-1H-cyclopropa-[b]anthracen-1-yl)methylene)malonate 3o. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.26; brown sticky liquid; yield 62% (44 mg); ^1H NMR (500 MHz, $CDCl_3$)) δ 8.47 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.66 (s, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 6.57 (d, *J* = 11.0 Hz, 1H), 3.77 (s, 3H), 3.60 (s, 3H), 3.53-3.52 (m, 2H), 2.56-2.53 (m, 1H), 2.51-2.47 (m, 1H), 2.32-2.28 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.5, 165.2, 164.4, 151.3, 136.0, 133.4, 132.0, 129.8, 129.0, 128.8, 128.7, 127.7, 127.2, 126.7, 126.5, 52.6, 52.4, 35.7, 27.4, 27.3, 24.4. FT-IR (neat) 2954, 1730, 1673, 1626, 1437, 1356, 1233 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{21}H_{18}O_5Na$: 373.1046; Found 373.1046.

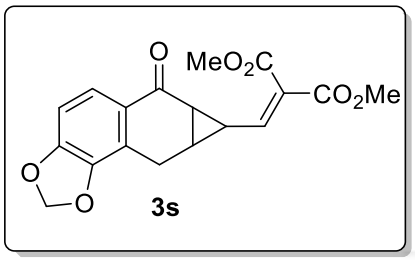


Dimethyl 2-((6-(3-(adamantan-1-yl)-4-methoxyphenyl)-2-oxo-1a,2,9,9a-tetrahydro-1H-cyclopropa[b]anthracen-1 yl)methylene)-malonate 3q. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.31; brown sticky liquid; yield 57% (34 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.98 (d, *J* = 8.8 Hz, 1H), 7.92 (s, 1H), 7.76-7.73 (m, 1H), 7.70 (s, 1H), 7.59-7.58 (m, 1H), 7.54-7.52 (m, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.58 (d, *J* = 10.4 Hz, 1H), 3.90 (s, 3H), 3.77 (s, 3H), 3.61 (s, 3H), 3.53 (s, 2H), 2.56-2.47 (m, 2H), 2.33-2.28 (m, 1H), 2.18 (s, 6H), 2.10 (s, 3H), 1.80 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.3, 165.2, 164.4, 159.1, 151.2, 141.9, 139.2, 136.5, 133.7, 132.6, 130.9, 130.2, 128.6, 128.5, 127.7, 126.8, 126.4, 126.1, 125.8, 124.1, 112.2, 55.3, 52.6, 52.3, 40.7, 37.3, 37.2, 35.7, 29.2, 27.5, 27.4, 24.5; FT-IR (neat) 2903, 1721, 1672, 1625, 1492, 1235, 1200, 1143 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{38}H_{38}O_6Na$: 613.2561; Found: 613.2566.

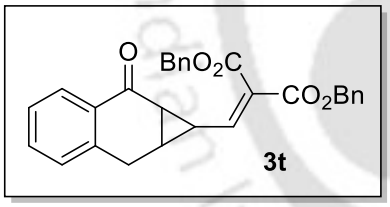


Dimethyl 2-((4-(5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl)-2-oxo-1a,2,7,7a-tetrahydro-1H-cyclopropa[b]naphthalen-1-yl)methylene)-malonate 3r. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.25; brown sticky liquid; yield 52% (33 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.30-8.28 (m, 1H), 8.25-8.21 (m, 1H), 7.63-7.59 (m, 1H), 7.37-7.33 (m, 2H), 7.31-7.27 (m, 1H), 6.55 (d, *J* = 10.5 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 3H), 3.46-3.39 (m, 2H), 2.54-2.48 (m, 2H), 2.29-2.26 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.8, 173.2 (J_{C-F} = 4.0 Hz), 168.0, 165.2, 164.4, 161.8 (J_{C-F} = 259.0 Hz), 150.8, 141.3, 134.9 (J_{C-F} = 8.5 Hz), 132.3, 131.4, 131.1, 129.9, 127.1, 126.9, 126.5, 124.9 (J_{C-F} = 3.9 Hz), 117.3 (J_{C-F} = 20.7 Hz), 112.8 (J_{C-F} = 10.9 Hz), 52.6 (J_{C-F} = 26.5 Hz), 35.2, 27.3, 26.7, 23.7; ^{19}F NMR

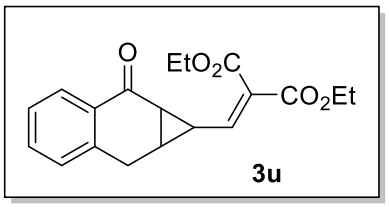
(470 MHz, $CDCl_3$) δ -108.15; FT-IR (neat) 2953, 1721, 1674, 1619, 1252, 1226, 1068, 755 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{25}H_{19}FN_2O_6Na$: 485.1119; Found 485.1128.



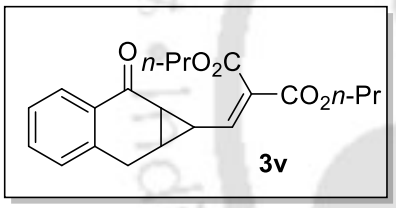
Dimethyl 2-((8-oxo-6a,7,7a,8-tetrahydro-6H-cyclopropa-[6,7]naphtho[1,2-d][1,3]dioxol-7-yl)methylene)malonate 3s. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.28; brown solid; mp 134-135 °C; yield 63% (45 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.52 (d, *J* = 11.0 Hz, 1H), 6.07 (d, *J* = 12.5 Hz, 2H), 3.77 (s, 3H), 3.72 (s, 3H), 3.39-3.35 (m, 1H), 3.12-3.07 (m, 1H), 2.46-2.42 (m, 1H), 2.40-2.38 (m, 1H), 2.22-2.18 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.9, 165.4, 164.4, 151.7, 145.1, 126.6, 125.0, 123.3, 119.6, 107.7, 102.2, 52.6, 52.4, 34.8, 26.9, 23.8, 20.6; FT-IR (KBr) 2954, 1722, 1670, 1625, 1462, 1438, 1364, 1285, 1252 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{18}H_{16}O_7Na$: 367.0788; Found 367.0787.



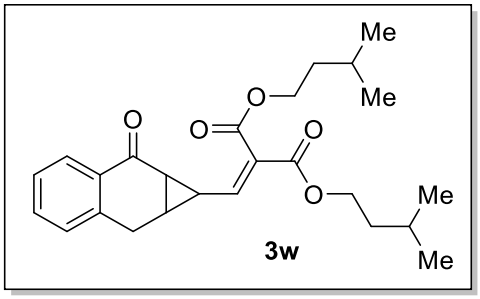
Dibenzyl 2-((2-oxo-1a,2,7,7a-tetrahydro-1H-cyclopropa[b]-naphthalen-1-yl)methylene)malonate 3t. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.28; yellow sticky liquid; yield 47% (55 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.29-7.26 (m, 2H), 7.24-7.22 (m, 3H), 7.19-7.18 (m, 2H), 7.15-7.12 (m, 2H), 7.09 (d, *J* = 8.0 Hz, 1H), 7.06-7.04 (m, 2H), 6.50 (d, *J* = 10.5 Hz, 1H), 5.13 (s, 2H), 5.02- 5.01 (m, 2H), 3.31-3.27 (m, 1H), 3.21-3.18 (m, 1H), 2.39-2.35 (m, 2H), 2.14-2.11 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.5, 164.6, 163.8, 151.6, 138.3, 135.5, 135.1, 133.8, 130.7, 129.1, 128.7, 128.6, 128.43, 128.40, 128.29, 128.26, 127.5, 127.4, 126.8, 67.3, 67.2, 35.3, 27.0, 26.8, 23.8; FT-IR (neat) 3032, 1720, 1669, 1454, 1340, 1285, 1214 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{29}H_{24}O_5Na$: 475.1516; Found 475.1523.



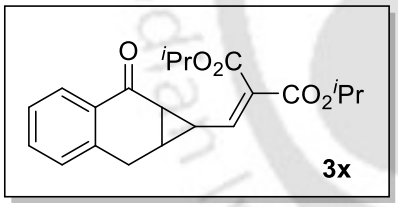
Diethyl 2-((2-oxo-1a,2,7,7a-tetrahydro-1H-cyclopropa[b]-naphthalen-1-yl)methylene)malonate 3u. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.35; brown sticky liquid; yield 42% (35 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.50-7.47 (m, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 6.52-6.50 (m, 1H), 4.24 (q, *J* = 7.5 Hz, 2H), 4.13 (q, *J* = 7.0 Hz, 2H), 3.41- 3.37 (m, 1H), 3.34-3.30 (m, 1H), 2.48-2.45 (m, 1H), 2.44-2.40 (m, 1H), 2.24-2.20 (m, 1H), 1.28 (t, *J* = 7.5 Hz, 3H), 1.05 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.9, 164.8, 164.0, 149.9, 138.3, 133.8, 130.9, 129.1, 127.7, 127.5, 127.3, 61.5, 61.3, 35.2, 27.2, 26.9, 23.6, 14.2, 13.9; FT-IR (neat) 2981, 1723, 1673, 1339, 1289, 1253, 1218, 1067 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{19}H_{20}O_5Na$: 351.1203; Found 351.1211.



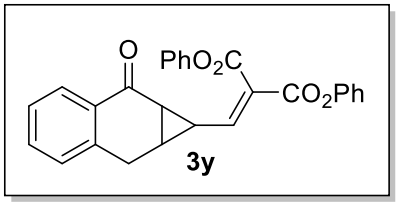
Dipropyl 2-((2-oxo-1a,2,7,7a-tetrahydro-1H-cyclopropa[b]-naphthalen-1-yl)methylene)malonate 3v. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.31; yellow sticky liquid; yield 52% (50 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 1H), 6.51 (d, *J* = 10.8 Hz, 1H), 4.13 (t, *J* = 6.6 Hz, 2H), 4.03 (t, *J* = 6.6 Hz, 2H), 3.41-3.37 (m, 1H), 3.33-3.30 (m, 1H), 2.47-2.46 (m, 1H), 2.43-2.40 (m, 1H), 2.24-2.21 (m, 1H), 1.70-1.64 (m, 2H), 1.48-1.42 (m, 2H), 0.93 (t, *J* = 7.8 Hz, 3H), 0.74 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.8, 165.0, 164.1, 149.8, 138.3, 133.8, 130.9, 129.1, 127.7, 127.5, 127.4, 67.1, 67.0, 35.3, 27.2, 26.9, 23.6, 22.0, 21.8, 10.5, 10.4; FT-IR (neat) 2968, 1722, 1672, 1457, 1340, 1286, 1253 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{25}O_5$: 379.1516; Found 379.1516.



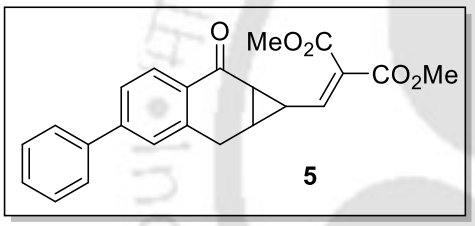
Diisopentyl 2-((2-oxo-1a,2,7,7a-tetrahydro-1H-cyclopropa[b]naphthalen-1-yl)methylene)malonate 3w. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.29; colorless sticky liquid; yield 48% (50 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.50-7.46 (m, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.19-7.18 (m, 1H), 6.48-6.46 (m, 1H), 4.19 (t, *J* = 7.0 Hz, 2H), 4.08 (t, *J* = 7.0 Hz, 2H), 3.41-3.36 (m, 1H), 3.33-3.29 (m, 1H), 2.46-2.44 (m, 1H), 2.41-2.37 (m, 1H), 2.23-2.19 (m, 1H), 1.69-1.63 (m, 2H), 1.55-1.50 (m, 2H), 1.34-1.30 (m, 2H), 0.91-0.90 (m, 6H), 0.79-0.77 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 165.0, 164.0, 149.7, 138.3, 133.8, 130.9, 129.1, 127.6, 127.5, 127.3, 64.2, 64.1, 37.3, 37.0, 35.2, 27.1, 26.8, 25.1, 25.0, 24.9, 23.6, 22.5, 22.44, 22.40; FT-IR (neat) 2958, 1721, 1672, 1458, 1340, 1285, 1250, 1215 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{25}H_{32}O_5Na$: 435.2142; Found 435.2144.



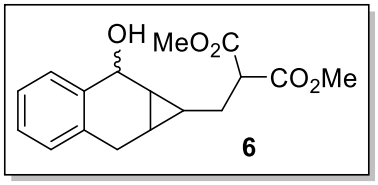
Diisopropyl 2-((2-oxo-1a,2,7,7a-tetrahydro-1H-cyclopropa[b]-naphthalen-1-yl)methylene)malonate 3x. Analytical TLC on silica gel, 2:8 ethyl acetate/hexane R_f = 0.32; yellow sticky liquid; yield 44% (22 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.2 Hz, 1H), 7.50-7.46 (m, 1H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.19 (d, *J* = 7.2 Hz, 1H), 6.46 (d, *J* = 10.8 Hz, 1H), 5.11-5.05 (m, 1H), 5.02-4.96 (m, 1H), 3.41-3.36 (m, 1H), 3.32-3.28 (m, 1H), 2.47-2.44 (m, 1H), 2.40-2.36 (m, 1H), 2.24-2.19 (m, 1H), 1.26-1.25 (m, 6H), 1.09 (d, *J* = 6.4 Hz, 3H), 1.03 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.0, 164.4, 163.5, 148.5, 138.3, 133.7, 131.0, 129.0, 128.6, 127.5, 127.3, 69.1, 69.0, 35.2, 27.3, 26.9, 23.4, 21.8, 21.5; FT-IR (neat) 2971, 1723, 1619, 1574, 1442, 1258, 1140 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{25}O_5$: 357.1697; Found 357.1697.



Diphenyl 2-((2-oxo-1a,2,7,7a-tetrahydro-1H-cyclopropa[b]-naphthalen-1-yl)methylene)malonate 3y. Analytical TLC on silica gel, 2:8 ethyl acetate/hexane R_f = 0.30; yellow sticky liquid; yield 35% (15 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.91 (m, 1H), 7.52-7.48 (m, 1H), 7.42-7.35 (m, 3H), 7.33-7.28 (m, 3H), 7.21 (d, *J* = 7.6 Hz, 2H), 7.17-7.15 (m, 2H), 6.96-6.94 (m, 2H), 6.88 (d, *J* = 11.2 Hz, 1H), 3.48-3.36 (m, 2H), 2.76-2.71 (m, 1H), 2.63-2.60 (m, 1H), 2.40-2.35 (m, 1H).^{13}C NMR (125 MHz, $CDCl_3$) δ 193.4, 163.2, 162.4, 154.5, 150.6, 150.3, 138.2, 134.0, 130.8, 129.7, 129.6, 129.2, 127.7, 127.5, 126.3, 126.1, 121.5, 121.4, 35.8, 27.3, 27.2, 24.2; FT-IR (neat) 2919, 1738, 1714, 1457, 1378, 1259, 1084 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{27}H_{20}O_5Na$: 447.1203; Found 447.1205.

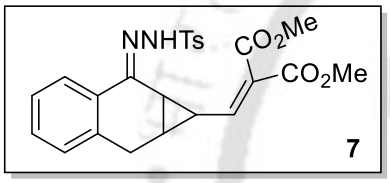


Dimethyl 2-((2-oxo-5-phenyl-1a,2,7,7a-tetrahydro-1H-cyclopropa[b]naphthalen-1-yl)methylene)malonate 5. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.32; brown sticky liquid; yield 50% (34 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 7.2 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.41-7.38 (m, 2H), 6.56 (d, *J* = 10.2 Hz, 1H), 3.77 (s, 3H), 3.69 (s, 3H), 3.47-3.43 (m, 1H), 3.42-3.39 (m, 1H), 2.51-2.47 (m, 2H), 2.26-2.23 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.3, 165.3, 164.4, 151.4, 146.5, 139.8, 138.9, 129.5, 129.0, 128.4, 128.0, 127.6, 127.3, 126.8, 126.4, 52.6, 52.4, 35.2, 27.3, 26.8, 23.9; FT-IR (neat) 2952, 1724, 1671, 1436, 1341, 1257, 1140, 1070 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{23}H_{20}O_5Na$: 399.1203; Found 399.1205.



Dimethyl 2-((2-hydroxy-1a,2,7,7a-tetrahydro-1H-cyclopropa-[b]naphthalen-1-yl)methyl)malonate 6. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.25; colorless sticky liquid; yield 82% (41 mg); 4:1 mixture of

diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.5 Hz, 1H, major), 7.65 (d, *J* = 8.0 Hz, 0.27H, minor), 7.44 (t, *J* = 7.5 Hz, 1H, major), 7.29 (t, *J* = 7.5 Hz, 1H, major), 7.23-7.22 (m, 0.29H, minor), 7.16 (d, *J* = 8.0 Hz, 1.29H, major + minor), 7.01 (d, *J* = 7.5 Hz, 0.27H, minor), 4.94 (bs, 0.30H, minor), 3.74 (s, 3H), 3.73-3.72 (m, 4H, major + minor), 3.68 (s, 1H), 3.46 (t, *J* = 7.5 Hz, 1H, major), 3.41 (t, *J* = 8.0 Hz, 0.31H, minor), 3.30-3.25 (m, 1.17H, major + minor), 3.19-3.15 (m, 1.21H, major + minor), 3.00-2.98 (m, 0.52H, minor), 2.06-2.02 (m, 2.31H, major + minor), 1.98-1.95 (m, 1H, major), 1.77-1.74 (m, 1H, major), 1.44-1.40 (m, 0.31H, minor); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 169.8, 169.5, 169.4, 138.9, 138.0, 133.3, 133.0, 131.5, 128.9, 128.3, 127.2, 127.1, 126.7, 125.8, 67.2, 52.9, 52.7, 51.9, 51.2, 32.4, 31.9, 31.3, 28.8, 27.8, 25.6, 24.3, 21.2, 17.3, 12.8; FT-IR (neat) 3476, 3006, 1731, 1665, 1603, 1435, 1338, 1286 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{17}H_{20}O_5Na$: 327.1203; Found 327.1206.



Dimethyl-2-((2-(2-tosylhydrazineylidene)-1a,2,7,7a tetra-hydro-1H-cyclopropa[b]naphthalen-1-yl)methylene)malonate 7. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.30; colorless sticky liquid; yield 52% (41 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.2 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.30-7.27 (m, 1H), 7.20-7.17 (m, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.66 (d, *J* = 9.5 Hz, 1H), 3.77 (s, 3H), 3.62 (s, 3H), 3.28-3.15 (m, 2H), 2.48-2.45 (m, 1H), 2.43 (s, 3H), 2.06-2.00 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.6, 164.3, 152.8, 151.6, 144.2, 135.3, 134.2, 130.7, 129.6, 129.2, 129.0, 128.5, 127.1, 127.0, 126.1, 52.6, 52.4, 26.9, 25.3, 23.4, 23.2, 21.7; FT-IR (neat) 3070, 1738, 1671, 1599, 1437, 1166, 1085 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{24}H_{25}N_2O_6SNa$: 491.1247; Found 491.1251.

Sample Preparation for Crystal Growth. The compound **3g** was dissolved in minimum volume of dichloromethane and methanol and kept at room temperature for slow evaporation (2 days). Block shaped crystals were formed, which were then subjected to *X*-ray diffraction.

Crystal Structure and Data of 3g.

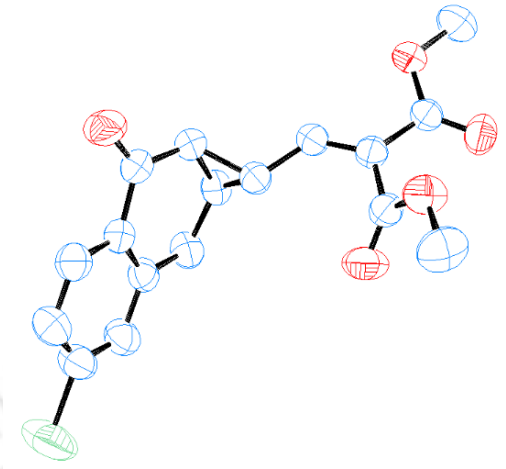


Figure 1. ORTEP diagram of Dimethyl 2-((5-chloro-2-oxo-1a,2,7,7a-tetrahydro-1H-cyclopropa[b]naphthalen-1-yl)methylene)malonate **3g** (CCDC No 2206044) with 50% ellipsoid. H-Atoms are omitted for clarity.

CCDC No.	2206044
Identification code	**3g**
Empirical formula	$C_{17}H_{15}ClO_5$
Formula weight	334.74
Crystal habit, colour	Block, Brown
Temperature, *T*/K	297K
Wavelength, λ/Å	0.71073 Å
Crystal system	Monoclinic
Space group	P 21/c
Unit cell dimensions	a = 9.0255(8) Å b = 8.5463(7) Å c = 20.7124(17) Å α= 90 β=100.229(2) γ = 90

Volume, V/Å^3	1572.3(2) Å^3
Z	4
Calculated density, Mg·m^{-3}	1.414
Absorption coefficient, μ/mm^{-1}	0.266
F (000)	696
θ range for data collection	2.29 to 24.49
Limiting indices	-10 ≤ h ≤ 10, -10 ≤ k ≤ 10, -24≤ l ≤ 24
Reflection collected / unique	2758/2163
Completeness to θ	99.4 %
Absorption correction	Multi-scan
Refinement method	'SHELXL-2019/1 (Sheldrick, 2019)'
Data / restraints / parameters	2758/ 0 / 210
Goodness-of-fit on F^2	1.041
Final R indices [I >2sigma(I)]	R1 = 0.0571, wR2 = 0.1442
R indices (all data)	R1 = 0.0755, wR2 = 0.1749

1.5 References

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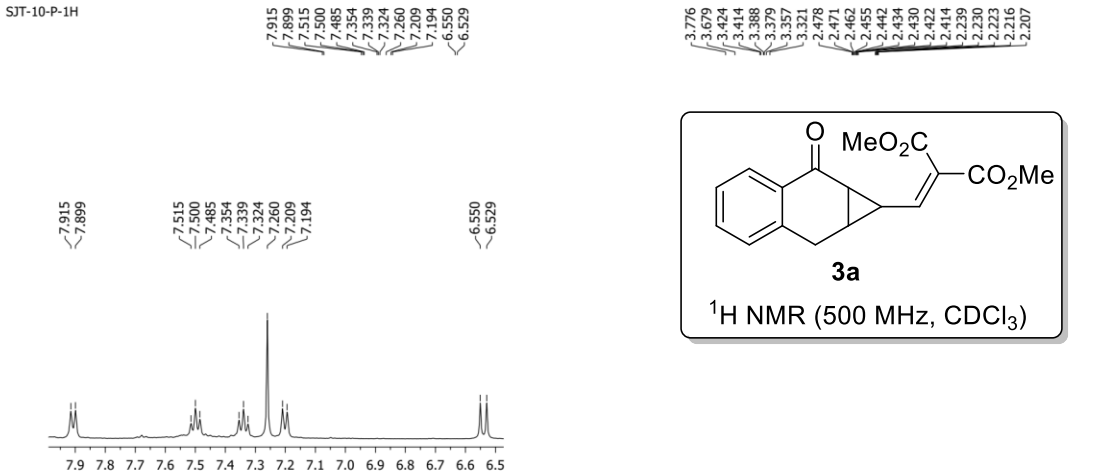
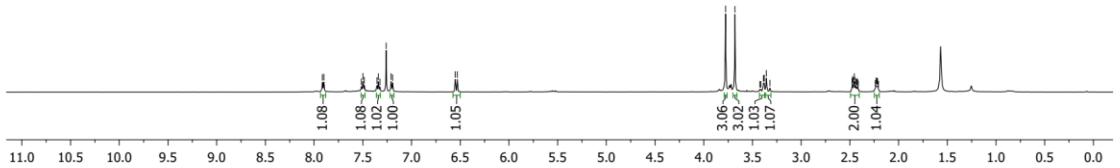
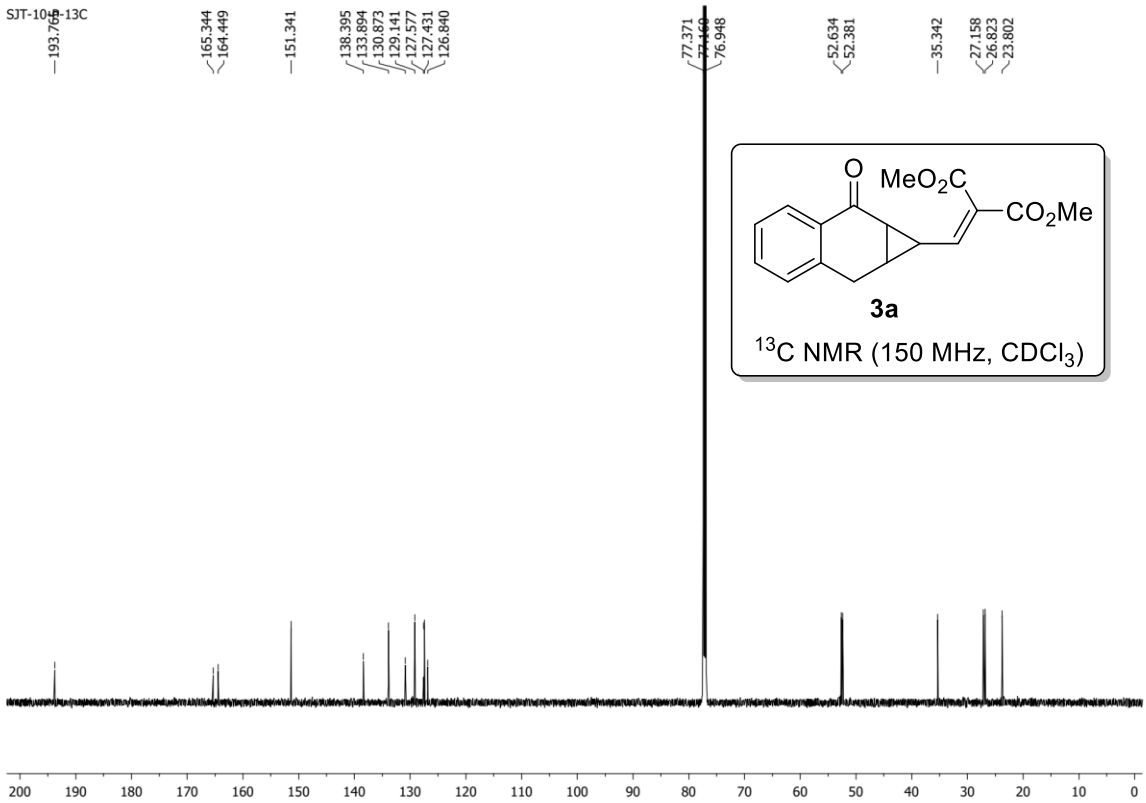
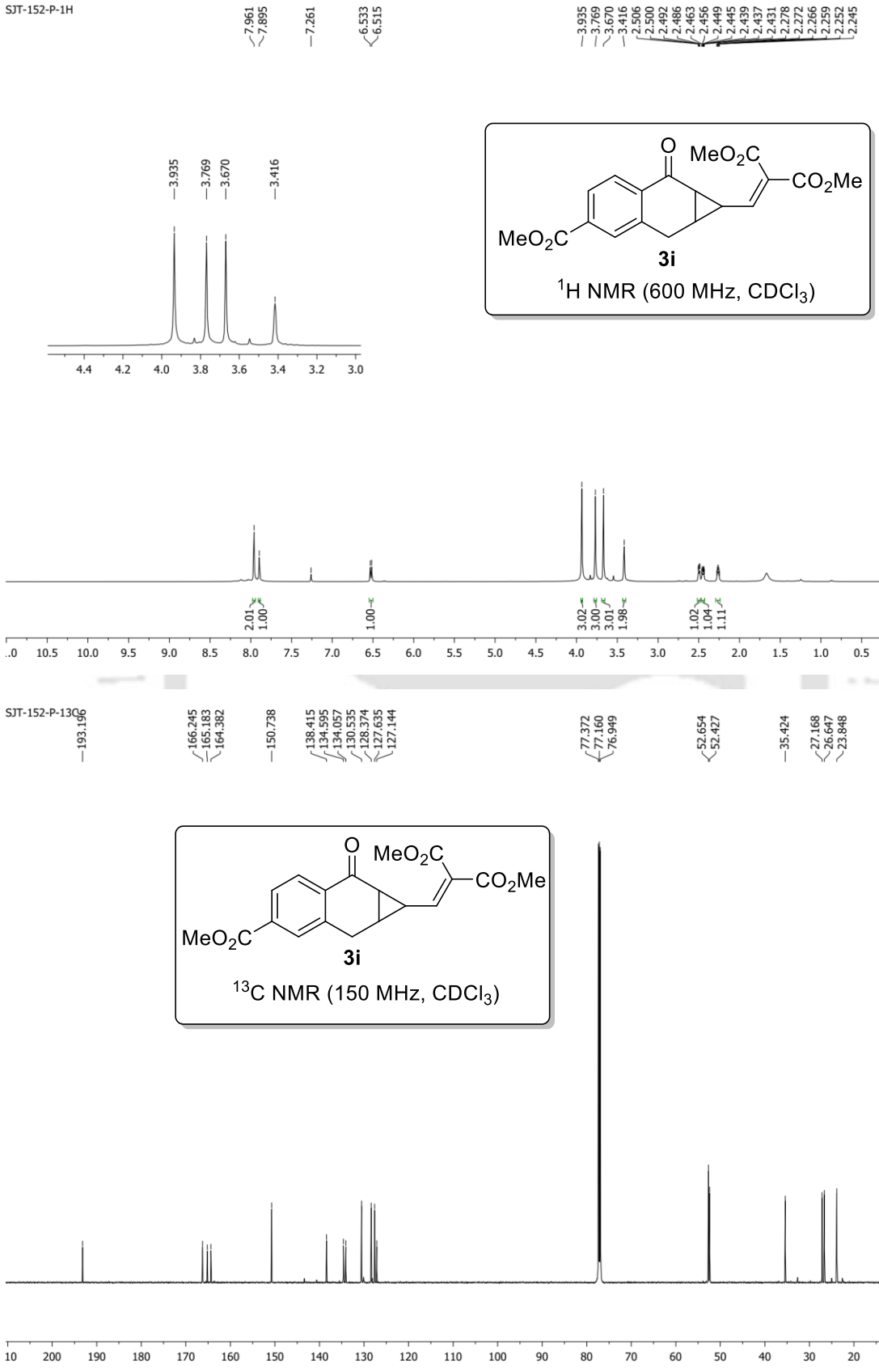
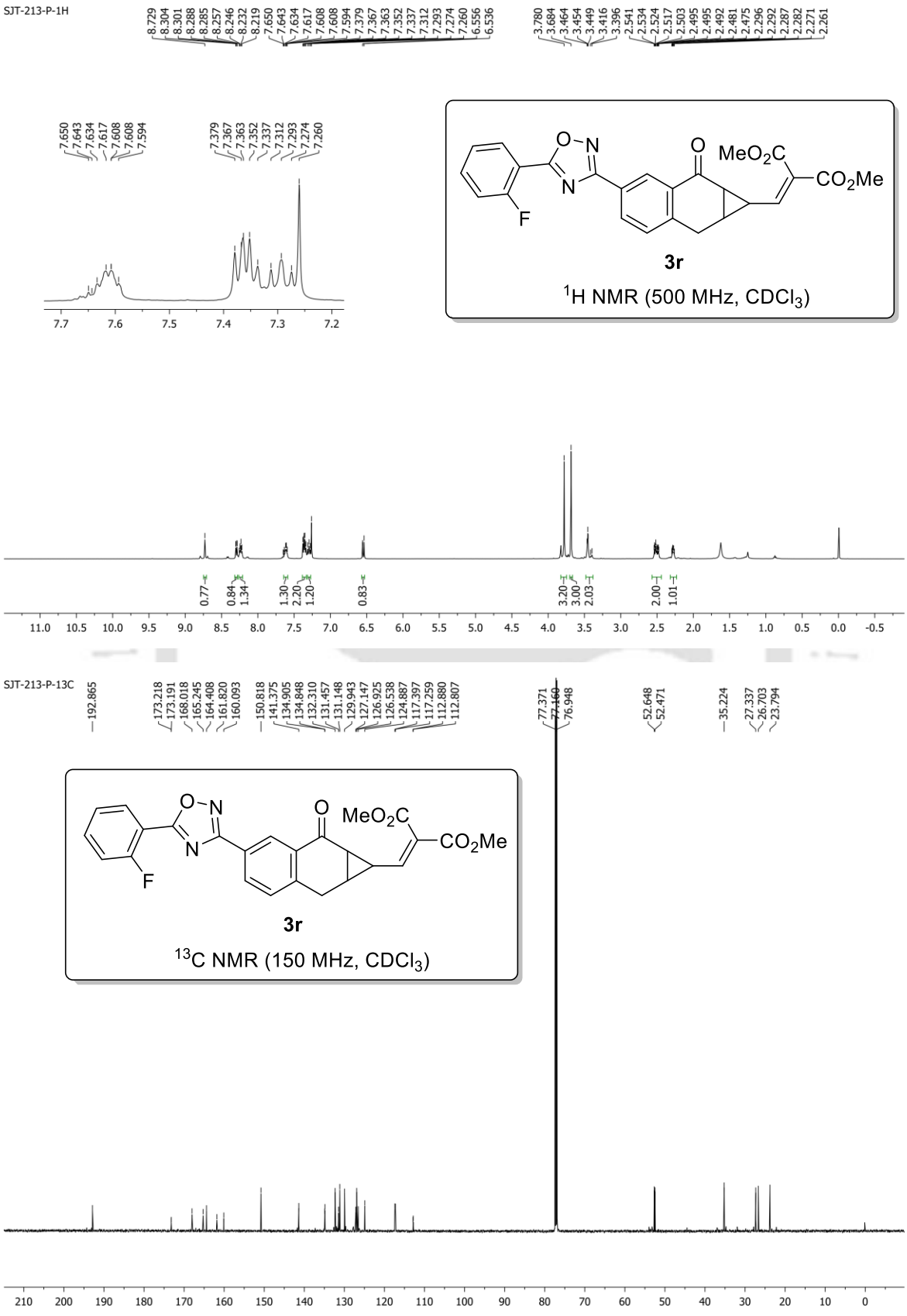
1.6 Selected NMR Spectra

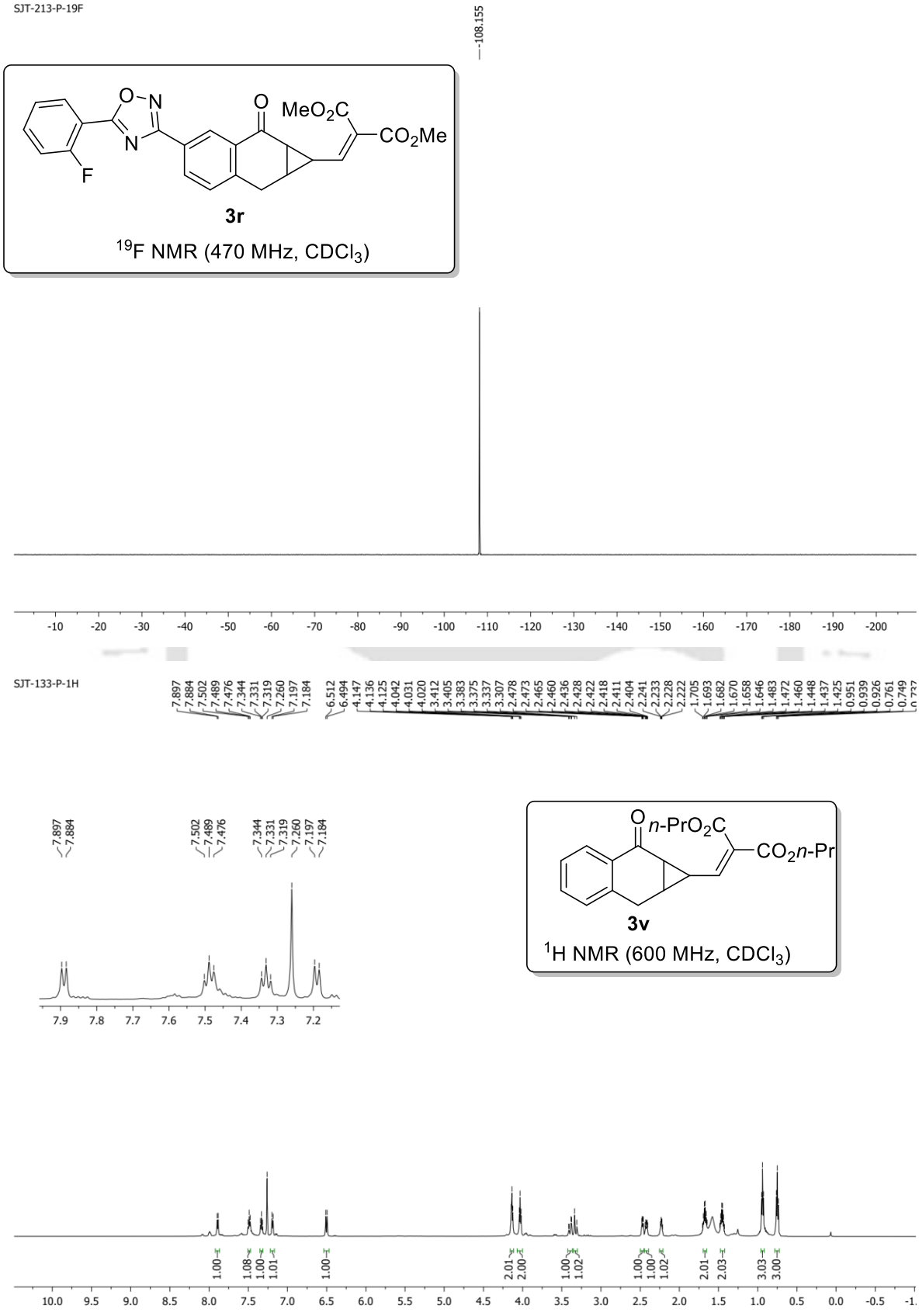


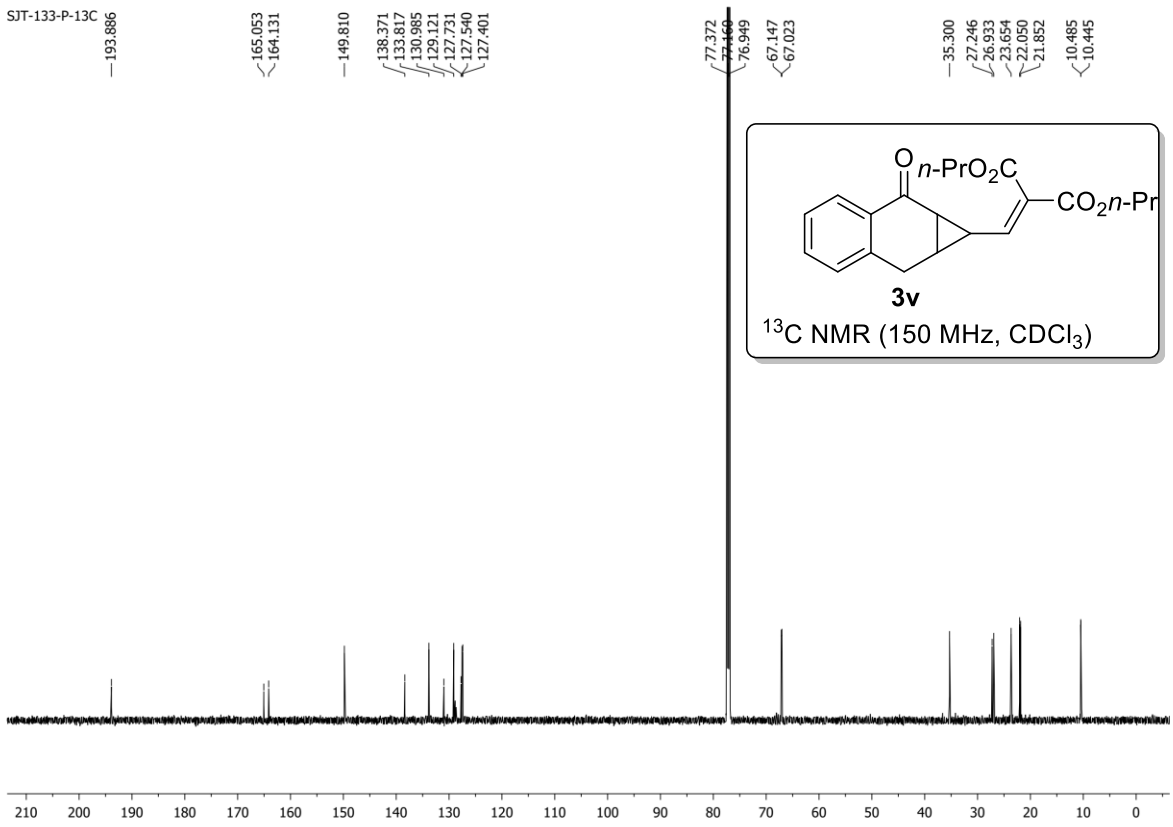






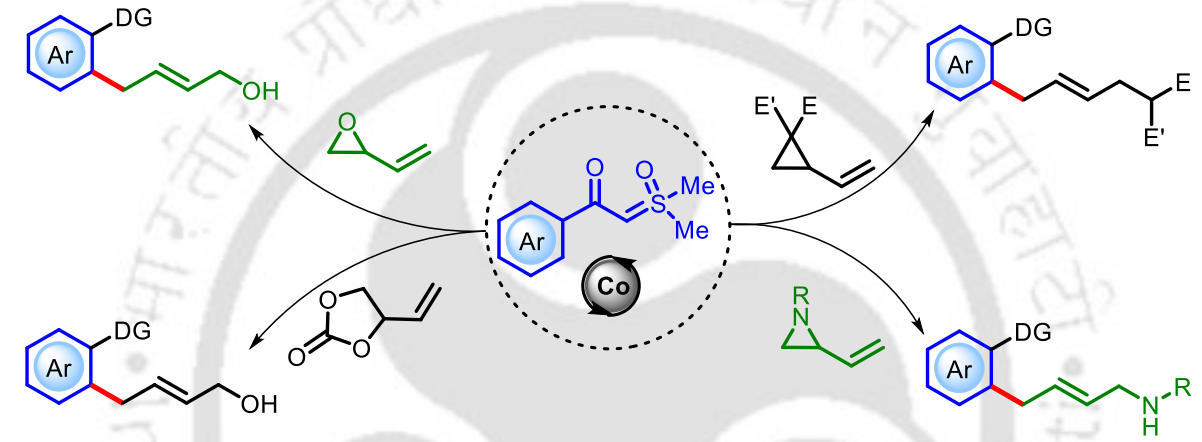






Chapter 2

Co-Catalyzed C-H Allylation of Benzoyl Sulfoxonium Ylides with Vinyl Strained Rings



♠ **Weak chelation** ♠ **Ring opening/C-C/C-het bond formation** ♠ **Versatile allylic motifs**

Chem. Commun. **2023**, *59*, 14173.

Co-Catalyzed C–H Allylation of Benzoyl Sulfoxonium Ylides with Vinyl Strained Rings

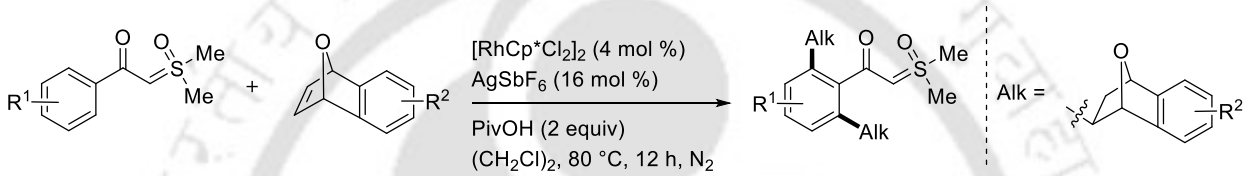
Weakly coordinating DG-assisted C–H functionalization has become an appealing platform in modern catalysis, offering operationally simple and step-economical routes to value-added scaffolds from readily available arenes.[1] Recently, organosulfur motifs are increasingly recognized as privileged structures in medicinal chemistry and functional materials, driving continued development of efficient strategies for their synthesis and late-stage modification of sulfur-based frameworks.[2] Within this manifold, sulfoxonium ylides have emerged as particularly attractive carbene surrogates[3] owing to their high thermal stability, low toxicity, ease of handling and have enabled a broad spectrum of redox-neutral C–H activation/annulation processes.[5] Classical sulfur ylide chemistry including epoxidation, cyclopropanation and rearrangement provided access to many carbo- and heterocyclic frameworks.[4] Recently, transition-metal-catalyzed protocols have been developed benzoyl sulfoxonium ylides as traceless or bifunctional DGs for the assembly of complex architectures *via* tandem C–H activation/annulation with olefinic coupling partners and VCPs.[6] Concurrently, vinyl strained rings have proven to be versatile allyl synthons in directed C–H allylation, where ring-opening C–C activation enables formal allylation of arenes and heteroarenes under transition-metal catalysis.[7-9] These transformations elegantly merge C–H/C–C activation with ring cleavage and typically deliver allylated products with regio- and stereocontrol. However, C–H functionalization of sulfoxonium ylides under weak chelation assistance, combined with ring-opening of strained vinyl carbo-/heterocycles using inexpensive first-row transition metals, remains scarcely explored. From the standpoint of step and atom economy, the use of modular vinyl ring systems as latent, tunable allyl synthons is highly attractive, as they can, in principle, deliver a range of substituted allylic motifs in a single catalytic blueprint. However, the installation of diverse allyl fragments onto sulfoxonium ylides *via* unified C–H/C–C/C–heteroatom activation remains a formidable task, often requiring separate conditions for each allyl source. Moreover, key challenges include discriminating between olefinic[13-14] versus aryl C–H activation on the ylide scaffold and maintaining efficient catalyst turnover in the presence of a strongly coordinating sulfur center. In addition, the resulting allyl fragments and the sulfoxonium-derived directing element can be leveraged in C–H functionalization, cyclization or oxidation

reactions to provide strategic opportunities for the construction of structurally diverse and functionally enriched carbo-/heterocyclic scaffolds.

2.1 Literature

2.1.1 Sulfoxonium Ylide Directed C–H Functionalization

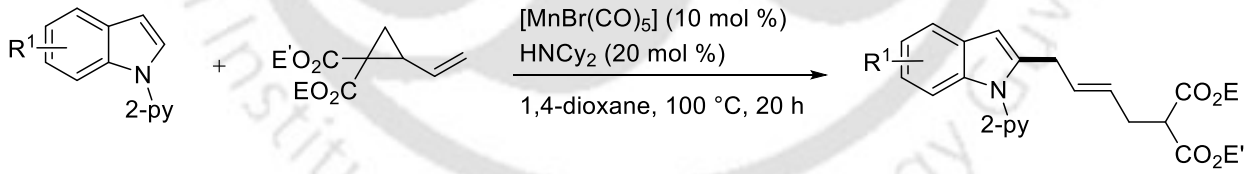
Li and co-workers developed a Rh-catalyzed C–H dialkylation of sulfoxonium ylides with oxaazabicyclic olefins employing $[Cp^*RhCl_2]_2$ as the catalyst and PivOH as the additive. The redox-neutral protocol shows substrate scope, functional group tolerance and sulfoxonium ylide act as weak-chelation assisted DG (Scheme 1).[8]



Scheme 1. Rh-Catalyzed C–H dialkylation of Sulfoxonium Ylides with Oxaazabicyclic Olefins

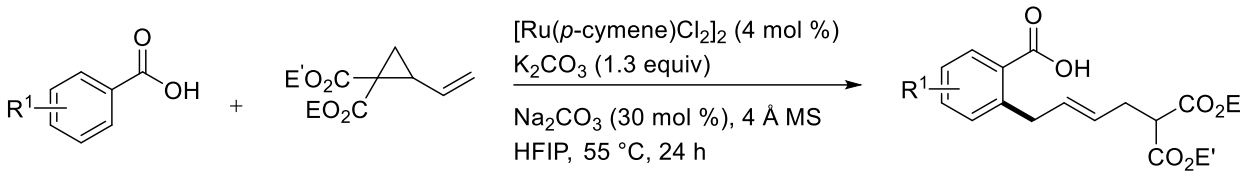
2.1.2 Vinyl Strained Rings in C–H Functionalization

Ackermann and co-workers described a Mn-catalyzed C–H/C–C activation of indoles and pyrroles with VCPs to deliver *E*-selective allyl arenes (up to 14:1 *E*/*Z*). The protocol features silver-free condition, substrate scope, site-selectivity and late-stage amino acid diversification (Scheme 2).[6d]



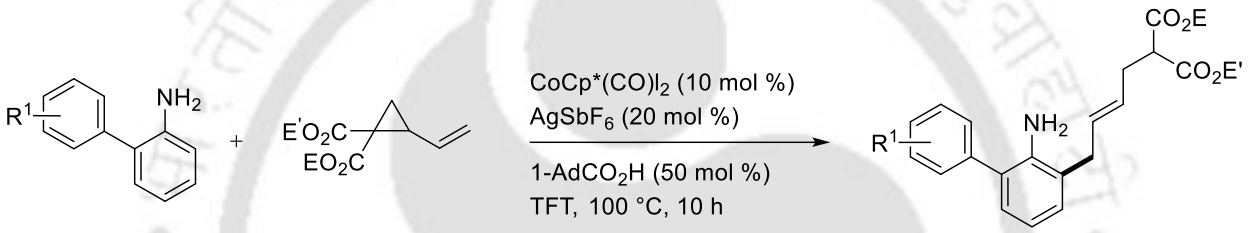
Scheme 2. Mn-Catalyzed C–H Allylation of Indoles with VCPs

Gooßen and co-workers developed a Ru-catalyzed ring-opening *ortho*-C–H allylation of benzoic acids with VCPs, merging C–H/C–C activation to deliver allyl arenes (up to 16:1 *E*/*Z*). The protocol features functional group tolerance, gram-scale synthesis and utility in isocoumarin/dihydroisocoumarin synthesis *via* follow-up cyclization reactions (Scheme 3).[7]



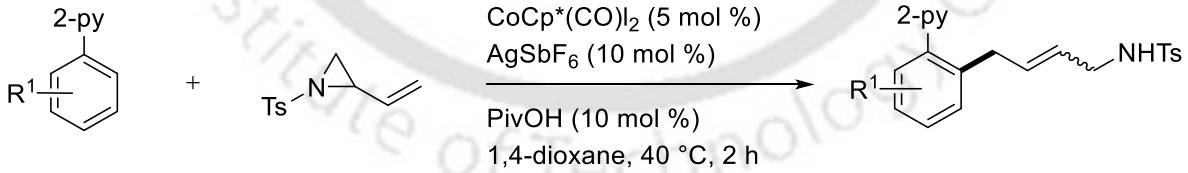
Scheme 3. Ru-Catalyzed Allylation of Benzoic Acids with VCPs

Baidya and co-workers established a Co-catalyzed free-amine-directed C–H allylation of 2-aminobiaryls with VCPs to produce *E*-selective allyl arenes (Scheme 4).[6g] The protocol proceeds through strained four-membered metallacycle formation *via* electrophilic C–H metalation, substrate scope and DFT study confirming rate-determining VCP insertion and *ortho*-selectivity from thermodynamic stability.



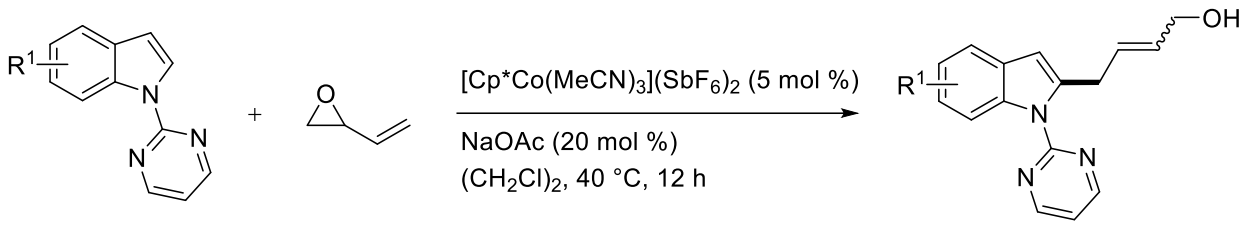
Scheme 4. Co-catalyzed Allylation of Free Amines with Vinyl Cyclopropane

Clavier and co-workers established a Co-catalyzed C–H allylation of 2-phenylpyridine with vinylaziridines, delivering allyl arenes *via* *β*-nitrogen elimination (Scheme 5).[9] The protocol features mild reaction conditions, substrate scope and functional group tolerance, though with modest *E*/*Z* selectivity (~1:1).



Scheme 5. Co-Catalyzed Allylation of 2-Phenylpyridine with Vinyl Aziridines

Li and co-workers established a Co-catalyzed C–H allylation of (hetero)arenes with 2-vinyloxirane to give allylic alcohols (Scheme 6).[10] The mild protocol features broad substrate scope, functional group tolerance, *β*-oxygen elimination, selectivity and low catalyst loadings.

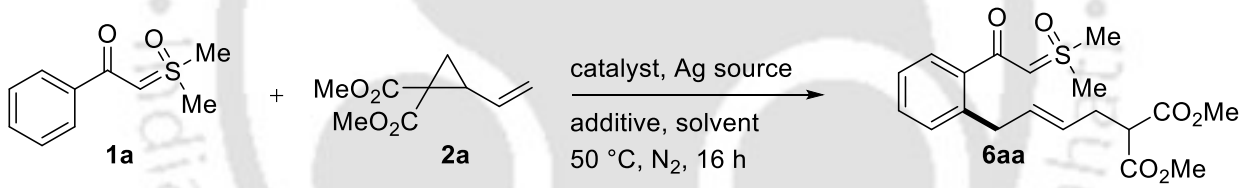


Scheme 6. Co-Catalyzed C–H Allylation of Indoles with Vinyl Oxiranes

1.3 Present Study

We herein describe a Co-catalyzed C–H allylation of arenes employing vinyl strained rings such as VCPs, 2-vinylaziridines, 2-vinyloxirane and 4-vinyl-1,3-dioxolan-2-one as coupling partner. The transformation proceeds *via* C–H and C–C/C–het activation using sulfoxonium ylide as a weakly coordinating DG. This protocol features site selectivity, functional group tolerance, substrate scope and mild reaction conditions.

Table 1. Optimization of the Reaction Conditions[a]



Entry	Catalyst	[Ag] source	Additive	Solvent	Yield (%)[b]	*E*/*Z*[c]
1	$[Cp^*Co(CO)I_2]$	$AgSbF_6$	NaOPiv	$(CH_2Cl)_2$	32	16:1
2	$[Cp^*Co(CO)I_2]$	$AgSbF_6$	CsOPiv	$(CH_2Cl)_2$	21	12:1
3	$[Cp^*Co(CO)I_2]$	$AgSbF_6$	NaOAc	$(CH_2Cl)_2$	76	17:1
4	$[Cp^*Co(CO)I_2]$	$AgSbF_6$	CsOAc	$(CH_2Cl)_2$	33	14:1
5	$[Cp^*Co(CO)I_2]$	$AgSbF_6$	1-Ad-CO_2H	$(CH_2Cl)_2$	25	8:1
6	$[Cp^*Co(CO)I_2]$	$AgSbF_6$	MesCO_2H	$(CH_2Cl)_2$	trace	-
7	$[Cp^*Co(CH_3CN)_3](SbF_6)_2$	$AgSbF_6$	NaOAc	$(CH_2Cl)_2$	72	15:1
8	$[Cp^*Co(CO)I_2]$	$AgSbF_6$	CH_3CO_2H	$(CH_2Cl)_2$	trace	-
9	$[Cp^*Co(CO)I_2]$	$AgSbF_6$	PivOH	$(CH_2Cl)_2$	22	9:1
10	**$[Cp^*Co(CO)I_2]$**	**$AgSbF_6$**	**-**	**$(CH_2Cl)_2$**	**88**	**21:1**

11	-	$AgSbF_6$	NaOAc	$(CH_2Cl)_2$	n.d	-
12	$[Cp^*Co(CO)I_2]$	$AgBF_4$	-	$(CH_2Cl)_2$	n.d.	-
13	$[Cp^*Co(CO)I_2]$	AgOTf	-	$(CH_2Cl)_2$	trace	-
14	$[Cp^*Co(CO)I_2]$	AgOAc	-	$(CH_2Cl)_2$	24	6:1
15	$[Cp^*Co(CO)I_2]$	$AgSbF_6$	-	THF	trace	-
16	$[Cp^*Co(CO)I_2]$	$AgSbF_6$	-	MeOH	n.d.	-
17	$[Cp^*Co(CO)I_2]$	$AgSbF_6$	-	TFE	n.d.	-
18	$[Cp^*Co(CO)I_2]$	$AgSbF_6$	-	CH_3CN	trace	-
19[d]	$[Cp^*Co(CO)I_2]$	$AgSbF_6$	-	$(CH_2Cl)_2$	68	16:1
20[e]	$[Cp^*Co(CO)I_2]$	$AgSbF_6$	-	$(CH_2Cl)_2$	22	17:1
21[f]	$[Cp^*Co(CO)I_2]$	$AgSbF_6$	-	$(CH_2Cl)_2$	trace	-
22[g]	$[Cp^*Co(CO)I_2]$	$AgSbF_6$	-	$(CH_2Cl)_2$	34	16:1
23	$[Cp^*RhCl_2]_2$	$AgSbF_6$	-	$(CH_2Cl)_2$	trace	-
24	$[Ru(p\text{-cymene})Cl_2]_2$	$AgSbF_6$	-	$(CH_2Cl)_2$	trace	-
25	$Pd(OAc)_2$	$AgSbF_6$	-	$(CH_2Cl)_2$	n.d	-
26	$Ir(ppy)_3$	$AgSbF_6$	-	$(CH_2Cl)_2$	n.d	-

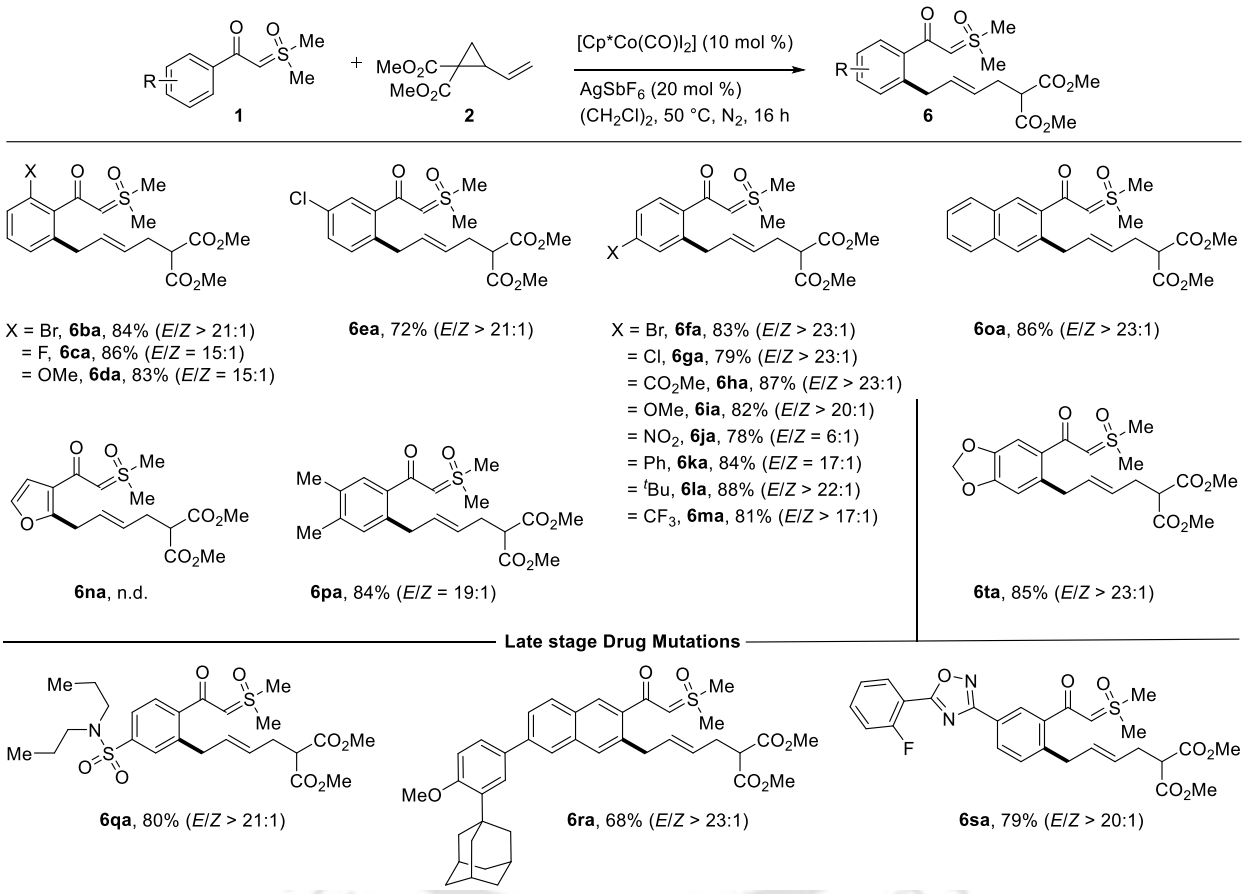
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst (10 mol %), [Ag] source (20 mol %), additive (20 mol %), solvent (2 mL), 50 °C, 16 h, N_2 atmosphere. [b]Isolated yield. [c]Determined by ^1H NMR. [d]At 80 °C. [e]Room temperature. [f]Under air. [g]At 120 °C. n.d. = not detected. TFE = 2,2,2-trifluoroethanol.

We initiated our studies using sulfoxonium ylide **1a** and VCP **2a** as model substrates (Table 1). Gratifyingly, reaction with $[Cp^*Co(CO)I_2]$ (10 mol %) and $AgSbF_6$ (20 mol %) in $(CH_2Cl)_2$ at 50 °C for 16 h under N_2 delivered allylated **6aa** in 88% yield with 21:1 *E*/*Z* selectivity. Notably, $[Cp^*Co(CO)I_2]$ outperformed $[Cp^*Co(CH_3CN)_3](SbF_6)_2$, while alternative solvents such as THF, CH_3CN, MeOH and TFE led to diminished the efficiency. Screening of additives showed no further improvement. Control experiments confirmed that no reaction occurred in the absence of the Co-catalyst, with recovery of the starting materials.

With the optimized conditions, we evaluated the scope of the allylation using sulfoxonium ylides bearing diverse aryl substituents **1b-t** with VCP **2a** as the standard coupling partner (Table 2). *Ortho*-substituted ylides containing 2-bromo **1b**, 2-fluoro **1c** and 2-methoxy **1d** groups

smoothly delivered **6ba-da** in 83-86% yields with ≥15:1 *E*/*Z*-diastereoselectivity, while the 3-chloro-substituted ylide **1e** afforded **6ea** in 72% yield and >21:1 *E*/*Z*-diastereoselectivity. Para-substituted ylides bearing bromo **1f**, chloro **1g**, ester **1h**, methoxy **1i**, nitro **1j**, phenyl **1k**, *tert*-butyl **1l** and trifluoromethyl **1m** groups were well tolerated, furnishing **6fa-ma** in 78-88% yields with

Table 2. Substrate Scope of Sulfoxonium Ylides[a,b]

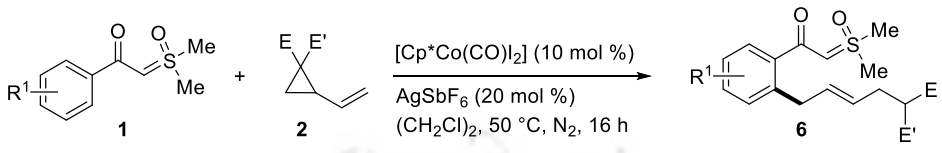


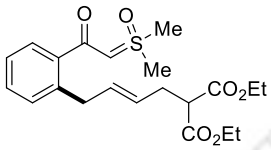
[a]Reaction conditions: **1b-t** (0.2 mmol), **2a** (0.3 mmol), [Cp*Co(CO)I_2] (10 mol %), $AgSbF_6$ (20 mol %), $(CH_2Cl)_2$ (2 mL), N_2, 50 °C, 16 h. [b]Isolated yield. n.d. = not detected.

≥6:1 *E*/*Z*-diastereoselectivities. In contrast, the heteroaryl 3-furoyl sulfoxonium ylide **1n** was unreactive, likely due to catalyst chelation. Notably, naphthyl-substituted ylide **1o** provided **6oa** in 86% yield with >23:1 *E*/*Z*-diastereoselectivity and the 3,4-dimethyl substituted ylide **1p** delivered **6pa** in 84% yield. Moreover, ylides derived from bioactive motifs including probenecid **1q**,

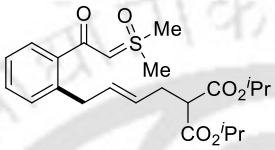
adapalene **1r**, ataluren **1s** and piperonylic acid **1t** participated in allylation to accomplish **6qa-ta** in 68-85% yields with excellent *E*/*Z*-diastereoselectivities (>20:1).

Table 3. Substrate Scope of VCPs [a,b]

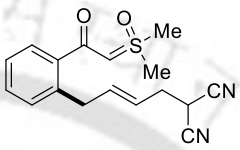




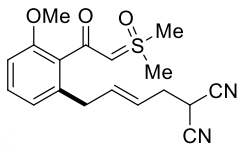
6ab, 87% (*E*/*Z* > 21:1)



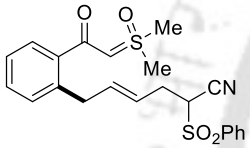
6ac, 85% (*E*/*Z* > 21:1)



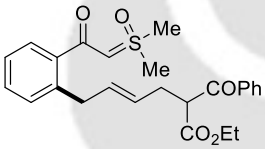
6ad, n.d.



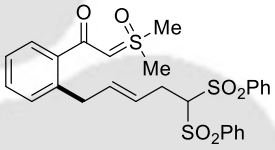
6id, trace



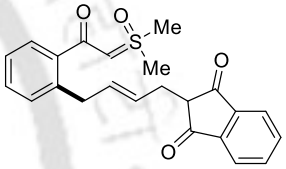
6ae, 83% (*E*/*Z* > 21:1)



6af, 87% (*E*/*Z* > 23:1)



6ag, 85% (*E*/*Z* > 23:1)



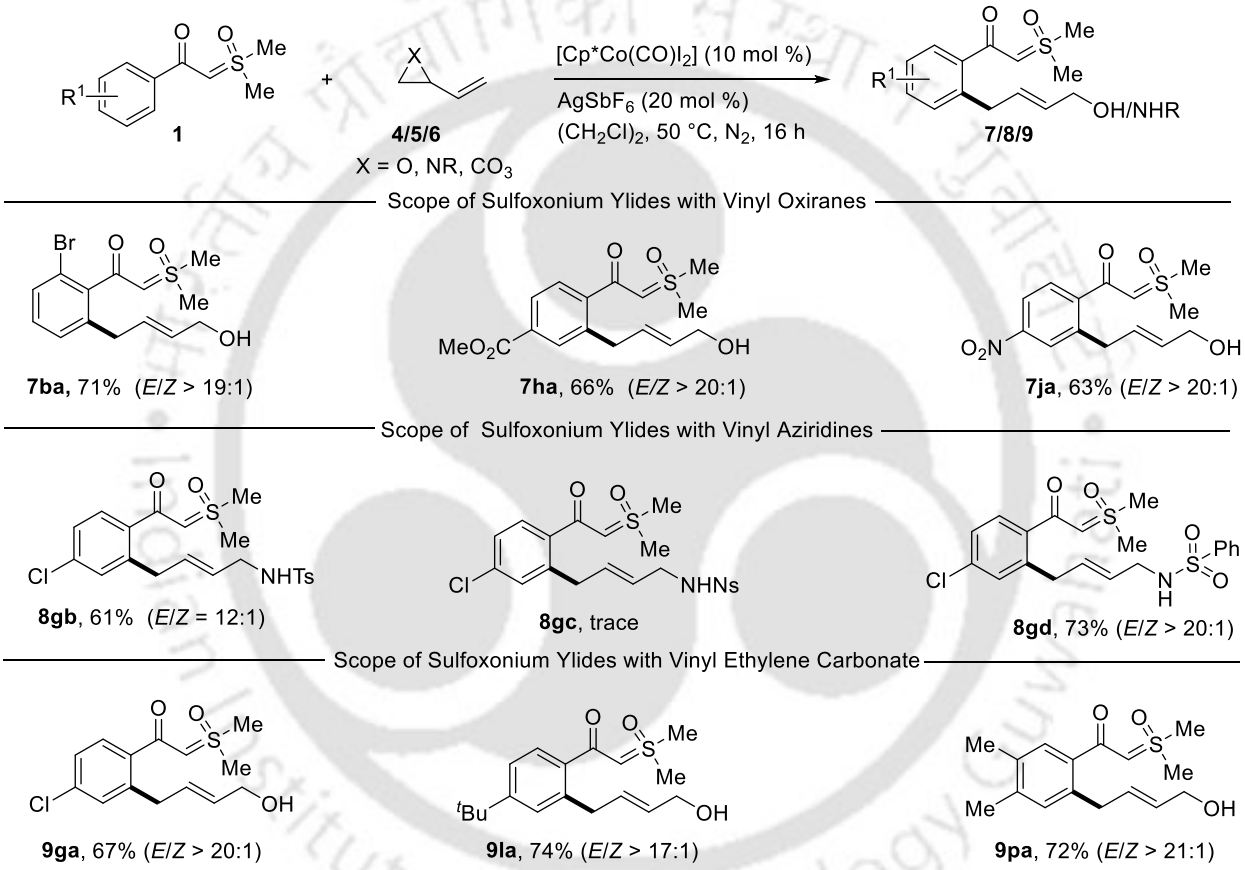
6ah, 79% (*E*/*Z* > 23:1)

[a]Reaction conditions: **1a, 1i** (0.2 mmol), **2b-h** (0.3 mmol), [Cp*Co(CO)I_2] (10 mol %), $AgSbF_6$ (20 mol %), $(CH_2Cl)_2$ (2 mL), N_2, 50 °C, 16 h. [b]Isolated yield. n.d. = not detected.

The scope of the procedure was next explored using VCPs **2b-h** with ylide **1a** as the representative coupling partner (Table 3). VCPs bearing ethyl analogue **2b** and isopropyl analogue **2c** furnished the allylated **6ab** and **6ac** in 87% and 85% yields, respectively, with a >21:1 *E*/*Z*-diastereoselectivities. In contrast, the dicyano-substituted VCP **2d** remained unreactive toward both **1a** and **1i**, presumably due to coordination of the nitrile group to the Co-catalyst. On the other hand, VCPs bearing phenylsulfonyl cyano **2e**, keto-ester **2f**, sulfonyl **2g** and indandione **2h** groups underwent coupling to deliver **6ae-6ah** in 79-87% yields with >21:1 *E*/*Z*-diastereoselectivities. To reveal the generality, vinyl strained-ring systems, 2-vinyloxirane **3** and 2-vinylaziridines **4** were examined with sulfoxonium ylides **1b**, **1h**, **1j** and **1g** as representative substrates (Table 4). The allylation proceeded, affording **7ba**, **7ha**, **7ja**, **8gb** and **8gd** in 61-73% yields with ≥12:1 (*E*/*Z*)-diastereoselectivities, whereas aziridine **4c** afforded only trace amount of **8gc**. Encouraged by the successful allylation of three membered vinyl strained systems, the coupling of 4-vinyl-1,3-

dioxolan-2-one (VEC) **5** was further examined to assess the scope of the methodology (Table 4). Sulfoxonium ylide **1g** coupled smoothly with VEC **5** to furnish **9ga** in 67% yield with >20:1 *E*/*Z*-diastereoselectivity. Similarly, ylides with 4-*tert*-butyl **1l** and 3,4-dimethyl **1p** groups afforded **9la** and **9pa** in 74% and 72% yields respectively with >17:1 *E*/*Z*-diastereoselectivities. These results demonstrate the broad applicability of the protocol across diverse substrate classes.

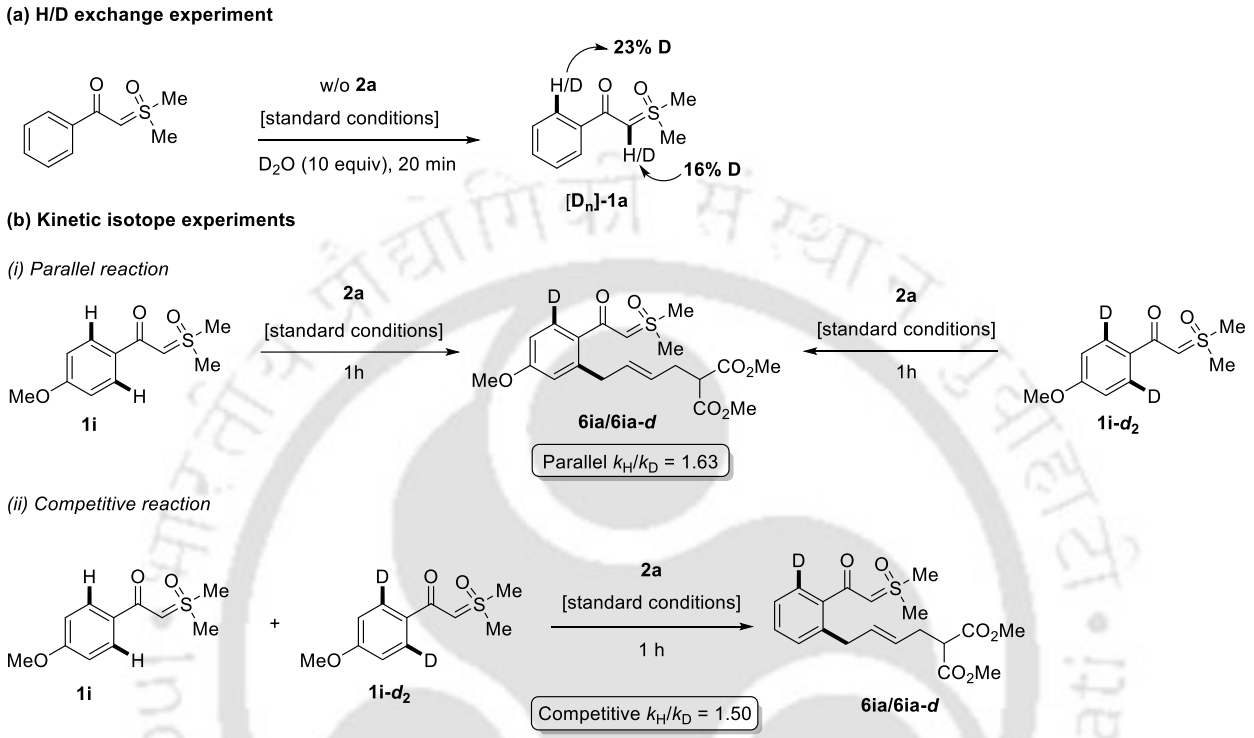
Table 4. Substrate Scope of Vinyl Oxiranes, Vinyl Aziridines and Vinyl Ethylene Carbonates [a,b]



[a]Reaction conditions: **1** (0.2 mmol), **4/5/6** (0.3 mmol), [Cp*Co(CO)I_2] (10 mol %), $AgSbF_6$ (20 mol %), $(CH_2Cl)_2$ (2 mL), N_2, 50 °C, 16 h. [b]Isolated yield.

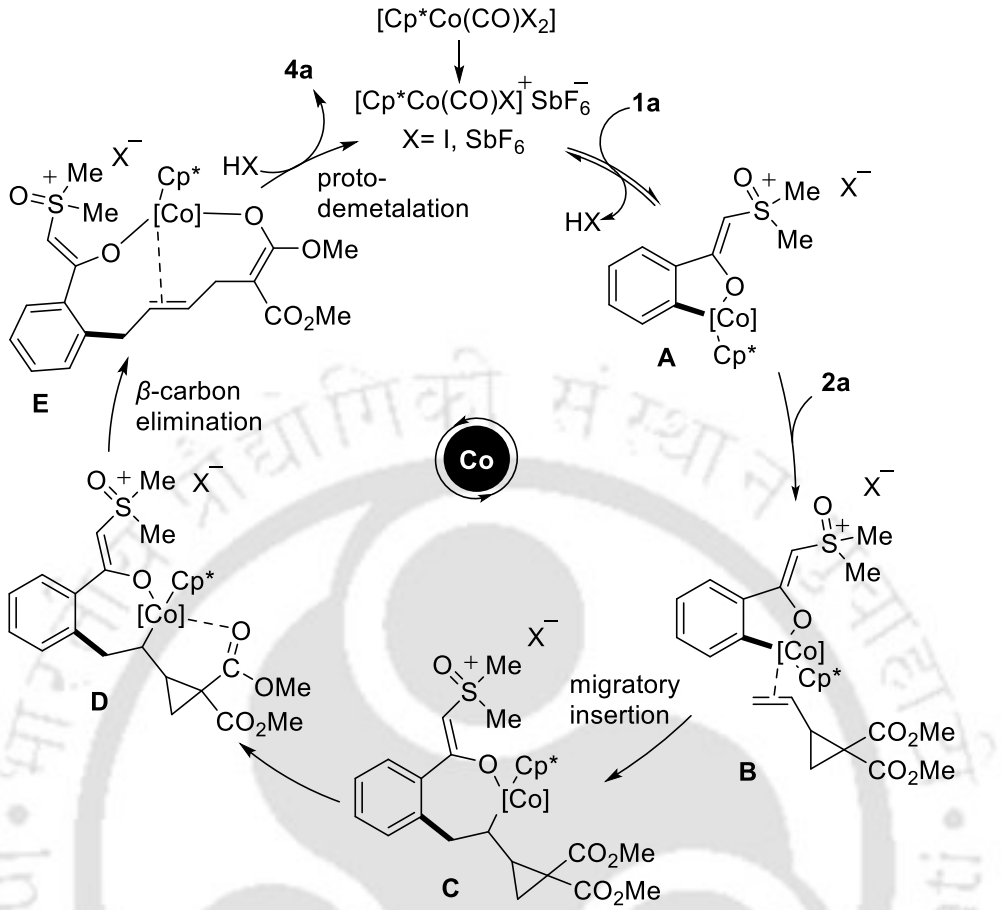
To probe the reaction mechanism, deuterium labeling experiment was conducted using D_2O as a cosolvent (Scheme 7). Treatment of **1a** with D_2O resulted 23% deuterium incorporation at the o*rtho*-position of the benzoyl ring and 16% at the *α*-position of the carbonyl group of sulfoxonium ylide, indicating that the C–H cleavage process might be reversible. Notably, no H/D exchange was occurred in the absence of [Cp*Co(CO)I_2], underscoring the essential role of the

[Cp*Co(CO)I_2] in C–H activation. Furthermore, kinetic isotope effect studies using **1i** and **1i-*d*$_2$** with **2a** revealed k_H/k_D values of 1.63 (parallel) and 1.50 (competitive), indicating that C–H bond cleavage is likely to be involved in the rate-determining step.

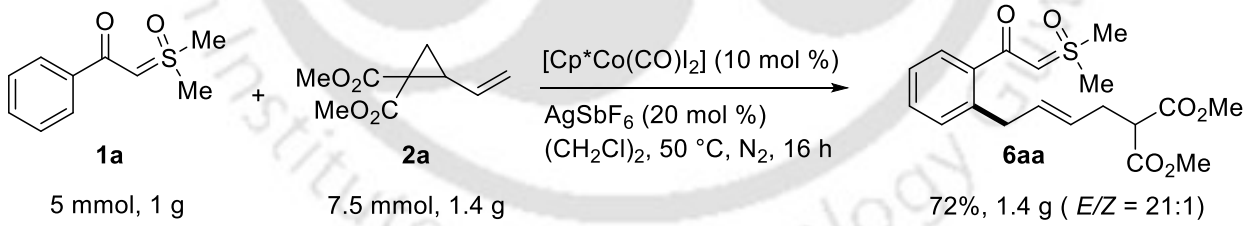


Scheme 7. Preliminary Mechanistic Investigations

These experimental results and literature precedents[11] suggest that, the substrate **1a** with active Co(III) species may generate five-membered cobaltacycle **A** by a concerted metalation-deprotonation (CMD) process (Scheme 8). Subsequent olefin coordination of VCP **2a** can generate **B**, which may undergo migratory insertion to afford cobaltacycle **C**. Further coordination of the ester moiety of the VCP to the Co-center may lead to intermediate **D**, thereby facilitating a thermodynamically favored *β*-carbon elimination and C–C bond cleavage to form **E**. Finally, protodemetalation of **E** can release the allylated product **6aa** and regenerates the active catalyst, thus completing the catalytic cycle.

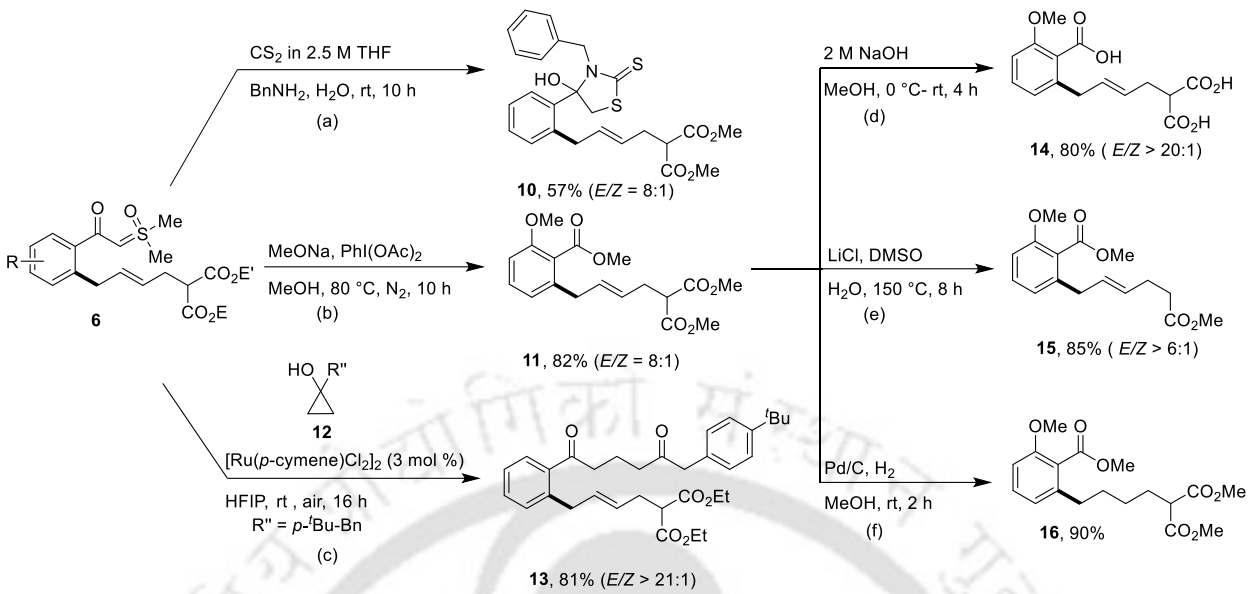


Scheme 8. Plausible Reaction Pathway



Scheme 9. Scale-up Synthesis

To demonstrate the synthetic versatility of the methodology, the C(olefinic)–H bond of the sulfoxonium ylide derived products were further diversified (Scheme 10). For instance, cyclization of **6aa** with CS_2 and $BnNH_2$ afforded **10** in 57% yield with 8:1 *E*/*Z*-diastereoselectivity. Likewise, Krapcho decarboxylation of **11** gave **15** in 85% yield with >6:1 *E*/*Z* diastereoselectivity, whereas Pd/C-mediated hydrogenation afforded **16** in 90% yield. In addition, Ru-catalyzed alkylation of



[a]Reaction conditions: (a) **6aa** (0.1 mmol), CS_2 in 2.5 M THF (0.3 mmol), $BnNH_2$ (0.2 mmol), H_2O (1 mL), rt, 10 h. (b) **6da** (0.1 mmol), MeONa (0.3 mmol), $PhI(OAc)_2$ (0.1 mmol), MeOH (1 mL), 80 °C, N_2, 10 h. (c) **6ab** (0.1 mmol), **12** (R''= *p*-^{t}Bu-Bn, 0.13 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (3 mol %), HFIP (1 mL), rt , air, 16 h. (d) **11** (0.1 mmol), 2 M NaOH (0.22 mmol), MeOH (0.5 mL), 0 °C-rt , 4 h. (e) **11** (0.1 mmol), LiCl (0.5 mmol), DMSO (1 mL), H_2O (0.5 mmol), 150 °C, 8 h. (f) **11** (0.1 mmol), Pd/C (1.0 mmol), H_2, MeOH (1 mL), rt, 2 h.

Scheme 10. Post-Synthetic Transformations

6ab with substituted cyclopropanol **12** delivered **13** in 81% yield with >21:1 *E*/*Z*-selectivity.[12] Notably, the protocol was scalable; treatment of **1a** with **2a** produced **6aa** in 72% yield with 21:1 *E*/*Z* diastereoselectivity (Scheme 9).

In summary, we have showed a Co-catalyzed C–H allylation of sulfoxonium ylides employing strained vinyl rings as coupling partners. The use of sulfoxonium ylides as weak DGs, substrate generality, diverse C–C/C–heteroatom bond formation, Co-catalysis and applicability to late-stage drug modification, highlights the practical utility of this method.

2.3 Experimental Section

General Information. $Co_2(CO)_8$ (≥90%), $AgSbF_6$ (98%), NaOPiv (98%), CsOPiv (>98%), NaOAc (99%), CsOAc (>98%), Cu_2O (≥99.99%), AgOAc (≥99.99%), Cs_2CO_3 (>98%), CH_3COOH (>98%), PivOH (>98%), 1-AdCOOH (>98%), MesCOOH (>98%), 2,2,2-trifluoroethanol (TFE) and carboxylic acids were purchased from Aldrich and TCI chemicals and used as received. Acetonitrile (CH_3CN), tetrahydrofuran (THF), MeOH and $(CH_2Cl)_2$ (1,2-dichloroethane) were dried prior as per the standard procedure. Silica gel-G/GF254 plates (Merck) were used for TLC analysis with a mixture of hexane and ethyl acetate as the eluent. Column chromatography was carried out using Rankem silica gel (60-120 mesh). Bruker Avance III 400, 500 and 600 MHz NMR spectrometers were used to record (^1H, ^{13}C, ^{19}F and NOESY) spectra using $CDCl_3$ and DMSO-d_6 as the solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) and spin-spin coupling constant (*J*) are reported in parts per million and hertz (Hz), respectively, and to describe peak patterns following abbreviations were used when appropriate: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Melting point of the products was measured on Büchi melting point apparatus, MPB-540. Open capillary tubes were used for the measurements and are uncorrected. Mestre nova software was used throughout the spectral analysis. Q-Tof ESI-MS instrument was used for recording HRMS data. Infrared spectra were recorded on Perkin Elmer FT-IR instrument. HPLC analysis was carried out using Waters 515 system bearing C18 column with iso-propanol and hexane as an eluent.

General Procedure for the Preparation of Sulfoxonium Ylides 1.

Sulfoxonium ylides **1** were synthesized according to the procedure outlined in chapter 1 (Experimental Section 1.3).

General Procedure for the Preparation of VCPs 2.

VCPs **2** were synthesized according to the procedures outlined in chapter 1 (Experimental Section 1.3).

General Procedure for the Preparation of Vinyl Aziridines 4.

Step-I: To a stirred solution of sulfonamide (20 mmol, 3.42 g) and potassium hydroxide (50 mmol, 2.8 g) in MeOH (80 mL), (diacetoxyiodo)benzene (20 mmol, 6.44 g) was added portion wise at 0 °C. The resulting mixture was stirred at room temperature for 3 h and poured into water (200 mL). The solution was kept in refrigerator overnight to precipitate a yellow solid, which was recrystallized to afford PhI=NR.

Step-II: To a stirred solution of PhI=NR (10 mmol, 3.37 g) and $Cu(OTf)_2$ (1 mmol, 0.36 g) in MeCN (20 mL), 1,3-butadiene (10 mmol, 0.84 mL) was added at 0 °C under N_2 atmosphere. The reaction was stirred at room temperature for 3 h. After completion, the residue was poured into 1M NaOH (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by silica gel flash chromatography (hexane/ethyl acetate 10:1) to afford the vinyl aziridines **4**.

General Procedure of Cobalt-Catalyzed Ring opening of Strain Rings *via* Sulfoxonium Ylide 6/7/8/9. Sulfoxonium ylide **1** (0.2 mmol), vinyl cyclopropane **2** (0.3 mmol/2-vinyloxirane **3** (0.3 mmol)/2-vinylaziridines **4** (0.3 mmol)/4-vinyl-1,3-dioxolan-2-one **5** (0.3 mmol), $[Cp^*Co(CO)I_2]$ (10 mol %, 0.02 mmol, 10 mg) and $AgSbF_6$ (20 mol %, 0.04 mmol, 13 mg) were stirred in $(CH_2Cl)_2$ (2 mL) at 50 °C under N_2 atmosphere in a preheated oil bath for 16 h. After completion (monitored by TLC), the reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and filtered through a short pad of celite. Evaporation of the solvent gave a residue, which was purified using silica gel chromatography (hexane: ethyl acetate =1:4) to afford the ring opening allylated products **6/7/8/9**.

Scale-up Synthesis of 6aa. 2-(Dimethyl(oxo)-l6-sulfaneylidene)-1-phenylethan-1-one **1a** (5 mmol, 1 g), 1-dimethyl 2-vinylcyclopropane-1,1-dicarboxylate **2a** (7.5 mmol, 1.4 g), $[Cp^*Co(CO)I_2]$ (10 mol %, 0.5 mmol, 242 mg) and $AgSbF_6$ (20 mol %, 1 mmol, 350 mg) were stirred in $(CH_2Cl)_2$ (100 mL) at 50 °C under N_2 atmosphere in a preheated oil bath for 16 h. After completion (monitored by TLC), the reaction mixture was cooled to room temperature, diluted with ethyl acetate (60 mL) and filtered through a celite pad. Evaporation of the solvent gave a

residue, which was purified using silica gel chromatography (hexane: ethyl acetate =2:8) to afford the ring opening allylated **6aa** in 72% (1.4 g) yield.

Post-Synthetic Modifications

Synthesis of 10. To a stirred solution of CS_2 (2.5 M in THF, 0.3 mmol, 0.12 mL) and benzyl amine (0.2 mmol, 22.5 mg) in water (0.7 mL), dimethyl (*E*)-2-(4-(2-(2-(dimethyl(oxo)-l6-sulfaneylidene)acetyl)phenyl)but-2-en-1-yl)malonate **6aa** (0.1 mmol, 40 mg) was added and the reaction mixture was stirred at room temperature for 10 h. After completion (monitored by TLC), it was extracted with ethyl acetate (3 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue, which was purified using silica gel chromatography (hexane/ethyl acetate = 9:1) to afford **10** in 57% (19 mg) yield.

Synthesis of 11. To a stirred solution of **6da** (0.1 mmol, 50 mg) in MeOH (2 mL) was added MeONa (0.3 mmol, 17.5 mg) and $PhI(OAc)_2$ (0.1 mmol, 32.5 mg) and the mixture was stirred at 80 °C for 12 h under N_2 atmosphere. After completion (monitored by TLC), all the volatiles were evaporated using rotary evaporator to give a residue, which was purified using silica gel chromatography (hexane/ethyl acetate = 7:3) to afford **11** in 82% (40 mg) yield.

Synthesis of 13. To a stirred solution of **6ab** (0.1 mmol, 50 mg) in HFIP (2 mL), [Ru(*p*-cymene)Cl_2]$_2$ (0.03 mmol, 4 mg) and cyclopropanol **12** (0.12 mmol, 25 mg) were added and the reaction was allowed to stir at room temperature for 16 h. After completion (monitored by TLC), all the volatiles were evaporated using rotary evaporator. The resulting residue was purified using silica gel chromatography (hexane/ethyl acetate = 9:1) to afford **13** in 81% (26 mg) yield.

Synthesis of 14. To a stirred solution of **11** (0.1 mmol, 35 mg) in MeOH (1 mL) was added 2M NaOH solution (0.25 mmol, 0.15 mL) at 0 °C and the mixture was stirred at room temperature for 4 h. After completion (monitored by TLC), all the volatiles were evaporated using rotary evaporator. The resulting residue was added 1M HCl solution and white solid compound was formed, which was filtered through sintered funnel and the filtrate was washed with water (10 mL) to afford **14** in 80% (35 mg) yield.

Synthesis of 15. Compound **11** (0.1 mmol, 35 mg) and LiCl (0.5 mmol, 21 mg) were stirred in DMSO (1 mL) and H_2O (0.5 mmol, 10 µL) for 12 h at 150 °C under N_2 atmosphere. After

completion (monitored by TLC), it was extracted with ethyl acetate (3 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue, which was purified using silica gel chromatography (hexane/ethyl acetate = 9:1) to afford **15** as a sticky liquid in 85% (17 mg) yield.

Synthesis of 16. Compound **11** (0.1 mmol, 35 mg) and Pd/C (10 mol %, 12 mg) were stirred in MeOH (1 mL) under H_2 balloon for 2 h at room temperature. After completion (monitored by TLC), the reaction mixture was passed through a short Celite pad using ethyl acetate (10 mL). The volatile was evaporated using rotary evaporator and the resulting residue was purified using silica gel chromatography (hexane/ethyl acetate = 9:1) to afford **16** as a colorless liquid in 90% (15 mg) yield.

Mechanistic Investigation

H/D Exchange Experiment of 1a with D_2O in Absence of 2a. To a stirred solution of 2-(dimethyl(oxo)-l6-sulfaneylidene)-1-phenylethan-1-one **1a** (0.2 mmol, 50 mg), [Cp*Co(CO)I_2] (10 mol %, 0.02 mmol, 10 mg) and $AgSbF_6$ (20 mol %, 0.04 mmol, 13 mg) in $(CH_2Cl)_2$ (5 mL), D_2O (2 mmol, 0.05 mL) was added and the resultant mixture was stirred at 50 °C in an oil bath for 20 minutes under N_2 atmosphere. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and passed through a short pad of celite. Substrate **1a** was recovered using silica gel chromatography (ethyl acetate: methanol = 9:1) to afford [D_n]-**1a**. The deuterium incorporation was observed as 23% at C2-H, 16% at the H of α-C of carbonyl group of [D_n]-**1a** based on 400 MHz ^{1}H NMR.

Preparation of 2-(Dimethyl(oxo)-l6-sulfaneylidene)-1-(4-methoxyphenyl-2,6-d2)ethan-1-one 1i-*d_2*.

Compound **1i-*d_2*** was synthesized according to the procedure outlined in chapter 1 (Experimental Section 1.3).

Kinetic Isotope Effect Experiments

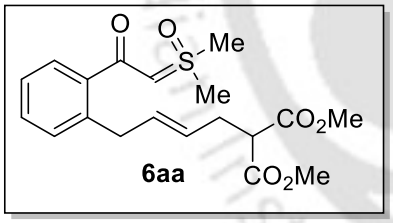
Parallel Reactions. [Cp*Co(CO)I_2] (10 mol %, 0.02 mmol, 10 mg), 2-(dimethyl(oxo)-l6-sulfaneylidene)-1-(4 methoxyphenyl)ethan-1-one (**1i** or **1i-*d_2***, 0.2 mmol, 50 mg), dimethyl 2-vinylcyclopropane-1,1-dicarboxylate **2a** (0.3 mmol, 61 mg) and $(CH_2Cl)_2$ (5 mL) were subjected

to the standard conditions for 1 h. The reaction was then cooled to room temperature, diluted with ethyl acetate (10 mL) and filtered through a short pad of celite. The solvent was removed under vacuum and purification was performed as described in the general procedure to afford **6ia** and **6ia-*d***. The KIE value was determined to be k_H/k_D = 1.63 on the basis of ^{1}H NMR analysis.

Competitive Reactions. A mixture of 2-(dimethyl(oxo)-l6-sulfaneylidene)-1-(4 methoxyphenyl)ethan-1-one **1i** (0.25 mmol, 46 mg) and 2-(dimethyl(oxo)-l6 sulfaneylidene)-1-(4-methoxyphenyl-2,6-d2)ethan-1-one **1i-*d*$_2$** (0.3 mmol, 48 mg) [93% D] was reacted with dimethyl 2-vinylcyclopropane-1,1-dicarboxylate **2a** (0.3 mmol, 165 mg) in $(CH_2Cl)_2$ (8 mL) for 1 h at standard reaction conditions. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (15 mL) and passed through a short pad of celite. Then the solvent was removed under vacuum and the purification was performed as described in the general procedure to afford mixture of **6ia/ 6ia-*d*** in 32% yield and the KIE value was determined to be k_H/k_D = 1.50, based on ^{1}H NMR analysis.

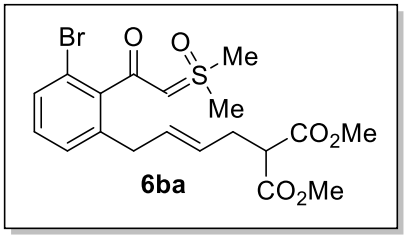
2.4 Characterization data

Characterization Data of the Products

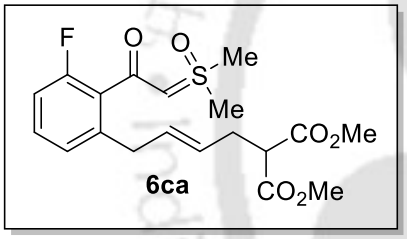


6aa

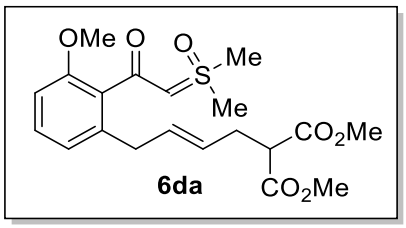
Dimethyl (*E*)-2-(4-(2-(2-(dimethyl(oxo)-l6-sulfaneylidene)-acetyl)phenyl)but-2-en-1-yl)malonate 6aa. Analytical TLC on silica gel, 9:1 ethyl acetate/hexane R_f = 0.28; brown liquid; yield 88% (89 mg); major diastereomer (*E*/*Z* > 21:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.2 Hz, 1H), 7.29-7.26 (m, 1H), 7.19-7.16 (m, 2H), 5.71-5.66 (m, 1H), 5.41-5.36 (m, 1H), 4.67 (bs, 1H), 3.72 (s, 6H), 3.67 (s, 0.29H, minor), 3.65-3.63 (m, 2H), 3.53 (s, 6H), 3.45 (t, *J* = 7.8 Hz, 1H), 2.75 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 186.8, 169.6, 132.2, 129.9, 129.4, 127.7, 126.0, 125.2, 71.8, 52.7, 51.7, 42.3, 31.0, 27.0; FT-IR (neat) 3025, 1723, 1542, 1382, 1328, 1255, 1121 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{25}O_6S$: 381.1366; Found 381.1373.



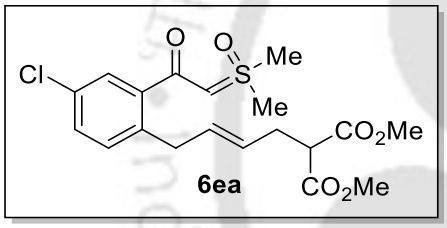
Dimethyl (*E*)-2-(4-(3-bromo-2-(2-(dimethyl(oxo)-l6-sulfaneylidene)acetyl)phenyl)but-2-en-1-yl)malonate 6ba. Analytical TLC on silica gel, 9:1 ethyl acetate/hexane R_f = 0.25; brown liquid; yield 84% (70 mg); major diastereomer (*E*/*Z* > 21:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.5 Hz, 1H), 7.13-7.07 (m, 2H), 5.71-5.66 (m, 1H), 5.44-5.39 (m, 1H), 4.55 (s, 1H), 3.72 (s, 6H), 3.65 (s, 0.18H, minor), 3.57 (s, 6H), 3.52 (d, *J* = 7.0 Hz, 2H), 3.44 (t, *J* = 7.5 Hz, 1H), 2.74 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.2, 169.5, 142.8, 139.1, 131.3, 130.4, 129.3, 127.9, 125.9, 120.0, 72.7, 52.7, 51.6, 42.2, 31.1, 27.1; FT-IR (neat) 3009, 1720, 1536, 1375, 1321, 1240, 1128 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{24}BrO_6S$: 459.0471; Found 459.0464.



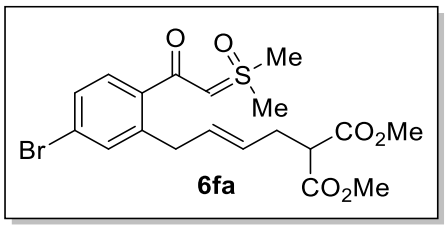
Dimethyl (*E*)-2-(4-(2-(2-(dimethyl(oxo)-l6-sulfaneylidene)acetyl)-3-fluorophenyl)but-2-en-1-yl)malonate 6ca. Analytical TLC on silica gel, 9:1 ethyl acetate/hexane R_f = 0.26; brown sticky liquid; yield 86% (80 mg); major diastereomer (*E*/*Z* = 15:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20-7.16 (m, 1H), 6.96-6.93 (m, 1H), 6.88 (t, *J* = 8.5 Hz, 1H), 5.71-5.66 (m, 1H), 5.43-5.38 (m, 1H), 4.64 (s, 1H), 3.72 (s, 6H), 3.68 (s, 0.40H, minor), 3.55-3.53 (m, 8H), 3.44 (t, *J* = 7.5 Hz, 1H), 2.74 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 180.8, 169.6, 159.9 (J_{C-F} = 244.1 Hz), 140.2 (J_{C-F} = 3.3 Hz), 131.4, 130.0 (J_{C-F} = 18.2 Hz), 129.5 (J_{C-F} = 8.6 Hz), 125.7, 124.7 (J_{C-F} = 2.9 Hz), 113.4 (J_{C-F} = 22.5 Hz), 73.9, 52.7, 51.6, 42.4, 30.5, 27.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ -116.97; FT-IR (neat) 3007, 1722, 1574, 1436, 1252, 1150, 1128 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{25}FO_6S$: 399.1272; Found 399.1275.



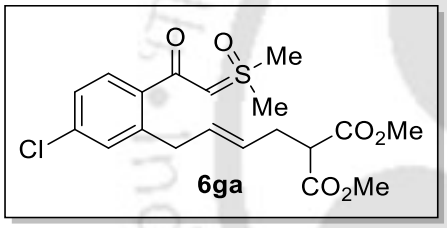
Dimethyl (*E*)-2-(4-(2-(2-(dimethyl(oxo)-l6-sulfaneylidene)-acetyl)-3-methoxyphenyl)but-2-en-1-yl)malonate 6da. Analytical TLC on silica gel, 8:2 ethyl acetate/hexane R_f = 0.27; yellow sticky liquid; yield 83% (75 mg); major diastereomer (*E*/*Z* = 15:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, *J* = 8.0 Hz, 1H), 6.78-6.72 (m, 2H), 5.74-5.67 (m, 1H), 5.42-5.35 (m, 1H), 4.57 (bs, 1H), 3.79 (s, 3H), 3.72 (s, 6H), 3.69 (s, 0.40H, minor), 3.55-3.53 (m, 6H), 3.48-3.46 (m, 2H), 3.44-3.42 (m, 1H), 2.74 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 184.6, 169.6, 156.1, 138.4, 132.0, 131.9, 128.9, 125.2, 121.2, 108.9, 72.9, 56.0, 52.7, 51.7, 42.5, 30.5, 27.1; FT-IR (neat) 2957, 1731, 1673, 1438, 1345, 1283, 1257, 1153, 1022 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{27}O_7S$: 411.1472; Found 411.1476.



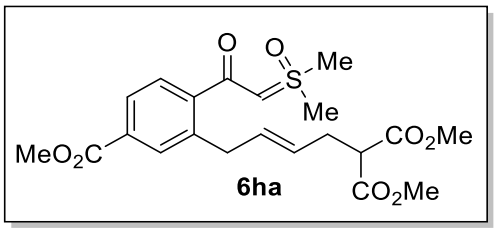
Dimethyl (*E*)-2-(4-(4-chloro-2-(2-(dimethyl(oxo)-l6-sulfaneylidene)acetyl)phenyl)but-2-en-1-yl)malonate 6ea. Analytical TLC on silica gel, 8:2 ethyl acetate/hexane R_f = 0.27; yellow sticky liquid; yield 72% (65 mg); major diastereomer (*E*/*Z* > 21:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.24-7.22 (m, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 5.66-5.62 (m, 1H), 5.41-5.37 (m, 1H), 4.65 (bs, 1H), 3.72 (s, 6H), 3.69 (s, 0.30H, minor), 3.58 (d, *J* = 7.8 Hz, 2H), 3.53 (s, 6H), 3.44 (t, *J* = 7.8 Hz, 1H), 2.73 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.0, 169.6, 137.6, 136.7, 131.7, 131.6, 131.2, 129.2, 127.6, 125.6, 72.2, 52.7, 51.7, 42.3, 30.4, 27.1; FT-IR (neat) 2973, 1718, 1573, 1385, 1283, 1121, 1084 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{24}ClO_6S$: 415.0977; Found 415.0978.



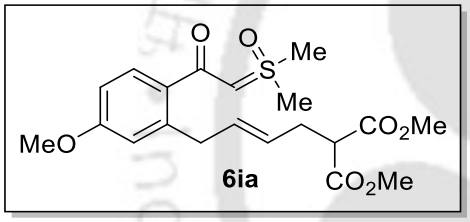
Dimethyl (*E*)-2-(4-(5-bromo-2-(2-(dimethyl(oxo)-l6-sulfaneylidene)acetyl)phenyl)but-2-en-1-yl)malonate 6fa. Analytical TLC on silica gel, 8:2 ethyl acetate/hexane R_f = 0.27; brown sticky liquid; yield 83% (75 mg); major diastereomer (*E*/*Z* > 23:1);^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32-7.29 (m, 2H), 7.27-7.25 (m, 1H), 5.66-5.62 (m, 1H), 5.44-5.40 (m, 1H), 4.64 (s, 1H), 3.73 (s, 6H), 3.69 (s, 0.20H, minor), 3.60 (d, *J* = 7.2 Hz, 2H), 3.53 (s, 6H), 3.45 (t, *J* = 7.8 Hz, 1H), 2.74 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.5, 169.6, 140.5, 139.9, 132.6, 131.3, 129.2, 129.0, 125.9, 123.3, 72.1, 52.8, 51.6, 42.2, 30.7, 27.0; FT-IR (neat) 3013, 1729, 1543, 1385, 1328, 1256, 1165, 1023 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{24}BrO_6S$: 459.0471; Found 459.0470.



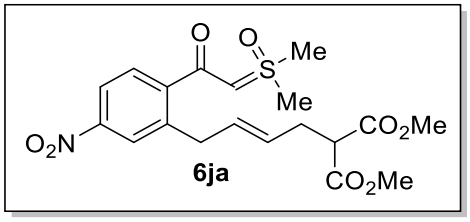
Dimethyl (*E*)-2-(4-(5-chloro-2-(2-(dimethyl(oxo)-l6-sulfaneylidene)acetyl)phenyl)but-2-en-1-yl)malonate 6ga. Analytical TLC on silica gel, 8:2 ethyl acetate/hexane R_f = 0.27; yellow sticky liquid; yield 79% (80 mg); major diastereomer (*E*/*Z* > 23:1) mixture of diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.0 Hz, 1H), 7.16-7.14 (m, 2H), 5.68-5.63 (m, 1H), 5.45-5.40 (m, 1H), 4.63 (bs, 1H), 3.73 (s, 6H), 3.70 (s, 0.27H, minor), 3.62 (d, *J* = 7.5 Hz, 2H), 3.52-3.51 (m, 6H), 3.47-3.44 (m, 1H), 2.74 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.6, 169.6, 140.3, 139.5, 135.0, 131.4, 129.8, 129.0, 126.0, 125.9, 72.1, 52.7, 51.6, 42.4, 30.8, 27.0; FT-IR (neat) 2953, 1722, 1673, 1438, 1345, 1283, 1257, 1159, 1067 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{24}ClO_6S$: 415.0977; Found 415.0967.



Dimethyl (*E*)-2-(4-(2-(2-(dimethyl(oxo)-l6-sulfaneylidene)acetyl)-5-(methoxycarbonyl)phenyl)but-2-en-1-yl)malonate 6ha. Analytical TLC on silica gel, 9:1 ethyl acetate/hexane R_f = 0.27; yellow sticky liquid; yield 87% (75 mg); major diastereomer (*E*/*Z* > 23:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85-7.83 (m, 2H), 7.43 (d, *J* = 8.0 Hz, 1H), 5.71-5.66 (m, 1H), 5.45-5.40 (m, 1H), 4.67 (bs, 1H), 3.90 (s, 3H), 3.73 (s, 6H), 3.68-3.66 (m, 2H), 3.55 (s, 6H), 3.46 (t, *J* = 7.5 Hz, 1H), 2.76 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.7, 169.6, 166.9, 145.5, 138.5, 131.6, 131.0, 130.6, 127.6, 127.3, 125.8, 72.3, 52.7, 52.3, 51.7, 42.4, 30.8, 27.1; FT-IR (neat) 3012, 1733, 1728, 1381, 1243, 1221, 1159, 1033 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{27}O_8S$: 439.1421; Found 439.1419.

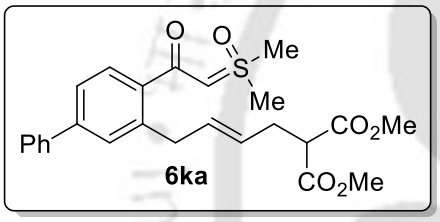


Dimethyl (*E*)-2-(4-(2-(2-(dimethyl(oxo)-l6-sulfaneylidene)acetyl)-5-methoxyphenyl)but-2-en-1-yl)malonate 6ia. Analytical TLC on silica gel, 9:1 ethyl acetate/hexane R_f = 0.27; brown liquid; yield 82% (73 mg); major diastereomer (*E*/*Z* > 20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.4 Hz, 1H), 6.73-6.72 (m, 1H), 6.70-6.67 (m, 1H), 5.71-5.64 (m, 1H), 5.42-5.36 (m, 1H), 4.63 (bs, 1H), 3.80 (s, 3H), 3.72 (s, 6H), 3.68-3.66 (m, 2H), 3.50 (s, 6H), 3.45 (t, *J* = 8.0 Hz, 1H), 2.75 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 186.5, 169.6, 160.4, 140.6, 133.6, 132.2, 129.5, 125.2, 115.5, 110.9, 71.0, 55.4, 52.7, 51.8, 42.5, 31.3, 27.0; FT-IR (neat) 2956, 1733, 1431, 1345, 1270, 1257, 1153, 1012 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{27}O_7S$: 411.1472; Found 411.1476.

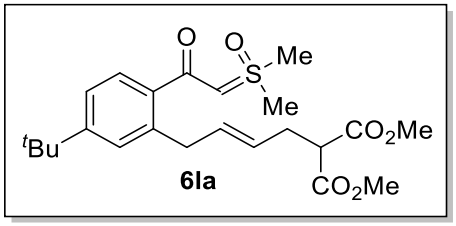


Dimethyl (*E*)-2-(4-(2-(2-(dimethyl(oxo)-l6-sulfaneylidene)acetyl)-5-nitrophenyl)but-2-en-1-yl)malonate 6ja. Analytical TLC on silica gel, 8:2 ethyl

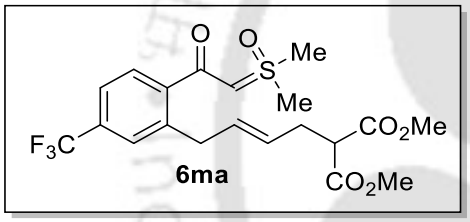
acetate/hexane R_f = 0.27; yellow sticky liquid; yield 78% (75 mg); major diastereomer (*E*/*Z* = 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06-8.02 (m, 2H, major + minor), 7.54-7.50 (m, 1H, major + minor), 5.72-5.65 (m, 1H, major + minor), 5.53-5.46 (m, 1H, major + minor), 4.68-4.67 (m, 1H, major + minor), 3.74 (m, 6H, major), 3.73 (m, 1H, minor), 3.71-3.70 (m, 2H, major + minor), 3.56 (s, 6H, major), 3.55 (s, 1H, minor), 3.47 (t, *J* = 7.6 Hz, 1H, major + minor), 2.75 (t, *J* = 7.2 Hz, 2H, major + minor); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.1 (major + minor), 171.7 (minor) 169.5 (major), 148.1 (major + minor), 147.2 (major + minor), 140.2 (major + minor), 130.6 (minor), 130.5 (major), 129.9 (minor), 128.5 (minor), 128.3 (major), 126.9 (major), 125.0 (minor), 124.7 (major), 121.5 (minor), 121.2 (major), 73.0 (minor), 72.9 (major), 53.0 (minor), 52.8 (major), 51.5 (major + minor), 42.3 (major), 42.2 (minor), 30.7 (major + minor), 27.1 (major + minor); FT-IR (neat) 2980, 1722, 1675, 1438, 1330, 1283, 1252, 1160, 1068 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{24}NO_8S$: 426.1217; Found 426.1223.



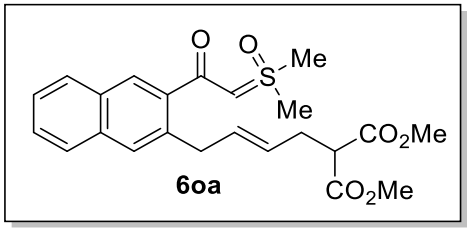
Dimethyl (*E*)-2-(4-(4-(2-(dimethyl(oxo)-l6-sulfaneyli-dene)acetyl)-[1,1'-biphenyl]-3-yl)but-2-en-1-yl)malonate 6ka. Analytical TLC on silica gel, 8:2 ethyl acetate/hexane R_f = 0.32; brown sticky liquid; yield 84% (70 mg); major diastereomer (*E*/*Z* = 17:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.2 Hz, 2H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.44-7.40 (m, 4H), 7.34 (t, *J* = 7.8 Hz, 1H), 5.76-5.71 (m, 1H), 5.43-5.39 (m, 1H), 4.71 (s, 1H), 3.73-3.70 (m, 8H), 3.63 (s, 0.36H, minor), 3.55 (s, 6H), 3.46 (t, *J* = 7.8 Hz, 1H), 2.79 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 186.5, 169.6, 142.1, 140.7, 139.8, 138.8, 132.3, 128.9, 128.7, 128.2, 127.6, 127.3, 125.2, 124.6, 71.7, 52.7, 51.7, 42.3, 31.1, 27.0; FT-IR (neat) 3031, 1730, 1438, 1345, 1281, 1260, 1155, 1020 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{25}H_{29}O_6S$: 457.1679; Found 457.1671.



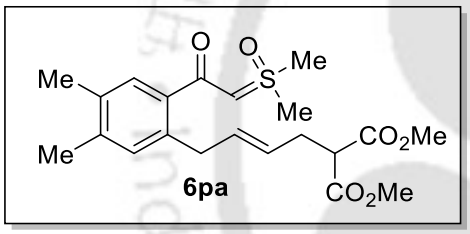
Dimethyl (*E*)-2-(4-(5-(*tert*-butyl)-2-(2-(dimethyl(oxo)-l6-sulfaneylidene)acetyl)phenyl)but-2-en-1-yl)malonate 6la. Analytical TLC on silica gel, 8:2 ethyl acetate/hexane R_f = 0.27; yellow sticky liquid; yield 88% (79 mg); major diastereomer (*E*/*Z* > 22:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.5 Hz, 1H), 7.20-7.18 (m, 2H), 5.72-5.67 (m, 1H), 5.40-5.35 (m, 1H), 4.64 (bs, 1H), 3.73 (s, 6H), 3.65 (d, *J* = 7.5 Hz, 2H), 3.53-3.51 (m, 6H), 3.47-3.44 (m, 1H), 2.77 (t, *J* = 7.0 Hz, 2H), 1.29 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.9, 169.6, 152.5, 138.2, 137.9, 132.7, 127.6, 127.0, 124.8, 122.8, 71.2, 52.7, 51.8, 42.4, 34.8, 31.4, 31.2, 27.1; FT-IR (neat) 2956, 1733, 1673, 1438, 1283, 1257, 1153, 1022 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{33}O_6S$: 437.1992; Found 437.1995.



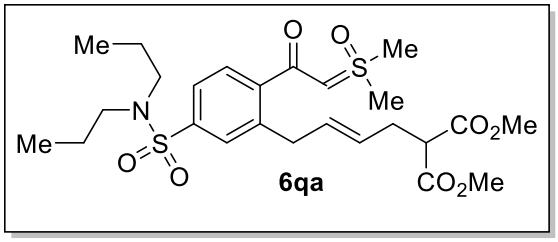
Dimethyl (*E*)-2-(4-(2-(2-(dimethyl(oxo)-l6-sulfaneylidene)acetyl)-5-(trifluoromethyl)phenyl)but-2-en-1-yl)malonate 6ma. Analytical TLC on silica gel, 9:1 ethyl acetate/hexane R_f = 0.27; yellow liquid; yield 81% (73 mg); major diastereomer (*E*/*Z* > 17:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.8 Hz, 1H), 7.45-7.43 (m, 2H), 5.70-5.65 (m, 1H), 5.47-5.42 (m, 1H), 4.65 (s, 1H), 3.73 (s, 6H), 3.72 (s, 0.26H, minor), 3.67 (d, *J* = 7.8 Hz, 2H), 3.55 (s, 6H), 3.45 (t, *J* = 7.2 Hz, 1H), 2.75 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.2, 169.6, 144.6, 139.1, 131.2, 131.1 ($J_{C\text{-}F}$ = 35.3 Hz), 127.83 ($J_{C\text{-}F}$ = 245.1 Hz), 127.81, 126.6 ($J_{C\text{-}F}$ = 3.8 Hz), 126.2, 122.9 ($J_{C\text{-}F}$ = 3.9 Hz), 72.3, 52.7, 51.6, 42.4, 30.8, 27.1; ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.62; FT-IR (neat) 2957, 1722, 1437, 1280, 1240, 1152, 1029 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{24}F_3O_6S$: 449.1240; Found 449.1233.



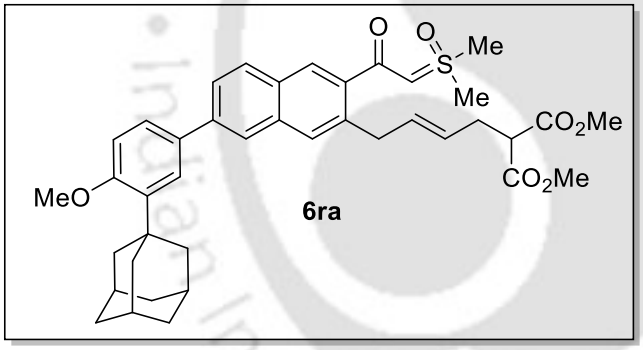
Dimethyl (*E*)-2-(4-(3-(2-(dimethyl(oxo)-l6-sulfaneylidene)acetyl)naphthalen-2-yl)but-2-en-1-yl)malonate 6oa. Analytical TLC on silica gel, 8:2 ethyl acetate/hexane R_f = 0.27; yellow sticky liquid; yield 86% (76 mg); major diastereomer (*E*/*Z* > 23:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.80-7.74 (m, 2H), 7.62 (s, 1H), 7.48-7.40 (m, 2H), 5.81-5.75 (m, 1H), 5.49-5.42 (m, 1H), 4.81 (bs, 1H), 3.79 (d, *J* = 7.2 Hz, 2H), 3.72 (s, 6H), 3.56 (s, 6H), 3.47 (t, *J* = 8.0 Hz, 1H), 2.80 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 186.8, 169.6, 136.0, 133.9, 132.1, 131.6, 128.1, 128.0, 127.3, 127.2, 126.83, 126.82, 125.9, 125.5, 71.9, 52.7, 51.8, 42.4, 31.2, 27.1; FT-IR (neat) 2953, 1727, 1438, 1351, 1288, 1259, 1187, 1067 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{27}O_6S$: 431.1523; Found 431.1516.



Dimethyl (*E*)-2-(4-(2-(2-(dimethyl(oxo)-l6-sulfaneylidene)acetyl)-4,5-dimethylphenyl)but-2-en-1-yl)malonate 6pa. Analytical TLC on silica gel, 8:2 ethyl acetate/hexane R_f = 0.27; brown sticky liquid; yield 84% (80 mg); major diastereomer (*E*/*Z* = 19:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (s, 1H), 6.94 (s, 1H), 5.69-5.64 (m, 1H), 5.38-5.33 (m, 1H), 4.62 (bs, 1H), 3.73 (s, 6H), 3.69 (s, 0.31H, minor), 3.58 (d, *J* = 7.5 Hz, 2H), 3.51 (s, 6H), 3.45 (t, *J* = 7.5 Hz, 1H), 2.76 (t, *J* = 7.5 Hz, 2H), 2.21 (d, *J* = 5.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.0, 169.6, 138.6, 137.9, 135.5, 134.0, 132.8, 131.2, 129.0, 124.7, 71.1, 52.6, 51.8, 42.4, 30.6, 27.0, 19.7, 19.3; FT-IR (neat) 2987, 1731, 1441, 1355, 1285, 1237, 1153, 1065 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{29}O_6S$: 409.1679; Found 409.1679.

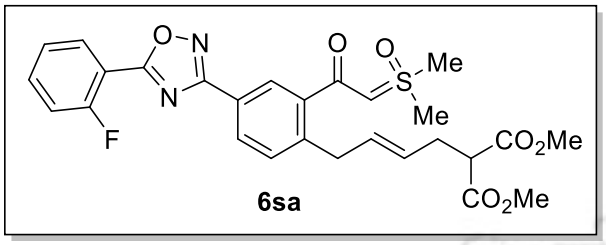


Dimethyl (*E*)-2-(4-(2-(2-(dimethyl(oxo)-l6-sulfaneylidene)acetyl)-5-(*N*,*N*-dipropylsulfamoyl)phenyl)but-2-en-1-yl)malonate 6qa. Analytical TLC on silica gel, 8:2 ethyl acetate/hexane R_f = 0.28; brown liquid; yield 80% (63 mg); major diastereomer (*E*/*Z* > 21:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.59 (m, 2H), 7.47 (d, *J* = 8.0 Hz, 1H), 5.68-5.62 (m, 1H), 5.46-5.40 (m, 1H), 4.68 (s, 1H), 3.74 (s, 6H), 3.69-3.67 (m, 2H), 3.55 (s, 6H), 3.45 (t, *J* = 7.6 Hz, 1H), 3.07-3.03 (m, 4H), 2.73 (t, *J* = 7.2 Hz, 2H), 1.59-1.49 (m, 4H), 0.87 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.0, 169.6, 144.9, 140.4, 139.5, 131.1, 128.2, 128.1, 126.3, 124.7, 72.6, 52.8, 51.5, 50.2, 42.3, 30.8, 29.8, 27.1, 22.2, 11.3; FT-IR (neat) 2954, 1722, 1625, 1462, 1438, 1364, 1285, 1252,1165, 1088, 1023 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{25}H_{38}NO_8S_2$: 544.2033; Found 544.2043.



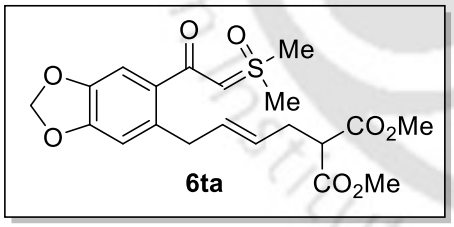
Dimethyl 2-((*E*)-4-(7-(3-((3r,5r,7r)-adamantan-1-yl)-4-methoxyphenyl)-3-(2-(dimethyl(oxo)-l6 sulfaneylidene)acetyl)naphthalen-2-yl)but-2-en-1-yl)malonate 6ra. Analytical TLC on silica gel, 8:2 ethyl acetate/hexane R_f = 0.31; brown sticky liquid; yield 68% (40 mg); major diastereomer (*E*/*Z* > 23:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 5.2 Hz, 2H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.69-7.66 (m, 2H), 7.59-7.58 (m, 1H), 7.53-7.51 (m, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 5.84-5.78 (m, 1H), 5.50-5.44 (m, 1H), 4.81 (bs, 1H), 3.90 (s, 3H), 3.81 (d, *J* = 7.2 Hz, 2H), 3.73 (s, 6H), 3.68 (s, 0.26H, minor), 3.57 (s, 6H), 3.48 (t, *J* = 8.4 Hz, 1H), 2.81 (t, *J* = 7.6 Hz, 2H), 2.18 (s, 6H), 2.10 (s, 3H), 1.80 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.9, 169.7, 158.8, 139.0, 136.3, 134.3, 133.2, 133.1, 132.2, 131.7, 130.4, 129.6, 128.4, 128.1, 126.0, 125.7, 125.5, 124.8, 124.4, 124.2, 112.3, 77.4, 55.3, 52.7, 51.8, 47.9,

42.5, 40.8, 40.2, 37.3, 31.2, 29.3, 27.1; FT-IR (neat) 2903, 1721, 1643, 1495, 1255, 1202, 1143, 1034 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{40}H_{47}O_7S$: 671.3037; Found: 671.3030.



6sa

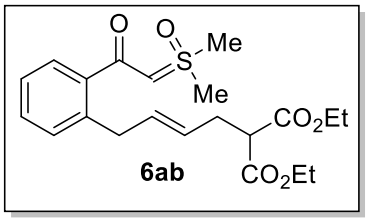
Dimethyl (*E*)-2-(4-(2-(2-(dimethyl(oxo)-l6-sulfaneylidene)acetyl)-4-(5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl)phenyl)but-2-en-1-yl)-malonate 6sa. Analytical TLC on silica gel, 8:2 ethyl acetate/hexane R_f = 0.25; yellow sticky liquid; yield 79% (60 mg); major diastereomer (*E*/*Z* > 20:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24-8.19 (m, 2H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.62-7.58 (m, 1H), 7.35-7.33 (m, 2H), 7.28 (d, *J* = 9.5 Hz, 1H), 5.73-5.68 (m, 1H), 5.46-5.41 (m, 1H), 4.81 (bs, 1H), 3.73-3.68 (m, 8H), 3.58 (s, 6H), 3.46 (t, *J* = 7.5 Hz, 1H), 2.77 (t, *J* = 7.0 Hz, 2H), 2.61 (0.11H, minor); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.0, 169.6, 168.4, 161.8, 160.0, 134.8 (J_{C-F} = 8.6 Hz), 131.3, 131.2, 130.7, 130.6, 130.5, 126.9, 126.0, 124.9, 124.8 (J_{C-F} = 3.6 Hz), 124.6, 117.3 (J_{C-F} = 20.7 Hz), 113.0 (J_{C-F} = 11.6 Hz), 67.6, 52.7, 51.7, 42.2, 31.1, 27.1; ^{19}F NMR (377 MHz, $CDCl_3$) δ -108.34; FT-IR (neat) 3012, 1720, 1252, 1226, 1067, 757 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{27}H_{28}FN_2O_7S$: 543.1596; Found 543.1578.



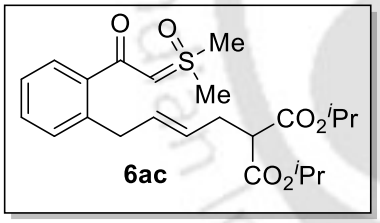
6ta

Dimethyl (*E*)-2-(4-(6-(2-(dimethyl(oxo)-l6-sulfaneylidene)acetyl)benzo[d][1,3]dioxol-5-yl)but-2-en-1-yl)malonate 6ta. Analytical TLC on silica gel, 8:2 ethyl acetate/hexane R_f = 0.28; yellow sticky liquid; yield 85% (75 mg); major diastereomer (*E*/*Z* > 23:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (d, *J* = 8.0 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 5.96 (s, 2H), 5.70-5.65 (m, 1H), 5.35-5.29 (m, 1H), 4.62 (bs, 1H), 3.72 (s, 6H), 3.66 (s, 0.20H, minor), 3.60 (d, *J* = 7.0 Hz, 2H), 3.50 (s, 6H), 3.45 (t, *J* = 7.5 Hz, 1H), 2.77 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.7, 169.7, 147.9, 146.5, 135.4, 131.0, 125.0, 122.2, 120.7, 105.8, 101.2, 70.9, 52.6, 51.8, 42.4, 27.0, 25.2; FT-IR (neat) 2959, 1722, 1670, 1462, 1438, 1364,

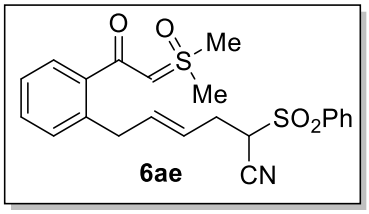
1255, 1243 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{25}O_8S$: 425.1265; Found 425.1273.



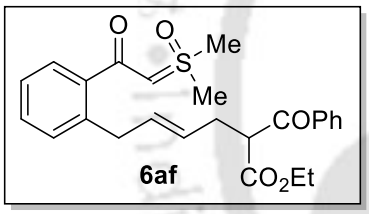
Diethyl (*E*)-2-(4-(2-(2-(dimethyl(oxo)-l6-sulfaneylidene)-acetyl)phenyl)but-2-en-1-yl)malonate 6ab. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.35; brown sticky liquid; yield 87% (95 mg); major diastereomer (*E*/*Z* > 21:1); ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.5 Hz, 1H), 7.27-7.24 (m, 1H), 7.19-7.14 (m, 2H), 5.70-5.65 (m, 1H), 5.41-5.36 (m, 1H), 4.65 (bs, 1H), 4.18 (q, *J* = 7.0 Hz, 4H), 3.63 (d, *J* = 7.5 Hz, 2H), 3.52 (s, 6H), 3.39 (t, *J* = 7.5 Hz, 1H), 2.74 (t, *J* = 7.5 Hz, 2H), 2.60-2.56 (m, 0.09H, minor), 1.25 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 186.8, 169.2, 141.1, 138.1, 132.0, 129.8, 129.2, 127.5, 125.9, 125.3, 71.9, 61.5, 52.0, 42.3, 31.0, 26.9, 14.2; FT-IR (neat) 2981, 1726, 1336, 1277, 1296, 1212, 1067 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{29}O_6S$: 409.1679; Found 409.1689.



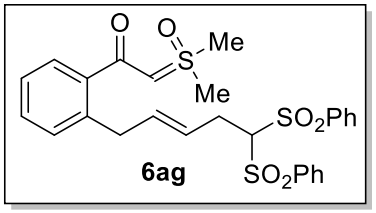
Diisopropyl (*E*)-2-(4-(2-(2-(dimethyl(oxo)-l6-sulfaneylidene)acetyl)phenyl)but-2-en-1-yl)malonate 6ac. Analytical TLC on silica gel, 8:2 ethyl acetate/hexane R_f = 0.32; yellow sticky liquid; yield 85% (50 mg); major diastereomer (*E*/*Z* > 21:1); ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.5 Hz, 1H), 7.28-7.25 (m, 1H), 7.20-7.14 (m, 2H), 5.69-5.64 (m, 1H), 5.42-5.37 (m, 1H), 5.06-5.01 (m, 2H), 3.63 (d, *J* = 7.0 Hz, 2H), 3.53 (s, 6H), 3.32 (t, *J* = 7.5 Hz, 1H), 2.71 (t, *J* = 7.0 Hz, 2H), 2.57 (t, *J* = 7.0 Hz, 0.09H, minor), 1.24-1.22 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 186.8, 168.8, 141.1, 138.2, 131.8, 129.8, 129.3, 127.6, 125.9, 125.5, 69.0, 52.4, 42.3, 31.1, 26.8, 21.8, 21.7; FT-IR (neat) 2971, 1720, 1574, 1442, 1258, 1144 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{33}O_6S$: 437.1992; Found 437.1992.



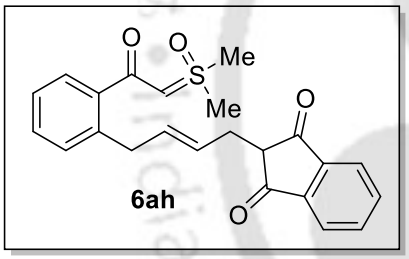
(*E*)-6-(2-(2-(dimethyl(oxo)-l6-sulfaneylidene)acetyl)phenyl) -2-(phenylsulfonyl)hex-4-enenitrile 6ae. Analytical TLC on silica gel, 9:1 ethyl acetate/hexane R_f = 0.35; brown sticky liquid; yield 83% (48 mg); major diastereomer (*E*/*Z* > 21:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.2 Hz, 2H), 7.76 (t, *J* = 7.2 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 2H), 7.38 (d, *J* = 7.2 Hz, 1H), 7.28-7.26 (m, 1H), 7.19-7.14 (m, 2H), 5.93-5.88 (m, 1H), 5.39-5.34 (m, 1H), 4.72 (s, 1H), 4.03-4.00 (m, 1H), 3.79-3.78 (m, 0.05H, minor), 3.70-3.67 (m, 1H), 3.54 (s, 4H), 3.45 (s, 3H), 2.90-2.88 (m, 1H), 2.58-2.52 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 187.1, 141.0, 136.9, 136.8, 135.6, 135.4, 130.4, 129.7, 129.4, 127.7, 126.3, 122.0, 114.2, 72.4, 57.7, 42.2, 42.0, 36.2, 30.2; FT-IR (neat) 3012, 1725, 1339, 1289, 1253, 1218, 1052 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{22}H_{24}NO_4S_2$: 430.1141; Found 430.1141.



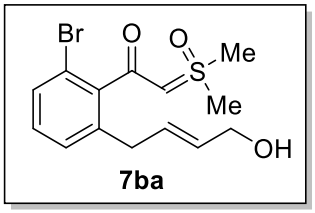
Ethyl (*E*)-2-benzoyl-6-(2-(2-(dimethyl(oxo)-l6-sulfaneylidene)acetyl)phenyl)hex-4-enoate 6af. Analytical TLC on silica gel, 8:2 ethyl acetate/hexane R_f = 0.35; brown sticky liquid; yield 87% (51 mg); major diastereomer (*E*/*Z* > 23:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.8 Hz, 2H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.40 (d, *J* = 7.2 Hz, 1H), 7.27 (d, *J* = 6.6 Hz, 1H), 7.20-7.17 (m, 2H), 5.71-5.67 (m, 1H), 5.47-5.43 (m, 1H), 4.67 (bs, 1H), 4.40 (t, *J* = 7.2 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.67 (s, 2H), 3.52 (d, *J* = 6.0 Hz, 6H), 2.92-2.83 (m, 2H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.1, 186.9, 169.7, 141.2, 138.2, 136.4, 133.7, 132.0, 129.8, 129.2, 128.9, 128.8, 127.5, 125.9, 125.7, 71.8, 61.6, 54.2, 42.3, 31.0, 27.2, 14.1; FT-IR (neat) 2987, 1723, 1673, 1323, 1272, 1221, 1210, 1053 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{25}H_{29}O_5S$: 441.1730; Found 441.1728.



(*E*)-1-(2-(5,5-bis(phenylsulfonyl)pent-2-en-1-yl)phenyl)-2-(dimethyl(oxo)-l6-sulfaneylidene)ethan-1-one 6ag. Analytical TLC on silica gel, 8:2 ethyl acetate/hexane R_f = 0.35; brown sticky liquid; yield 85% (60 mg); major diastereomer (*E*/*Z* > 23:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.5 Hz, 4H), 7.66 (t, *J* = 7.0 Hz, 2H), 7.52 (t, *J* = 7.5 Hz, 4H), 7.41 (d, *J* = 7.0 Hz, 1H), 7.30-7.28 (m, 1H), 7.22-7.19 (m, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 5.63-5.57 (m, 1H), 5.46-5.41 (m, 1H), 4.50 (t, *J* = 5.0 Hz, 1H), 3.53 (s, 8H), 2.85 (t, *J* = 5.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 186.9, 141.2, 137.8, 137.3, 134.8, 134.6, 130.3, 129.8, 129.3, 129.2, 127.7, 126.2, 124.6, 83.7, 72.3, 42.2, 36.2, 29.0; FT-IR (neat) 3010, 1723, 1673, 1340, 1290, 1253, 1220, 1067 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{27}H_{29}O_6S_3$: 545.1121; Found 545.1127.

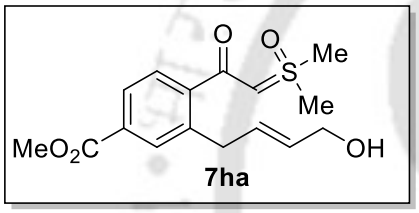


(*E*)-2-(4-(2-(2-(dimethyl(oxo)-l6-sulfaneylidene)acetyl)-phenyl)but-2-en-1-yl)-1H-indene-1,3(2H)-dione 6ah. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.35; brown sticky liquid; yield 79% (89 mg); major diastereomer (*E*/*Z* > 23:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.93 (m, 2H), 7.84-7.82 (m, 2H), 7.43-7.37 (m, 1H), 7.34-7.32 (m, 1H), 7.14-7.10 (m, 1H), 6.92-6.90 (m, 1H), 6.70-6.68 (m, 0.04H, minor), 5.74-5.67 (m, 1H), 5.38-5.30 (m, 1H), 4.58 (bs, 1H), 3.51 (s, 6H), 3.42 (d, *J* = 6.8 Hz, 2H), 3.06 (t, *J* = 5.6 Hz, 1H), 2.71 (t, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7, 186.8, 142.8, 140.9, 137.7, 135.8, 133.8, 130.9, 129.8, 129.1, 128.3, 127.5, 126.7, 125.8, 125.5, 123.2, 71.5, 53.8, 42.7, 42.4, 36.0, 30.0; FT-IR (neat) 2980, 1723, 1681, 1339, 1276, 1253, 1250, 1061 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{23}O_4S$: 351.1203; Found 351.1211.



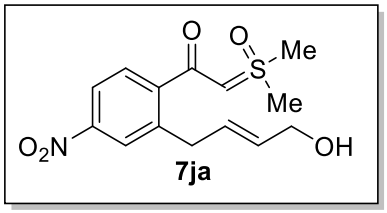
7ba

(*E*)-1-(2-bromo-6-(4-hydroxybut-2-en-1-yl)phenyl)-2-(dimethyl-(oxo)-l6-sulfaneylidene)ethan-1-one 7ba. Analytical TLC on silica gel, 9:1 ethyl acetate/hexane R_f = 0.35; yellow sticky liquid; yield 71% (45 mg); major diastereomer (*E*/*Z* > 19:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.6 Hz, 1H), 7.14-7.07 (m, 2H), 5.86-5.79 (m, 1H), 5.72-5.65 (m, 1H), 4.54 (s, 1H), 4.08 (d, *J* = 5.6 Hz, 2H), 3.58 (s, 0.20H, minor), 3.55 (s, 6H), 3.48 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.1, 142.8, 138.6, 131.3, 130.9, 130.6, 129.4, 128.6, 120.2, 72.9, 63.6, 42.3, 36.6; FT-IR (neat) 3020, 2920, 1732, 1549, 1382, 1162, 1094 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{14}H_{18}BrO_3S$: 345.0155; Found 345.0175.



7ha

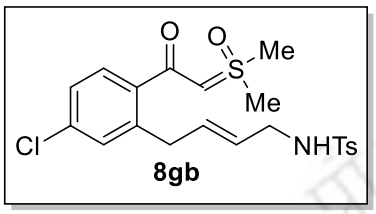
Methyl (*E*)-4-(2-(dimethyl(oxo)-l6-sulfaneylidene)acetyl)-3-(4-hydroxybut-2-en-1-yl)benzoate 7ha. Analytical TLC on silica gel, 9:1 ethyl acetate/hexane R_f = 0.35; brown sticky liquid; yield 66% (42 mg); major diastereomer (*E*/*Z* > 20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.85 (m, 2H), 7.44 (d, *J* = 8.4 Hz, 1H), 5.89-5.82 (m, 1H), 5.70-5.63 (m, 1H), 4.68 (bs, 1H), 4.21 (d, *J* = 6.0 Hz, 0.07H, minor), 4.09 (d, *J* = 6.0 Hz, 2H), 3.91 (s, 3H), 3.64 (d, *J* = 6.0 Hz, 2H), 3.53 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.8, 166.9, 145.4, 138.0, 131.6, 131.4, 130.7, 127.7, 127.5, 72.5, 64.4, 63.8, 52.3, 42.4, 41.1, 36.1; FT-IR (neat) 3015, 2903, 1725, 1567, 1370, 1162, 1093 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{21}O_5S$: 325.1104; Found 325.1105.



7ja

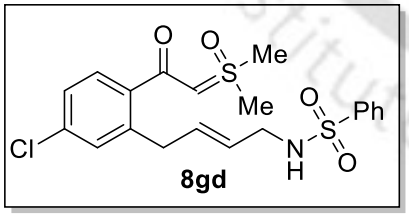
(*E*)-2-(dimethyl(oxo)-l6-sulfaneylidene)-1-(2-(4-hydroxy-but-2-en-1-yl)-4-nitrophenyl)ethan-1-one 7ja. Analytical TLC on silica gel, 9:1 ethyl acetate/hexane R_f = 0.35; brown sticky liquid; yield 63% (41 mg); major diastereomer (*E*/*Z* > 20:1); ^{1}H NMR (400

MHz, $CDCl_3$) δ 8.06-8.03 (m, 2H), 7.51 (d, *J* = 7.6 Hz, 1H), 5.88-5.81 (m, 1H), 5.74-5.67 (m, 1H), 4.69 (s, 1H), 4.12 (d, *J* = 5.6 Hz, 2H), 3.68 (d, *J* = 6.0 Hz, 2H), 3.56-3.55 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.2, 148.1, 147.1, 139.8, 131.6, 130.1, 128.5, 125.2, 121.4, 73.0, 63.5, 42.3, 36.0; FT-IR (neat) 3036, 2915, 1732, 1550, 1381, 1161, 1093 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{14}H_{18}NO_5S$: 312.0900; Found 312.0916.



8gb

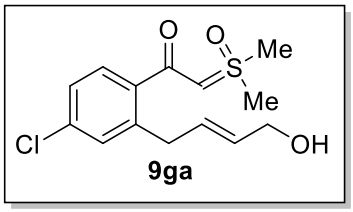
(*E*)-*N*-(4-(5-chloro-2-(2-(dimethyl(oxo)-l6-sulfaneylidene)-acetyl)phenyl)but-2-en-1-yl)-4-methylbenzenesulfonamide 8gb. Analytical TLC on silica gel, 8:2 ethyl acetate/hexane R_f = 0.32; brown sticky liquid; yield 61% (30 mg); major diastereomer (*E*/*Z* = 12:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74-7.68 (m, 2H, major + minor), 7.34 (d, *J* = 8.5 Hz, 0.2H, minor), 7.30 (d, *J* = 8.0 Hz, 1H), 7.26-7.25 (m, 2H, major + minor), 7.17-7.15 (m, 1H), 7.12-7.11 (m, 0.2H, minor), 7.08-7.07 (m, 1H, major), 5.73-5.67 (m, 1H, major), 5.35-5.29 (m, 1H, major), 5.05 (t, *J* = 5.5 Hz, 1H, major), 4.79 (bs, 1H, major), 3.61 (m, 0.51H, minor), 3.54-3.51 (m, 8H, major + minor), 3.45 (t, *J* = 6.0 Hz, 2H, major), 2.40 (s, 3H, major + minor); ^{13}C NMR (150 MHz, $CDCl_3$) δ 186.4, 143.5, 139.4, 137.1, 135.0, 133.0, 130.5, 129.8, 129.1, 128.5, 128.1, 127.2, 127.1, 126.3, 126.1, 73.2, 45.4, 42.1, 35.9, 21.6; FT-IR (neat) 3392, 2963, 1734, 1605, 1520, 1385, 1182 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{25}ClNO_4S_2$: 454.0908; Found 454.0912.



8gd

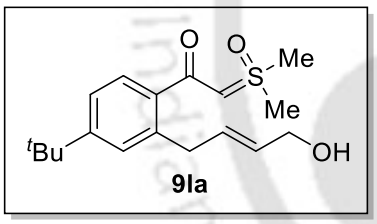
(*E*)-*N*-(4-(5-chloro-2-(2-(dimethyl(oxo)-l6-sulfaneylidene)-acetyl)phenyl)but-2-en-1-yl)benzenesulfonamide 8gd. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.35; brown sticky liquid; yield 72% (30 mg); major diastereomer (*E*/*Z* > 20:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.5 Hz, 2H), 7.90 (d, *J* = 7.5 Hz, 0.09H, minor), 7.55 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.18-7.15 (m, 2H), 7.04 (t, *J* = 5.5 Hz, 1H), 5.54-5.49 (m, 1H), 5.47-5.42 (m, 1H), 4.74 (bs, 1H), 3.58 (s, 6H), 3.56-3.51 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.8, 140.4, 140.3, 138.4, 135.5, 133.9, 132.6, 131.0, 130.0,

129.2, 127.2, 126.5, 123.7, 73.9, 43.1, 39.4, 32.3; FT-IR (neat) 3373, 2941, 1737, 1592, 1512, 1343, 1080 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{22}ClNO_4S_2$: 440.0752; Found 440.0754.



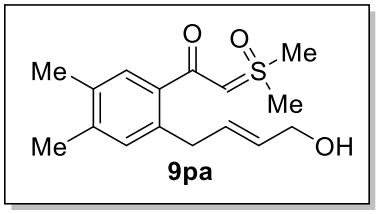
9ga

(*E*)-1-(4-chloro-2-(4-hydroxybut-2-en-1-yl)phenyl)-2-(dimethyl(oxo)-l6-sulfaneylidene)ethan-1-one 9ga. Analytical TLC on silica gel, 9:1 ethyl acetate/hexane R_f = 0.35; brown sticky liquid; yield 67% (46 mg); major diastereomer (*E*/*Z* > 20:1); ^1H NMR (600 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.8 Hz, 1H), 7.17-7.16 (m, 2H), 5.85-5.80 (m, 1H), 5.69-5.64 (m, 1H), 4.65 (bs, 1H), 4.19 (d, *J* = 7.2 Hz, 0.10H, minor), 4.10 (d, *J* = 6.0 Hz, 2H), 3.59 (d, *J* = 6.6 Hz, 2H), 3.51 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.8, 139.9, 139.5, 131.2, 130.8, 130.3, 129.1, 126.2, 72.1, 63.7, 42.4, 36.0; FT-IR (neat) 3010, 2920, 1731, 1539, 1383, 1154, 1087 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{14}H_{18}ClO_3S$: 301.0660; Found 301.0664.



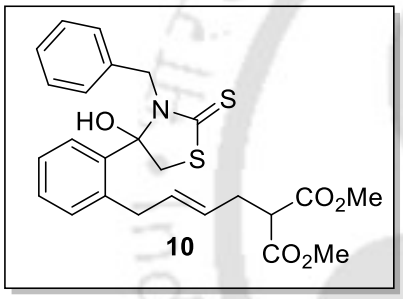
9la

(*E*)-1-(4-(*tert*-butyl)-2-(4-hydroxybut-2-en-1-yl)phenyl)-2-(dimethyl(oxo)-l6-sulfaneylidene)ethan-1-one 9la. Analytical TLC on silica gel, 9:1 ethyl acetate/hexane R_f = 0.35; brown sticky liquid; yield 74% (24 mg); major diastereomer (*E*/*Z* > 19:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.0 Hz, 1H), 7.22-7.18 (m, 2H), 5.90-5.83 (m, 1H), 5.69-5.64 (m, 1H), 4.67 (bs, 1H), 4.07 (d, *J* = 5.6 Hz, 2H), 3.63 (d, *J* = 6.0 Hz, 2H), 3.52 (s, 1H), 3.50 (s, 6H), 1.30 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.2, 141.8, 138.3, 137.4, 132.7, 129.8, 127.7, 127.6, 123.1, 71.4, 63.9, 42.4, 41.2, 36.7, 34.8, 31.4; FT-IR (neat) 3023, 2921, 1730, 1543, 1375, 1160, 1076 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{18}H_{27}O_3S$: 323.1675; Found 323.1690.



9pa

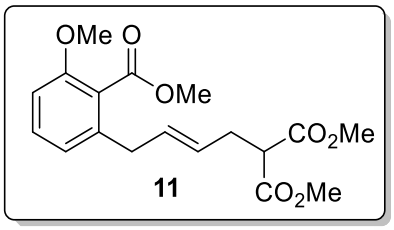
(*E*)-2-(dimethyl(oxo)-l6-sulfaneylidene)-1-(2-(4-hydroxybut-2-en-1-yl)-4,5-dimethylphenyl)ethan-1-one 9pa. Analytical TLC on silica gel, 9:1 ethyl acetate/hexane R_f = 0.35; brown sticky liquid; yield 72% (22 mg); major diastereomer (*E*/*Z* > 21:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (s, 1H), 6.94 (s, 1H), 5.88-5.81 (m, 1H), 5.67-5.61 (m, 1H), 4.66 (bs, 1H), 4.06 (d, *J* = 5.6 Hz, 2H), 3.55 (d, *J* = 6.4 Hz, 2H), 3.51 (s, 6H), 2.22 (d, *J* = 4.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.2, 138.5, 138.0, 135.0, 134.3, 132.8, 131.8, 129.7, 129.1, 71.5, 64.4, 63.9, 42.4, 35.9, 19.7, 19.3; FT-IR (neat) 3054, 2923, 1718, 1539, 1389, 1140, 1091 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{23}O_3S$: 295.1362; Found 295.1382.



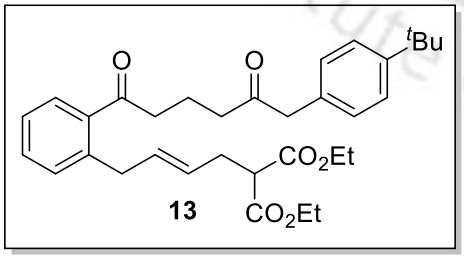
10

Dimethyl (*E*)-2-(4-(2-(3-benzyl-4-hydroxy-2-thioxothiazolidin-4-yl)phenyl)but-2-en-1-yl)malonate 10. Analytical TLC on silica gel, 2:8 ethyl acetate/hexane R_f = 0.30; colorless sticky liquid; yield 57% (19 mg); major diastereomer (*E*/*Z* = 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.6 Hz, 1H, major + minor), 7.68 (bs, 1H, major + minor), 7.45 (t, *J* = 7.2 Hz, 1H, major + minor), 7.37-7.30 (m, 7H, major + minor), 7.22 (s, 1H, major + minor), 5.66-5.60 (m, 1H, major + minor), 5.44-5.38 (m, 2H, major + minor), 4.90 (d, *J* = 5.2 Hz, 1H, major + minor), 4.67 (s, 1H, major + minor), 4.27 (d, *J* = 14.4 Hz, 1H, major + minor), 3.74 (s, 1H, minor), 3.72-3.69 (m, 6H, major), 3.66-3.62 (m, 2H, major + minor), 3.45-3.42 (m, 1H, major + minor), 2.74 (t, *J* = 7.6 Hz, 2H, major + minor); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5 (major), 196.09 (minor), 169.6 (major), 169.5 (minor), 141.2 (major + minor), 136.6 (major), 136.4 (minor), 136.0 (major + minor), 132.3 (major + minor), 131.3 (major + minor), 131.0 (major + minor), 130.0 (major + minor), 129.1 (major + minor), 128.9 (major + minor), 128.7 (major + minor), 128.5 (major + minor), 128.3 (major + minor), 126.7 (major + minor), 126.3 (major + minor), 126.0 (major + minor), 52.8 (major + minor), 52.7 (major + minor), 51.8 (minor), 51.7

(major), 51.5 (major + minor), 45.2 (major + minor), 31.6 (major + minor), 27.1(minor), 27.0 (major); FT-IR (neat) 3015, 2936, 1750, 1532, 1361, 1156, 1182 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{25}H_{27}NO_5S_2Na$: 508.1223; Found 508.1222.

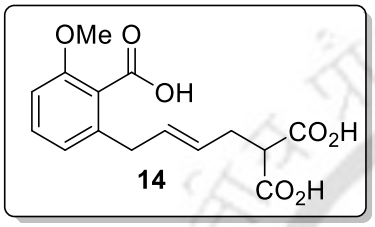


Dimethyl (*E*)-2-(4-(3-methoxy-2-(methoxycarbonyl)-phenyl)but-2-en-1-yl)malonate 11. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.25; colorless sticky liquid; yield 82% (40 mg); major diastereomer (*E*/*Z* = 8:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 (m, 1H, major + minor), 6.79-6.76 (m, 2H, major + minor), 5.66-5.59 (m, 1H, major + minor), 5.48-5.41 (m, 1H, major + minor), 3.90 (s, 0.4H, minor) 3.89 (s, 3H, major), 3.81 (s, 3H, major + minor), 3.74 (s, 0.8H, minor), 3.71 (s, 6H, major), 3.42 (t, *J* = 7.6 Hz, 1H, major + minor), 3.36 (d, *J* = 7.2 Hz, 0.35H, minor), 3.26 (d, *J* = 6.8 Hz, 2H, major), 2.73 (t, *J* = 7.2 Hz, 0.39H, minor), 2.60 (t, *J* = 7.2 Hz, 2H, major); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5 (major + minor), 168.7 (major + minor), 156.6 (major + minor), 139.1(minor), 138.9 (major), 131.5 (major), 130.72 (minor), 130.67 (minor), 130.62 (major) 127.4 (major), 126.0 (minor), 123.5 (major + minor), 121.6 (major), 121.5 (major + minor), 109.1(major + minor), 56.1 (major + minor), 52.7 (minor), 52.6 (major), 52.4 (minor), 52.3 (major), 51.9 (major), 51.7 (minor), 36.5 (major), 31.9 (major), 31.2 (minor), 26.9 (minor); FT-IR (neat) 2979, 2932, 1715, 1600, 1575, 1454, 1432, 1259, 1102 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{18}H_{22}O_7Na$: 373.1258; Found 373.1258.

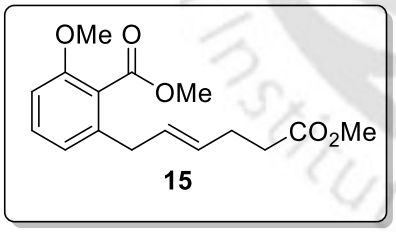


Diethyl (*E*)-2-(4-(2-(6-(4-(*tert*-butyl)phenyl)-5-oxohexanoyl)phenyl)but-2-en-1-yl)malonate 13. Analytical TLC on silica gel, 2:8 ethyl acetate/hexane R_f = 0.30; colorless sticky liquid; yield 81% (26 mg); major diastereomer (*E*/*Z* > 21:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.6 Hz, 1H), 7.40-7.32 (m, 3H), 7.27 (s, 1H),

7.24-7.22 (m, 1H), 7.12 (d, J = 8.4 Hz, 2H), 5.61-5.54 (m, 1H), 5.44-5.38 (m, 1H), 4.20 (q, J = 7.2 Hz, 4H), 3.66 (s, 2H), 3.60 (d, J = 7.2 Hz, 2H), 3.40 (t, J = 7.6 Hz, 1H), 2.86 (t, J = 7.2 Hz, 2H), 2.75 (t, J = 7.6 Hz, 2H), 2.58 (t, J = 7.2 Hz, 2H), 1.99-1.92 (m, 2H), 1.30 (s, 9H), 1.26 (t, J = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.3, 204.2, 169.2, 150.0, 140.3, 138.2, 131.5, 131.4, 131.2, 131.0, 129.2, 128.5, 126.2, 125.9, 125.8, 61.6, 52.1, 49.8, 41.0, 40.7, 34.6, 31.7, 31.5, 26.9, 18.4, 14.2; FT-IR (neat) 3070, 1738, 1671, 1599, 1437, 1166, 1085 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{33}H_{42}O_6Na$: 557.2874; Found 557.2874.

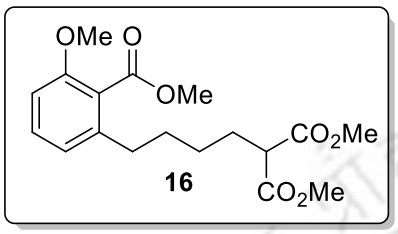


(*E*)-2-(4-(2-carboxy-3-methoxyphenyl)but-2-en-1-yl)malonic acid 14. Analytical TLC on silica gel, 1:9 methanol/ethyl acetate R_f = 0.22; colorless solid; mp 115-116 °C; yield 80% (35 mg); major diastereomer (E/Z > 20:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.27 (t, J = 8.0 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 6.76 (d, J = 7.6 Hz, 1H), 5.58-5.51 (m, 1H), 5.48-5.40 (m, 1H), 3.73 (s, 3H), 3.25-3.23 (m, 1H), 3.19 (d, J = 6.4 Hz, 2H), 2.39 (t, J = 6.8 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.9, 169.2, 155.7, 137.7, 130.4, 130.3, 128.5, 125.0, 121.4, 109.5, 56.0, 51.9, 35.9, 31.7; FT-IR (neat) 3476, 3006, 1731, 1665, 1603, 1435, 1338, 1286 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{15}H_{16}O_7Na$: 331.0788; Found 331.0790.



Methyl (*E*)-2-methoxy-6-(6-methoxy-6-oxohex-2-en-1-yl)-benzoate 15. Analytical TLC on silica gel, 2:8 ethyl acetate /hexane R_f = 0.30; colorless sticky liquid; yield 85% (17 mg); major diastereomer (E/Z > 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 (m, 1H, major + minor), 6.82-6.77 (m, 2H, major + minor), 5.60-5.44 (m, 2H, major + minor), 3.90-3.89 (m, 3H, major + minor), 3.82 (bs, 3H, major + minor), 3.67-3.65 (m, 3H, major + minor), 3.38 (d, J = 6.8 Hz, 0.31H, minor) 3.28 (d, J = 6.4 Hz, 2H, major), 2.45-2.30 (m, 5H, major + minor); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.7 (major), 173.6 (minor), 168.83 (minor), 168.76 (major), 156.6 (major + minor), 139.4 (minor), 139.3 (major), 130.7 (minor), 130.6 (major), 130.2

(major), 129.3 (major), 129.0 (minor), 128.8 (minor), 123.5 (major + minor), 121.7 (major), 121.5 (minor), 109.0 (major + minor), 56.08 (minor), 56.06 (major), 52.4 (minor), 52.3 (major), 51.73 (minor), 51.67(major), 36.6 (major), 34.0 (minor), 33.9 (major), 31.1 (minor), 27.9 (major), 22.9 (minor); FT-IR (neat) 1728, 1725, 1612, 1439, 1357, 1280 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{16}H_{21}O_5Na$: 315.1203; Found 315.1203.



Dimethyl 2-(4-(3-methoxy-2-(methoxycarbonyl)-phenyl)-butyl)malonate 16. Analytical TLC on silica gel, 2:8 ethyl acetate /hexane R_f = 0.32; colorless sticky liquid; yield 90% (15 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.24 (m, 1H), 6.80-6.75 (m, 2H), 3.90 (s, 3H), 3.81 (s, 3H), 3.73 (s, 6H), 3.37-3.31 (m, 1H), 2.56-2.52 (m, 2H), 1.94-1.88 (m, 2H), 1.65-1.59 (m, 2H), 1.38-1.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 169.0, 156.5, 140.8, 130.5, 123.7, 121.6, 108.7, 56.0, 52.6, 52.3, 51.7, 33.2, 30.7, 28.7, 27.2; FT-IR (neat) 1732, 1722, 1665, 1555, 1338, 956 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{18}H_{24}O_7Na$: 375.1414; Found 375.1419.

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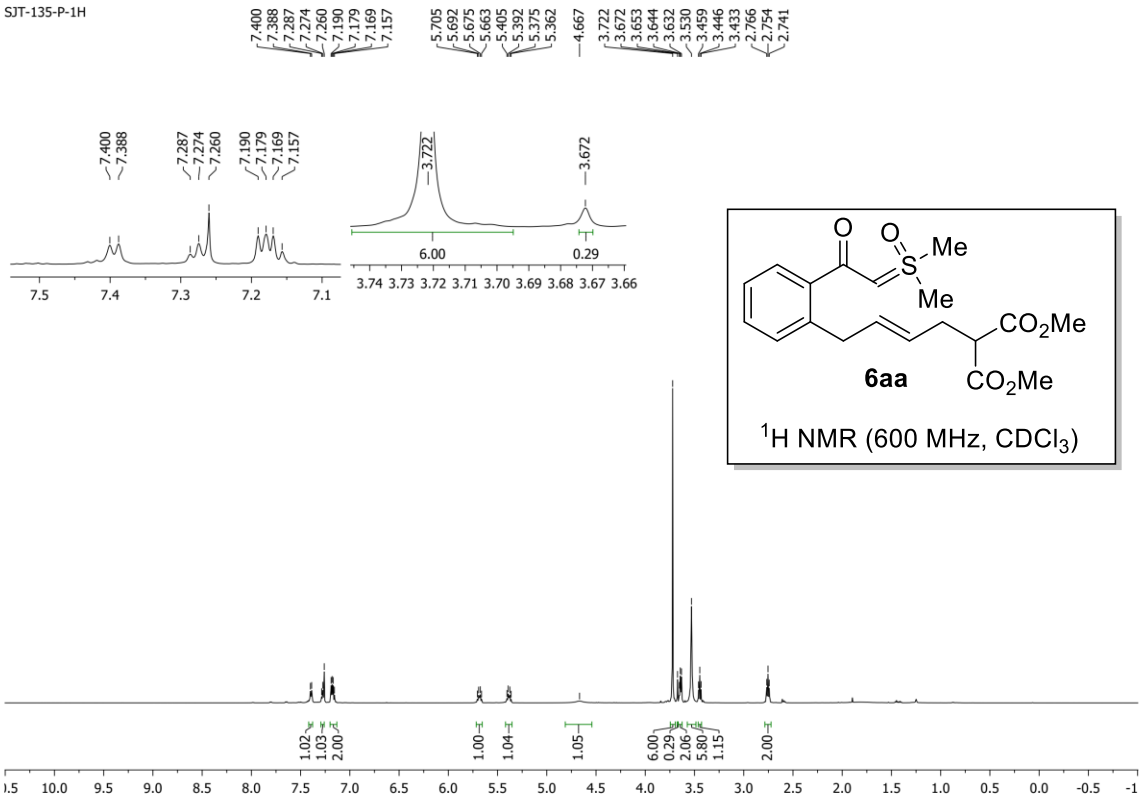
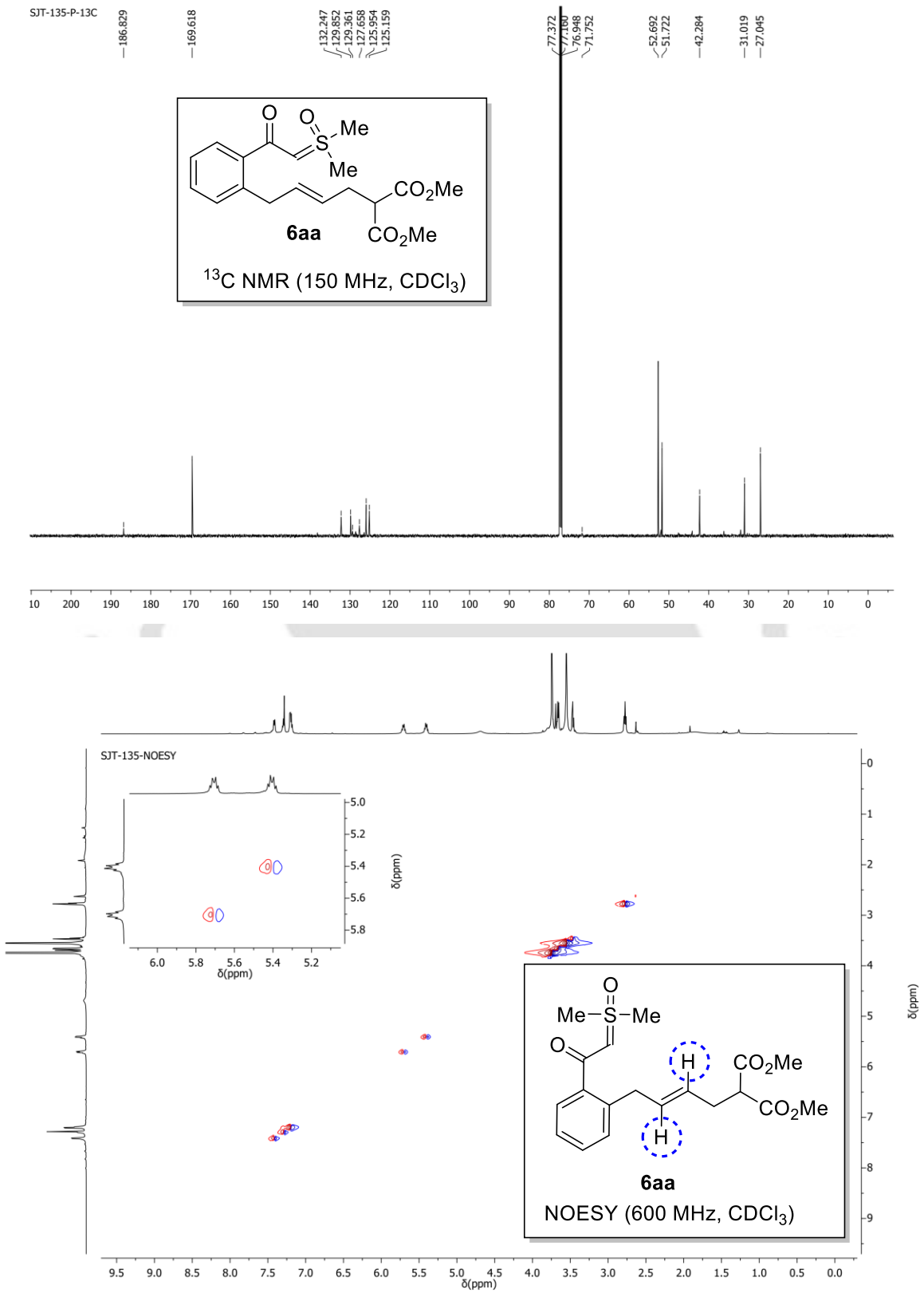
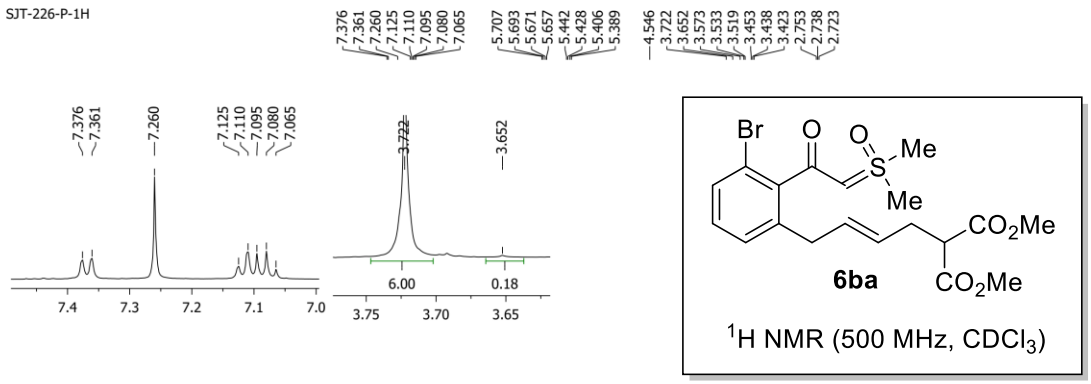
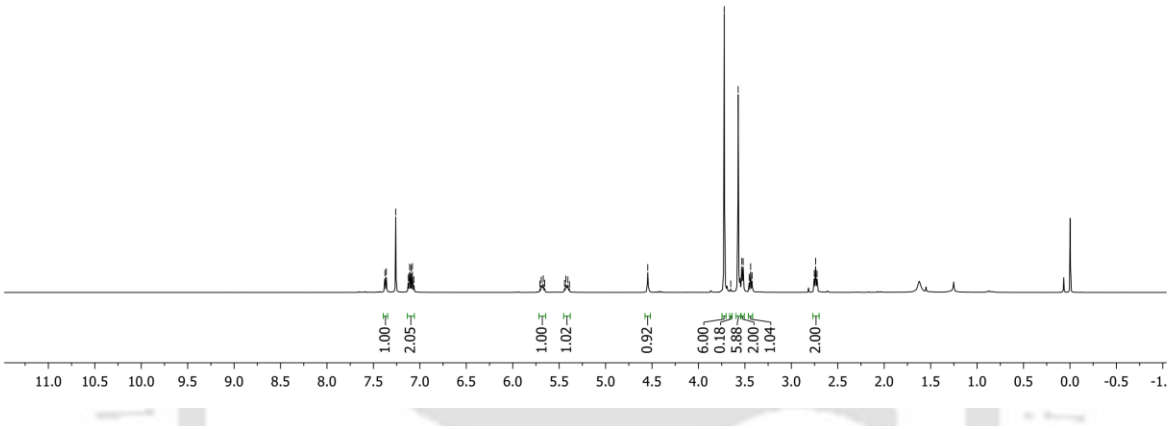
2.6 Selected NMR Spectra and HPLC Chromatogram

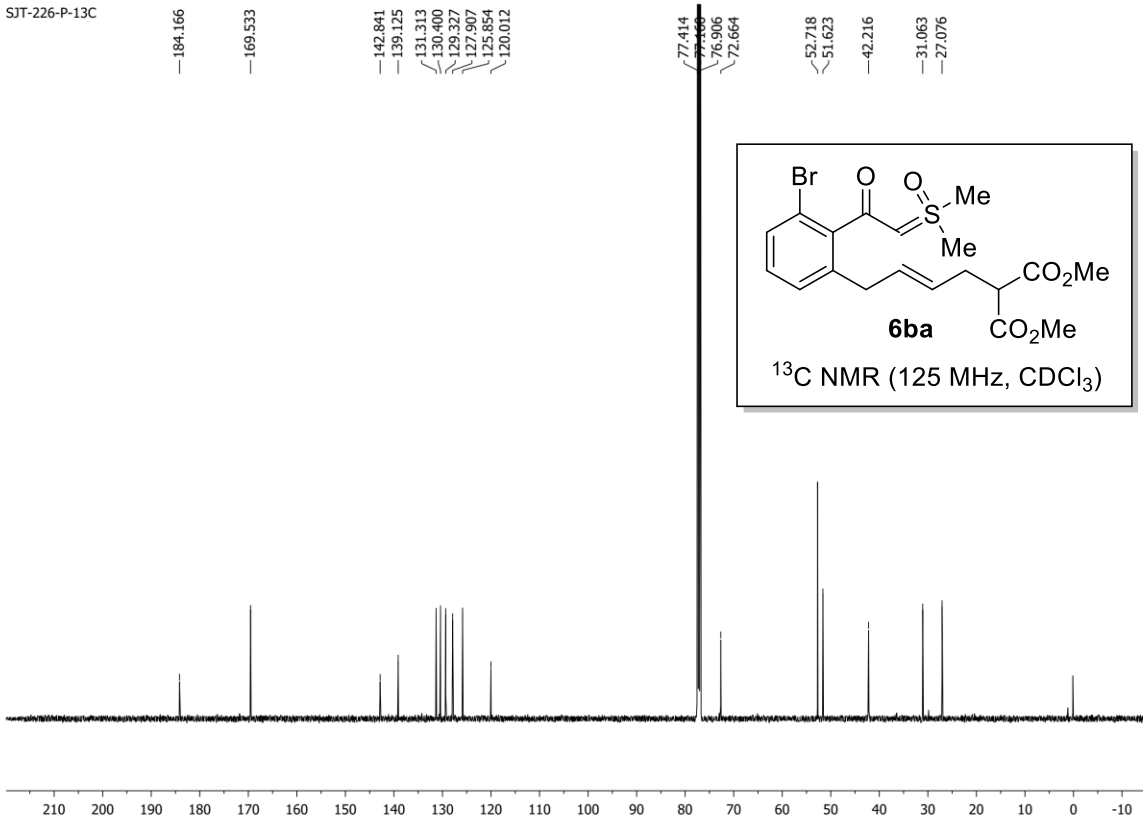




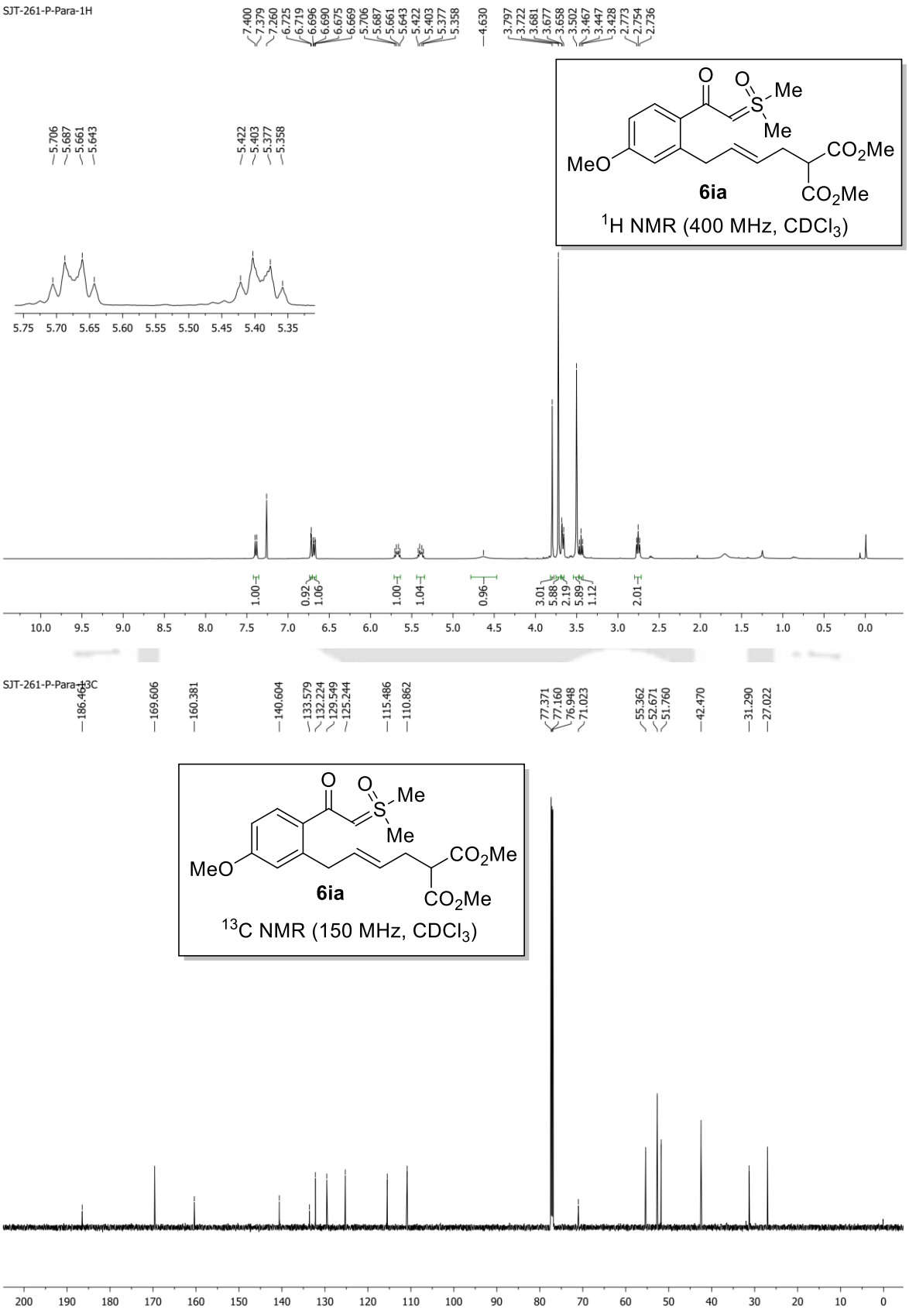


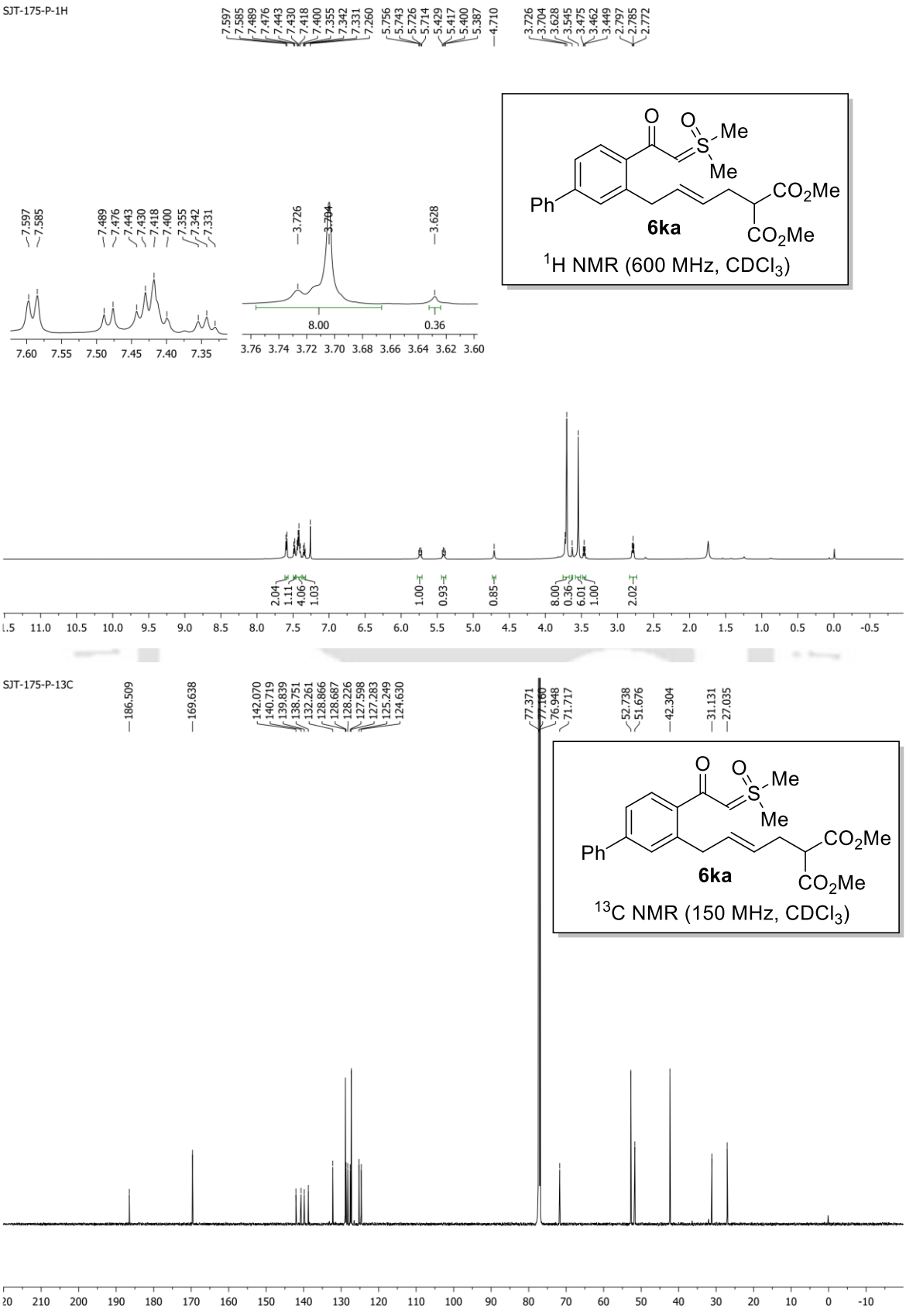
^{1}H NMR (500 MHz, $CDCl_3$)

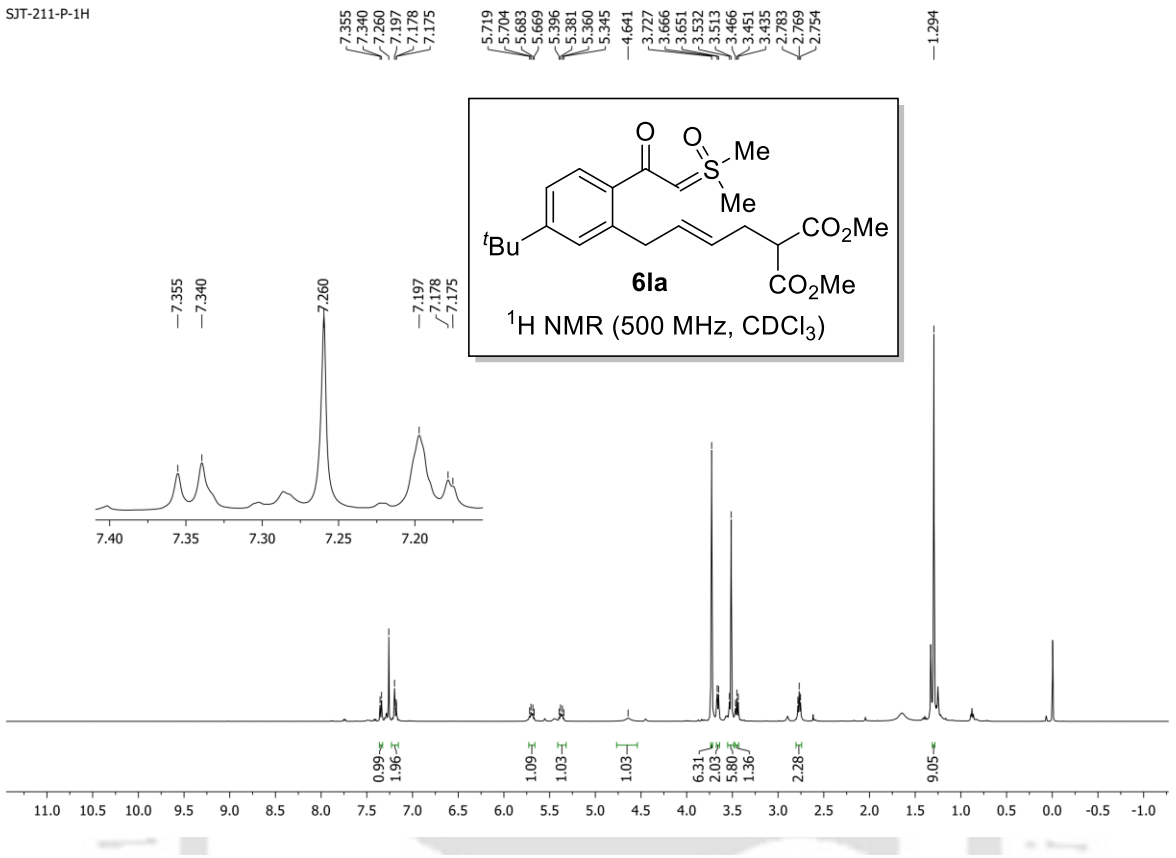


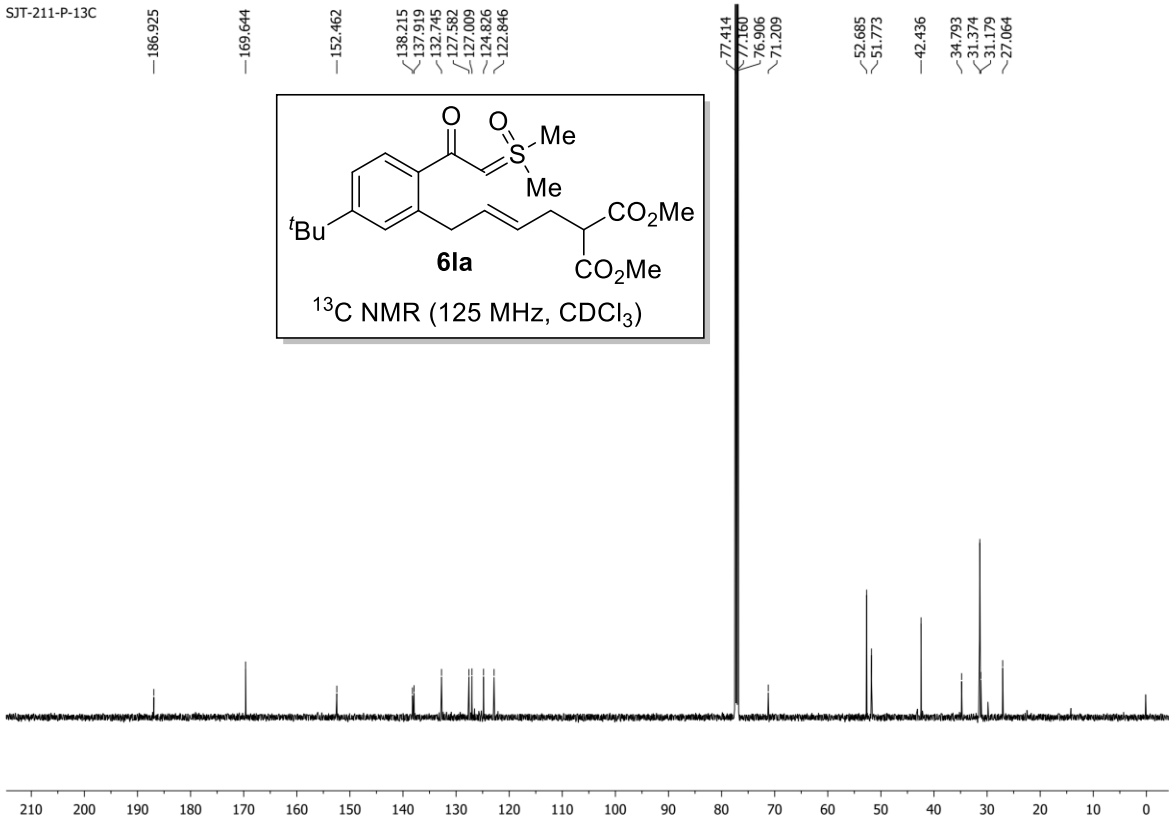


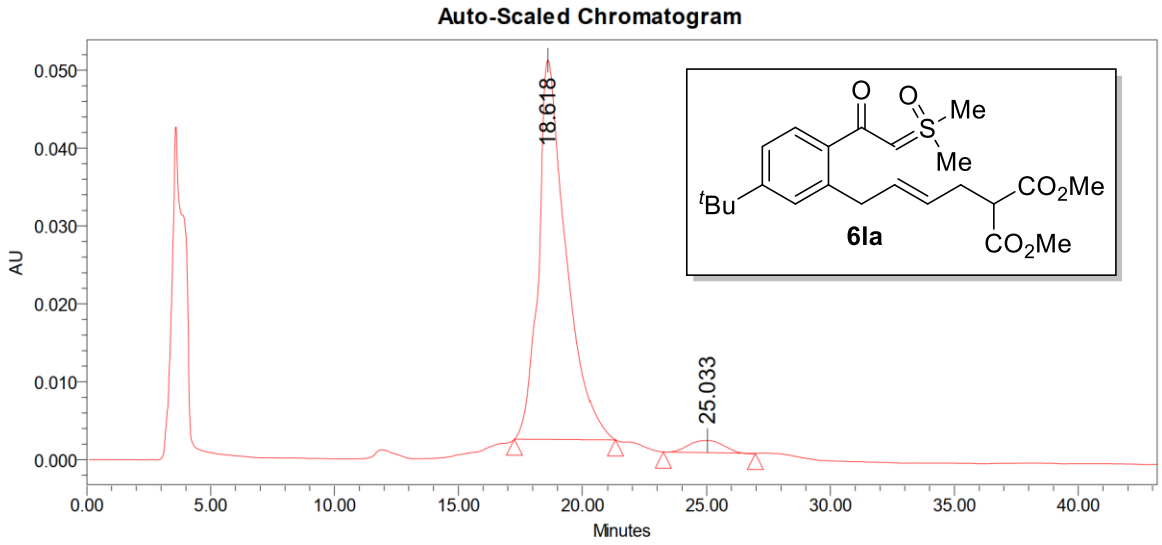
^{13}C NMR (125 MHz, $CDCl_3$)





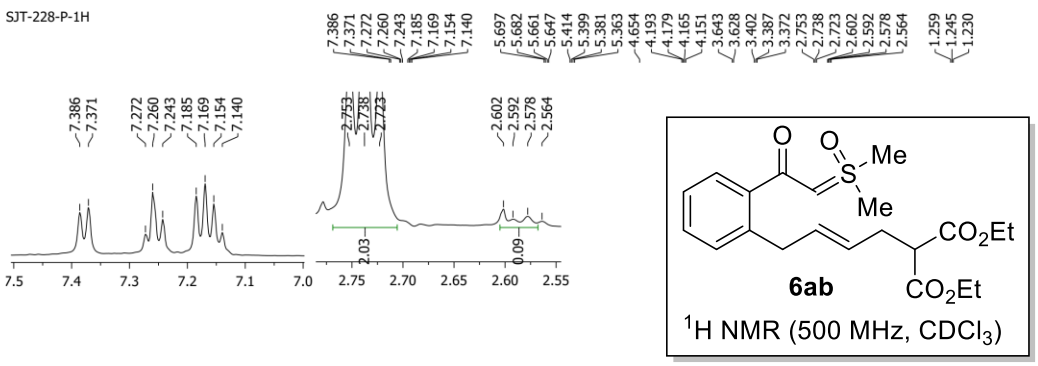


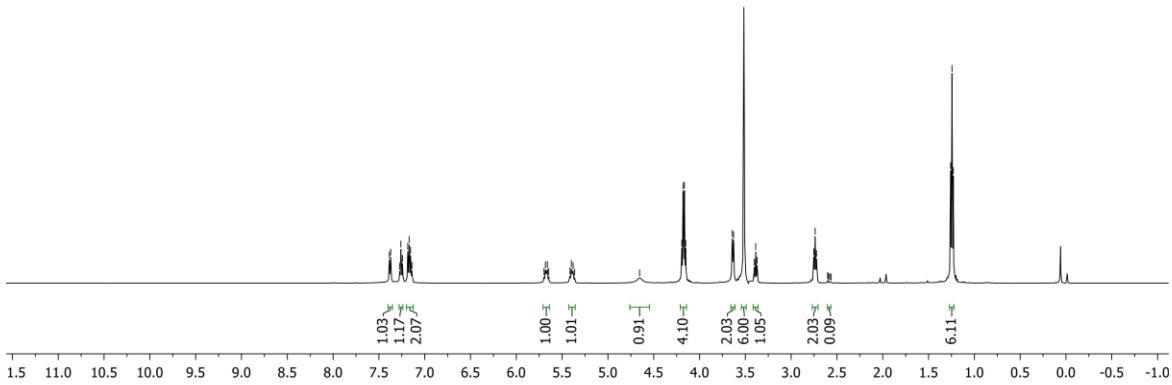


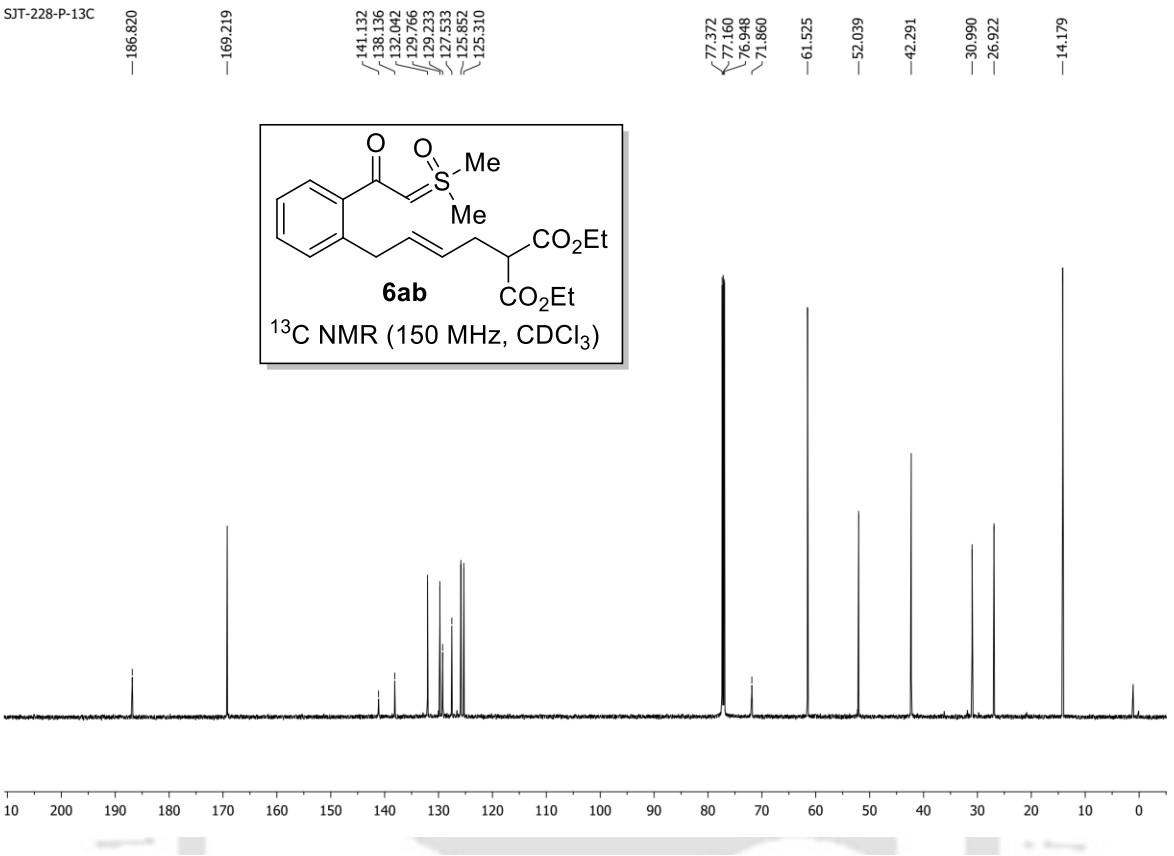


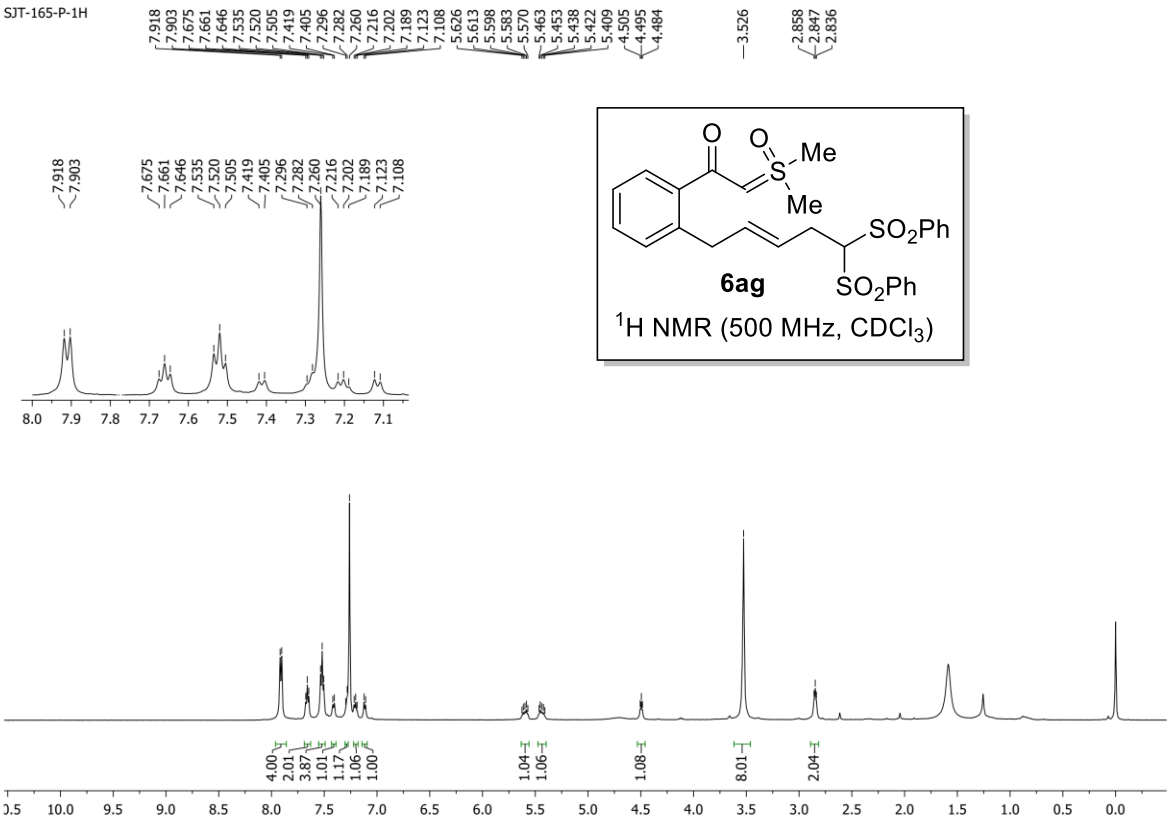
Peak Results

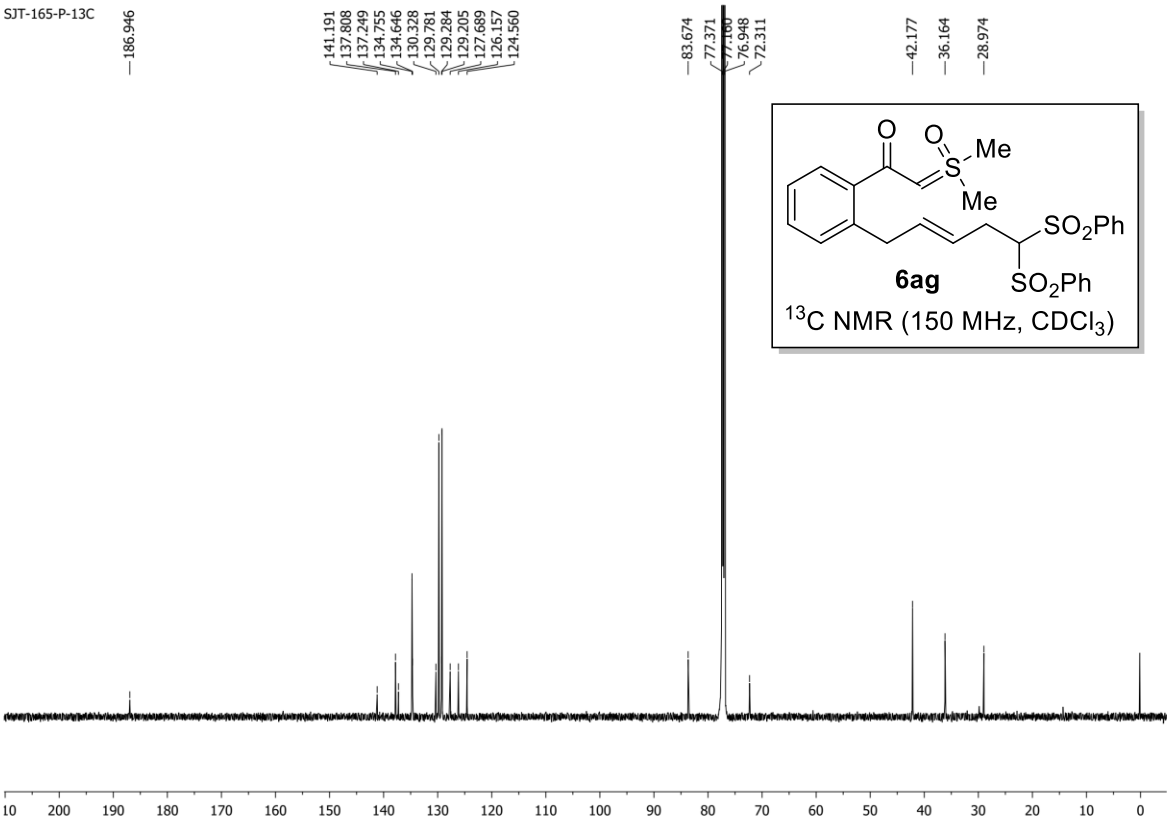
	Start Time (min)	End Time (min)	RT	Height (μV)	% Area
1	17.267	21.317	18.618	48679	96.13
2	23.250	26.967	25.033	1558	3.87

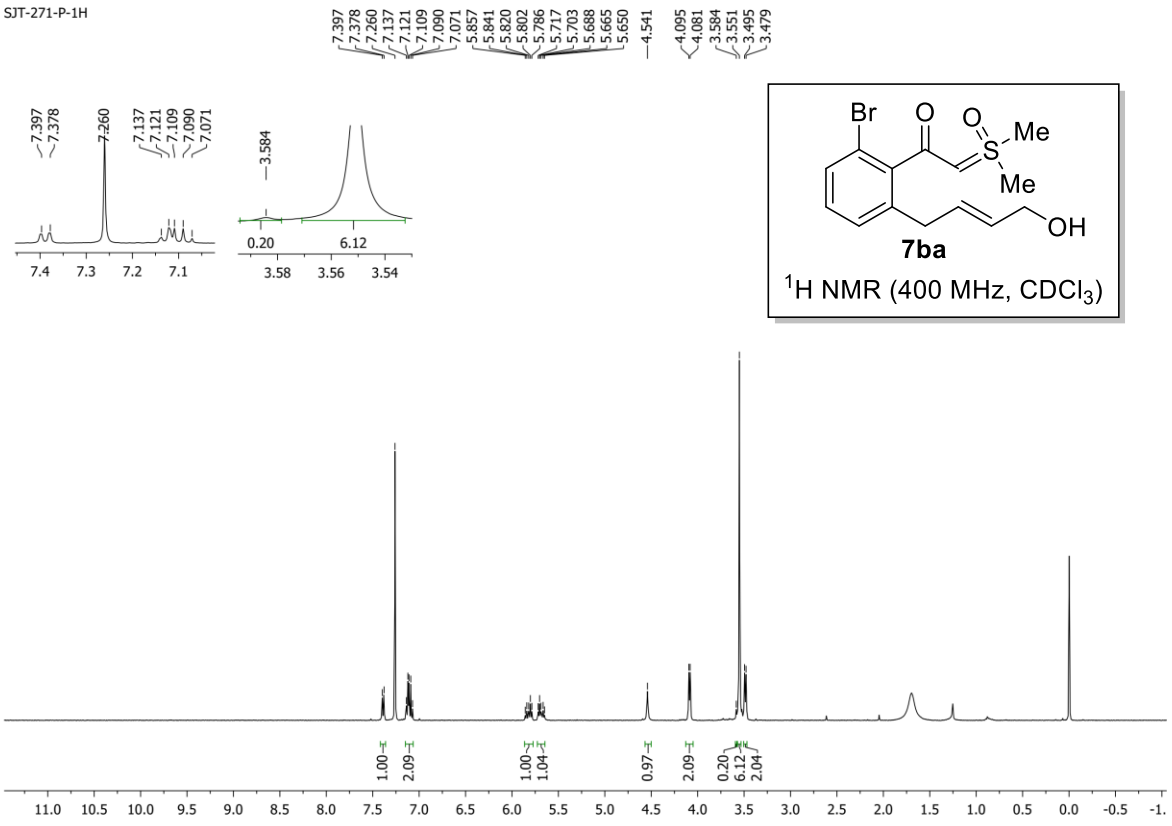


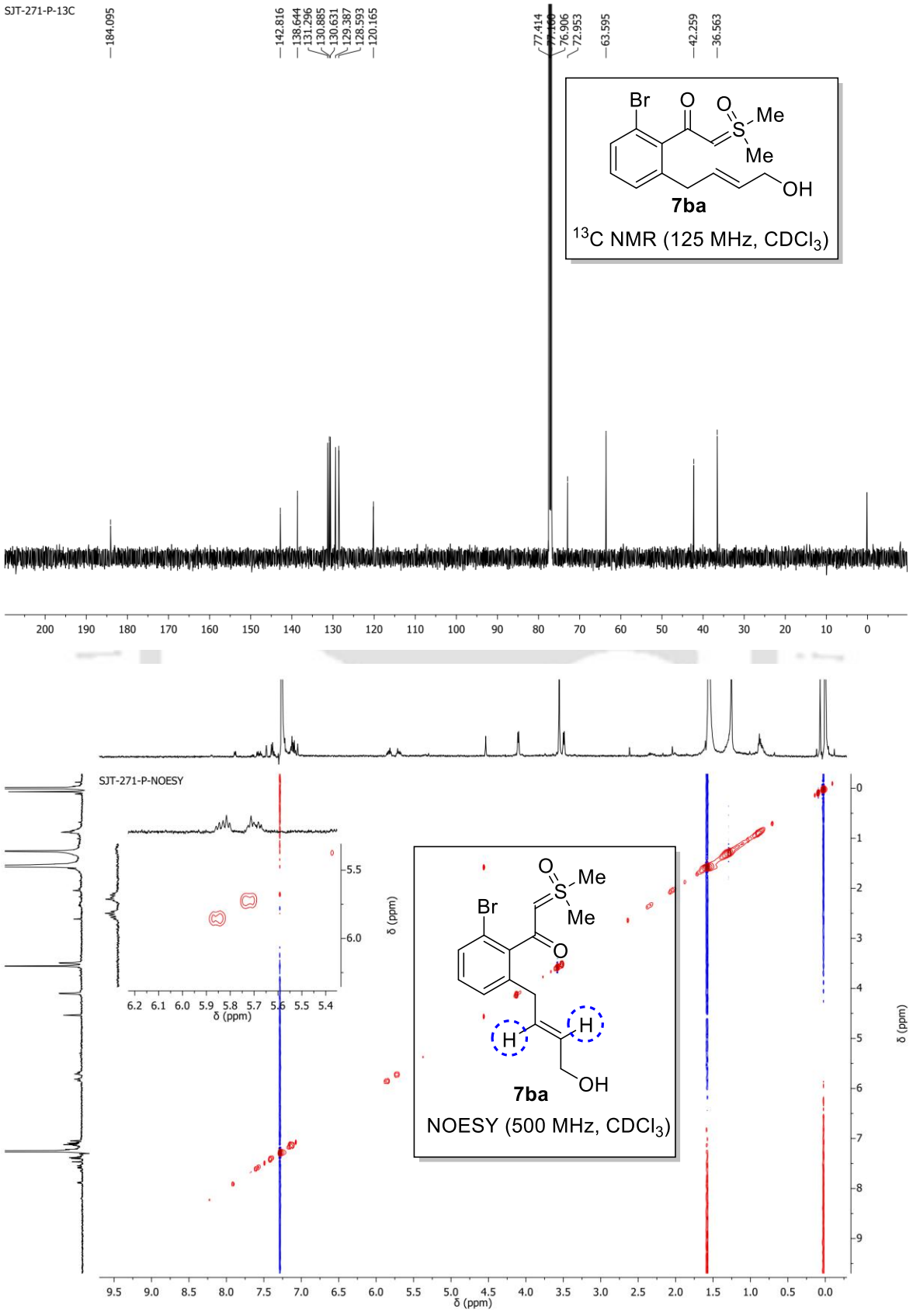


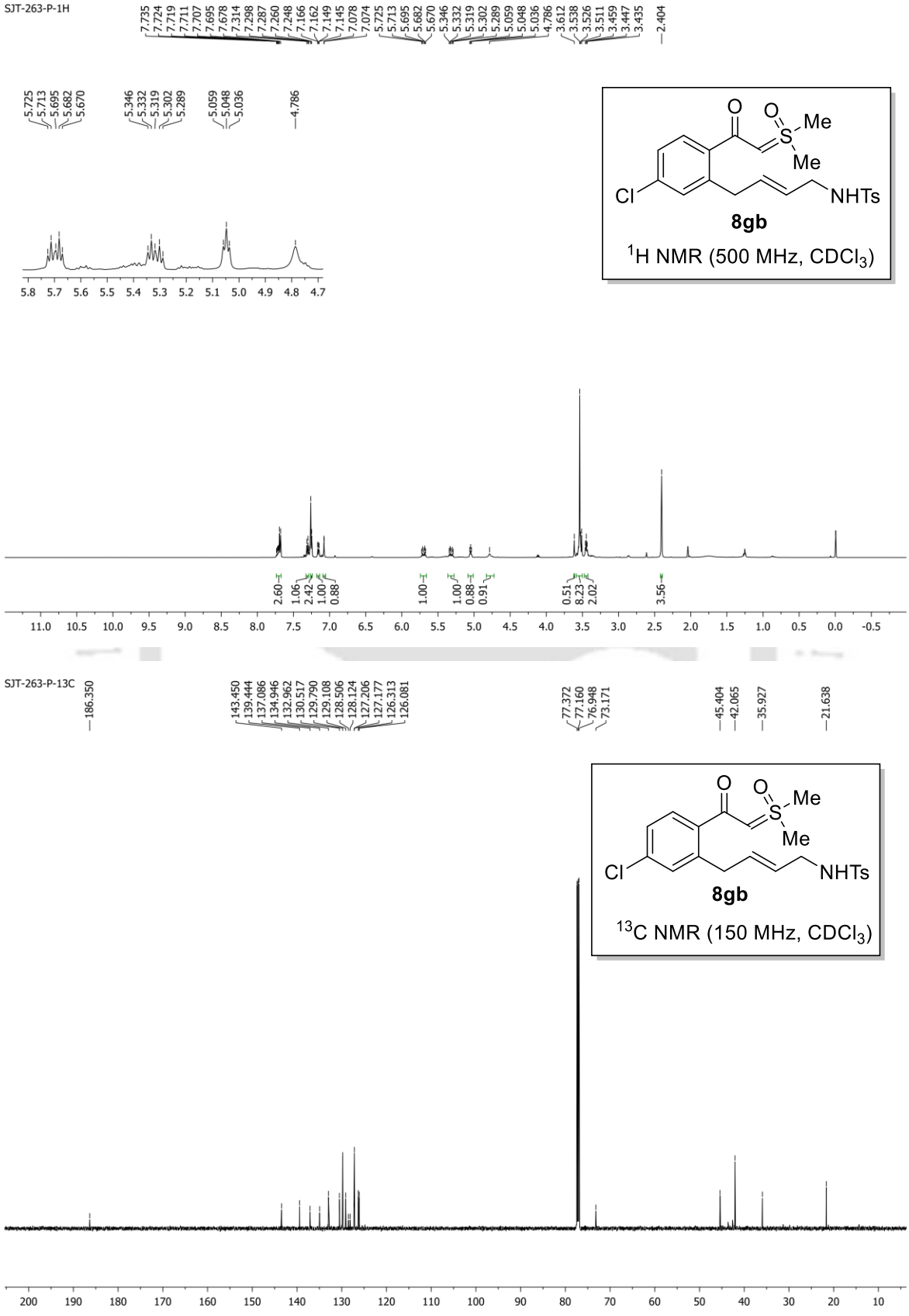


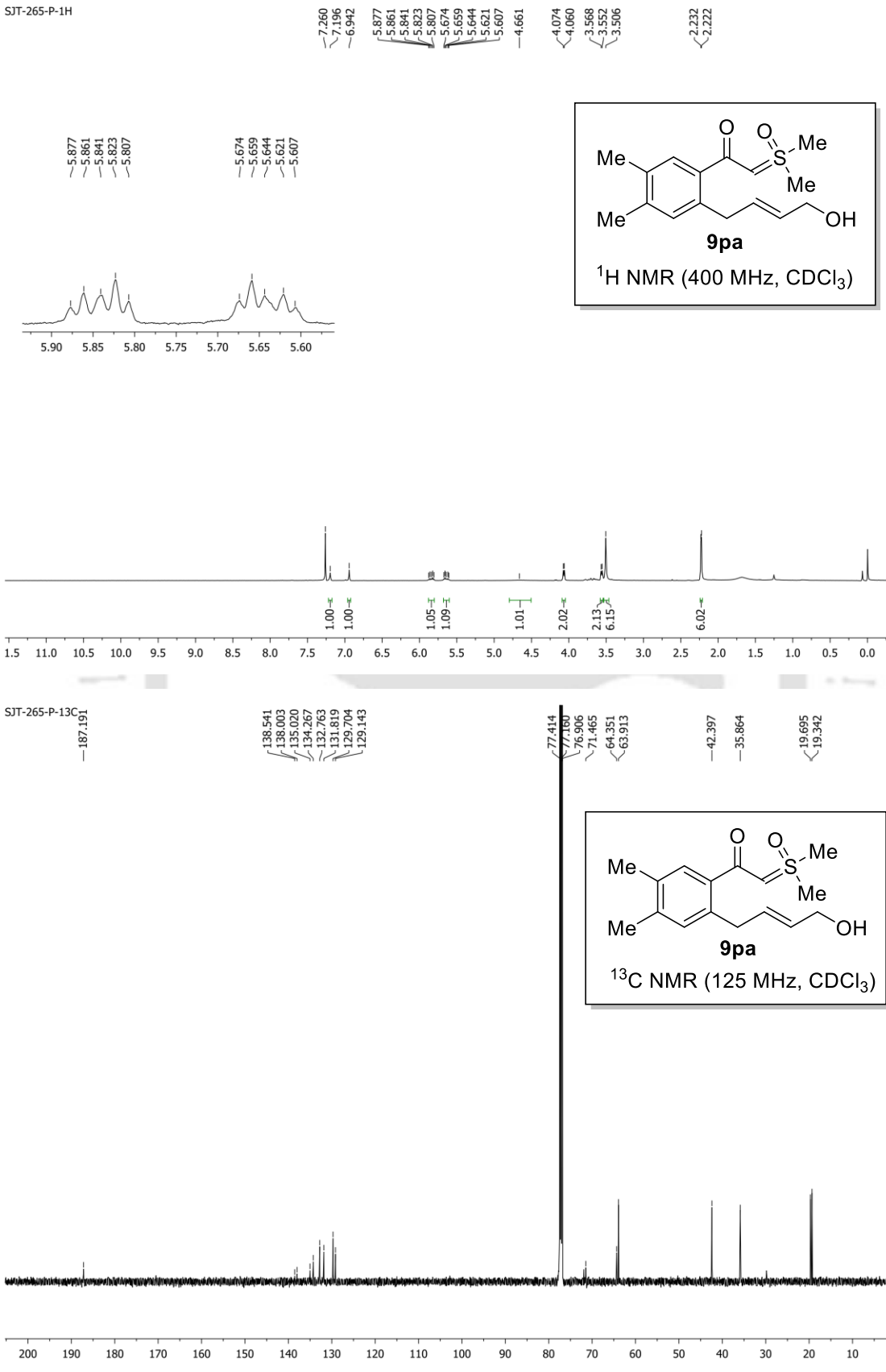






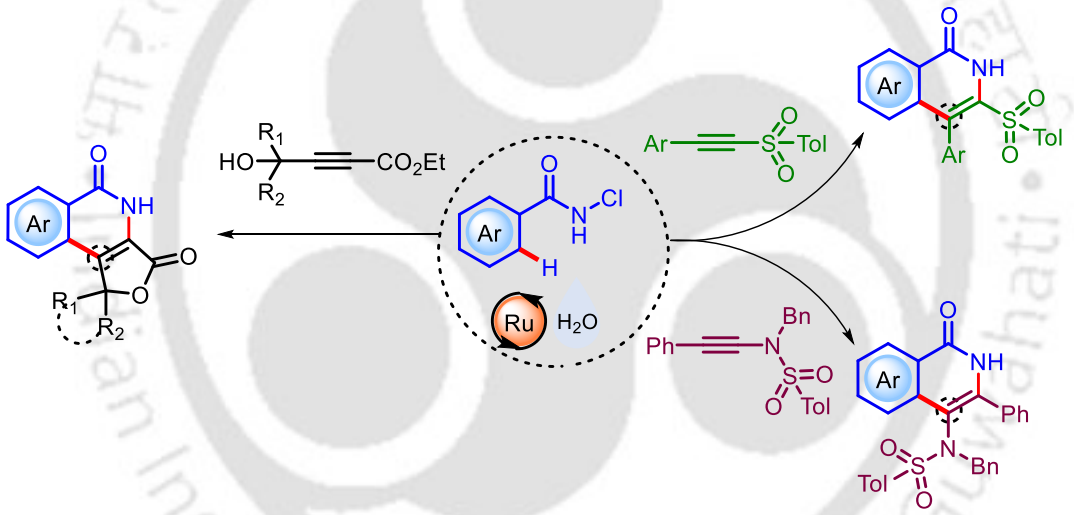






Chapter 3

Ru-Catalyzed C-H Annulation of N-Chlorobenzamides with Unsymmetrical Alkynes



♠ Unique regioselectivity ♠ Mild reaction condition ♠ Green solvent ♠ Versatile heteroatom handler

J. Org. Chem. **2024**, *89*, 16850.

Ru-Catalyzed C-H Annulation of *N*-Chlorobenzamides with Unsymmetrical Alkynes

Transition-metal-catalyzed directed C–H functionalization has evolved into effective strategy for the site-selective construction of C–C and C–heteroatom bond formation from simple arenes.[1] In this context, benzamide-type auxiliaries have played a crucial role, enabling annulation with unsaturated coupling partners to construct nitrogen-containing heterocyclic architectures, including isoquinolones and other heterocyclic motifs that are widely embedded in natural products and bioactive molecules.[2] Nevertheless, most of these oxidative annulations rely on external stoichiometric oxidants and often require an extra step for removal of the DG, which compromises step economy and generates substantial waste. To address these limitations, oxidizing DGs such as *N*-chlorobenzamides have emerged as attractive alternatives that merge coordination control with internal oxidation. In recent times, *N*-chlorobenzamides have been leveraged in Co-catalysis to enable room-temperature C–H activation/annulation with alkynes to access cobaltacycles followed by isoquinolones with mechanistic insight.[3] Despite these advances, a general strategy that combines oxidizing DGs with environmentally benign media, such as water, remains underdeveloped, even though aqueous C–H functionalization is highly desirable from the perspective of safety, abundance and simplified product isolation.[4] In particular, isoquinolone cores serve as privileged scaffolds in medicinal chemistry and functional materials.[5] Moreover, transition-metal-catalyzed oxidative annulations with symmetric internal alkynes are well established.[6-10] However, unsymmetrical and heteroatom-functionalized alkynes pose persistent challenges in terms of regioselectivity, compatibility and downstream diversification. Recent studies show that, 4-hydroxy-2-alkynoates and related heteroatom-functionalized unsymmetrical alkynes are particularly appealing as coupling partners because they can participate in cascade C–H activation/annulation/lactonization sequences, giving access to furanone-fused and N,O-bridged frameworks in a single operation, but often at elevated temperatures and in the presence of stoichiometric metal oxidants.[9] Moreover, these protocols rely on bidentate auxiliaries such as 8-aminoquinoline or on *N*-alkoxycarboxamides in few cases, which either require additional steps for auxiliary removal or limit the functional group tolerance on the amide backbone. In addition, these strategies still largely rely on organic solvents and in many cases, on external silver or copper

oxidants, which detract from their sustainability profile. Against this backdrop, the development of annulation of *N*-chlorobenzamides with heteroatom-functionalized unsymmetrical alkynes in water as the reaction medium would be valuable. Such transformations would unite (i) oxidizing DG control (*N*-Cl as DG/internal oxidant), (ii) regioselective C–H activation with challenging unsymmetrical alkynes and (iii) in situ lactonization to deliver furanone-fused and heteroatom-rich isoquinolone frameworks in a single step under oxidant-free aqueous conditions. The resulting densely functionalized isoquinolones and their embedded DGs could be manipulated through subsequent C–H activation, cross-coupling or heterocycle-forming reactions, thereby providing a versatile entry to structurally complex *N*-heterocycles of potential relevance in medicinal chemistry and materials science.

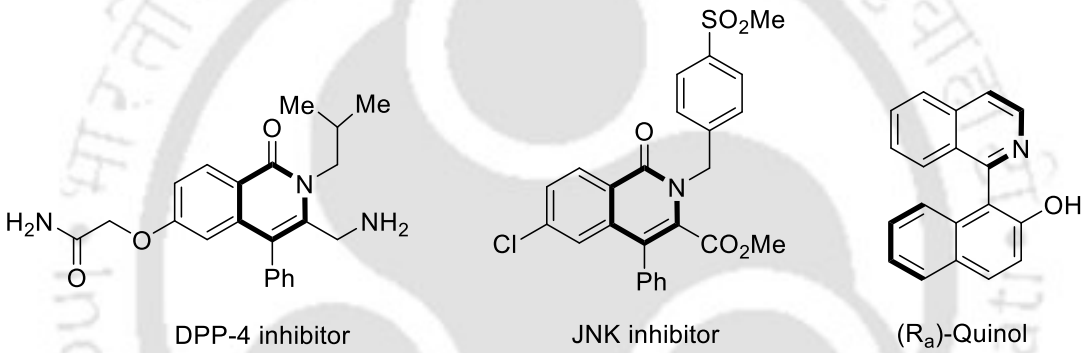
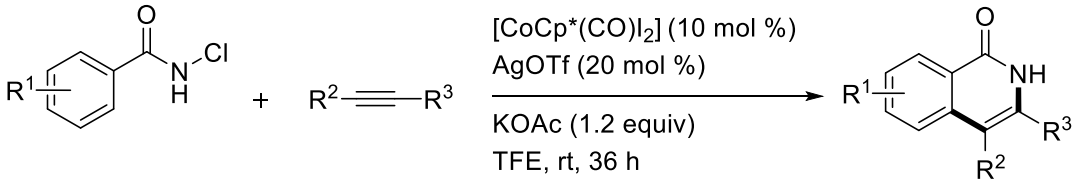


Figure 1. Biologically Important Isoquinolones and Isoquinolines

3.1 Literature

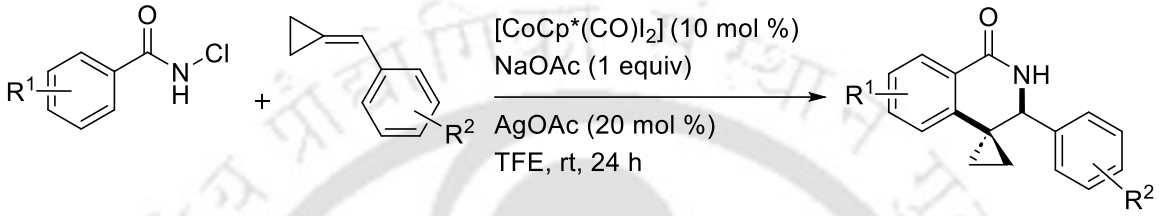
3.1.1 Benzamide Directed C-H Functionalization and Annulation

Zhu and co-workers a developed Co-catalyzed oxidative annulation of *N*-chlorobenzamides with internal alkynes. *N*-chloro benzamide functions as internal oxidizing DG to promote *ortho*-C-H activation and deliver diversely substituted isoquinolones with substrate scope (Scheme 1).[3a]



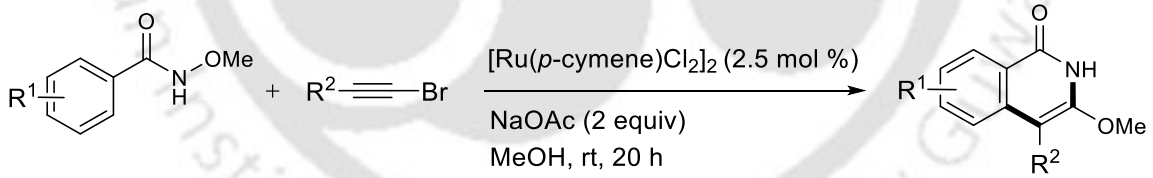
Scheme 1. Co-Catalyzed Annulation of *N*-Cl Benzamides with Internal Alkynes

Jeganmohan group showed a Co-catalyzed [4+2]-annulation of alkylidenecyclopropanes with *N*-chlorobenzamides/acrylamides at room temperature to access 3,4-dihydroisoquinolinone frameworks (Scheme 2).[3d] This methodology proceeds without an external oxidant, exploiting the *N*-Cl bond as an internal oxidant, tolerates diverse functional groups on both the benzamide and alkylidenecyclopropane partners and delivers the annulated products in moderate to excellent yields.



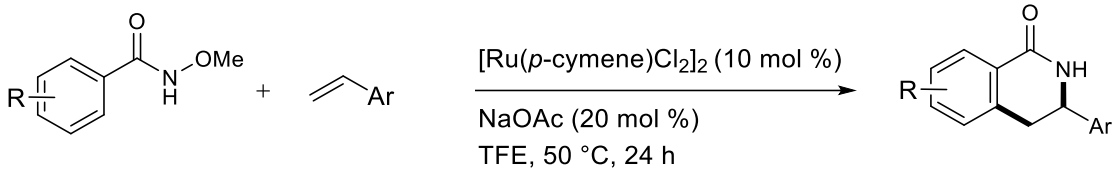
Scheme 2. Co-Catalyzed [4+2]-Annulation of *N*-chlorobenzamides/Acrylamides with Alkylidenecyclopropanes

Ackermann and co-workers established a Ru-catalyzed *N*-methoxybenzamide-assisted C-H/N-O activation using 1-bromoalkynes as coupling partner at room temperature (Scheme 3).[6] The reaction furnished 3-alkoxyisoquinolones with complementary distal-selective alkyne annulation under mild conditions.



Scheme 3. Ru-Catalyzed Annulation of *N*-methoxybenzamide with 1-Bromoalkynes

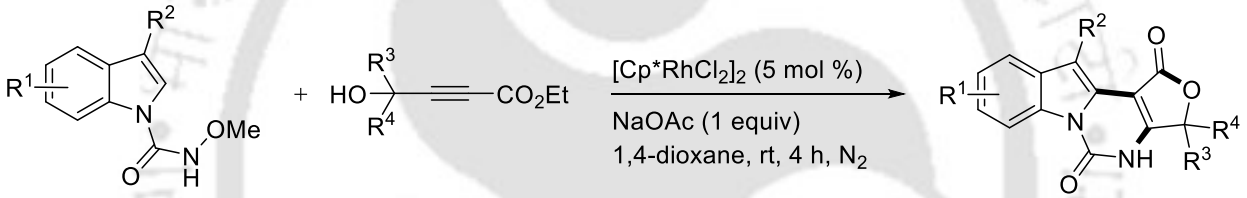
Wang and co-workers demonstrated a Ru-catalyzed oxidative C-H olefination of *N*-methoxybenzamides with styrene to produce 3,4-dihydroisoquinolinone derivatives with substrate scope and functional group tolerance (Scheme 4).[7] This method stands out for its use of an internal oxidizing DG, mild conditions and ensuring exclusive *ortho*- and mono-selectivity.



Scheme 4. Ru-catalyzed Annulation of *N*-methoxybenzamides with Styrene

3.1.2 Hydroxy Alkynoates in C-H Functionalization and Annulation

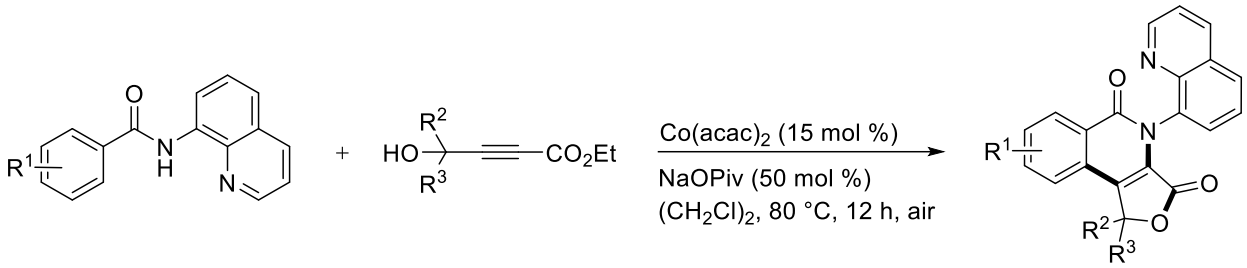
Zhao and co-workers reported a Rh-catalyzed redox-neutral [4+2]-annulation/lactonization of *N*-methoxy indole carboxamides with 4-hydroxy-2-alkynoates at room temperature to provide furo[3,4-*f*][4,5-pyrimido][1,6-*a*]indole-1,5(3*H*,4*H*)-diones (Scheme 5).[8] This protocol features mild conditions, compatibility with diverse indoles, regioselectivity and affords the indole-fused polyheterocycles in good to excellent yields.



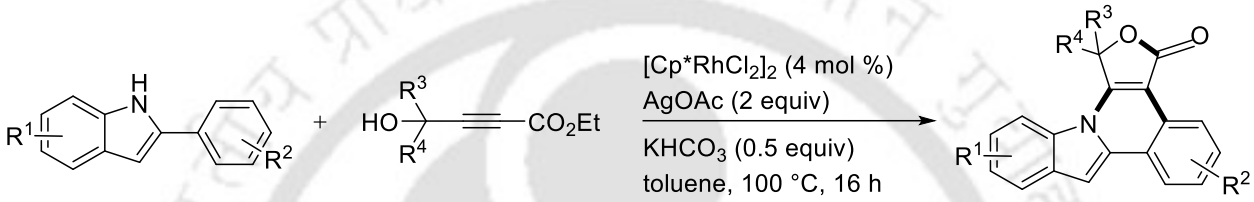
Scheme 5. Rh-Catalyzed [4+2]-Annulation/ Lactonization of *N*-methoxy Indole Carboxamides and 4-Hydroxy-2-alkynoates

Prabhu group showed a Co-catalyzed [4+2]-annulation/lactonization of 8-aminoquinoline-derived benzamides with 4-hydroxy-2-alkynoates to produce 1,4-dihydrofuro[3,4-*c*]isoquinoline-3,5-diones (Scheme 6).[9] This operationally simple and sustainable protocol uses air as the sole oxidant, displays substrate scope with functional group compatibility and provides the annulated products in good to excellent yields with regioselectivity.

Cui and co-workers developed a Rh-catalyzed cascade C-H activation/annulation/lactonization of 2-arylindoles with 4-hydroxy-2-alkynoates to furnish furo[3,4-*c*]indolo[2,1-*a*]isoquinolin-3-1*H*-ones in one-pot. This protocol constructs multiple rings *via* sequential C-H/C-C/C-O activation exhibits regioselectivity, substrate scope, functional group tolerance and delivers the polycyclic products in good to high yields (Scheme 7).[10]



Scheme 6. Co-Catalyzed Annulation/Lactonization of 8-Aminoquinoline Benzamides with 4-Hydroxy-2-alkynoates

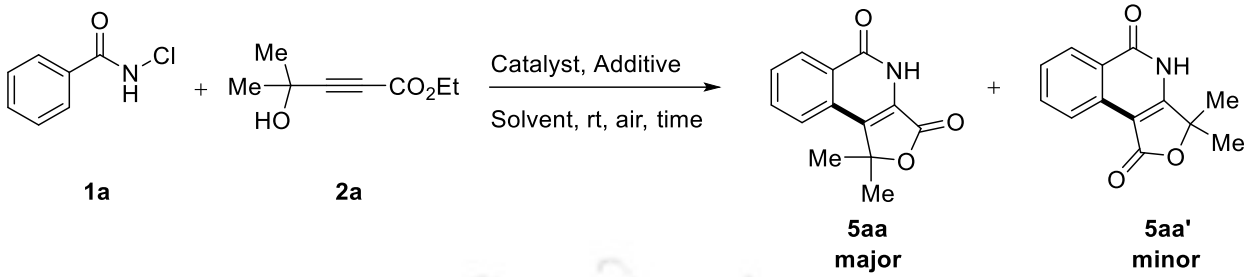


Scheme 7. Rh-Catalyzed C-H activation/Annulation/Lactonization of 2-Arylindoles with 4-Hydroxy-2-alkynoates

1.4 Present Study

We herein report a Ru-catalyzed annulation of *N*-chlorobenzamides with unsymmetrical 4-hydroxy-2-alkynoates, alkynyl sulfones and sulfonyl-based ynamides that proceeds efficiently at room temperature in water. Notably, the reaction occurs upon simple stirring of the alkynes and *N*-chlorobenzamides with a Ru catalyst and KOAc in aqueous medium, highlighting the simplicity and mildness of the protocol. Our studies were initiated using *N*-chlorobenzamide **1a** and ethyl 4-hydroxy-4-methylpent-2-ynoate **2a** as model substrates (Table 1). Under the action of [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol %) and KOAc (2 equiv) in water at room temperature under air in 1 h, the annulation proceeded smoothly to afford isoquinolones **5aa** and **5aa′** in 65% and 10% yields, respectively. Among the additives screened, KOAc proved optimal, whereas LiOAc, NaOAc, CsOAc, and PivOH resulted in diminished efficiency. Notably, water was identified as the solvent of choice, while TFE, MeOH, and EtOH delivered moderate outcomes. Control experiments established that both the Ru-catalyst and the acetate additive are essential for the annulation.

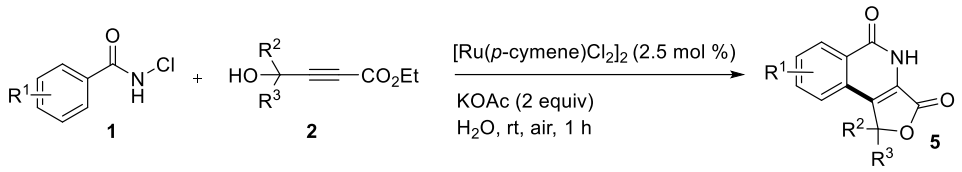
Table 1. Optimization of the Reaction Conditions[a]

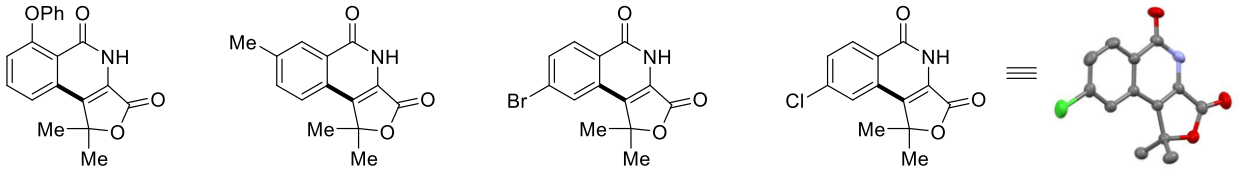


Entry	Catalyst	Base	Solvent	Yield (%)[b]	
				5aa	**5aa'**
1	**[Ru(*p*-cymene)Cl$_2$]$_2$**	**KOAc**	**H$_2$O**	**65**	**10**
2[e]	[Ru(*p*-cymene)Cl$_2$]$_2$	KOAc	H$_2$O	56	15
3	[Ru(*p*-cymene)Cl$_2$]$_2$	NaOAc	H$_2$O	57	22
4	[Ru(*p*-cymene)Cl$_2$]$_2$	LiOAc	H$_2$O	trace	trace
5	[Ru(*p*-cymene)Cl$_2$]$_2$	CsOAc	H$_2$O	21	13
6	[Ru(*p*-cymene)Cl$_2$]$_2$	NaOPiv	H$_2$O	17	11
7	[Ru(*p*-cymene)Cl$_2$]$_2$	PivOH	H$_2$O	n.d.	n.d.
8	[Ru(*p*-cymene)Cl$_2$]$_2$	KOAc	TFE	60	21
9	[Ru(*p*-cymene)Cl$_2$]$_2$	KOAc	MeOH	56	16
10	[Ru(*p*-cymene)Cl$_2$]$_2$	KOAc	EtOH	62	18
11[c]	[Ru(*p*-cymene)Cl$_2$]$_2$	KOAc	H$_2$O	52	14
12[d]	[Ru(*p*-cymene)Cl$_2$]$_2$	KOAc	H$_2$O	32	13
13	[Ru(*p*-cymene)Cl$_2$]$_2$	-	H$_2$O	n.d.	n.d.
14	-	KOAc	H$_2$O	n.d.	n.d.
15	[Cp*Co(CO)I$_2$]	NaOAc	TFE	n.d.	n.d.

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst (2.5 mol %), additive (2 equiv), solvent (1 mL), rt, 1 h, air. [b]Isolated yield. [c]3 equiv KOAc. [d]1 equiv KOAc. [e]At 60 °C. n.d. = not detected. TFE = 2,2,2-trifluoroethanol.

Table 2. Substrate Scope of *N*-Cl Benzamides[a,b]





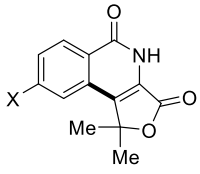
5ba, 61% (trace)[d]

5ca, 41% (9%)[d]

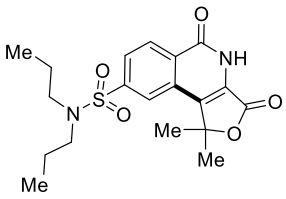
5da, 64% (trace)[d]
5fa, 58% (7%)[d]

5ea, 62% (trace)[d]

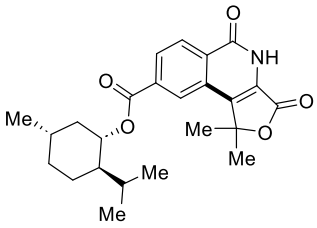
(*CCDC* 2352164)



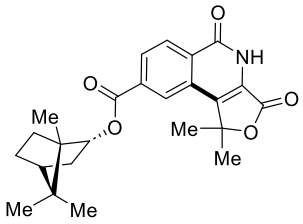
X = ^{t}Bu, **5ga**, 63% (10%)[d]
= NO_2, **5ha**, trace



5ia, 60%[c] (trace)[d]
from probenecid



5ja, 62%[c] (8%)[d]
from *L*-menthol



5ka, 64%[c] (9%)[d]
from (-)-borneol

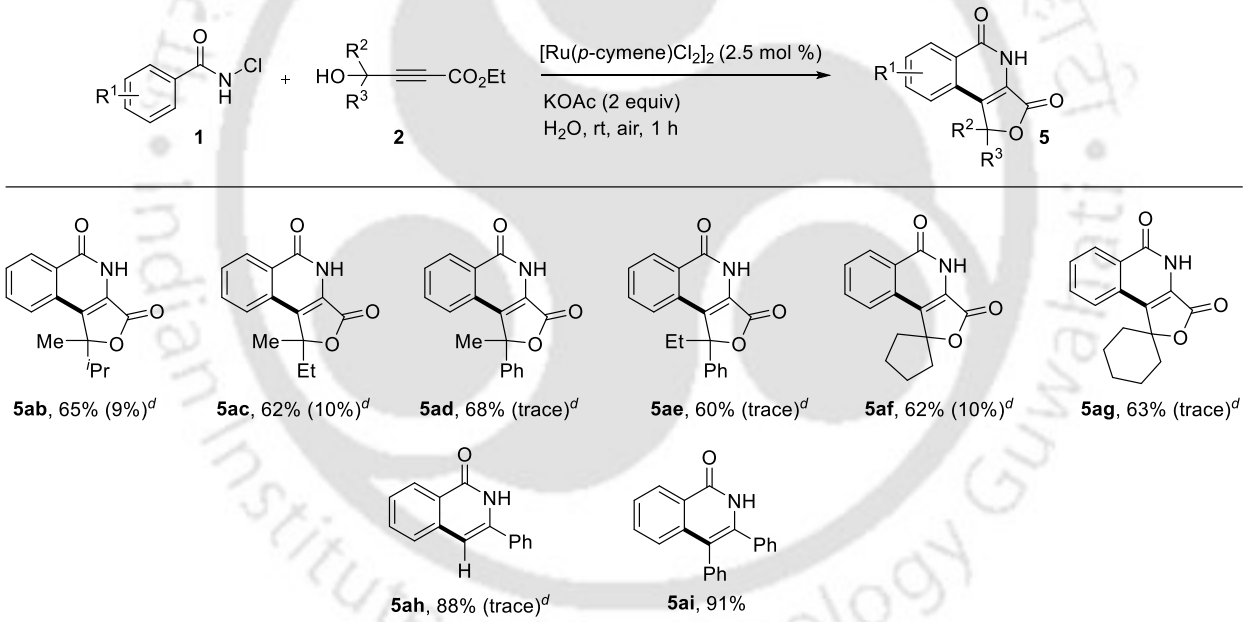
[a]Reaction conditions: **1a-k** (0.2 mmol), **2a-i** (0.3 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol %), KOAc (0.4 mmol), H_2O (1 mL), rt, air, 1 h. [b]Isolated yield. [c]H_2O/EtOH (1:1). [d]The value in parentheses indicates the isolated yield of the minor regioisomers.

With the optimized conditions established, the substrate scope was evaluated using a series of *N*-chlorobenzamides **1b-k** with 4-hydroxy-4-methylpent-2-ynoate **2a** as the standard coupling partner (Table 2). *N*-chlorobenzamide bearing a sterically bulky 2-phenoxy substituent **1b** delivered **5ba** in 61% yield, while the 3-methyl-substituted analogue **1c** afforded **5ca** in 41% yield. Halogenated substrates, including 4-bromo **1d**, 4-chloro **1e** and 4-fluoro **1f** *N*-chlorobenzamides, were well tolerated, furnishing **5da-fa** in 58-64% yields, the structure of **5ea** was confirmed by single-crystal *X*-ray analysis (CCDC 2352164). Electron-rich 4-*tert*-butyl-substituted *N*-chlorobenzamides **1g** underwent smooth annulation to afford **5ga** in 63% yield, whereas the strongly electron-deficient 4-nitro derivative **1h** was providing only trace amounts of **5ha**. Notably, *N*-chlorobenzamides derived from bioactive scaffolds, including probenecid **1i**, *L*-

menthol **1j** and (–)-borneol **1k**, participated efficiently to deliver the heterocycles **5ia-ka** in 60–64% yields.

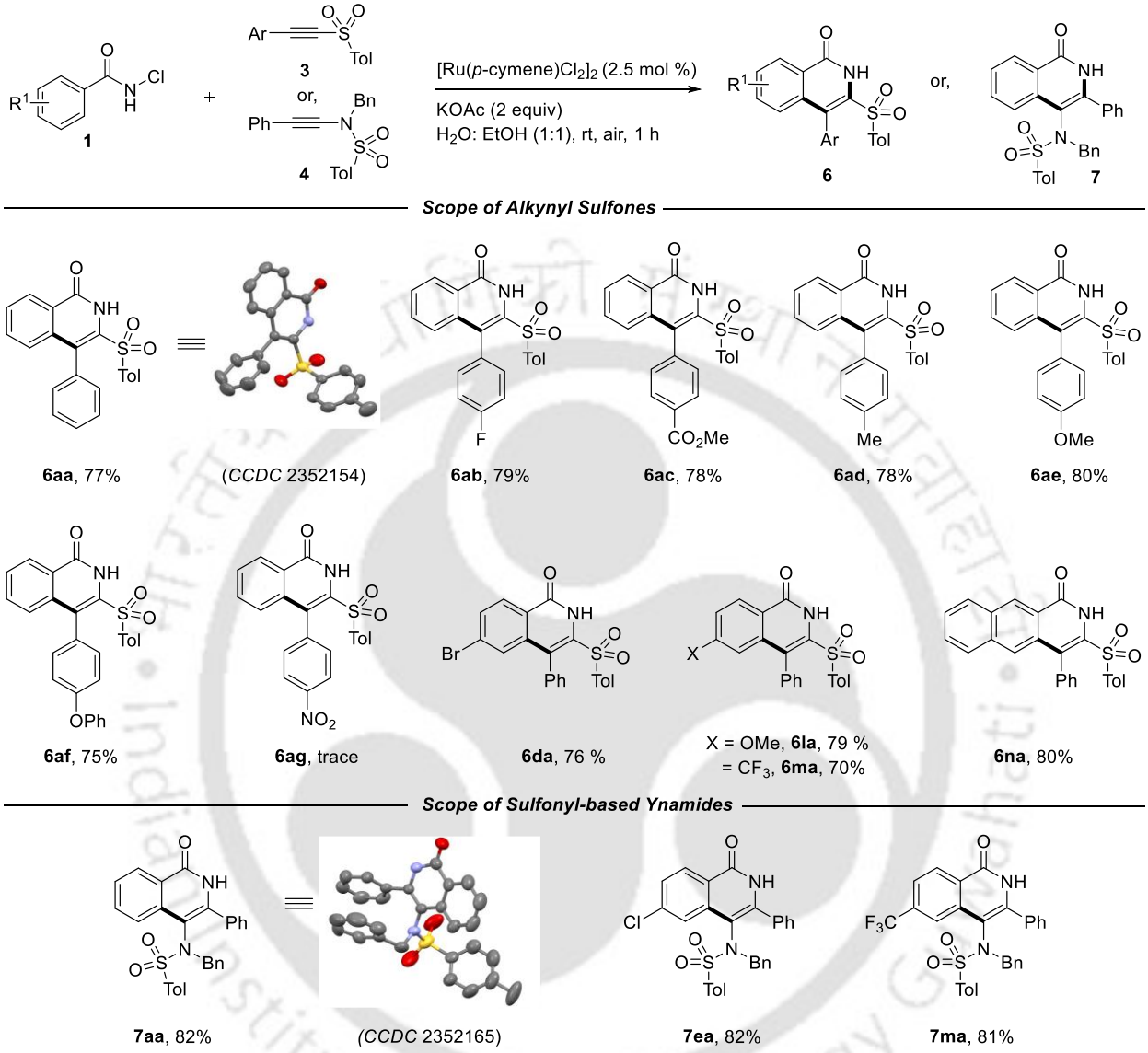
Next, the scope of the protocol was examined using a series of hydroxyalkynoates **2b-g** with *N*-chlorobenzamide **1a** as the standard substrate (Table 3). Alkynoates bearing methyl and isopropyl **2b**, methyl and ethyl **2c**, methyl and phenyl **2d** and ethyl and phenyl **2e** substituents smoothly underwent annulation to deliver isoquinolones **5ab-5ae** in 60-68% yields. Cyclic hydroxyalkyl-substituted propiolates, including ethyl 3-(1-hydroxycyclopentyl) **2f** and ethyl 3-(1-hydroxycyclohexyl) **2g** were compatible to furnish **5af** and **5ag** in 62% and 63% yields respectively. Notably, phenylacetylene **2h** and diphenylacetylene **2i** proved effective, furnishing **5ah** and **5ai** in 88% and 91% yields respectively.

Table 3. Substrate Scope of Hydroxy-Alkynoates and Other Alkynes[a,b]



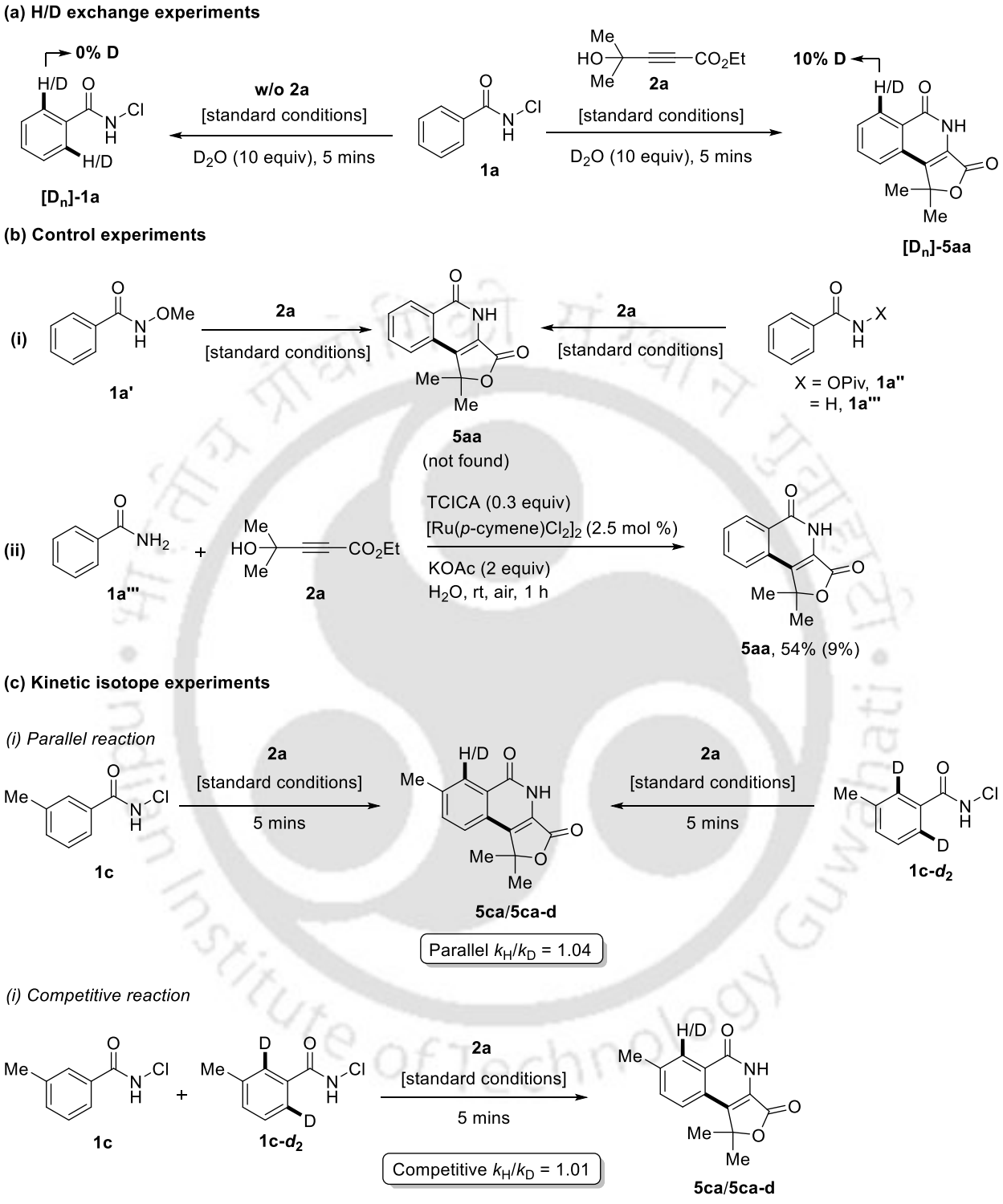
[a]Reaction conditions: **1a-k** (0.2 mmol), **2a-i** (0.3 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol %), KOAc (0.4 mmol), H_2O (1 mL), rt, air, 1 h. [b]Isolated yield. [c]H_2O/EtOH (1:1). [d]The value in parentheses indicates the isolated yield of the minor regioisomers.

Table 4. Substrate Scope of *N*-Chlorobenzamides, Alkynyl Sulfones and Ynamides[a,b]

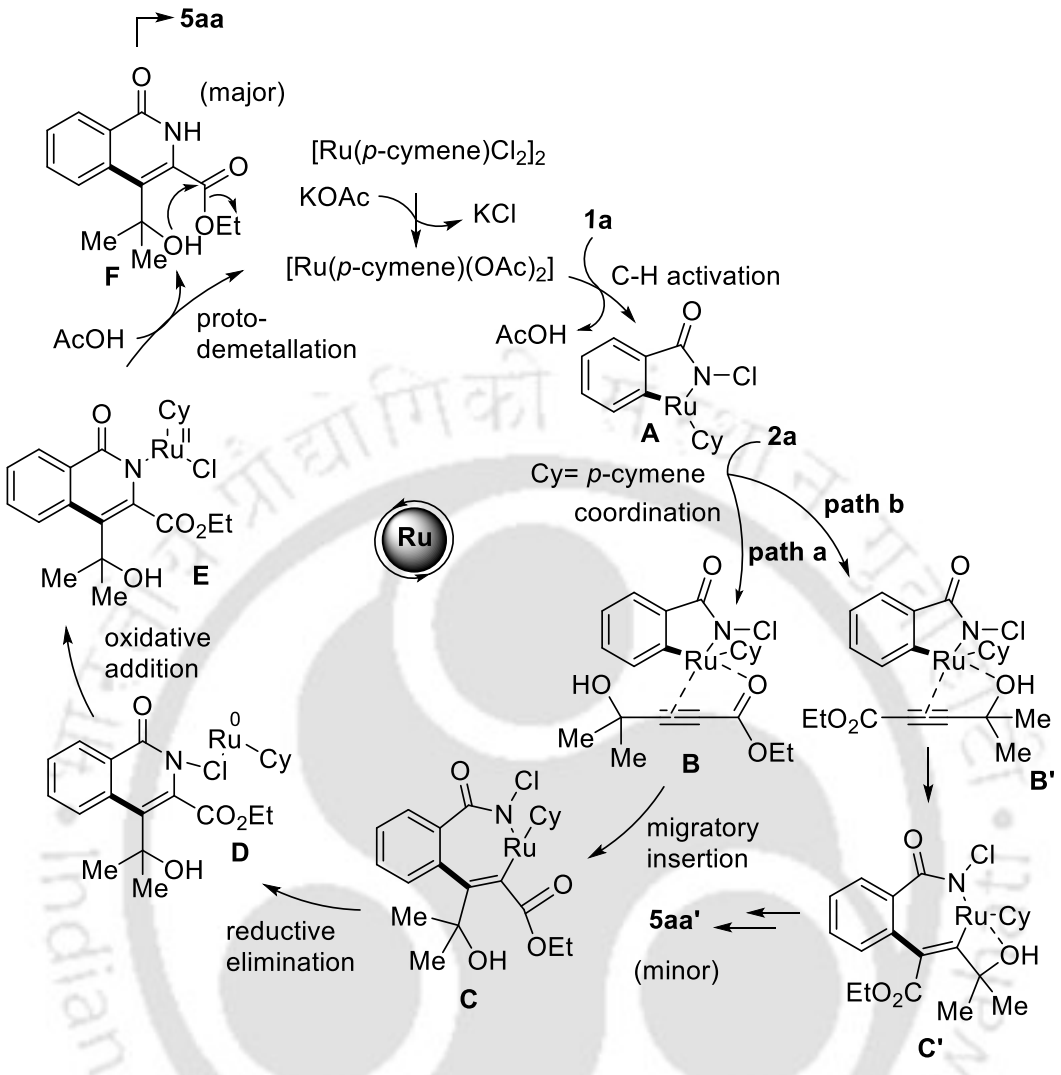


[a]Reaction conditions: **1** (0.2 mmol), **3** or **4** (0.3 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol %), KOAc (0.4 mmol), H_2O: EtOH (1:1, 1 mL), rt, air, 1 h. [b]Isolated yield.

Encouraged by the annulation of *N*-chlorobenzamides with hydroxy-alkynoates, we next examined alkynyl sulfone **3a** as coupling partner (Table 4). Using *N*-chlorobenzamide **1a**, the reaction furnished sulfone-containing isoquinolone **6aa** in 77% yield as a single regioisomer and the structure was confirmed by single-crystal *X*-ray analysis (CCDC 2352154). Para-substituted aryl alkynyl sulfones bearing fluoro **3b**, ester **3c**, methyl **3d**, methoxy **3e** and phenoxy **3f** groups were well tolerated, affording **6ab-af** in 75-80% yields, whereas the nitro-substituted analogue **3g**



Scheme 8. Preliminary Mechanistic Investigations



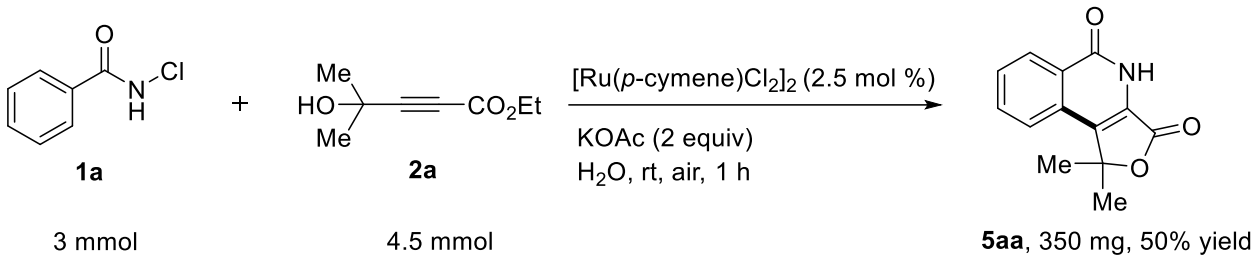
Scheme 9. Plausible Reaction Pathway

was largely unreactive. Moreover, *N*-chlorobenzamides substituted with 4-bromo **1d**, 4-methoxy **1l**, 4-trifluoromethyl **1m** and naphthyl **1n** groups smoothly underwent annulation to deliver **6da**, **6la**, **6ma** and **6na** in 70-80% yields.

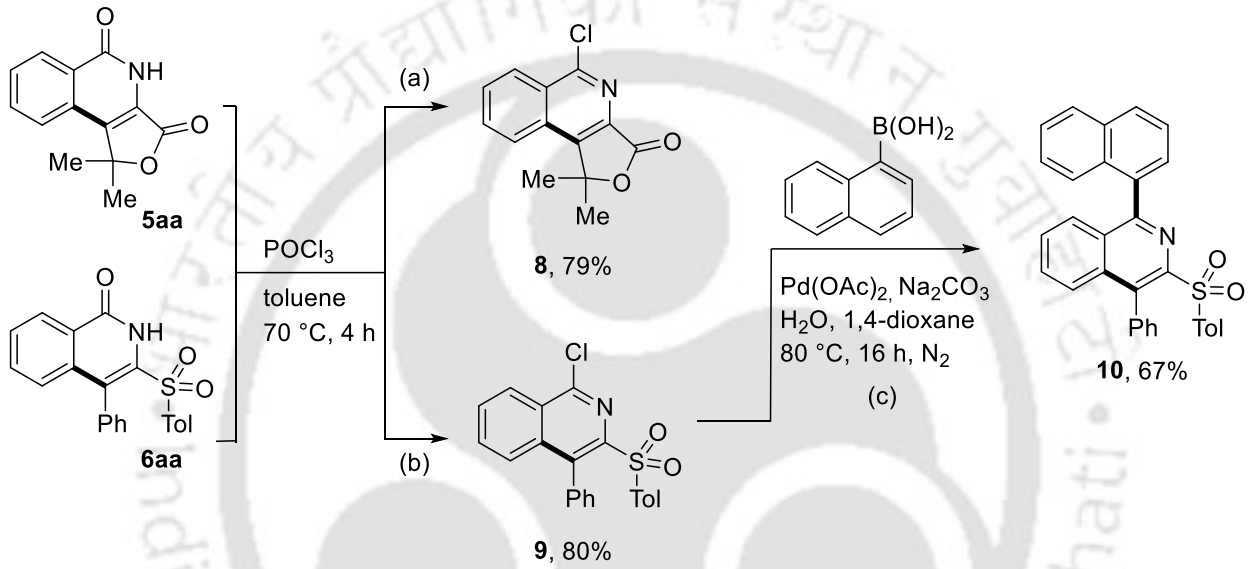
Following the successful synthesis of isoquinolones with two distinct coupling partners, the protocol was next evaluated using sulfonyl-based ynamides (Table 4). *N*-Chlorobenzamide **1a** reacted with sulfonyl-based ynamide **4a** to deliver **7aa** in 82% yield as a single regioisomer. *N*-Chlorobenzamides bearing 4-chloro **1e** and 4-trifluoromethyl **1m** substituents similarly furnished **7ea** and **7ma** in 82% and 81% yields respectively. The structure of **7aa** was unambiguously confirmed by single-crystal *X*-ray analysis (CCDC 2352165).

To gain insight into the reaction pathway, deuterium labeling experiments were conducted using D_2O as co-solvent. In absence of **2a**, no deuterium incorporation at the *ortho*-position of *N*-chlorobenzamide **1a** was detected (Scheme 8), indicating that the C–H activation step is likely to be irreversible. In contrast, in the presence of **2a**, 10% deuterium incorporation was observed at the *ortho*-position of the isoquinolone derivative. Parallel and competitive kinetic isotope effect experiments using **1c** and **1c-*d*₂** with **2a** provided k_H/k_D = 1.04 and 1.01 respectively, suggesting that C–H bond cleavage is not involved in the rate-determining step. In addition, no formation of **5aa** was observed under the standard conditions when using **1a′**, **1a″** or **1a‴**, indicating that the N–Cl bond acting as an internal oxidant, which is crucial for isoquinolone formation. Finally, a control experiment starting from benzamide **1a‴** and TCICA to achieve in situ *N*-chlorination, followed by addition of **2a** under the standard conditions, enabled a one-pot annulation to furnish **5aa**, albeit in a lower yield of 54%.

On the basis of these experimental observations and prior literatures,[8,11] activation of [Ru(*p*-cymene)Cl_2]$_2$ by KOAc can generate the catalytically active Ru(II) species, which may undergo irreversible C–H activation to form a five-membered ruthenacycle **A** (Scheme 9). Subsequent coordination of alkyne **2a** to intermidiate **A** can afford intermediate **B** (*path a*), followed by regioselective migratory insertion of the triple bond to deliver a seven-membered ruthenacycle **C**. Reductive elimination from **C** may yield intermediate **D**, which may undergo oxidative addition to give **E**. Proto-demetallation of **E** may furnish annulated intermediate **F** with concurrent regeneration of the Ru-catalyst and intramolecular lactonization of **F** affords heterocycle **5aa**. The observed regioselectivity is rationalized by preferential orientation of the gem-dimethyl substituents away from the *p*-cymene ligand, together with a stabilizing secondary interaction between the Ru center and the carbonyl group. In contrast, weaker chelation of **2a** to **A** can lead to intermediate **B′** (*path b*), resulting in the formation of the minor regioisomer **5aa′**. For alkynes **3**, enhanced secondary interaction between the Ru center and the sulfonyl group is proposed to govern regioselectivity,[12] whereas in the case of alkynes **4**, steric repulsion directs bulky substituents away from the *p*-cymene ligand during migratory insertion, thereby influencing the regiochemical outcome.



Scheme 10. Scale-up Synthesis



[a]Reaction conditions: (a) **5aa** (0.2 mmol), $POCl_3$ (1.5 mmol), toluene (3 mL), 70 °C, 4 h. (b) **6aa** (0.2 mmol), $POCl_3$ (1.5 mmol), toluene (3 mL), 70 °C, 4 h. (c) **9** (0.07 mmol), naphthalen-1-yl boronic acid (0.08 mmol), Na_2CO_3 (0.14 mL), H_2O (0.05 mL), $Pd(OAc)_2$ (10 mol %), 1,4-dioxane (0.3 mL), 80 °C, 16 h, N_2.

Scheme 11. Post-Synthetic Transformations

To highlight the synthetic utility of the method, a gram-scale reaction was performed using **1a** (3 mmol) and **2a** (4.5 mmol) under the optimized conditions (Scheme 10), delivering isoquinolone **5aa** in 50% yield. Furthermore, treatment of annulated product **5aa** with $POCl_3$ afforded 1-chloroisoquinoline **8** in 79% yield (Scheme 11). Similarly, tosyl-substituted isoquinolone **6aa** underwent $POCl_3$ mediated chlorination to provide 1-chloroisoquinoline **9** in 80% yield, which

was further diversified *via* Pd-catalyzed C–C cross-coupling with boronic acid to furnish product **10** in 67% yield.

In summary, we have developed a Ru-catalyzed annulation of *N*-chlorobenzamides with heteroatom-substituted unsymmetrical alkynes in water, enabling efficient access to structurally diverse isoquinolones bearing furanone, ynamide and sulfone motifs. The operational simplicity, use of water as a green solvent, redox-neutral conditions, regioselectivity and broad functional group tolerance underscore the practical utility of this transformation.

3.3 Experimental Section

General Information. [Ru(*p*-cymene)Cl_2]$_2$ (98%), NaOPiv (98%), CsOPiv (>98%), NaOAc (99%), KOAc (99%), CsOAc (>98%), PivOH (>98%), 2,2,2-trifluoroethanol (TFE) and carboxylic acids were purchased from Aldrich and TCI chemicals and used as received. Acetonitrile, dichloromethane, tetrahydrofuran, MeOH and EtOH were dried prior as per the standard procedure. Silica gel-G/GF254 plates (Merck) were used for TLC analysis. Column chromatography was carried out using Rankem silica gel (60-120 mesh). Bruker Avance III 400, 500 and 600 MHz NMR spectrometers were used to record (^{1}H, ^{13}C and ^{19}F) NMR spectra using $CDCl_3$ and DMSO-d_6 with tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) and spin-spin coupling constant (*J*) are reported in parts per million and hertz (Hz), respectively, and to describe peak patterns following abbreviations used when appropriate: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Melting point was measured on Büchi melting point apparatus, MPB-540, with open capillary tubes and are uncorrected. Mestrenova software was used throughout the spectral analysis. Q-Tof ESI-MS instrument was used for recording HRMS. Infrared spectra were recorded on Perkin Elmer FT-IR instrument. Single crystal *X*-ray data were collected on a Bruker SMART APEX equipped with a CCD area detector using Mo/-Kα radiation and the structure was solved by direct method using SHELXL-16 (Göttingen, Germany).

Preparation of *N*-Chlorobenzamides 1.

Step-I. To a stirred solution of a carboxylic acid (3 mmol, 1 equiv) and DMF (1 drop) in CH_2Cl_2 (10 mL), $(COCl)_2$ (0.34 mL, 4 mmol, 1.3 equiv) was added dropwise. The solution was allowed to

stir at room temperature for 12 h and the resulting solution was concentrated in vacuo and dissolved in THF (10 mL), which was used in subsequent steps.

Step-II. To a stirred solution of acid chloride (5 mmol, 1equiv) (obtained in **Step-I**) in CH_2Cl_2 (10 mL), aqueous NH_3 (20 mL, 25 mmol, 5 equiv) was added. The resultant mixture was stirred for 2 h at room temperature. After completion (monitored by TLC), 10 mL of 1 N HCl was added dropwise and the aqueous solution was extracted with ethyl acetate (3 x 10 mL). The combined organic solution was dried (Na_2SO_4) and evaporated to give a residue that was used in subsequent reaction.

Step-III. To a stirred solution of the amide (5 mmol, 1 equiv) in MeOH (10 mL), trichloroisocyanuric acid (1.8 mmol, 0.36 equiv) was added. The resultant mixture was stirred for 1 h at room temperature. The solid was filtered and washed with ethyl acetate. The filtrate was evaporated to give *N*-chlorobenzamides **1**.

Preparation of 4-Hydroxy-2-Alkynoates 2. To a stirred solution of diisopropylamine (11 mmol, 1.1 equiv) in THF (10 mL), *n*-butyllithium (hexane, 1 M, 11 mmol, 1.1 equiv) was added dropwise at 0 °C. After stirring for 1 h at 0 °C, the reaction mixture was cooled to -78 °C and propargyl ester (10.2 mmol, 1 equiv) in THF (4 mL) was added dropwise. After stirring for 1 h at -78 °C, the ketone (20.4 mmol, 2 equiv) was added dropwise and the stirring was continued for an additional 3 h at -78 °C. The reaction mixture was quenched with saturated NH_4Cl and extracted with ethyl acetate (3 x 25 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography (hexane: ethyl acetate = 4:1) to afford 4-hydroxy-2-alkynoates **2**.

Preparation of Alkynyl Sulfones 3. To a stirred solution of arylacetylene (5 mmol, 1 equiv) with sodium sulfinate (10 mmol, 2 equiv) and iodine (2.5 mmol, 0.5 equiv) in THF (20 mL), TBHP (70% in water, 15 mmol, 3 equiv) was added. The resulting mixture was stirred at room temperature for 16 h and quenched with aqueous $Na_2S_2O_3$ (15 mL). The solvent was evaporated and the resultant aqueous solution was extracted using ethyl acetate (3 x 25 mL). Drying (Na_2SO_4) and the evaporation of the solvent gave a residue that was purified on silica gel column chromatography (hexane: ethyl acetate = 4:1) to afford the alkynyl sulfones **3**.

Preparation of Ynamides 4. To a stirred solution of 1-bromoalkyne (1.9 mmol, 1 equiv) and amine (1.7 mmol, 0.9 equiv) in toluene (10 mL), $CuSO_4$•$5H_2O$ (10 mol %, 0.05 equiv), 1,10-phenanthroline (20 mol%, 0.10 equiv) and K_2CO_3 (3.8 mmol, 2 equiv) were added. The reaction mixture was stirred at 90 °C for 22 h. After completion (monitored by TLC), the mixture was cooled to room temperature and passed through a short pad of celite using ethyl acetate. The solvent was evaporated under reduced pressure and the residue was purified on silica gel column chromatography (hexane: ethyl acetate = 9:1) to afford ynamides **4**.

General Procedure of Ru-Catalyzed Annulation of *N*-Chlorobenzamides with 2/3/4. To a stirred solution of *N*-chlorobenzamide **1a** (0.1 mmol, 1 equiv) and **2a/3a/4a** (0.15 mmol, 1.5 equiv) in H_2O/ H_2O: EtOH (1:1) (1 mL), KOAc (0.2 mmol, 2 equiv) and [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol %, 0.25 equiv) were added at room temperature under air. The reaction mixture was stirred for 1 h and the solid was separated, and purified on silica gel column chromatography using CH_2Cl_2: ethyl acetate = 8:1 as eluent to separate the regioisomers of isoquinolones **5** and ethyl acetate: hexane = 2:3 as eluent as eluent to purify isoquinolones **6** and **7**.

Post-synthetic Transformations

Synthesis of 8. To a stirred solution of 1,1-dimethyl-1,4-dihydrofuro[3,4-*c*]isoquinoline-3,5-dione **5aa** (50 mg, 0.22 mmol, 1 equiv) in toluene (3 mL), phosphorus oxychloride (0.13 mL, 1.5 mmol, 6.8 equiv) was added. The resultant mixture was stirred at 70 °C for 4 h and then cooled to room temperature. The solution was poured into ice-cold water treated with a saturated $NaHCO_3$ (7 mL). The resultant mixture was extracted using ethyl acetate (3 x 15 mL) and dried over Na_2SO_4. Evaporation of the solvent provided a residue that was purified on silica gel column chromatography using hexane: ethyl acetate (5:1) to give 5-chloro-1,1-dimethylfuro[3,4-c]isoquinolin-3(1H)-one **8** in 32 mg (79% yield).

Synthesis of 9. 4-Phenyl-3-tosylisoquinolin-1(2*H*)-one **6aa** (50 mg, 0.13 mmol, 1 equiv) was subjected to the reaction conditions used for **8** to yield 1-Chloro-4-phenyl-3-tosylisoquinoline **9** in 83 mg (80% yield).

Synthesis of 10. To a stirred solution of 1-chloro-4-phenyl-3-tosylisoquinoline **9** (30 mg, 0.07 mmol, 1 equiv) and naphthalen-1-yl boronic acid (15 mg, 0.08 mmol, 1.1 equiv) in 1,4-dioxane

(0.3 mL) under nitrogen atmosphere, Na_2CO_3 (15 mg, 0.14 mmol, 2 equiv), H_2O (0.05 mL) and $Pd(OAc)_2$ (2 mg, 10 mol%, 0.1 equiv) were added. The resultant mixture was stirred at 80 °C for 16 h and diluted with ethyl acetate (30 mL). The solution was washed with water (5 mL) and dried (Na_2SO_4). Evaporation of the solvent gave a residue that was purified on silica gel chromatography to afford **10**.

Mechanistic Investigation

H/D Exchange Experiment of 1a with D_2O in Absence of 2a. To a stirred solution of **1a** (20 mg, 0.1 mmol, 1 equiv), [Ru(*p*-cymene)Cl_2]$_2$ (2 mg, 2.5 mol %, 0.1 equiv) and KOAc (20 mg, 0.2 mmol, 2 equiv) in H_2O (1 mL), D_2O (0.02 mL, 1.3 mmol, 12 equiv) was added. The resultant mixture was allowed to stir at room temperature for 5 mins and extracted with ethyl acetate (2 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography (ethyl acetate: hexane = 2:3) to afford [D_n]-**1a** whose 400 MHz ^{1}H NMR analysis showed no deuterium incorporation.

H/D Exchange Experiment of 1a with D_2O in Presence of 2a. To a stirred solution of **1a** (20 mg, 0.1 mmol, 1 equiv), **2a** (24 mg, 0.15 mmol, 1.5 equiv), [Ru(*p*-cymene)Cl_2]$_2$ (1 mg, 2.5 mol %, 0.25 equiv) and KOAc (20 mg, 0.2 mmol, 2 equiv) in H_2O (1 mL), D_2O (0.02 mL, 1.3 mmol, 12 equiv) was added and the resultant mixture was allowed to stir at room temperature for 5 mins. The reaction mixture was extracted with ethyl acetate (2 x 10 mL) and dried (Na_2SO_4). Evaporation of the solvent gave a residue, which was purified using silica gel column chromatography (CH_2Cl_2 : ethyl acetate = 8:1) to afford **[D_n]-5aa** in 43% yield along with recovered **1a**. 400 MHz ^{1}H NMR analysis showed 10% deuterium incorporation at *ortho*-position of **[D_n]-5aa**.

Preparation of *N*-Chloro-3-methylbenzamide-2,6-*d_2* 1c-*d_2*. Step-I. 3-Methylbenzoic acid (0.50 mmol, 76 mg, 1 equiv), [Ru(O_2CAd)$_2$(*p*-cymene)] (14.9 mg, 5 mol %, 0.1 equiv) and D_2O (0.18 mL, 10 mmol, 20 equiv) were stirred in 1,4-dioxane (3 mL) at 100 °C for 16 h under N_2 atmosphere. After cooling to room temperature, the residue was diluted with ethyl acetate (10 mL) and filtered through a short pad of celite. Evaporation of the solvent gave a residue that was purified using silica gel column chromatography (hexane: ethyl acetate: acetic acid = 8:1:0.1) to afford **[D]-1c** benzoic acid.

Step-II. To a stirred solution of **[D]-1c** benzoic acid (100 mg, 0.6 mmol, 1 equiv) and DMF (1 drop) in CH_2Cl_2 (2 mL), $(COCl)_2$ (0.07 mL, 0.8 mmol, 1.3 equiv) was added dropwise. The reaction mixture was allowed to stir at room temperature for 12 h. Then the solvent was evaporated under reduced pressure and the residue having **[D]-1c** acid chloride was used in the subsequent step.

Step-III. To a stirred solution of **[D]-1c** acid chloride (156 mg, 1 mmol, 1 equiv) (obtained in **Step-II**) in CH_2Cl_2 (2 mL), aqueous NH_3 (4 mL, 5 mmol, 5 equiv) was added at room temperature and the reaction was allowed to stir for 2 h at room temperature. After completion (monitored by TLC), 5 mL of 1 N HCl was added dropwise to the reaction mixture and then the aqueous part was extracted with ethyl acetate (3 x 20 mL). The combined organic layer was washed with brine (20 mL). Drying (Na_2SO_4) and evaporation of the solvent gave the residue **[D]-1c**, which was used in subsequent reaction.

Step-IV. To a stirred solution of **[D]-1c** (120 mg, 0.9 mmol, 1 equiv) in MeOH (2 mL), trichloroisocyanuric acid (73 mg, 0.3 mmol, 0.36 equiv) was added. The resultant mixture was stirred for 1 h at room temperature. The solid was filtered and washed with ethyl acetate. The filtrate was evaporated to give **1c-*d*$_2$** with 93% deuteriation.

Kinetic Isotope Effect Experiments

Parallel Reactions. *N*-Chloro-3-methylbenzamides **1c** and **1c-*d*$_2$** (0.1 mmol, 1 equiv) were separately reacted with ethyl 4-hydroxy-4-methylpent-2-ynoate **2a** (31 mg, 0.2 mmol, 2 equiv) in H_2O (1 mL) for 5 mins at the standard conditions. The reaction mixture was then extracted with ethyl acetate (2 x 10 mL) and dried (Na_2SO_4). Evaporation of the solvent gave a residue that was purified on silica gel column chromatography to give **5ca** and **5ca-*d***, whose 400 MHz ^{1}H NMR analysis showed k_H/k_D = 1.04.

Competitive Reactions. A mixture of *N*-chloro-3-methylbenzamide **1c** (20 mg, 0.1 mmol, 1 equiv) and *N*-chloro-3-methylbenzamide-2,6-d_2 **1c-*d*$_2$** (20 mg, 0.1 mmol, 1 equiv) [93% D] was reacted with ethyl 4-hydroxy-4-methylpent-2-ynoate **2a** (31 mg, 0.2 mmol, 2 equiv) in H_2O (1 mL) for 5 mins at standard reaction conditions. The reaction mixture extracted with ethyl acetate (2 x 10 mL) and dried (Na_2SO_4). Evaporation of the solvent gave a residue that was purified on silica

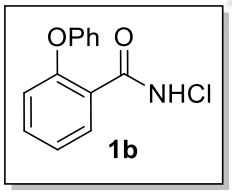
gel column chromatography to afford a mixture of **5ca**/**5ca-*d*** in 32% yield, whose 400 MHz ^{1}H NMR analysis showed $k_H/k_D = 1.01$.

Control Experiments: (i) *N*-Methoxybenzamide **1a'** (20 mg, 0.13 mmol) or *N*-(pivaloyloxy)benzamide **1a''** (20 mg, 0.1 mmol) or benzamide **1a'''** (20 mg, 0.16 mmol), **2a** (24 mg, 0.19 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (1 mg, 2.5 mol %, 0.25 equiv) and KOAc (20 mg, 0.26 mmol, 2 equiv) were stirred in H_2O (1 mL) at room temperature for 1 h under air. The formation of **5aa** was not observed.

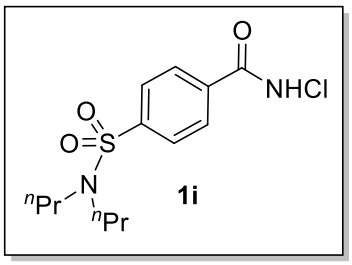
(ii) To a stirred solution of benzamide **1a'''** (20 mg, 0.16 mmol) in H_2O (1 mL), trichloroisocyanuric acid (TCICA) (14 mg, 0.06 mmol, 0.36 equiv) was added. The resultant mixture was stirred for 1 h at room temperature. After that, **2a** (31 mg, 0.19 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (1 mg, 2.5 mol %, 0.25 equiv) and KOAc (20 mg, 0.26 mmol, 2 equiv) were added and the reaction mixture was allowed to stir at room temperature for 1 h under air. After completion of the reaction (monitored by TLC), the solid was filtered and then extracted with ethyl acetate (2 x 10 mL) and dried (Na_2SO_4). Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using CH_2Cl_2: ethyl acetate = 8:1 as eluent to separate the regioisomers of isoquinolone **5aa** to give 54% yield.

3.4 Characterization data

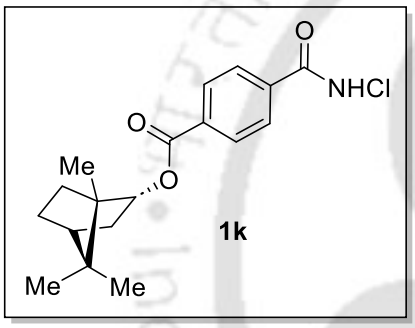
Characterization Data of Newly Synthesized *N*-Cl benzamides Adducts



***N*-Chloro-2-phenoxybenzamide 1b.** Analytical TLC on silica gel, 2:3 ethyl acetate/hexane $R_f = 0.27$; brown solid; yield 73% (145 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.27-8.24 (m, 1H), 7.47-7.38 (m, 3H), 7.30-7.28 (m, 1H), 7.20 (t, $J = 8.0$ Hz, 1H), 7.12 (d, $J = 7.6$ Hz, 2H), 6.80 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.9, 155.6, 154.1, 133.3, 132.4, 130.2, 129.9, 123.9, 123.4, 121.0, 119.8, 118.2; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{13}H_{11}ClNO_2$: 248.0473; Found 248.0463.

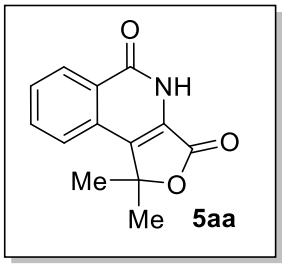


***N*-Chloro-4-(*N*,*N*-dipropylsulfamoyl)benzamide 1i**. Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.30; colorless solid; yield 43% (85 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.94 (m, 2H), 7.88-7.86 (m, 2H), 3.12-3.08 (m, 4H), 1.60-1.50 (m, 4H), 0.87 (t, *J* = 7.4 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.5, 143.6, 136.8, 128.3, 127.4, 50.1, 38.8, 22.1, 11.3; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{13}H_{20}ClN_2O_3S$: 319.0878; Found 319.0880.

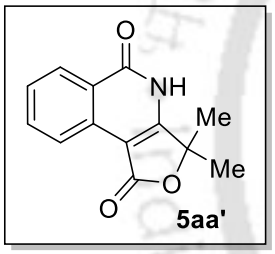


(1*S*,2*R*,4*R*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 4-(chlorocarbamoyl)benzoate 1k. Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.30; yellow solid; yield 40% (140 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.4 Hz, 2H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.21- 7.14 (m, 1H), 5.14 (d, *J* = 10.0 Hz, 1H), 2.52-2.46 (m, 1H), 2.13-2.04 (m, 1H), 1.86-1.79 (m, 1H), 1.77-1.76 (m, 1H), 1.46-1.39 (m, 1H), 1.35-1.32 (m, 1H), 1.14-1.10 (m, 1H), 0.97 (s, 3H), 0.92-0.91 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.5, 166.2, 135.8, 134.2, 130.0, 129.9, 127.9, 127.6, 81.6, 49.3, 48.1, 45.0, 37.0, 28.2, 27.5, 19.8, 19.0, 13.8; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{18}H_{23}ClNO_3$: 336.1361; Found 336.1341.

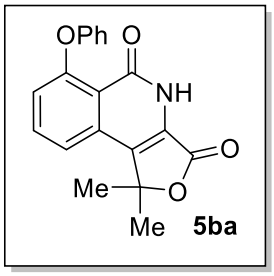
Characterization Data of the Products



1,1-Dimethyl-1,4-dihydrofuro[3,4-*c*]isoquinoline-3,5-dione 5aa. Analytical TLC on silica gel, 8:1 dichloromethane/ethyl acetate R_f = 0.28; colorless solid; mp > 300 °C; yield 65% (30 mg, major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (bs, 1H), 8.62 (d, *J* = 8.0 Hz, 1H), 7.87-7.83 (m, 1H), 7.75-7.71 (m, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 1.85 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.5, 162.3, 135.1, 133.7, 130.5, 130.3, 130.1, 129.1, 124.8, 123.9, 85.7, 26.9; FT-IR (neat) 2991, 1769, 1687, 1667, 1377, 1317, 1244 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{13}H_{12}NO_3$: 230.0812; Found 230.0812.

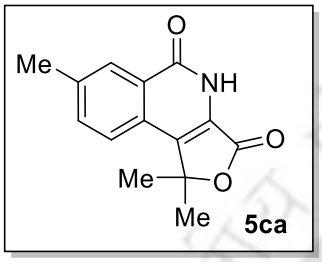


3,3-Dimethylfuro[3,4-*c*]isoquinoline-1,5(3*H*,4*H*)-dione 5aa'. Analytical TLC on silica gel, 8:1 dichloromethane/ethyl acetate R_f = 0.31; colorless solid; mp > 300 °C; yield 10% (7 mg, minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.15 (bs, 1H), 8.54 (d, *J* = 8.0 Hz, 1H), 8.44 (d, *J* = 8.0 Hz, 1H), 7.87 (t, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 8.4 Hz, 1H), 1.84 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.7, 166.3, 161.8, 134.8, 132.6, 128.3, 128.2, 124.4, 123.6, 100.9, 81.2, 25.5; FT-IR (neat) 2997, 1770, 1687, 1663, 1371, 1318, 1240 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{13}H_{12}NO_3$: 230.0812; Found 230.0812.

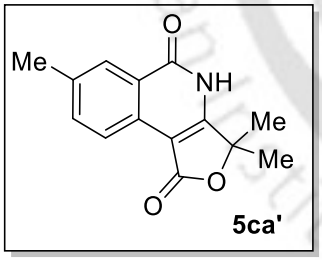


1,1-Dimethyl-6-phenoxy-1,4-dihydrofuro[3,4-*c*]isoquinoline-3,5-dione 5ba. Analytical TLC on silica gel, 8:1 dichloromethane/ethyl acetate R_f = 0.25; brown solid; mp

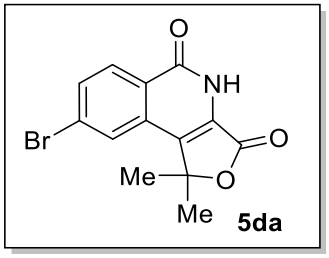
> 300 °C; yield 61% (38 mg, major); minor regioisomer (trace); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40-8.38 (m, 1H), 7.77 (t, *J* = 8.4 Hz, 1H), 7.35-7.31 (m, 2H), 7.13-7.06 (m, 2H), 6.89 (d, *J* = 7.6 Hz, 2H), 1.52 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 167.9, 167.6, 164.2, 158.2, 157.2, 135.9, 135.3, 130.0, 122.9, 120.9, 119.8, 119.6, 117.1, 80.9, 25.1; FT-IR (neat) 2994, 1772, 1687, 1660, 1372, 1319, 1240 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{16}NO_4$: 322.1074; Found 322.1081.



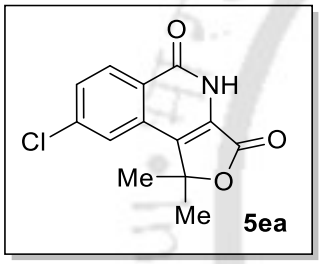
1,1,7-Trimethyl-1,4-dihydrofuro[3,4-*c*]isoquinoline-3,5-dione 5ca. Analytical TLC on silica gel, 8:1 dichloromethane/ethyl acetate R_f = 0.26; yellow solid; mp > 300 °C; yield 41% (20 mg, major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (bs, 1H), 8.42 (s, 1H), 7.65 (d, *J* = 9.6 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 2.57 (s, 3H), 1.83 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 162.4, 141.0, 135.5, 135.0, 130.1, 129.0, 128.1, 123.9, 123.8, 85.5, 26.9, 21.9; FT-IR (neat) 2991, 1770, 1686, 1662, 1370, 1320, 1241 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{14}H_{14}NO_3$: 244.0968; Found 244.0968.



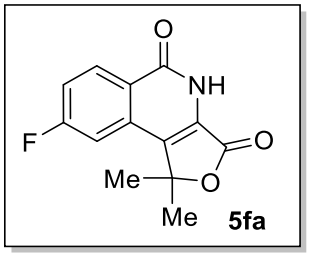
3,3,7-trimethylfuro[3,4-*c*]isoquinoline-1,5(3*H*,4*H*)-dione 5ca'. Analytical TLC on silica gel, 8:1 dichloromethane/ethyl acetate R_f = 0.30; light yellow solid; mp > 300 °C; yield 9% (7 mg, minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.09 (s, 1H), 8.42 (d, *J* = 8.4 Hz, 1H), 8.22 (s, 1H), 7.70-7.67 (m, 1H), 2.56 (s, 3H), 1.84 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 166.2, 161.0, 138.5, 136.2, 130.2, 127.9, 124.3, 123.5, 100.8, 81.2, 25.5, 21.8; FT-IR (neat) 2991, 1768, 1684, 1662, 1370, 1320, 1240 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{14}H_{14}NO_3$: 244.0968; Found 244.0970.



8-Bromo-1,1-dimethyl-1,4-dihydrofuro[3,4-*c*]isoquinoline-3,5-dione 5da. Analytical TLC on silica gel, 8:1 dichloromethane/ethyl acetate R_f = 0.27; yellow solid; mp = 240-241 °C; yield 64% (25 mg, major); minor regioisomer (trace); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (bs, 1H), 8.47 (d, *J* = 8.4 Hz, 1H), 7.83-7.81 (m, 1H), 7.75-7.74 (m, 1H), 1.84 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2, 162.1, 133.6, 133.3, 132.0, 131.9, 129.2, 127.7, 126.5, 126.2, 85.5, 26.9; FT-IR (neat) 2985, 1737, 1448, 1372, 1233, 1044, 937 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{13}H_{11}BrNO_3$: 307.9917; Found 307.9917.

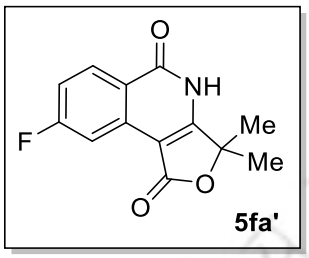


8-Chloro-1,1-dimethyl-1,4-dihydrofuro[3,4-*c*]isoquinoline-3,5-dione 5ea. Analytical TLC on silica gel, 8:1 dichloromethane/ethyl acetate R_f = 0.27; yellow solid; mp 230-231 °C; yield 62% (26 mg, major); minor regioisomer (trace); NMR (400 MHz, $CDCl_3$) δ 9.69 (bs, 1H), 8.54 (d, *J* = 8.8 Hz, 1H), 7.68-7.65 (m, 1H), 7.58-7.57 (m, 1H), 1.84 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.1, 161.6, 140.6, 133.7, 131.9, 131.8, 130.4, 127.4, 126.1, 123.5, 85.6, 26.9; FT-IR (neat) 2985, 1736, 1446, 1371, 1233, 1043, 938 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{13}H_{11}ClNO_3$: 264.0422; Found 264.0426.

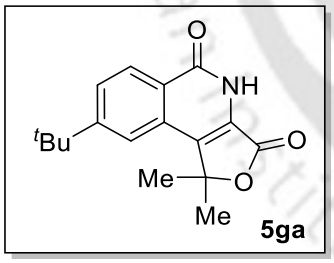


8-Fluoro-1,1-dimethyl-1,4-dihydrofuro[3,4-*c*]isoquinoline-3,5-dione 5fa. Analytical TLC on silica gel, 8:1 dichloromethane/ethyl acetate R_f = 0.27; brown solid; mp = 250-251 °C; yield 58% (25 mg, major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (bs, 1H), 8.64 (dd, *J* =

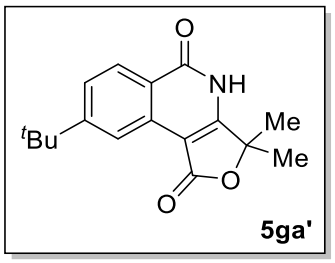
8.8, 5.6 Hz, 1H), 7.41 (td, J = 8.8, 2.4 Hz, 1H), 7.27-7.24 (m, 1H), 1.83 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 164.7, 164.2, 161.5, 134.0, 133.4 ($J_{C\text{-}F}$ = 10.3 Hz), 132.7 ($J_{C\text{-}F}$ = 11.1 Hz), 125.6 ($J_{C\text{-}F}$ = 72.8 Hz), 118.1 ($J_{C\text{-}F}$ = 22.8 Hz), 109.7 ($J_{C\text{-}F}$ = 23.0 Hz), 85.6, 26.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ -102.31; FT-IR (neat) 2983, 1764, 1667, 1611, 1238, 1175 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{13}H_{11}FNO_3$: 248.0717; Found 248.0723.



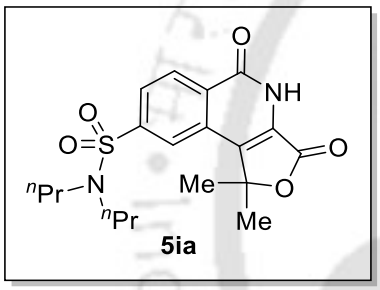
8-Fluoro-3,3-dimethylfuro[3,4-*c*]isoquinoline-1,5(3*H*,4*H*)-dione 5fa'. Analytical TLC on silica gel, 8:1 dichloromethane/ethyl acetate R_f = 0.30; colorless solid; mp = 254-255 °C; yield 7% (5 mg, minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.79 (s, 1H), 8.48-8.45 (m, 1H), 8.20-8.17 (m, 1H), 7.34-7.29 (m, 1H), 1.85-1.82 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 165.9, 165.3, 162.7, 135.0 ($J_{C\text{-}F}$ = 11.6 Hz), 131.6 ($J_{C\text{-}F}$ = 10.5 Hz), 120.9, 116.8 ($J_{C\text{-}F}$ = 23.5 Hz), 109.5 ($J_{C\text{-}F}$ = 23.4 Hz), 81.2, 77.0, 25.45; ^{19}F NMR (565 MHz, $CDCl_3$) δ -100.53; FT-IR (neat) 2985, 1763, 1667, 1611, 1238, 1172 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{13}H_{11}FNO_3$: 248.0717; Found 248.0720.



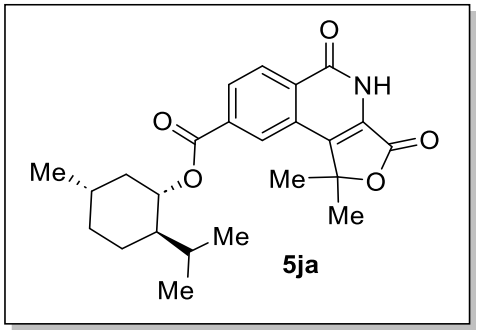
8-(*tert*-Butyl)-1,1-dimethyl-1,4-dihydrofuro[3,4-*c*]iso-quino-line-3,5-dione 5ga. Analytical TLC on silica gel, 8:1 dichloromethane/ethyl acetate R_f = 0.27; yellow solid; mp = 237-238 °C; yield 63% (26 mg, major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (bs, 1H), 8.53 (d, J = 8.8 Hz, 1H), 7.78-7.76 (m, 1H), 7.58-7.57 (m, 1H), 1.85 (s, 6H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 162.4, 157.6, 135.5, 130.5, 130.0, 128.1, 126.7, 124.8, 119.9, 85.5, 35.6, 31.2, 27.0; FT-IR (neat) 2985, 1738, 1447, 1373, 1234, 1044, 937 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{20}NO_3$: 286.1438; Found 286.1447.



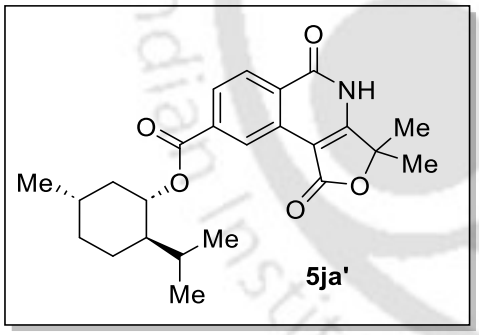
8-(*tert*-Butyl)-3,3-dimethylfuro[3,4-c]isoquinoline-1,5(3*H*,4*H*)-dione 5ga'. Analytical TLC on silica gel, 8:1 dichloromethane/ethyl acetate R_f = 0.31; light yellow solid; mp = 242-243 °C; yield 10% (10 mg, minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.97 (s, 1H), 8.55 (s, 1H), 8.35 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 9.6 Hz, 1H), 1.82 (s, 6H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 166.1, 161.8, 159.0, 132.7, 128.1, 126.1, 122.0, 119.8, 100.9, 81.0, 35.8, 31.2, 25.5; FT-IR (neat) 2982, 1735, 1447, 1372, 1234, 1044, 940 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{20}NO_3$: 286.1438; Found 286.1447.



1,1-Dimethyl-3,5-dioxo-*N*,*N*-dipropyl-1,3,4,5-tetrahydro-furo-[3,4-*c*]isoquinoline-8-sulfonamide 5ia. Analytical TLC on silica gel, 8:1 dichloromethane/ethyl acetate R_f = 0.27; yellow solid; mp > 300 °C; yield 60% (24 mg, major); minor regioisomer (trace); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (bs, 1H), 8.73 (d, *J* = 8.0 Hz, 1H), 8.05-8.02 (m, 2H), 3.19-3.15 (m, 4H), 1.87 (s, 6H), 1.62-1.52 (m, 4H), 0.88 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 161.4, 145.7, 134.1, 131.6, 131.3, 130.9, 127.1, 126.5, 122.6, 85.6, 50.0, 26.9, 22.0, 11.3; FT-IR (neat) 2986, 1738, 1448, 1372, 1230, 1044, 937 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{25}N_2O_5S$: 393.1479; Found 393.1479.

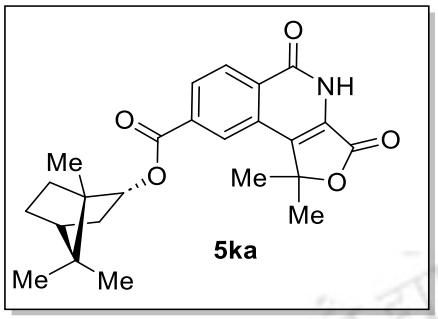


(1*S*,2*R*,5*S*)-2-*iso*-Propyl-5-methylcyclohexyl 1,1-dimethyl-3,5-dioxo-1,3,4,5-tetrahydrofuro[3,4-*c*]isoquinoline-8-carboxylate 5ja. Analytical TLC on silica gel, 8:1 dichloromethane/ethyl acetate R_f = 0.27; brown solid; mp > 300 °C; yield 62% (26 mg, major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (bs, 1H), 8.67 (d, *J* = 8.0 Hz, 1H), 8.32-8.30 (m, 2H), 5.21-5.17 (m, 1H), 2.57-2.49 (m, 1H), 2.13-2.07 (m, 1H), 1.88 (d, *J* = 2 Hz, 6H), 1.80 (t, *J* = 4.4 Hz, 1H), 1.37-1.28 (m, 3H), 1.19-1.15 (m, 1H), 1.00 (s, 3H), 0.95-0.94 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 164.2, 161.5, 135.6, 134.8, 131.8, 130.6, 130.5, 129.9, 125.5, 125.4, 85.8, 82.1, 49.4, 48.2, 45.1, 37.1, 28.2, 27.6, 26.9, 19.9, 19.1, 13.8; FT-IR (neat) 2987, 1735, 1450, 1372, 1231, 1044 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{24}H_{30}NO_5$: 412.2118; Found 412.2112.

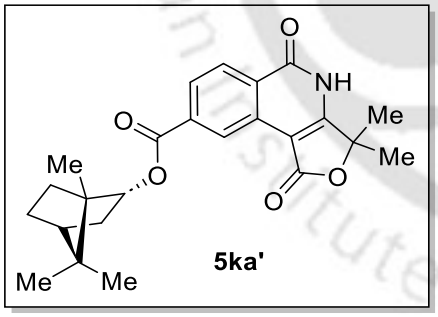


(1*S*,2*R*,5*S*)-2-*iso*-Propyl-5-methylcyclohexyl 3,3-dimethyl-1,5-dioxo-1,3,4,5-tetrahydrofuro[3,4-*c*]isoquinoline-8-carboxylate 5ja'. Analytical TLC on silica gel, 8:1 dichloromethane/ethyl acetate R_f = 0.32; colorless solid; mp > 300 °C; yield 8% (9 mg, minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.01 (s, 1H), 9.20-9.19 (m, 1H), 8.50 (d, *J* = 8.4 Hz, 1H), 8.25-8.22 (m, 1H), 5.18 (d, *J* = 9.2 Hz, 1H), 2.56-2.48 (m, 1H), 2.24-2.17 (m, 1H), 1.84 (s, 6H), 1.77 (t, *J* = 4.4 Hz, 1H), 1.52-1.40 (m, 2H), 1.37-1.33 (m, 1H), 1.20-1.16 (m, 1H), 0.99 (s, 3H), 0.94 (d, *J* = 4.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 165.8, 162.1, 136.5, 132.6, 128.6, 128.3, 126.9, 125.0, 101.1, 81.9, 81.2, 77.4, 49.4, 48.1, 45.1, 37.1, 28.3, 27.5, 25.5,

19.9, 19.1, 13.8; FT-IR (neat) 2985, 1730, 1450, 1372, 1231, 1048 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{24}H_{30}NO_5$: 412.2118; Found 412.2112.

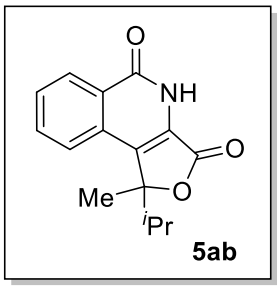


(1*S*,2*R*,4*R*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 1,1-dimethyl-3,5-dioxo-1,3,4,5-tetrahydrofuro[3,4-*c*]isoquinoline-8-carboxylate 5ka. Analytical TLC on silica gel, 8:1 dichloromethane/ethyl acetate R_f = 0.27; yellow solid; mp > 300 °C; yield 64% (22 mg, major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (bs, 1H), 8.68-8.66 (m, 1H), 8.30-8.28 (m, 2H), 5.01 (td, *J* = 10.8, 4.4 Hz, 1H), 2.18-2.15 (m, 1H), 1.97-1.93 (m, 1H), 1.89 (s, 3H), 1.87 (s, 3H), 1.80-1.74 (m, 3H), 1.21-1.13 (m, 2H), 0.95 (dd, *J* = 6.7, 4.0 Hz, 7H), 0.82 (d, *J* = 6.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 164.3, 161.7, 135.6, 134.9, 131.8, 130.6, 130.5, 130.0, 125.5, 125.4, 85.8, 77.4, 76.5, 47.4, 41.0, 34.3, 31.6, 27.0, 26.9, 24.0, 22.2, 20.8; FT-IR (neat) 2985, 1739, 1440, 1371, 1232, 1049 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{24}H_{28}NO_5$: 410.1962; Found 410.1955.

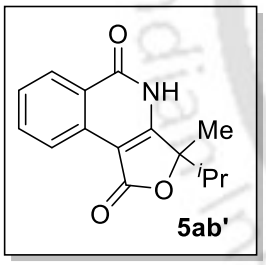


(1*S*,2*R*,4*R*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 3,3-dimethyl-1,5-dioxo-1,3,4,5-tetrahydrofuro[3,4-*c*]isoquinoline-8-carboxylate 5ka'. Analytical TLC on silica gel, 8:1 dichloromethane/ethyl acetate R_f = 0.30; light yellow solid; mp > 300 °C; yield 9% (8 mg, minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.13 (s, 1H), 9.14 (s, 1H), 8.49 (d, *J* = 8.4 Hz, 1H), 8.24-8.22 (m, 1H), 5.05-4.98 (m, 1H), 2.17-2.13 (m, 1H), 2.01- 1.92 (m, 1H), 1.85 (s, 5H), 1.78-1.74 (m, 2H), 1.68-1.59 (m, 3H), 1.25-1.10 (m, 3H), 0.94 (t, *J* = 6.0 Hz, 6H), 0.81 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 165.8, 165.1, 162.2, 136.5, 132.6, 130.1,

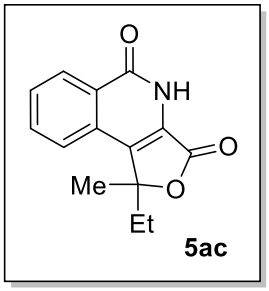
128.6, 128.5, 126.9, 125.0, 101.0, 81.2, 76.3, 47.2, 41.0, 34.4, 31.7, 26.8, 25.5, 23.9, 22.2, 20.8, 16.8; FT-IR (neat) 2982, 1740, 1440, 1371, 1230, 1046 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{24}H_{28}NO_5$: 410.1962; Found 410.1962.



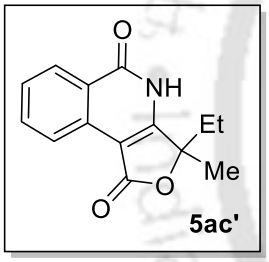
1-*iso*-Propyl-1-methyl-1,4-dihydrofuro[3,4-*c*]isoquinoline-3,5-dione 5ab. Analytical TLC on silica gel, 8:1 dichloromethane/ethyl acetate R_f = 0.32; brown solid; mp > 300 °C; yield 65% (32 mg, major); ^1H NMR (500 MHz, $CDCl_3$) δ 9.35 (bs, 1H), 8.62 (d, *J* = 8.0 Hz, 1H), 7.82 (t, *J* = 7.0 Hz, 1H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 2.46 (p, *J* = 7.0 Hz, 1H), 1.83 (s, 3H), 1.28 (d, *J* = 6.5 Hz, 3H), 0.65 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 162.2, 134.8, 133.7, 130.7, 130.3, 130.1, 129.0, 124.9, 123.9, 90.2, 35.7, 24.1, 17.2, 17.0; FT-IR (neat) 2982, 1736, 1449, 1371, 1235, 1098, 1046 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{15}H_{16}NO_3$: 258.1125; Found 258.1135.



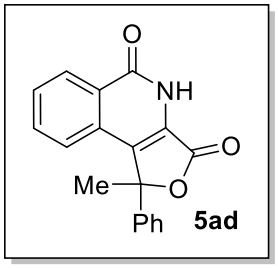
3-*iso*-Propyl-3-methylfuro[3,4-*c*]isoquinoline-1,5(3*H*,4*H*)-dione 5ab'. Analytical TLC on silica gel, 8:1 dichloromethane/ethyl acetate R_f = 0.35; colorless solid; mp > 300 °C; yield 9% (6 mg, minor); ^1H NMR (400 MHz, $CDCl_3$) δ 12.55 (s, 1H), 8.54 (d, *J* = 8.0 Hz, 1H), 8.42 (d, *J* = 8.4 Hz, 1H), 7.86 (t, *J* = 8.4 Hz, 1H), 7.63 (t, *J* = 8.4 Hz, 1H), 2.39 (p, *J* = 6.8 Hz, 1H), 1.80 (s, 3H), 1.23 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 165.9, 161.1, 134.8, 132.4, 128.3, 128.1, 124.3, 123.6, 101.7, 85.8, 77.4, 35.0, 22.5, 17.0; FT-IR (neat) 2980, 1737, 1449, 1370, 1238, 1098, 1050 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{15}H_{16}NO_3$: 258.1125; Found 258.1125.



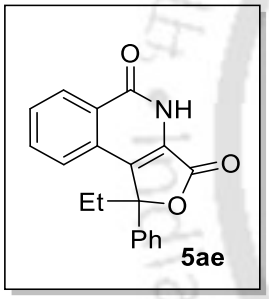
1-Ethyl-1-methyl-1,4-dihydrofuro[3,4-*c*]isoquinoline-3,5-dione 5ac. Analytical TLC on silica gel, 8:1 dichloromethane/ethyl acetate R_f = 0.27; yellow solid; mp > 300 °C; yield 62% (29 mg, major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.09 (bs, 1H), 8.65 (d, *J* = 8.0 Hz, 1H), 7.85-7.81 (m, 1H), 7.75-7.70 (m, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 2.36-2.27 (m, 1H), 2.18-2.09 (m, 1H), 1.83 (s, 3H), 0.78 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 162.7, 133.7, 133.5, 130.7, 130.3, 130.1, 129.0, 125.7, 123.7, 88.3, 32.1, 25.7, 7.9; FT-IR (neat) 2985, 1737, 1447, 1373, 1234, 1098, 1043 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{14}H_{14}NO_3$: 244.0968; Found 244.0969.



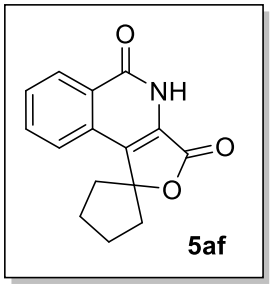
3-Ethyl-3-methylfuro[3,4-*c*]isoquinoline-1,5(3*H*,4*H*)-dione 5ac'. Analytical TLC on silica gel, 8:1 dichloromethane/ethyl acetate R_f = 0.30; brown solid; mp > 300 °C; yield 10% (9 mg, minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.16 (s, 1H), 8.55 (d, *J* = 8.0 Hz, 1H), 8.44 (d, *J* = 8.0 Hz, 1H), 7.87 (t, *J* = 8.4 Hz, 1H), 7.63 (t, *J* = 8.0 Hz, 1H), 2.29-2.12 (m, 2H), 1.82 (s, 3H), 0.91 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 166.3, 160.6, 134.8, 132.5, 128.3, 128.1, 124.3, 123.6, 102.0, 83.9, 77.4, 31.1, 24.1, 7.8; FT-IR (neat) 2985, 1737, 1447, 1373, 1234, 1098, 1043 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{14}H_{14}NO_3$: 244.0968; Found 244.0969.



1-Methyl-1-phenyl-1,4-dihydrofuro[3,4-*c*]isoquinoline-3,5-dione 5ad. Analytical TLC on silica gel, 9:1 dichloromethane/ethyl acetate R_f = 0.27; yellow solid; mp > 300 °C; yield 68% (32 mg, major); minor regioisomer (trace); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.77 (bs, 1H), 8.57 (d, *J* = 8.0 Hz, 1H), 8.41 (d, *J* = 8.0 Hz, 1H), 7.88 (t, *J* = 8.4 Hz, 1H), 7.66-7.62 (m, 3H), 7.41-7.34 (m, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 165.3, 161.1, 137.6, 134.8, 132.2, 129.4, 129.3, 128.4, 128.3, 125.4, 124.5, 123.8, 83.3, 77.4, 24.3; FT-IR (neat) 2977, 1722, 1437, 1280, 1240, 1152, 1029 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{18}H_{14}NO_3$: 292.0968; Found 292.0958.

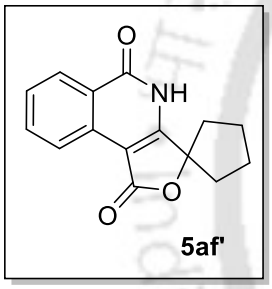


1-Ethyl-1-phenyl-1,4-dihydrofuro[3,4-*c*]isoquinoline-3,5-dione 5ae. Analytical TLC on silica gel, 9:1 dichloromethane/ethyl acetate R_f = 0.27; yellow solid; mp > 300 °C; yield 60% (35 mg, major); minor regioisomer (trace); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (bs, 1H), 8.62-8.60 (m, 1H), 7.70-7.68 (m, 2H), 7.44-7.37 (m, 6H), 2.95-2.86 (m, 1H), 2.61-2.52 (m, 1H), 0.81 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 162.4, 138.1, 133.7, 132.1, 131.1, 130.2, 130.0, 129.5, 129.1, 128.8, 126.7, 126.4, 124.5, 90.7, 29.8, 7.9; FT-IR (neat) 2985, 1737, 1447, 1373, 1234, 1098, 1043 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{16}NO_3$: 306.1125; Found 306.1133.



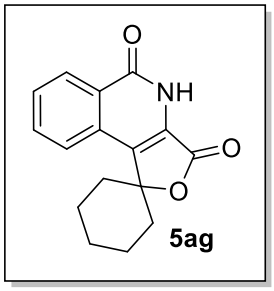
3'*H*-Spiro[cyclopentane-1,1'-furo[3,4-*c*]isoquinoline]-3',5'(4'*H*)-dione

5af. Analytical TLC on silica gel, 9:1 dichloromethane/ethyl acetate R_f = 0.27; brown solid; mp > 300 °C; yield 62% (30 mg, major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (bs, 1H), 8.62-8.60 (m, 1H), 7.85-7.80 (m, 1H), 7.74-7.70 (m, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 2.45-2.38 (m, 2H), 2.19-2.05 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.6, 162.0, 133.7, 131.8, 130.7, 130.3, 130.1, 129.1, 125.1, 123.6, 95.8, 38.4, 25.4; FT-IR (neat) 2987, 1731, 1441, 1355, 1285, 1237, 1153, 1065 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{15}H_{14}NO_3$: 256.0968; Found 256.0966.

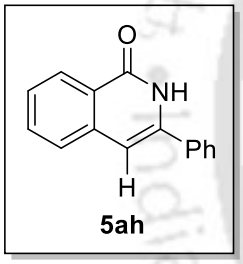


1'*H*-Spiro[cyclopentane-1,3'-furo[3,4-*c*]isoquinoline]-1',5'(4'*H*)-dione

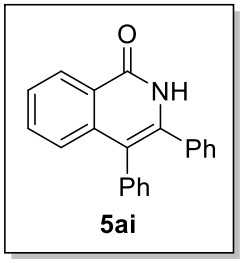
5af'. Analytical TLC on silica gel, 9:1 dichloromethane/ethyl acetate R_f = 0.30; light brown solid; mp > 300 °C; yield 10% (8 mg, minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.97 (s, 1H), 8.53 (d, *J* = 8.0 Hz, 1H), 8.37 (d, *J* = 8.0 Hz, 1H), 7.86 (t, *J* = 7.6 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 2.41-2.35 (m, 2H), 2.16 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.9, 166.1, 159.5, 134.8, 132.5, 128.2, 128.1, 124.4, 123.5, 101.9, 90.9, 38.2, 25.6; FT-IR (neat) 2990, 1730, 1441, 1355, 1285, 1236, 1153, 1064 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{15}H_{14}NO_3$: 256.0968; Found 256.0968.



3'*H*-spiro[cyclohexane-1,1'-furo[3,4-*c*]isoquinoline]-3',5'(4'*H*)-dione 5ag. Analytical TLC on silica gel, dichloromethane/ethyl acetate R_f = 0.28; brown solid; mp > 300 °C; yield 63% (32 mg, major); minor regioisomer (trace); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.28 (bs, 1H), 8.61 (d, *J* = 6.4 Hz, 1H), 7.83 (t, *J* = 6.4 Hz, 1H), 7.75 (d, *J* = 6 Hz, 1H), 7.71 (t, *J* = 6.4 Hz, 1H), 2.28-2.22 (m, 2H), 1.96-1.81 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 162.1, 135.2, 133.6, 130.8, 130.3, 130.0, 129.2, 124.9, 124.1, 87.6, 35.8, 24.8, 22.4; FT-IR (neat) 2985, 1738, 1661 1450, 1373, 1234, 1044 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{16}NO_3$: 270.1125; Found 270.1124.

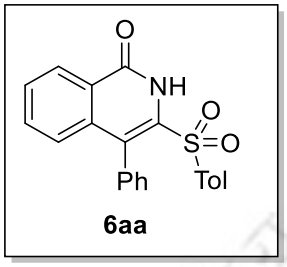


3-Phenylisoquinolin-1(2*H*)-one 5ah. Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.31; colorless solid; mp > 300 °C; yield 88% (32 mg, major); minor regioisomer (trace); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.84 (bs, 1H), 8.39 (d, *J* = 8.0 Hz, 1H), 7.81-7.79 (m, 2H), 7.69-7.65 (m, 1H), 7.61-7.59 (m, 1H), 7.55-7.45 (m, 4H), 6.80 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4, 139.8, 138.5, 134.4, 132.9, 129.6, 129.3, 127.6, 126.7, 126.6, 126.4, 125.1, 104.5; FT-IR (neat) 2980, 1730, 1661, 1450, 1360, 1234 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{15}H_{12}NO$: 222.0913; Found 222.0913.



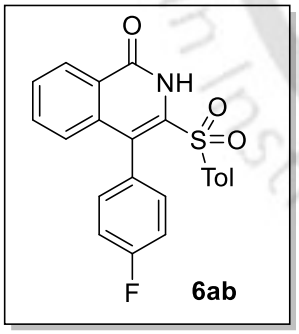
3,4-Diphenylisoquinolin-1(2*H*)-one 5ai. Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.31; colorless solid; mp > 300 °C; yield 91% (33 mg, major); ^{1}H NMR

(400 MHz, $CDCl_3$) δ 9.06 (bs, 1H), 8.50-8.48 (m, 1H), 7.61-7.57 (m, 1H), 7.53-7.48 (m, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.32-7.28 (m, 3H), 7.26-7.22 (m, 5H), 7.20-7.17 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8, 138.8, 137.1, 135.8, 135.3, 132.8, 132.0, 129.3, 128.8, 128.6, 128.5, 127.7, 127.5, 126.8, 125.8, 125.3, 117.4; FT-IR (neat) 2982, 1742, 1661, 1440, 1373, 1036 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{16}NO$: 298.1226; Found 298.1227.



6aa

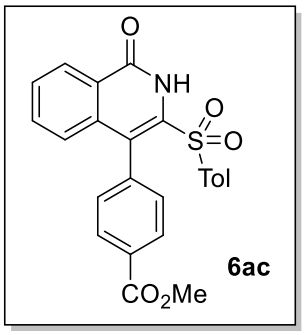
4-Phenyl-3-tosylisoquinolin-1(2*H*)-one 6aa. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.31; brown solid; mp = 247-248 °C; yield 77% (55 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (bs, 1H), 8.52-8.49 (m, 1H), 7.62-7.53 (m, 2H), 7.44 (t, J = 7.6 Hz, 1H), 7.32 (t, J = 8.0 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 7.6 Hz, 1H), 6.95 (d, J = 6.8 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7, 145.4, 138.0, 136.0, 134.9, 133.2, 131.9, 131.4, 129.6, 129.5, 128.8, 128.3, 128.2, 127.9, 127.8, 127.3, 122.3, 21.8; FT-IR (neat) 3060, 1669, 1600, 1508, 1337, 1222, 1168 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{22}H_{18}NO_3S$: 376.1002; Found: 376.1004.



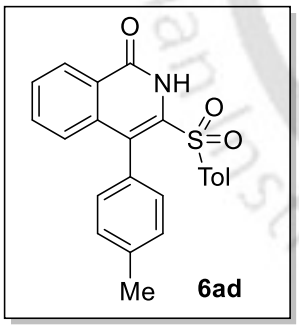
6ab

4-(4-Fluorophenyl)-3-tosylisoquinolin-1(2*H*)-one 6ab. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.35; brown solid; mp = 242-243 °C; yield 79% (55 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (bs, 1H), 8.52-8.50 (m, 1H), 7.64-7.55 (m, 2H), 7.20 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 7.03 (t, J = 8.4 Hz, 3H), 6.95-6.92 (m, 2H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.1, 162.1, 160.6, 145.6, 137.9, 136.1, 135.4, 133.7 ($J_{C\text{-}F}$ = 8.3 Hz), 133.4, 129.7, 128.2, 128.1, 127.8, 127.2 ($J_{C\text{-}F}$ = 3.5 Hz), 127.0, 121.1, 115.3 ($J_{C\text{-}F}$ = 21.5 Hz),

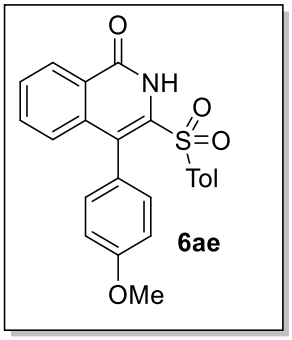
21.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ -112.28; FT-IR (neat) 3063, 1666, 1602, 1509, 1329, 1224, 1160 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{22}H_{17}FNO_3S$: 394.0908; Found 394.0915.



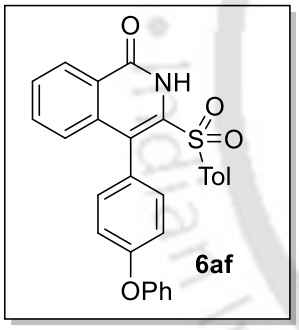
Methyl 4-(1-oxo-3-tosyl-1,2-dihydroisoquinolin-4-yl)-benzoate 6ac. Analytical TLC on silica gel, 9:1 ethyl acetate/hexane R_f = 0.35; brown solid; mp = 256-257 °C; yield 78% (63 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (bs, 1H), 8.50 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 2H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.57-7.53 (m, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 1H), 4.00 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 160.6, 145.8, 137.4, 136.5, 136.0, 135.1, 133.4, 132.0, 130.6, 129.8, 129.3, 128.3, 128.1, 127.8, 127.0, 121.1, 52.6, 21.8; FT-IR (neat) 3012, 1725, 1339, 1289, 1253, 1218, 1052 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{24}H_{20}NO_5S$: 434.1057; Found 434.1049.



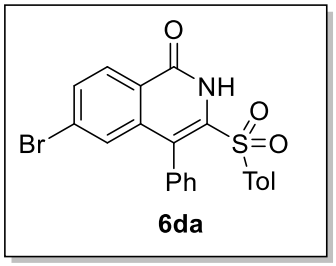
4-(*p*-Tolyl)-3-tosylisoquinolin-1(2*H*)-one 6ad. Analytical TLC on silica gel, 8:2 ethyl acetate/hexane R_f = 0.35; brown solid; mp = 249-250 °C; yield 78% (58 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (bs, 1H), 8.51-8.48 (m, 1H), 7.61-7.52 (m, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.14-7.06 (m, 5H), 6.83 (d, *J* = 8.0 Hz, 2H), 2.46 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7, 145.3, 138.7, 138.1, 136.2, 134.9, 133.2, 131.7, 129.5, 128.9, 128.4, 128.3, 127.9, 127.8, 127.4, 122.4, 21.8, 21.6; FT-IR (neat) 2987, 1723, 1671, 1320, 1272, 1215, 1053 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{20}NO_3S$: 390.1158; Found 390.1161.



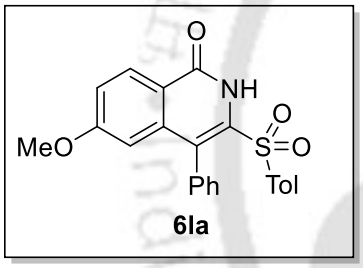
4-(4-Methoxyphenyl)-3-tosylisoquinolin-1(2*H*)-one 6ae. Analytical TLC on silica gel, 9:1 ethyl acetate/hexane R_f = 0.35; yellow solid; mp = 247-248 °C; yield 80% (62 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (bs, 1H), 8.51-8.49 (m, 1H), 7.62-7.54 (m, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.12-7.08 (m, 3H), 6.89-6.84 (m, 4H), 3.90 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7, 160.0, 145.3, 138.3, 136.2, 135.1, 133.2, 133.1, 129.6, 129.5, 128.3, 127.9, 127.8, 127.3, 123.2, 122.1, 113.7, 55.5, 21.8; FT-IR (neat) 3063, 1656, 1609, 1508, 1329, 1229, 1160 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{20}NO_4S$: 406.1108; Found 406.1103.



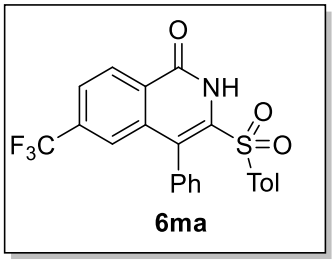
4-(4-Phenoxyphenyl)-3-tosylisoquinolin-1(2*H*)-one 6af. Analytical TLC on silica gel, 8:2 ethyl acetate/hexane R_f = 0.35; brown solid; mp = 260-261 °C; yield 75% (67 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (bs, 1H), 8.52-8.50 (m, 1H), 7.64-7.57 (m, 2H), 7.44 (t, *J* = 8.0 Hz, 2H), 7.27 (s, 1H), 7.25 (s, 2H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 3H), 7.10 (d, *J* = 7.2 Hz, 1H), 6.94-6.88 (m, 4H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 158.2, 156.5, 145.5, 138.1, 136.2, 135.2, 133.4, 133.3, 130.2, 129.7, 128.3, 128.0, 127.8, 127.2, 125.6, 124.3, 121.8, 119.8, 117.9, 21.9; FT-IR (neat) 3010, 1723, 1673, 1340, 1290, 1253, 1220, 1067 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{28}H_{22}NO_4S$: 468.1264; Found 468.1265.



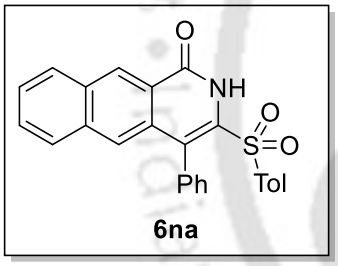
6-Bromo-4-phenyl-3-tosylisoquinolin-1(2*H*)-one 6da. Analytical TLC on silica gel, 8:2 ethyl acetate/hexane R_f = 0.28; yellow solid; mp > 300 °C; yield 76% (45 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.62 (bs, 1H), 8.34 (d, *J* = 8.5 Hz, 1H), 7.69 (d, *J* = 10.5 Hz, 1H), 7.46 (t, *J* = 6.5 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 2H), 7.14-7.13 (m, 3H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.92 (d, *J* = 8.0 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1, 145.6, 139.5, 136.3, 135.7, 132.9, 131.8, 130.6, 129.71, 129.69, 129.65, 129.1, 128.9, 128.5, 128.4, 126.5, 121.0, 21.8; FT-IR (neat) 2985, 1737, 1683, 1374, 1235, 1137, 1044 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{22}H_{17}BrNO_3S$: 454.0107; Found 454.0107.



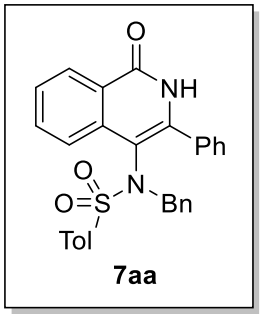
6-Methoxy-4-phenyl-3-tosylisoquinolin-1(2*H*)-one 6la. Analytical TLC on silica gel, 8:2 ethyl acetate/hexane R_f = 0.25; yellow solid; mp > 300 °C; yield 79% (58 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.50 (bs, 1H), 8.42 (d, *J* = 9.0 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.17-7.14 (m, 3H), 7.08 (d, *J* = 8.5 Hz, 2H), 6.94 (d, *J* = 7.5 Hz, 2H), 6.37 (s, 1H), 3.65 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 160.4, 145.3, 140.2, 136.1, 135.5, 131.8, 131.5, 130.0, 129.6, 128.8, 128.3, 128.2, 121.8, 121.4, 117.7, 109.7, 55.5, 21.8; FT-IR (neat) 2980, 1736, 1684, 1371, 1239, 1137, 1040 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{20}NO_4S$:406.1108; Found 406.1108.



4-Phenyl-3-tosyl-6-(trifluoromethyl)isoquinolin-1(2*H*)-one 6ma. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.35; brown solid; mp > 300 °C; yield 70% (42 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (bs, 1H), 8.62 (d, *J* = 8.4 Hz, 1H), 7.81-7.79 (m, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.28 (s, 1H), 7.14 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.96-6.94 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.7, 145.7, 138.3, 136.5, 135.5, 135.1 (J_{C-F} = 32.7 Hz), 131.8, 130.3, 130.0, 129.7, 129.3, 129.1, 128.6, 128.4, 125.6 (J_{C-F} = 2.5 Hz), 124.3 (J_{C-F} = 3.9 Hz), 124.2 (J_{C-F} = 271.5 Hz) 121.5, 21.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ -63.22; FT-IR (neat) 2983, 1738, 1684, 1372, 1234, 1137, 1044 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{17}F_3NO_3S$: 444.0876; Found 444.0885.

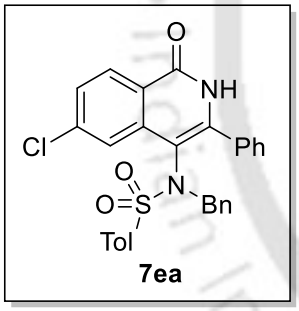


4-Phenyl-3-tosylbenzo[*g*]isoquinolin-1(2*H*)-one 6na. Analytical TLC on silica gel, 8:2 ethyl acetate/hexane R_f = 0.32; yellow solid; mp > 300 °C; yield 80% (50 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (bs, 1H), 9.10 (s, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.60-7.53 (m, 2H), 7.51-7.47 (m, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.04-7.02 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4, 145.3, 136.4, 135.3, 134.0, 133.8, 132.8, 132.0, 131.7, 129.6, 129.5, 129.4, 128.9, 128.8, 128.5, 128.28, 128.26, 127.8, 127.5, 124.8, 122.8, 21.8; FT-IR (neat) 2971, 1720, 1574, 1442, 1258, 1144 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{26}H_{20}NO_3S$: 426.1158; Found 426.1156.



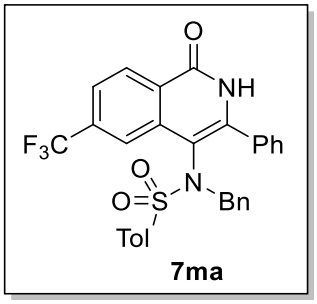
7aa

***N*-Benzyl-4-methyl-*N*-(1-oxo-3-phenyl-1,2-dihydroisoquinolin-4-yl)-benzenesulfonamide 7aa.** Analytical TLC on silica gel, 4:1 ethyl acetate/hexane R_f = 0.35; brown solid; mp > 300 °C; yield 82% (33 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.14 (bs, 1H), 8.33 (d, *J* = 8.0 Hz, 1H), 7.54-7.51 (m, 1H), 7.47-7.46 (m, 2H), 7.42-7.36 (m, 3H), 7.22-7.16 (m, 5H), 7.04 (t, *J* = 7.5 Hz, 2H), 6.91 (d, *J* = 7.5 Hz, 2H), 6.61 (d, *J* = 7.5 Hz, 2H), 4.57 (d, *J* = 13.5 Hz, 1H), 4.42 (d, *J* = 13.5 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0, 144.0, 143.6, 137.2, 136.7, 134.5, 133.3, 132.8, 130.2, 129.6, 129.3, 129.1, 128.5, 128.4, 128.3, 128.2, 127.0, 125.8, 124.4, 114.0, 54.0, 21.7; FT-IR (neat) 2985, 1737, 1447, 1373, 1234, 1044 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{29}H_{25}N_2O_3S$: 481.1580; Found 481.1584.

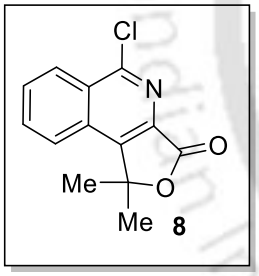


7ea

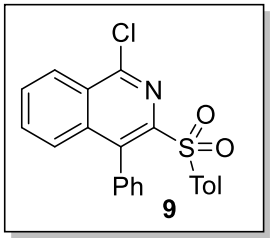
***N*-Benzyl-*N*-(6-chloro-1-oxo-3-phenyl-1,2-dihydroisoquinolin-4-yl)-4-methylbenzenesulfonamide 7ea.** Analytical TLC on silica gel, 8:2 ethyl acetate/hexane R_f = 0.32; colorless solid; mp > 300 °C; yield 82% (32 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (bs, 1H), 8.27 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.43-7.36 (m, 2H), 7.29-7.27 (m, 3H), 7.25 (s, 1H), 7.18-7.10 (m, 3H), 7.02 (t, *J* = 7.6 Hz, 2H), 6.93 (d, *J* = 2.0 Hz, 1H), 6.69 (d, *J* = 6.8 Hz, 2H), 4.59 (d, *J* = 13.6 Hz, 1H), 4.32 (d, *J* = 13.6 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 145.1, 144.5, 139.7, 137.9, 137.3, 134.3, 130.02, 130.00, 129.7, 128.9, 128.6, 128.5, 128.3, 128.2, 127.6, 124.0, 123.9, 113.3, 54.2, 21.8; FT-IR (neat) 2983, 1738, 1446, 1370, 1232, 1043 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{29}H_{24}ClN_2O_3S$: 515.1191; Found 515.1193.



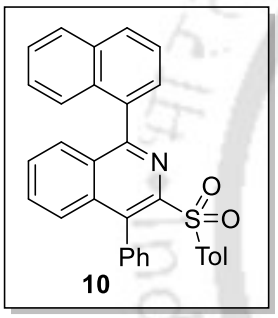
***N*-Benzyl-4-methyl-*N*-(1-oxo-3-phenyl-6-(trifluoromethyl)-1,2-dihydroisoquinolin-4-yl)benzenesulfonamide 7ma.** Analytical TLC on silica gel, 4:1 ethyl acetate/hexane R_f = 0.35; brown solid; mp > 300 °C; yield 81% (30 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (bs, 1H), 8.40 (d, *J* = 8.0 Hz, 1H), 7.59-7.56 (m, 3H), 7.49-7.45 (m, 1H), 7.36 (t, *J* = 8.0 Hz, 2H), 7.31-7.26 (m, 3H), 7.25 (s, 1H), 7.13-7.09 (m, 1H), 6.99 (t, *J* = 8.0 Hz, 2H), 6.71 (d, *J* = 7.2 Hz, 2H), 4.48-4.41 (m, 2H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 145.1, 144.6, 137.34, 137.28, 134.2, 133.9, 132.8, 130.1, 129.9, 129.2, 129.0, 128.7, 128.5, 128.4, 128.0, 127.6, 124.8, 123.1 (J_{C-F} = 3.1 Hz), 122.1, 121.6 (J_{C-F} = 4.2 Hz), 114.3, 54.4, 21.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ 63.2; FT-IR (neat) 2983, 1736, 1450, 1371, 1232, 1044 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{30}H_{24}F_3N_2O_3S$: 549.1454; Found 549.1443.



5-Chloro-1,1-dimethylfuro[3,4-*c*]isoquinolin-3(1*H*)-one 8. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.35; brown solid; mp > 300 °C; yield 79% (19 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, *J* = 8.4 Hz, 1H), 8.48 (d, *J* = 8.8 Hz, 1H), 8.00-7.96 (m, 1H), 7.84-7.80 (m, 1H), 1.77 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.9, 168.2, 159.2, 134.2, 133.7, 129.6, 127.8, 126.6, 123.7, 111.6, 85.5, 25.6; FT-IR (neat) 1737, 1447, 1370, 1234, 1034 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{13}H_{11}ClNO_2$: 248.0473; Found 248.0477.



1-Chloro-4-phenyl-3-tosylisoquinoline 9. Analytical TLC on silica gel, 9:1 ethyl acetate/hexane R_f = 0.35; brown solid; mp =230-231 °C; yield 80% (30 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 8.0 Hz, 1H), 7.81-7.77 (m, 1H), 7.71-7.68 (m, 3H), 7.53-7.46 (m, 4H), 7.26-7.22 (m, 4H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9, 148.1, 144.4, 138.9, 137.3, 134.2, 132.9, 132.2, 130.8, 130.4, 129.4, 129.2, 128.8, 128.1, 127.9, 127.8, 126.6, 21.8; FT-IR (neat) 1539, 1383, 1154, 1087, 1045 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{22}H_{17}ClNO_2S$: 394.0663; Found 394.0674.



1-(Naphthalen-1-yl)-4-phenyl-3-tosylisoquinoline 10. Analytical TLC on silica gel, 9:1 ethyl acetate/hexane R_f = 0.35; brown solid; mp =212-213 °C; yield 67% (25 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.63-7.48 (m, 9H), 7.44-7.43 (m, 2H), 7.29 (d, *J* = 8.5 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 148.8, 143.9, 137.9, 137.8, 135.5, 134.0, 133.9, 133.2, 132.3, 131.2, 130.7, 130.3, 129.6, 129.4, 129.28, 129.26, 129.0, 128.8, 128.6, 128.4, 128.2, 128.1, 128.0, 127.3, 126.4, 126.1, 126.0, 125.1, 21.7; FT-IR (neat) 1543, 1375, 1160, 1076, 947 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{32}H_{24}NO_2S$: 486.1522; Found 486.1530.

Sample Preparation for Crystal Growth. The compounds, **5ea** (10 mg), **6aa** (10 mg) and **7aa** (10 mg), were dissolved separately in a 1:1 mixture of CH_2Cl_2 and CH_3CN (2 mL) and kept at room temperature for slow evaporation (2 days). Block and needle shaped crystals were formed, which were then subjected to *X*-ray diffraction.

Crystal Structure and Data of 5ea.

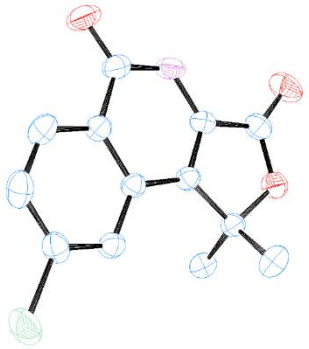


Figure 2. ORTEP diagram of 8-Chloro-1,1-dimethyl-1,4-dihydrofuro[3,4-*c*]isoquinoline-3,5-dione **5ea** (CCDC No 2352164) with 50% ellipsoid. H-Atoms are omitted for clarity.

CCDC No.	2352164
Identification code	**5ea**
Empirical formula	$C_{13}H_{10}ClNO_3$
Formula weight	263.67
Crystal habit, colour	Block, colorless
Temperature, *T*/K	293K
Wavelength, λ/Å	0.71073 Å
Crystal system	Monoclinic
Space group	P 21/c
Unit cell dimensions	a = 5.7676(3) Å b = 17.4337(10) Å c = 11.9763(8) Å α= 90 β=102.749(6) γ = 90
Volume, *V*/Å^3	1174.54(12) Å^3
Z	4

Calculated density, $Mg \cdot m^{-3}$	1.491
Absorption coefficient, μ/mm^{-1}	0.324
F (000)	544
2θ range for data collection	4.67 to 49.99
Limiting indices	$-6 \leq h \leq 4$, $-19 \leq k \leq 20$, $-10 \leq l \leq 14$
Reflection collected	4127
Completeness to θ	100 %
Absorption correction	Multi-scan
Refinement method	'SHELXL-2019/1'
Data / restraints / parameters	2061/0/165
Goodness-of-fit on F^2	1.052
Final R indices [I >2sigma(I)]	$R_1 = 0.0394$, $wR_2 = 0.0916$
R indices (all data)	$R_1 = 0.0510$, $wR_2 = 0.1031$

Crystal Structure and Data of 6aa.

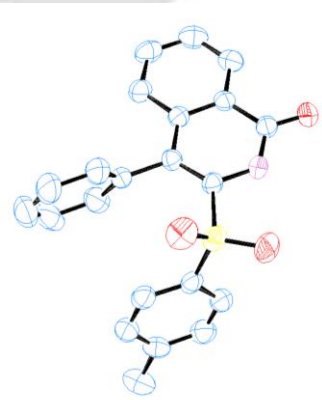


Figure 3. ORTEP diagram of 4-Phenyl-3-tosylisoquinolin-1(2*H*)-one **6aa** (CCDC No 2352154) with 50% ellipsoid. H-Atoms are omitted for clarity.

CCDC No.	2352154
Identification code	**6aa**
Empirical formula	$C_{22}H_{17}NO_3$
Formula weight	375.43
Crystal habit, colour	Block, colorless
Temperature, *T*/K	293K
Wavelength, λ/Å	0.71073 Å
Crystal system	Monoclinic
Space group	P 21/c
Unit cell dimensions	a = 9.6020 (8) Å b = 25.3981(18) Å c = 15.7561(14) Å α= 90 β=104.888(8) γ = 90
Volume, *V*/Å^3	3713.5(5) Å^3
Z	4
Calculated density, Mg·m^{-3}	1.343
Absorption coefficient, μ/mm^{-1}	0.197
F (000)	1569.9
2θ range for data collection	4.68 to 50
Limiting indices	$-12 \leq h \leq 6$, $-14 \leq k \leq 33$, $-20 \leq l \leq 21$
Reflection collected	16438
Completeness to *θ*	99.9 %
Absorption correction	Multi-scan
Refinement method	'SHELXL-2019/1 (Sheldrick, 2019)'
Data / restraints / parameters	6549/0/489
Goodness-of-fit on F^2	1.064
Final *R* indices [*I* >2sigma(*I*)]	R_1 = 0.0538, wR_2 = 0.1224

R indices (all data)	R_1 = 0.0756, wR_2 = 0.1408

Crystal Structure and Data of 7aa.

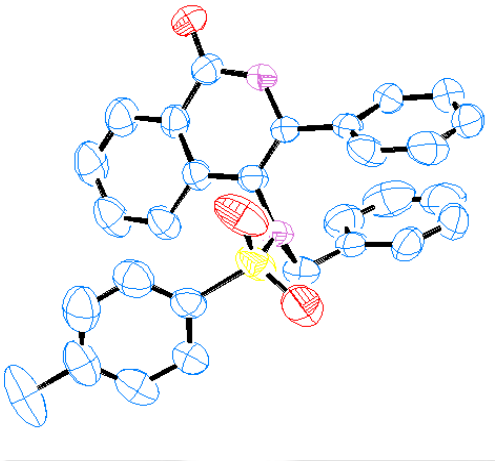


Figure 4. ORTEP diagram of *N*-benzyl-4-methyl-*N*-(1-oxo-3-phenyl-1,2-dihydroisoquinolin-4-yl)benzenesulfonamide **7aa** (CCDC No 2352165) with 50% ellipsoid. H-Atoms are omitted for clarity.

CCDC No.	2352165
Identification code	**7aa**
Empirical formula	$C_{29}H_{24}N_2O_3S$
Formula weight	480.56
Crystal habit, colour	Needle, colorless
Temperature, *T*/K	293K
Wavelength, λ/Å	0.71073 Å
Crystal system	triclinic
Space group	P -1

Unit cell dimensions	a = 8.4032 (4) Å b = 15.1793 (7) Å c = 20.1761 (9) Å α= 87.578 (4) β=87.716 (4) γ = 87.538 (4)
Volume, V/Å^3	2567.0(2) Å^3
Z	4
Calculated density, Mg·m^{-3}	1.243
Absorption coefficient, μ/mm^{-1}	0.159
F (000)	1008
2θ range for data collection	4.76 to 49.99
Limiting indices	$-9 \leq h \leq 9$, $-18 \leq k \leq 17$, $-23 \leq l \leq 23$
Reflection collected	15884
Completeness to θ	99.4 %
Absorption correction	Multi-scan
Refinement method	'SHELXL-2018/3'
Data / restraints / parameters	9005/0/633
Goodness-of-fit on F^2	1.047
Final R indices [I >2sigma(I)]	R_1 = 0.0613, wR_2 = 0.1291
R indices (all data)	R_1 = 0.1166, wR_2 = 0.1631

3.5 References

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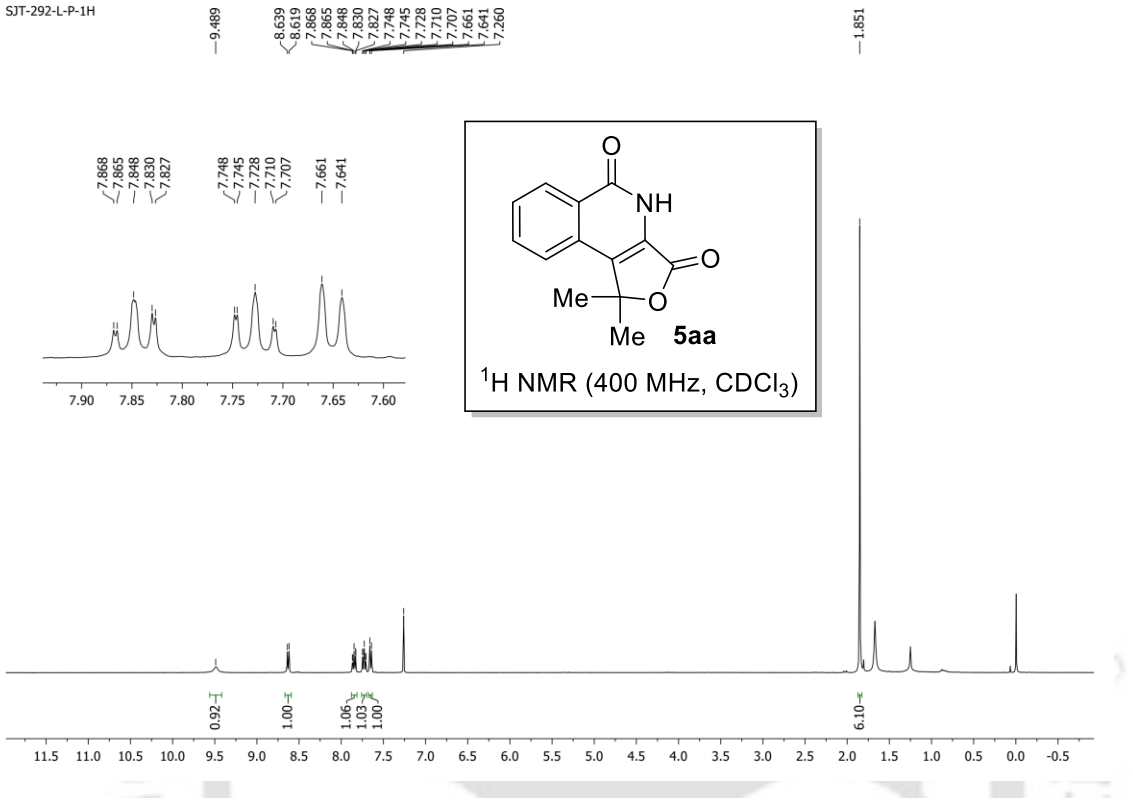
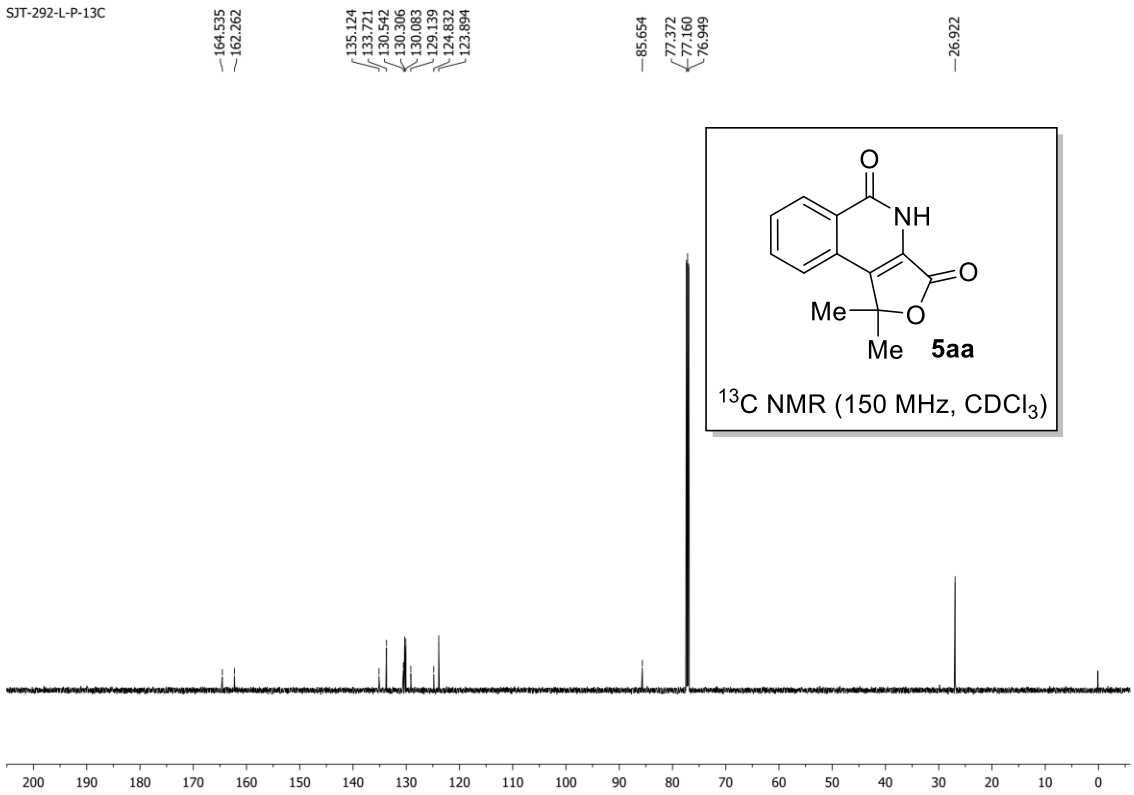
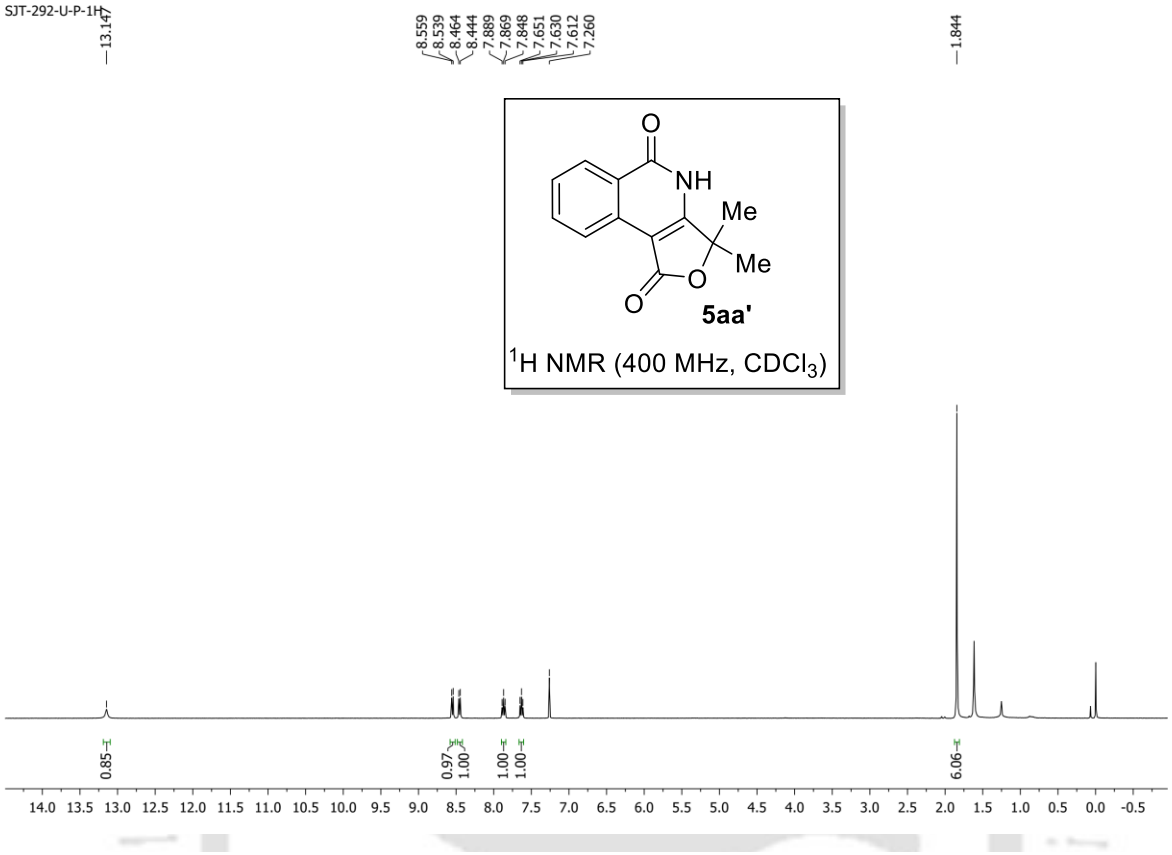
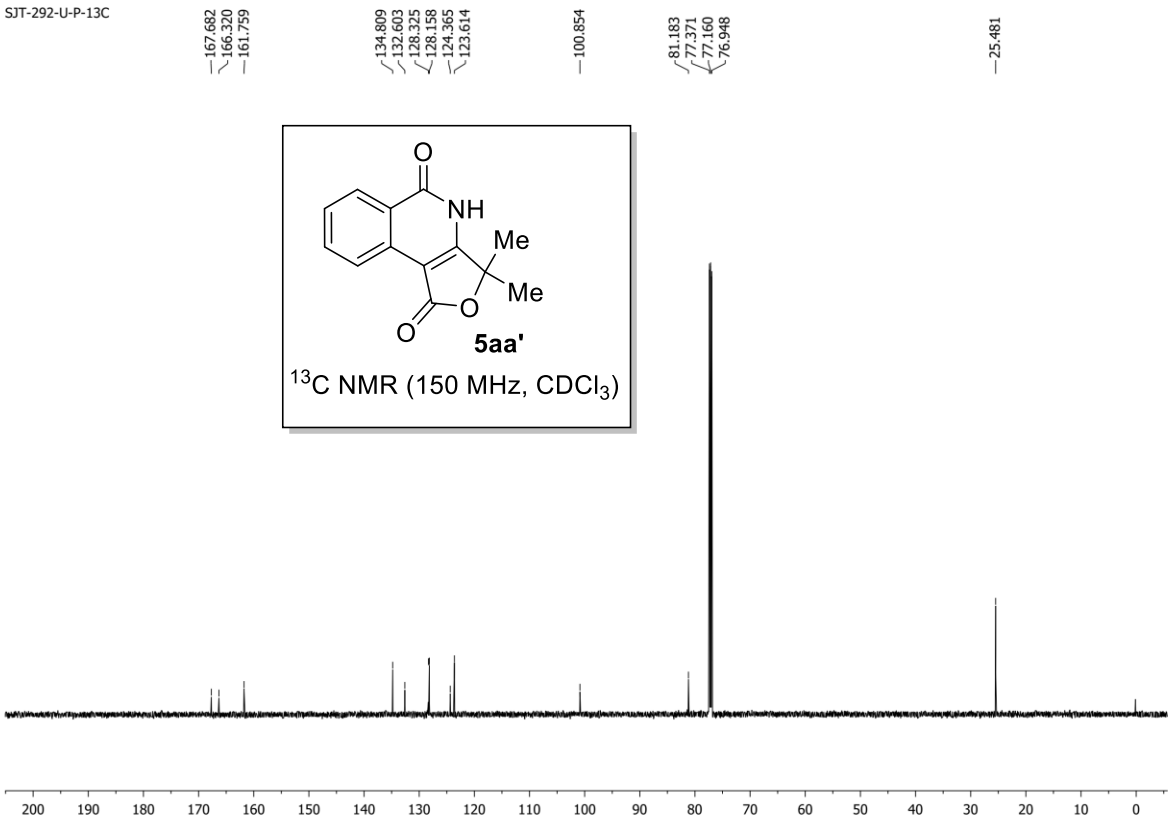
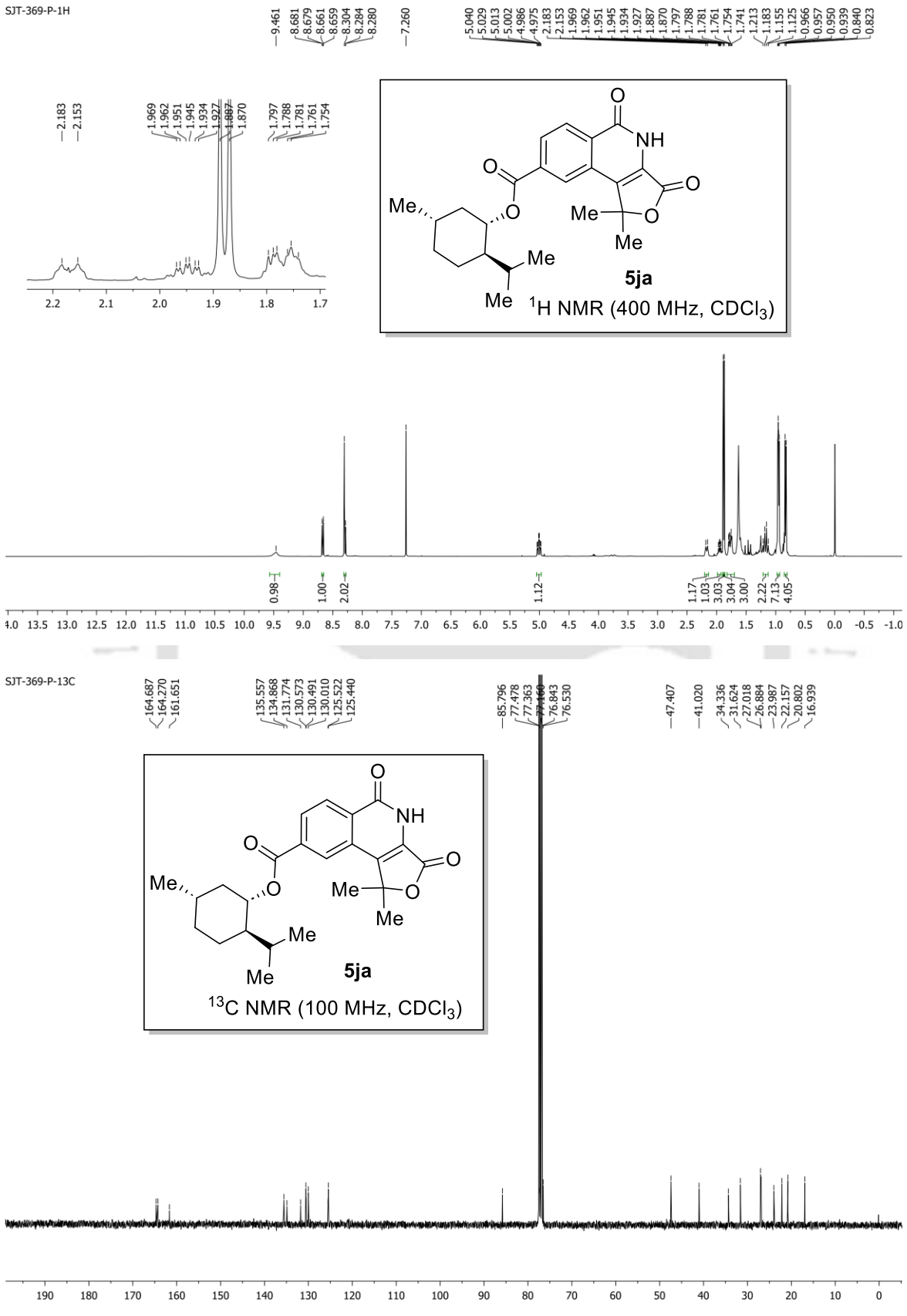
3.6 Selected NMR Spectra

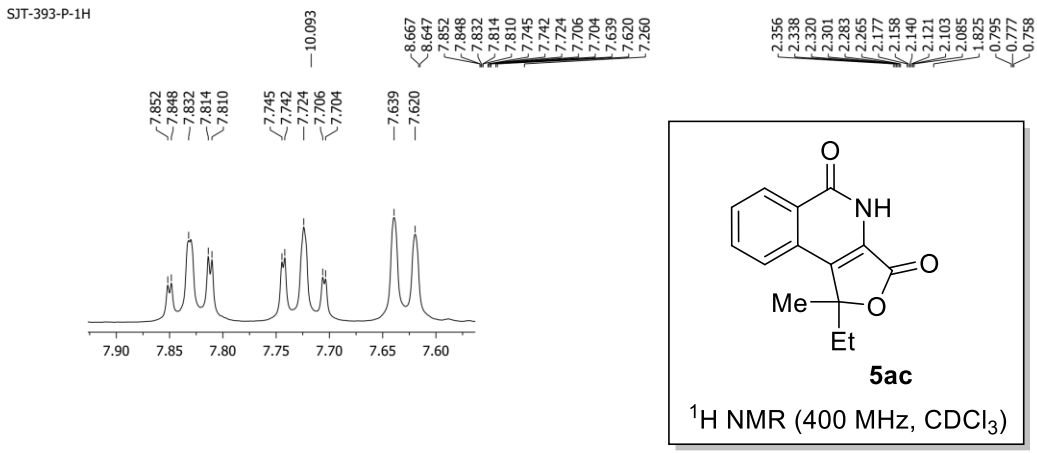


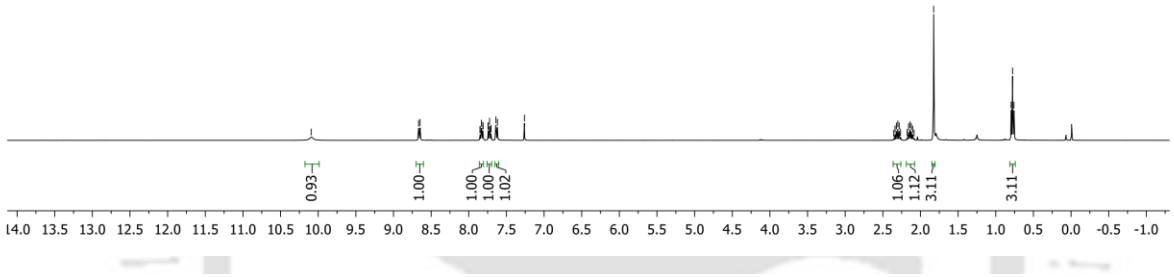


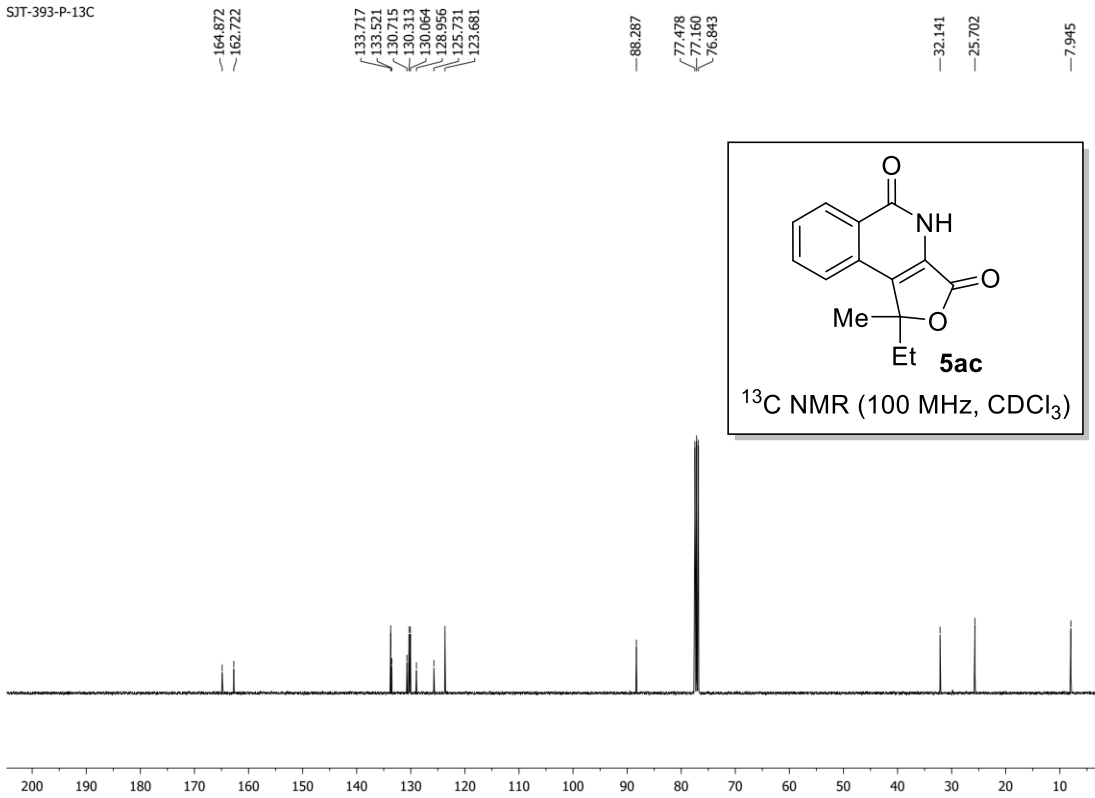


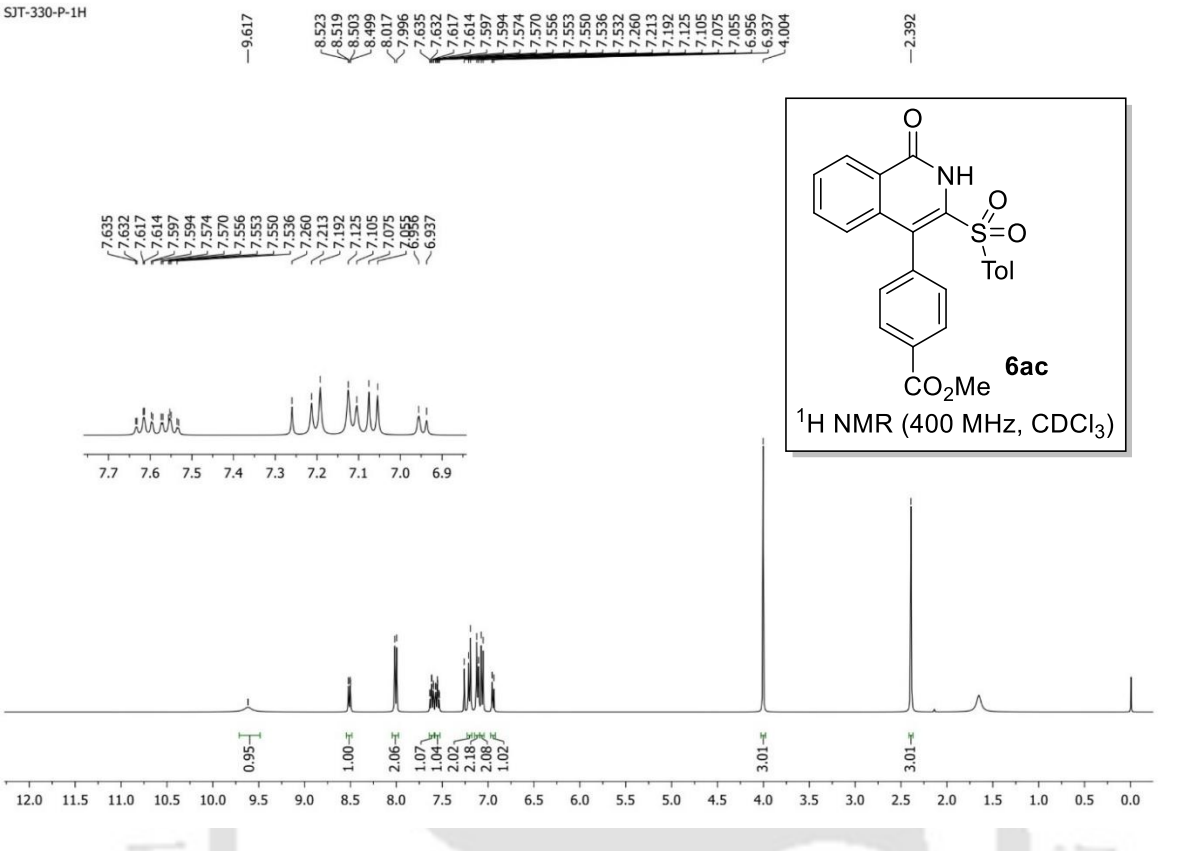


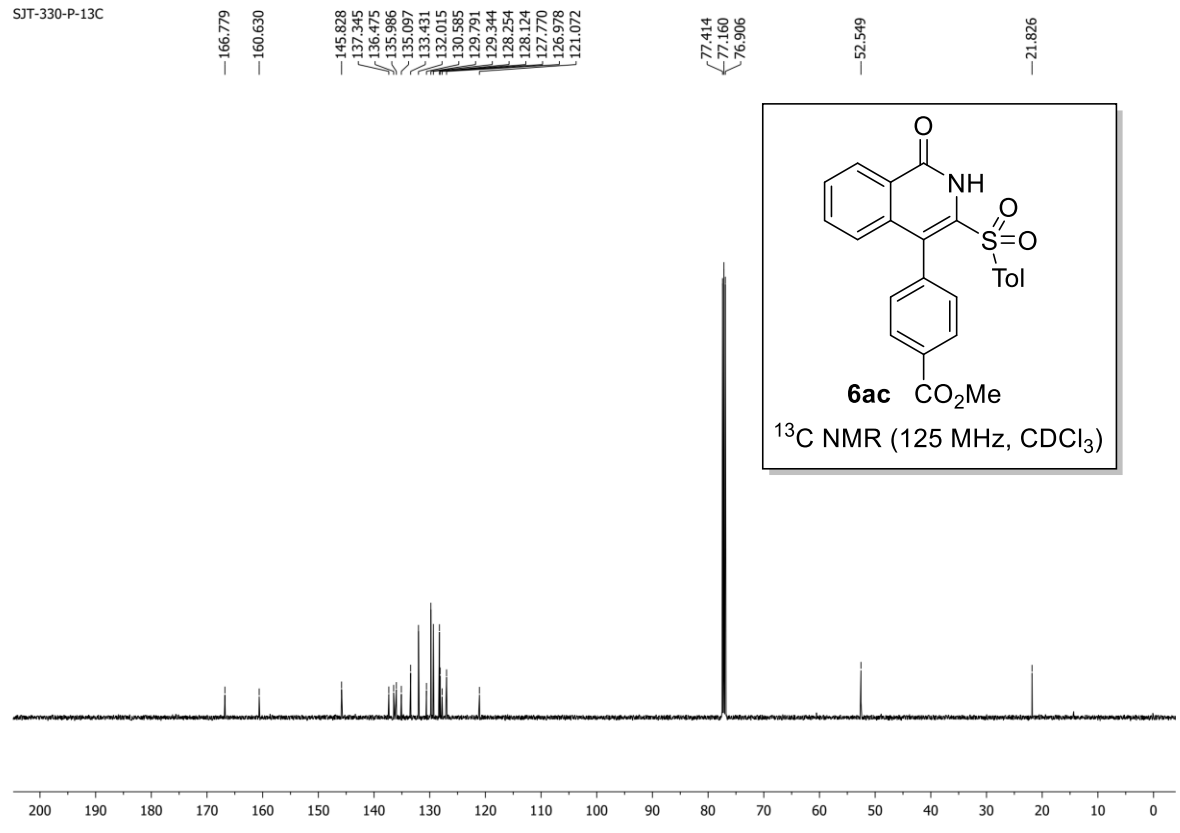


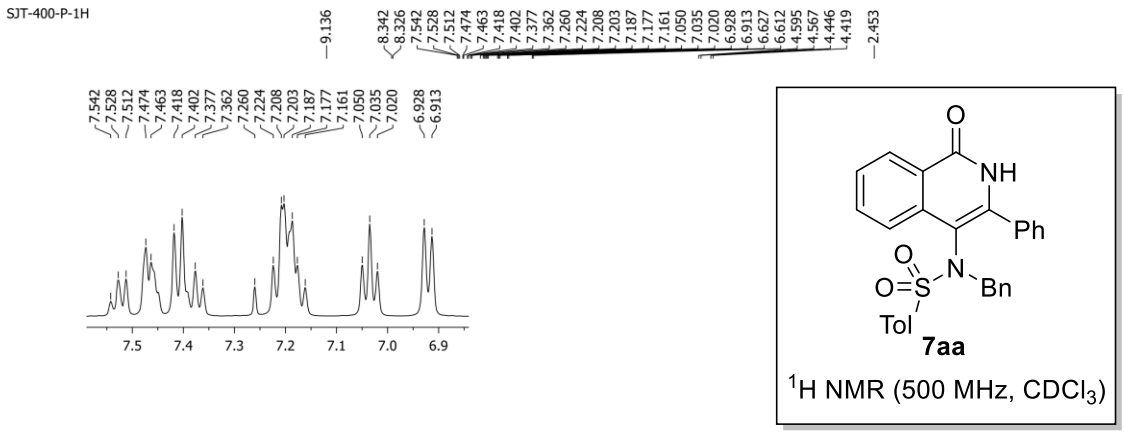


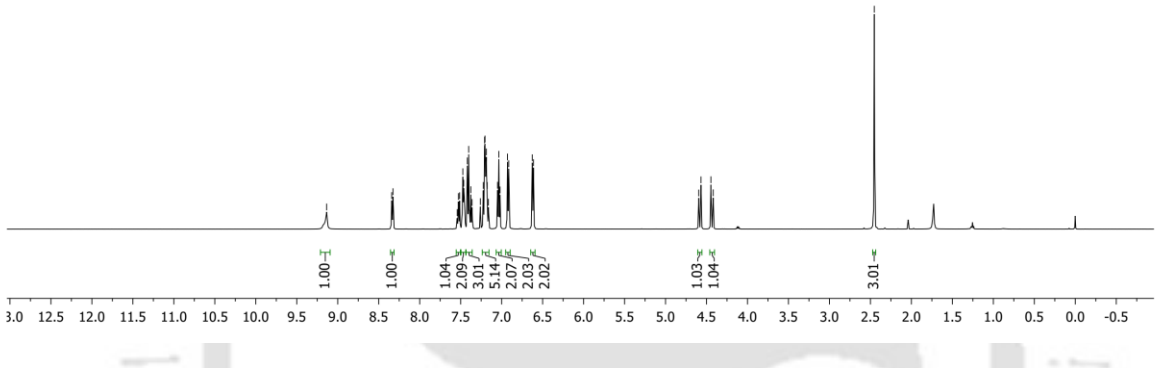


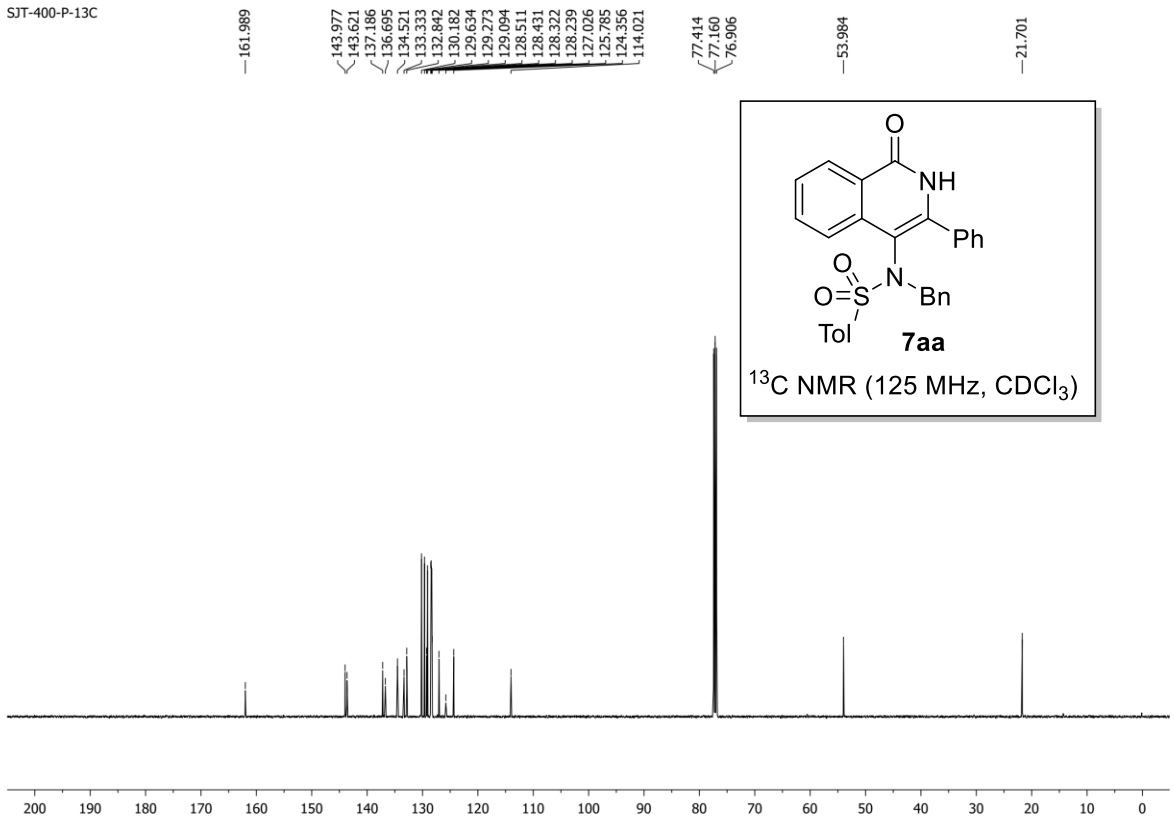






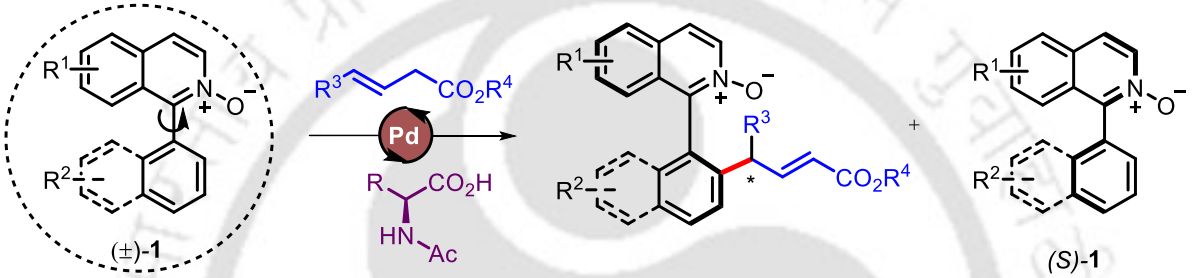






Chapter 4

Atroposelective C-H Allylation: Enabling Concurrent Axial and Central Chirality



♠ Axial & central chirality ♠ Open air reaction ♠ Upto 99% ee ♠ Kinetic Resolution

(Manuscript under preparation)

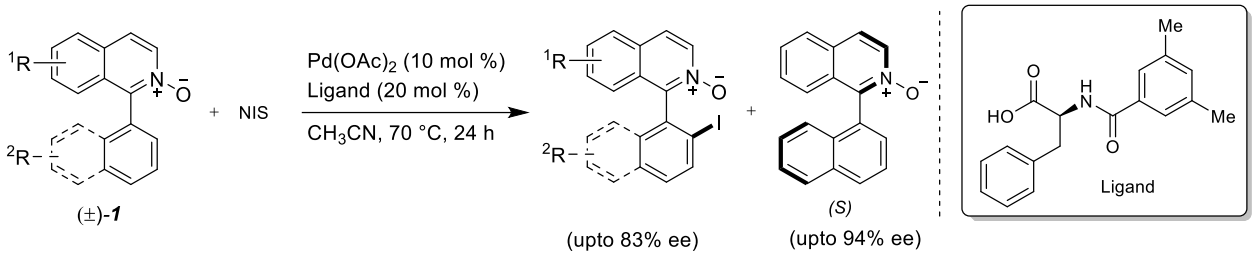
Atroposelective C-H Allylation: Enabling Concurrent Axial and Central Chirality

Axially chiral scaffolds are the privileged structural frameworks due to their interesting biological properties as well as their applications in asymmetric catalysis and functional materials.[1] Development of effective synthetic strategies to access these versatile motifs with structural diversity are thus valuable. Among them, the chiral transition-metal-catalyzed DG assisted enantioselective C-H functionalization is attractive as they have emerged as a reliable synthetic strategy for the site-selective carbon-carbon and carbon-heteroatom bond formation with step and atom economy to access the axially chiral frameworks,[2] while efforts are made on the development of synthetic routes to assemble diverse C-stereogenic scaffolds.[3] However, the transition-metal-catalysed concurrent generation of axial and central chirality with prochiral coupling partner poses a significant synthetic challenges, often leading to the formation of a mixture of stereoisomers.[4] Of the diverse classes of biaryl motifs, the axial heteroaryl scaffolds exhibit broad synthetic utilities, serving as chiral ligands and chiral catalysts for the enantioselective synthesis.[5] Recently, there has been thus considerable interest to explore synthetic approaches to access these axially chiral heteroaryl structural scaffolds.[6,7] In this context, internal alkenes such as *trans*-3-alkenoates[8] can enable the formation of allyl structural units merging the axial and central chirality. However, this approach can feature synthetic challenges such as alkenyl vs allyl selectivity as well as leading to the formation of a mixture of stereoisomers.

4.1 Literature

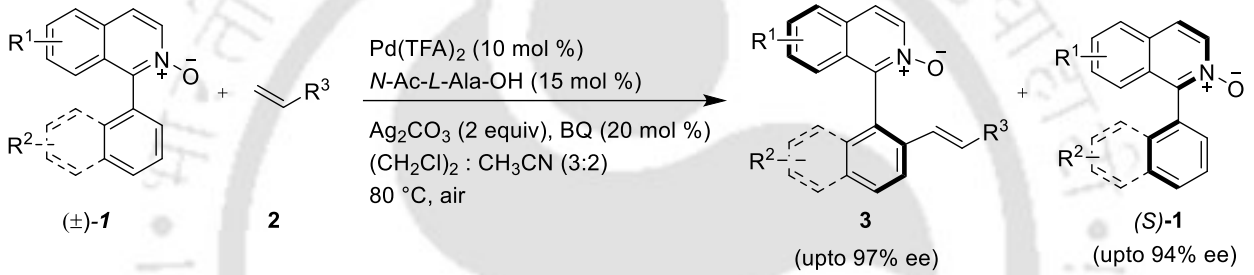
4.1.1 1-Arylisoquinoline *N*-oxide Directed Asymmetric C-H Functionalization

You and co-workers described a Pd-catalyzed intermolecular C-H iodination using axially chiral biaryl *N*-oxides and NIS *via* kinetic resolution with selectivity factor (S) up to 27 (Scheme 1).[6a] The resulting chiral iodides can readily be converted into aryl substituted pyridine *N*-oxides by Suzuki-Miyaura coupling which can function as organocatalysts in asymmetric allylation.



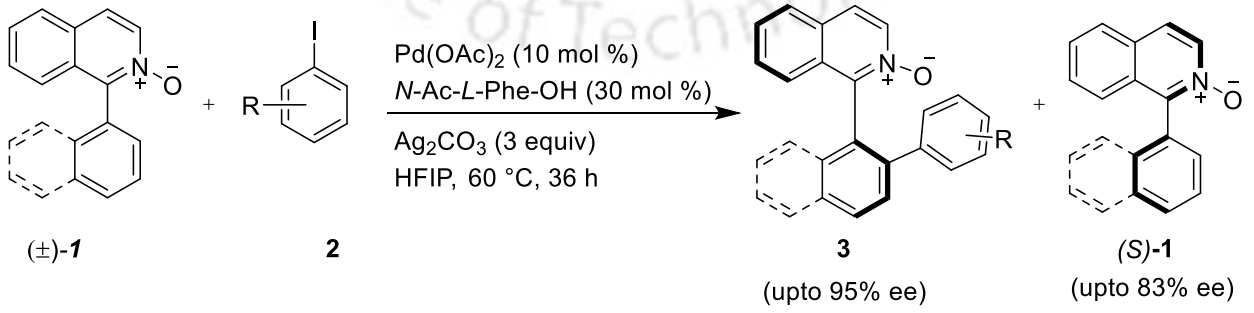
Scheme 1. Pd-Catalyzed Enantioselective C-H Iodination of *rac*-1-Arylisoquinoline *N*-oxides

Guo group developed a Pd-catalyzed asymmetric C-H alkenylation of heterobiaryl *N*-oxides, achieving kinetic resolution (S up to 102.7) and delivering both alkenylated products and recovered *N*-oxides with high ee (up to 97% and 94% ee) (Scheme 2).[6b]



Scheme 2. Pd-Catalyzed C-H Alkenylation of *rac*-1-Arylisoquinoline *N*-oxides

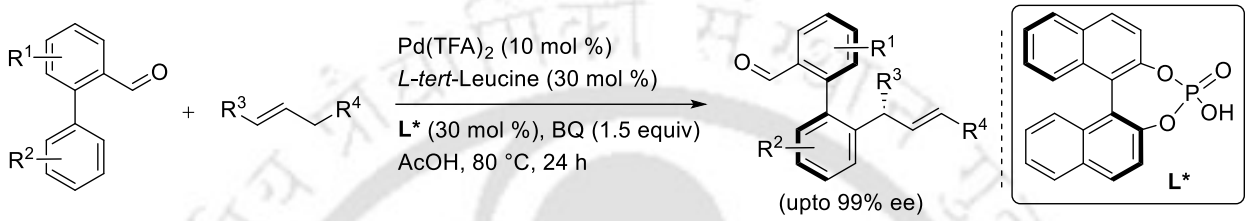
Recently, Sharma group developed a Pd-catalyzed atroposelective C(sp^2)-H arylation of 1-arylisoquinoline *N*-oxides *via* kinetic resolution using chiral MPAA ligand (*N*-Ac-*L*-Phe-OH), to accomplish axially chiral biaryls with selectivity factor (S) up to 60 (Scheme 3).[6c] The method furnishes configurationally stable atropoisomeric biaryls which is supported by experimental studies and DFT calculations.



Scheme 3. Pd-Catalyzed Atroposelective Arylation of 1-Arylisoquinoline *N*-oxides

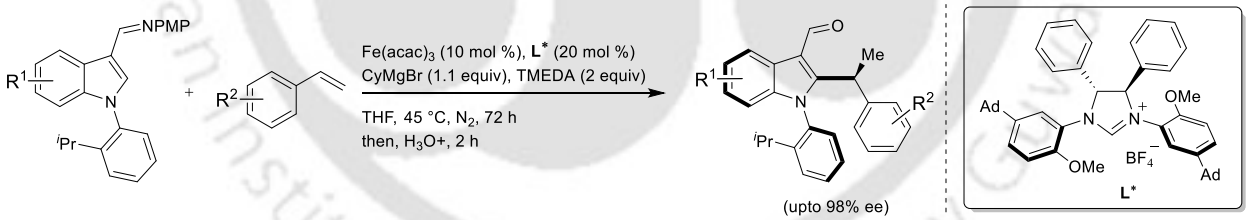
4.1.2 Prochiral Adducts in Asymmetric C-H Functionalization

Maiti and co-workers developed a Pd-catalyzed atroposelective *ortho*-allylation of *rac*-biaryl aldehydes using a combinatorial chiral amino acid and BINOL-phosphoric acid ligand system to achieve simultaneous control of axial and central chirality (>9:1 dr and up to 99% ee) (Scheme 4).[7b] The method employs unactivated internal olefins as allyl sources to deliver configurationally stable biaryls with stereocontrol rationalized by mechanistic and computational studies.



Scheme 4. Pd-Catalyzed Combinatorial Ligand assisted Stereoselective C-H Allylation

Ackermann and co-workers developed an Fe-catalyzed stereoselective C-H alkylation of indoles using a chiral *N*-heterocyclic carbene ligand to accomplish simultaneous construction of C-N axial and C-central chirality (>20:1 dr and up to 98% ee) (Scheme 5).[4a] The method enables broad substrate scope under Fe-catalysis with good stereocontrol rationalized by computational studies.



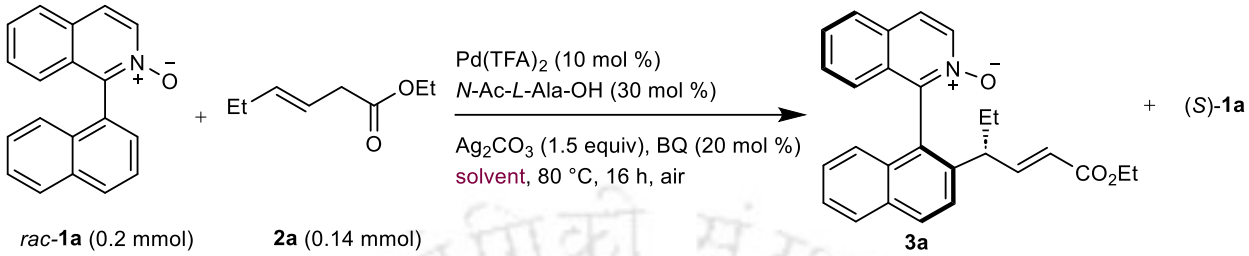
Scheme 5. Fe-Catalyzed Asymmetric C-H Alkylation

1.5 Present Study

We herein report an efficient atroposelective chiral Pd-MPAA-catalyzed C-H allylation of 1-aryl-isoquinoline *N*-oxides employing *trans*-3-alkenoates as coupling partner to accomplish the concurrent axial and central chirality. The enantioselective C-H allylation to achieve the axial and central chirality with heteroaryl compounds, isolation of two distinct diastereomers under tunable reaction conditions, kinetic resolution[9] with up to S =143, substrate scope and functional group diversity are the important practical features.

Table 1. Optimization of the Reaction Condition

Table 1.1. Screening of Solvents[a]

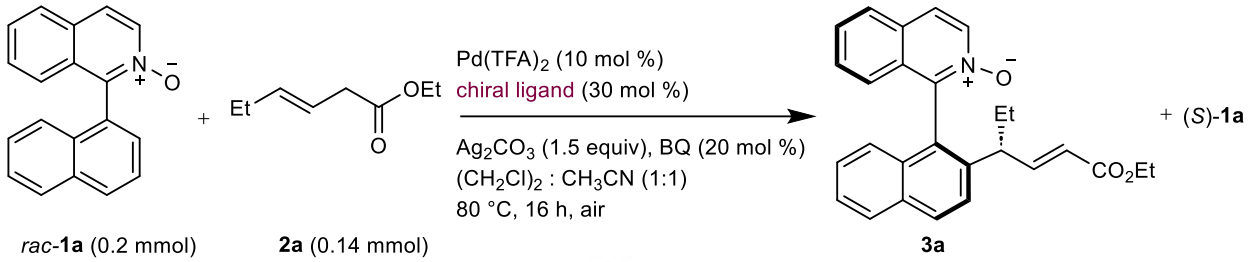


rac-**1a** (0.2 mmol) **2a** (0.14 mmol) **3a**

		Yield[b] (%)		ee[c] (%)			
Entry	Solvent	(*S*)-**1a**	**3a**	(*S*)-**1a**	**3a**	C[d] (%)	S[e]
1	$(CH_2Cl)_2$	45	42	44	54	45	5
2	TFE	52	35	33	52	39	4
3	HFIP	62	n.d.	-	-	-	-
4	CH_3CN	65	10	17	76	20	6
5	$(CH_2Cl)_2$: CH_3CN (9:1)	62	25	27	70	28	7
6	$(CH_2Cl)_2$: CH_3CN (3:2)	68	22	30	88	25	25
7	**$(CH_2Cl)_2$: CH_3CN (1:1)**	**70**	**17**	**22**	**91**	**19**	**38**

[a]Reaction conditions: *rac*-**1a** (0.2 mmol), **2a** (0.14 mmol), $Pd(TFA)_2$ (10 mol %), Ag_2CO_3 (1.5 equiv), *N*-Ac-*L*-Ala-OH (30 mol %), BQ (20 mol %), solvent (2 mL) at 80 °C, 16 h, air. [b]Yield was determined by ^1H NMR using CH_2Br_2 as an internal standard. [c]Determined by HPLC analysis on a chiral stationary phase. [d]Conversion, $C = ee_{SM}/(ee_{SM} + ee_{PR})$; [e]Selectivity factor, $(S) = \ln[(1-C)(1-ee_{SM})]/\ln[(1-C)(1+ee_{SM})]$. BQ = *p*-Benzoquinone.

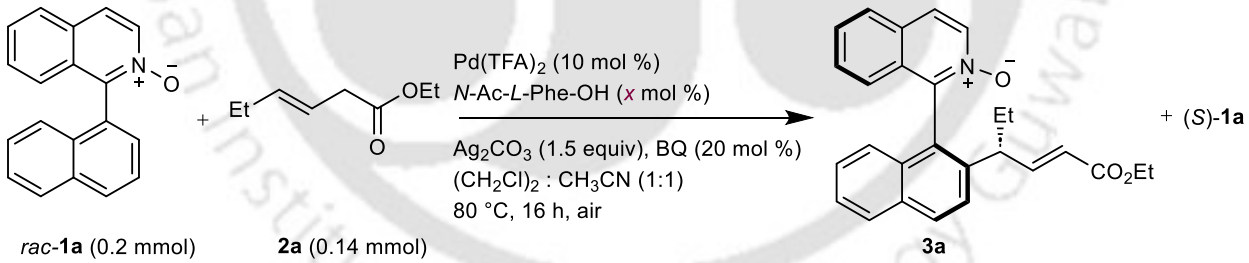
Table 1.2. Screening of Chiral Ligands



rac-**1a** (0.2 mmol) **2a** (0.14 mmol) **3a**

		Yield (%)		ee (%)			
Entry	Ligand	(*S*)-**1a**	**3a**	(*S*)-**1a**	**3a**	C (%)	S
1	*N*-Ac-*L*-Val-OH (**L2**)	78	trace	-	-	-	-
2	*N*-Ac-*L*-Leu-OH (**L3**)	75	10	10	71	12	7
3	***N*-Ac-*L*-Phe-OH (L4)**	**68**	**13**	**17**	**93**	**15**	**69**
4	*L*-Fmoc-Ala-OH (**L5**)	67	17	13	52	20	4
5	*L*-Boc-Ala-OH (**L6**)	70	trace	-	-	-	-
6	*L-tert*-Leucine **(L7)**	72	n.d.	-	-	-	-
7	*L-iso*-Leucine **(L8)**	75	n.d.	-	-	-	-

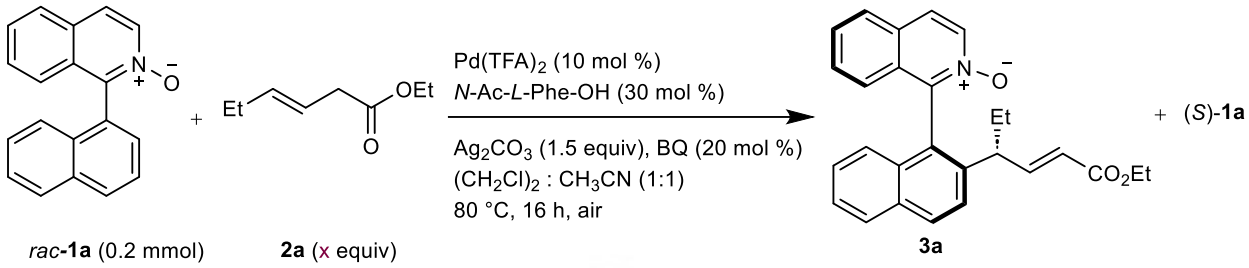
Table 1.3. Screening of Loading of Chiral Ligand



rac-**1a** (0.2 mmol) **2a** (0.14 mmol) **3a**

		Yield (%)		ee (%)			
Entry	x	(*S*)-**1a**	**3a**	(*S*)-**1a**	**3a**	C (%)	S
1	15	76	13	16	93	15	24
2	50	67	21	26	87	23	19
3	100	73	17	22	85	20	20

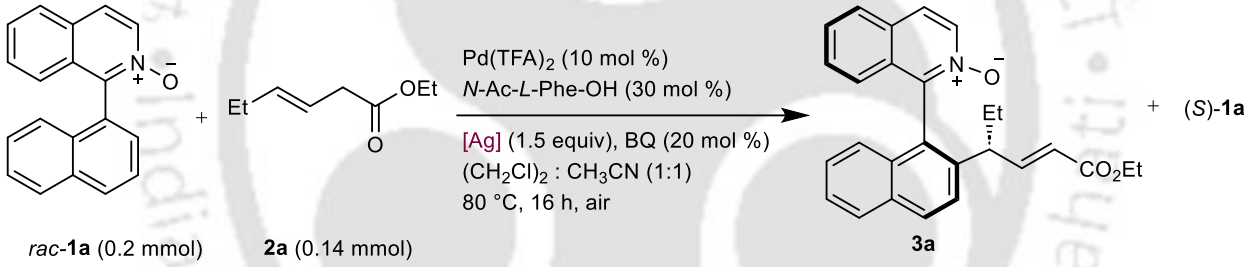
Table 1.4. Screening of Loading of Coupling Partner **2a**



rac-**1a** (0.2 mmol) **2a** (x equiv) **3a**

		Yield (%)		ee (%)			
Entry	x	(*S*)-**1a**	**3a**	(*S*)-**1a**	**3a**	C (%)	S
1	0.5	72	10	12	95	11	61
2	1	65	15	20	92	18	26
3	2	55	27	40	85	32	18

Table 1.5. Screening of [Ag] Additives



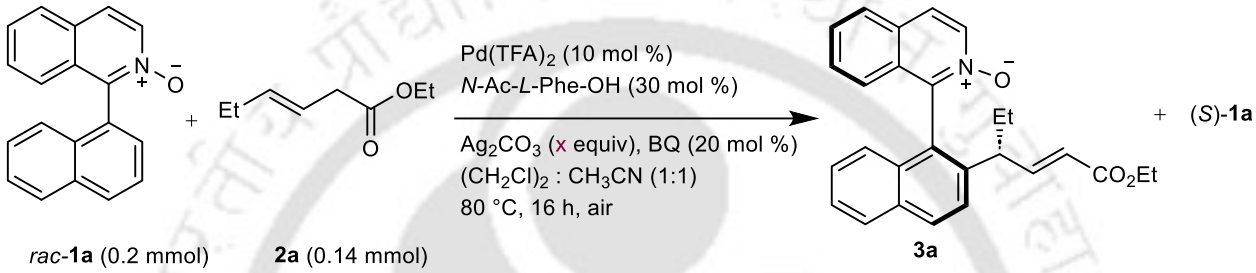
rac-**1a** (0.2 mmol) **2a** (0.14 mmol) **3a**

		Yield (%)		ee (%)			
Entry	[Ag]	(*S*)-**1a**	**3a**	(*S*)-**1a**	**3a**	C (%)	S
1	AgOAc	79	trace	-	-	-	-
2	AgTFA	81	n.d.	-	-	-	-
3	Ag_2O	85	n.d.	-	-	-	-

The optimization studies commenced employing 1-naphthyl-isoquinoline *N*-oxide (±)-**1a** (0.2 mmol) and *trans*-3-alkenoate **2a** (0.14 mmol) as the model substrates (Table 1). To our delight, the atroposelective allylation proceeded to deliver **3a** (diastereomer I) in 54% ee and 45% conversion (C), while the recovered (*S*)-**1a** exhibited 44% ee with S = 5 when the substrates **1a** and **2a** were reacted utilizing $Pd(TFA)_2$ (10 mol %), *N*-Ac-*L*-Ala-OH (30 mol %), Ag_2CO_3 (1.5 equiv) and BQ (20 mol %) in $(CH_2Cl)_2$ at 80 °C for 16 h. Screening of solvents revealed that a 1:1

mixture of $(CH_2Cl)_2$ and CH_3CN enhanced the enantioselectivity, affording **3a** in 91% ee, albeit in a modest conversion. Subsequent evaluation of the effect of a set MPAA (monoprotected amino acid ligands), *N*-Ac-*L*-Ala-OH **L1**, *N*-Ac-*L*-Val-OH **L2**, *N*-Ac-*L*-Leu-OH **L3** and *N*-Ac-*L*-Phe-OH **L4** led to increase the enantioselectivity of **3a** to 93% (C= 15% and S = 69) and the recovered (S)-**1a** showed 17% ee. Further, systematic evaluation of silver salt, additive and temperature revealed that the catalytic system having $Pd(TFA)_2$ (10 mol %), *N*-Ac-*L*-Phe-OH (30 mol %), Ag_2CO_3 (2

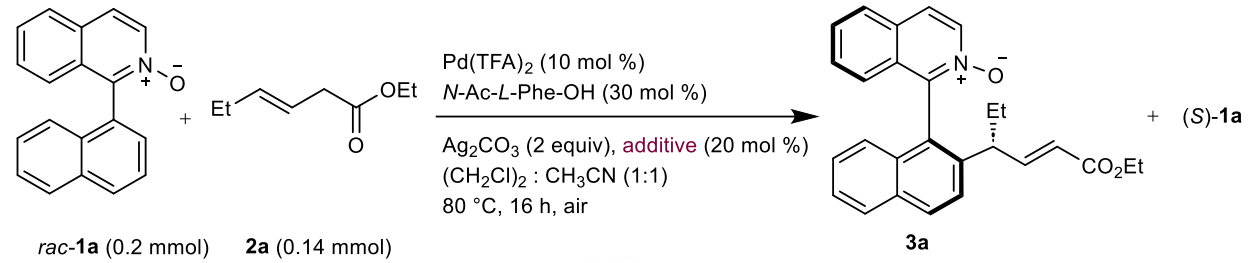
Table 1.6. Screening of Loading of Ag_2CO_3

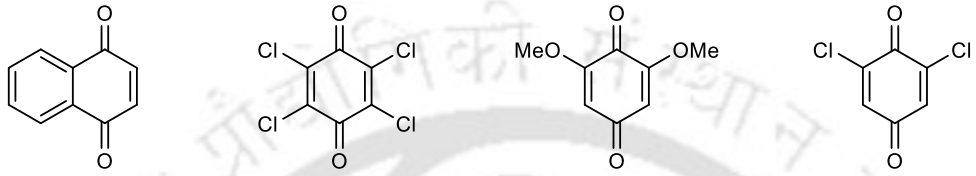


		Yield (%)		ee (%)			
Entry	x	(*S*)-**1a**	**3a**	(*S*)-**1a**	**3a**	C (%)	S
1	1	70	15	17	88	16	20
2	**2**	**67**	**23**	**25**	**95**	**21**	**40**
3	3	69	22	23	92	20	31

equiv) and BQ (20 mol %) in $(CH_2Cl)_2$: CH_3CN (1:1), 50 °C, 5 h, air, led the C-H allylation of (±)-**1a** (0.2 mmol) with **2a** (0.14 mmol) efficiently to furnish **3a** (Diastereomer-I) in 97% ee with S = 90, while the recovered (*S*)-**1a** exhibited 34% ee with a >10:1 diastereoselectivity. In addition, a catalytic system with $Pd(OAc)_2$ (10 mol %), *N*-Ac-*L*-Ala-OH (30 mol %), AgOAc (2 equiv) and BQ (20 mol %) in $(CH_2Cl)_2$: CH_3CN (1:1) at 80 °C for 16 h, afforded diastereomer-II **3a′** in 75% ee (21% yield) and (*S*)-**1a′** with S = 8. These results highlight the tunable stereochemical outcome achievable through subtle variation of the combination of Pd/MPAA and silver salts. Next, the scope of the procedure was examined for diastereomer-**I** (Table 3). Substrates bearing electron donating groups such as 6-*iso*propyl **1b** and 6-methoxy **1c** on the isoquinoline core reacted to afford **3b** and **3c** in 90% ee (27% yield) and 87% ee (10% yield), respectively, having diastereomeric ratio (d.r.) ≥ 3:1. The recovered (*S*)-**1b** and **1c** were obtained in 38% ee (61% yield and S = 41) and 10% ee (75% yield and S = 10.5), respectively.

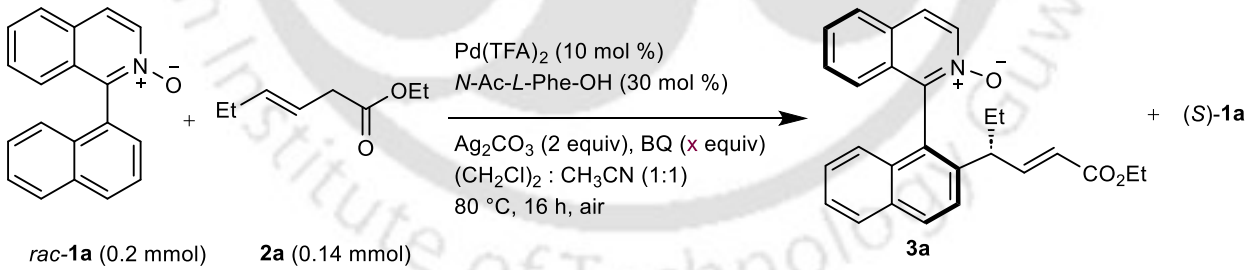
Table 1.7. Screening of Quinone Additives





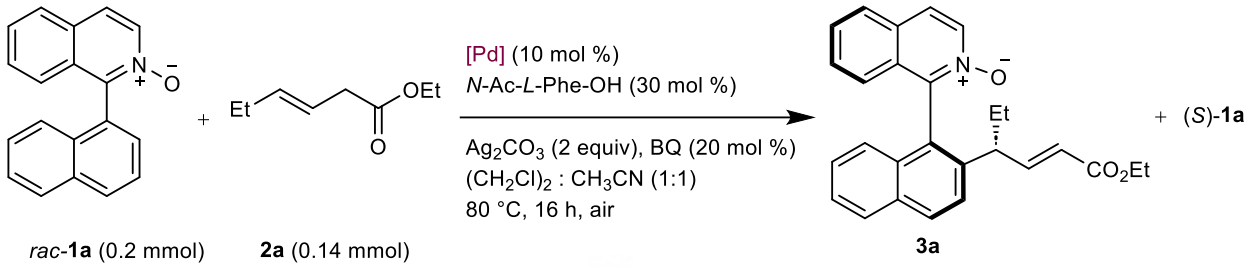
		Yield (%)		ee (%)			
Entry	Additive	(*S*)-**1a**	**3a**	(*S*)-**1a**	**3a**	C (%)	S
1	A1	62	23	30	90	25	26
2	A2	65	22	*rac*	88	-	-
3	A3	69	18	22	85	21	13
4	A4	78	6	8	86	10	7

Table 1.8. Screening of Loading of BQ



		Yield (%)		ee (%)			
Entry	x	(*S*)-**1a**	**3a**	(*S*)-**1a**	**3a**	C (%)	S
1	0.5	78	8	10	88	10	21
2	1	67	12	15	90	14	28
3	2	65	17	22	92	19	34

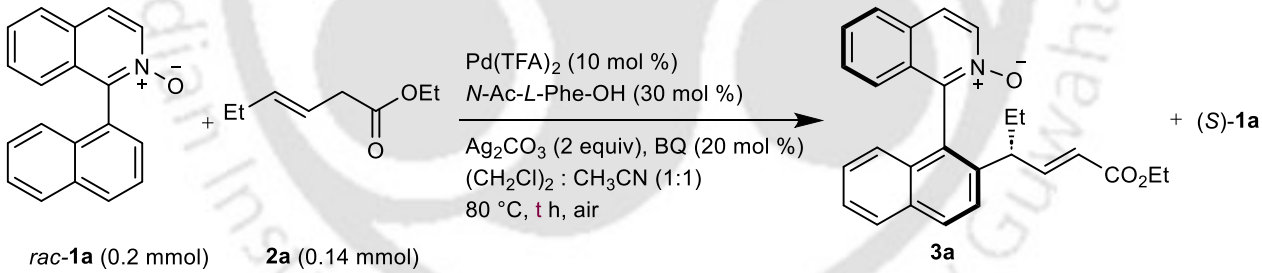
Table 1.9. Screening of Catalyst



rac-**1a** (0.2 mmol) **2a** (0.14 mmol) **3a**

		Yield (%)		ee (%)			
Entry	[Pd]	(*S*)-**1a**	**3a**	(*S*)-**1a**	**3a**	C (%)	S
1	$Pd(OAc)_2$	73	trace	-	-	-	-
2	$PdCl_2•(CH_3CN)_2$	68	12	15	76	16	10
3	$PdCl_2•(C_6H_5CN)_2$	75	trace	-	-	-	-
4	$Pd(acac)_2$	76	n.d.	-	-	-	-
5	$Pd(PPh_3)_2Cl_2$	78	n.d.	-	-	-	-
6	$PdCl_2$	71	trace	-	-	-	-

Table 1.10. Screening of Kinetic Resolution Time



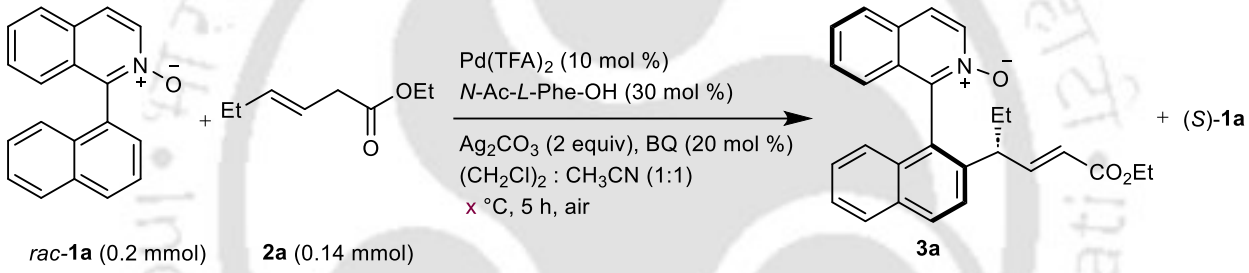
rac-**1a** (0.2 mmol) **2a** (0.14 mmol) **3a**

		Yield (%)		ee (%)			
Entry	Time (h)	(*S*)-**1a**	**3a**	(*S*)-**1a**	**3a**	C (%)	S
1	**5**	**58**	**26**	**35**	**91**	**28**	**27**
2	24	61	23	30	92	25	26
3	36	60	24	32	88	27	19
4	48	62	23	34	90	27	33

Likewise, the reaction of 4′-fluoro **1d**, 4′-methyl **1e** and 4′-methoxy **1f** substituents bearing naphthalene core furnished **3d-f** in 90-98% ee (15-27% yields) with d.r. ≥7:1 and the recovered

(*S*)-**1d-f** showed 18-37% ee (S = 29-53). In addition, polyarene *N*-oxide **1g** reacted to afford **3g** in 98% ee, while (*S*)-**1g** was recovered in 16% ee (76% yield and S = 12.5). Moreover, the reaction of di-substituted **1h** and **1i** produced **3h** and **3i** in 99% ee (22% yield) and 94% ee (10% yield, respectively, and recovered (*S*)-**1h** and **1i** exhibited 11% ee (S = 18) and 29% ee (S =101), respectively. In addition, the reaction of 1-(2-methylphenyl) **1j** and 1-(2-phenylphenyl) **1k** isoquinoline *N*-oxides led to the formation of **3j** and **3k** in 97 and 98% ee, respectively, with S=108. In contrast, 1-(2-fluorophenyl) isoquinoline *N*-oxide **1l** failed to provide the selectivity, which might be due to the reduced steric hindrance, whereas isoquinoline analogue **1m** was an unsuccessful substrate, presumably due to a competing desymmetrization pathway that precludes kinetic resolution.

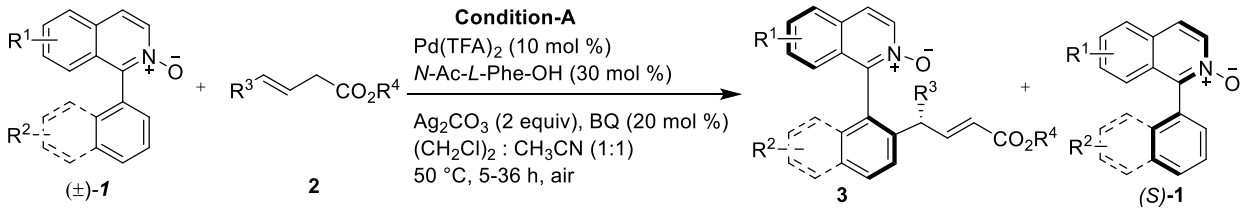
Table 1.11. Screening of Temperature



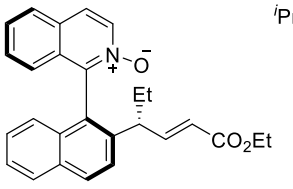
		Yield (%)		ee (%)			
Entry	Temp (°C)	(*S*)-**1a**	**3a**	(*S*)-**1a**	**3a**	C (%)	S
1	**50**	**55**	**36**	**56**	**97**	**37**	**75**
2	100	61	23	14	90	16	8
3	130	60	24	13	86	15	7

Having established these results, we extended the procedure to diversify the scope of olefinic coupling partner. *Trans*-3-hexenoates containing methyl **2b**, *iso*-propyl **2c**, n-butyl **2d**, *iso*-amyl **2e**, benzyl **2f** and *p*-tolylbenzyl **2g** were tolerated to produce **3n-s** in 96-99% ee (15-30% yields and S = 41-230) with d.r.>10:1. The recovered (*S*)-**1a** was obtained in 18-46% ee (58-74% yields), whereas methyl **2h** and ethyl **2i** substituted pent-3-enoates failed to deliver the allylated scaffolds. However, ester derived from carvacrol **2j** reacted to provide **3v** in 92% ee (20% yield) and the recovered (*S*)-**1a** exhibited 26% ee (S = 32), while (±)-tocopherol derived ester **2k** furnished **3w** in 27% yield with d.r.>10:1, that showcases the scope of the reaction in late-stage diversification.

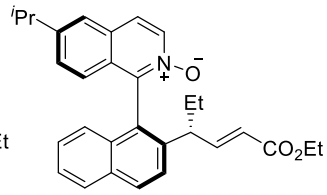
Table 2. Substrate Scope of 1-Arylisoquinoline *N*-oxides[a,b]



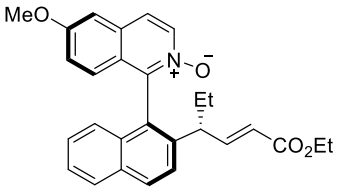
Scope of 1-arylisoquinoline *N*-oxides



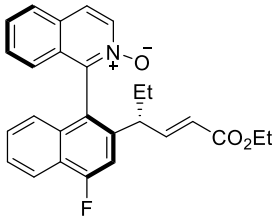
3a, 36%, 97% ee
(S)-**1a**, 55%, 56% ee
C = 37%, S = 75, 5 h
d.r. >10:1



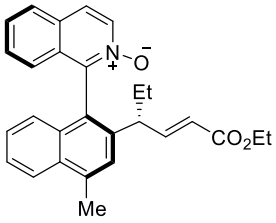
3b, 27%, 90% ee
(S)-**1b**, 61%, 38% ee
C = 29%, S = 41, 16 h
d.r. = 3:1



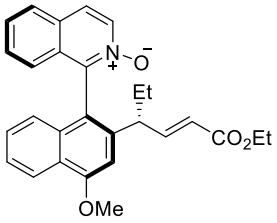
3c, 10%, 87% ee
(S)-**1c**, 75%, 10% ee
C = 11%, S = 10.5, 36 h
d.r. >10:1



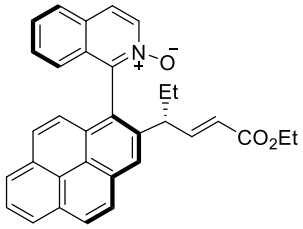
3d, 15%, 98% ee
(S)-**1d**, 73%, 18% ee
C = 16%, S = 47, 5 h
d.r.= 7:1



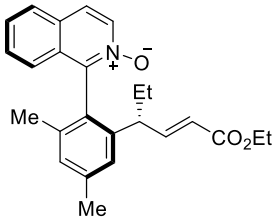
3e, 27%, 90% ee
(S)-**1e**, 60%, 37% ee
C = 29%, S = 29, 16 h
d.r. >10:1



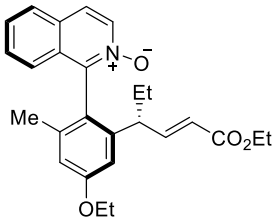
3f, 22%, 97% ee
(S)-**1f**, 64%, 30% ee
C = 24%, S = 53, 5 h
d.r. >10:1



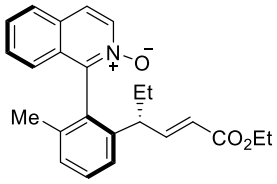
3g, 12%, 98% ee
(S)-**1g**, 76%, 16% ee
C = 14%, S = 12.5, 16 h
d.r. >10:1



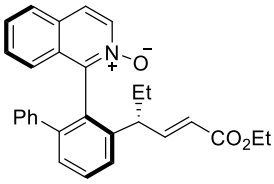
3h, 22%, 99% ee
(S)-**1h**, 68%, 29% ee
C = 29%, S = 101, 16 h
d.r. >10:1



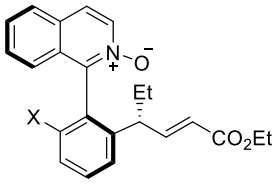
3i, 10%, 94% ee
(S)-**1i**, 77%, 11% ee
C = 11%, S = 18, 36 h
d.r. = 4:1



3j, 13%, 97% ee
(S)-**1j**, 74%, 16% ee
C = 14%, S = 108, 24 h
d.r. =5:1



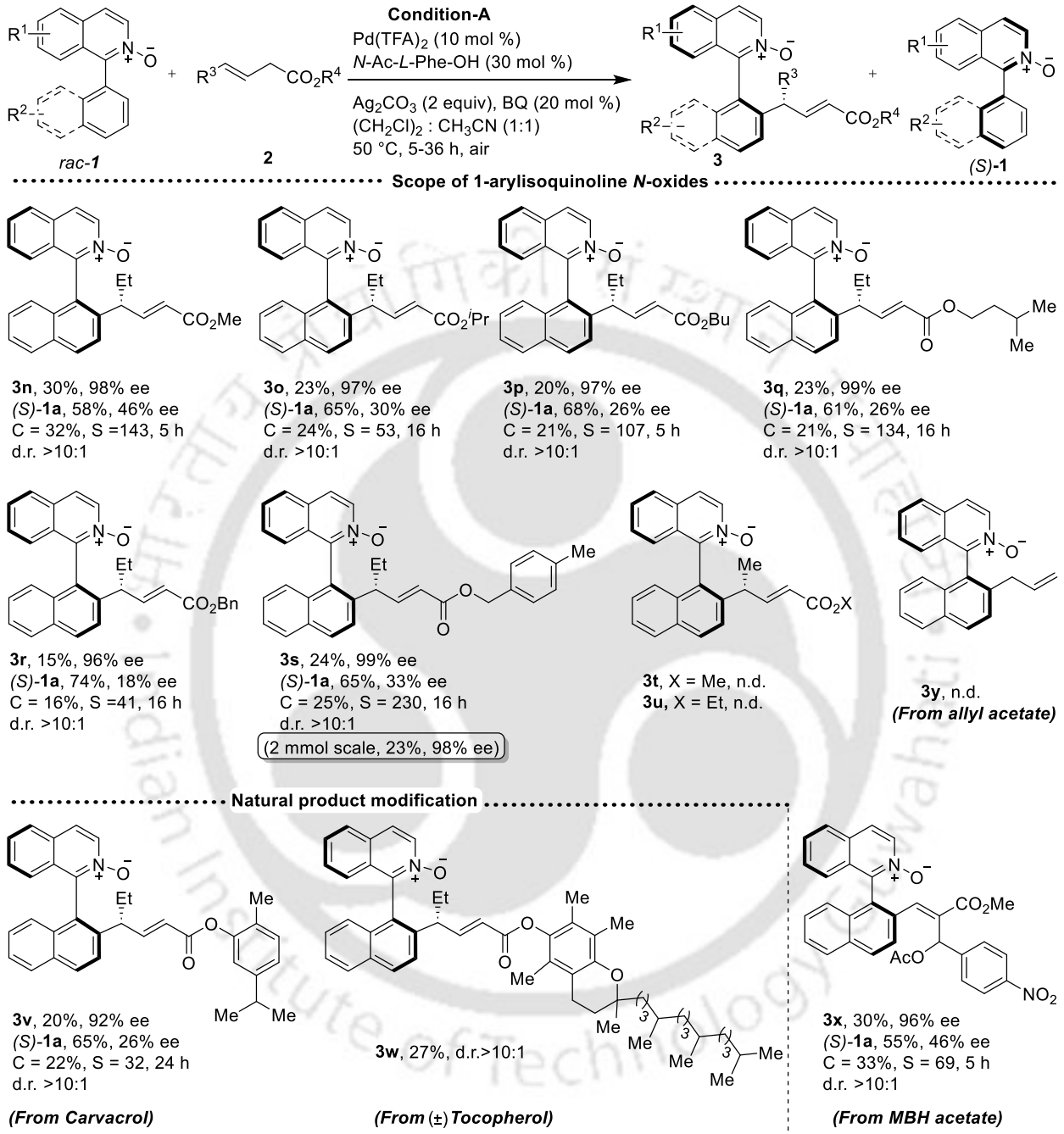
3k, 13%, 98% ee
(S)-**1k**, 76%, 16% ee
C = 14%, S = 108, 24 h
d.r. >10:1



X = F, **3l**, 32%, 5% ee
= H, **3m**, n.d.

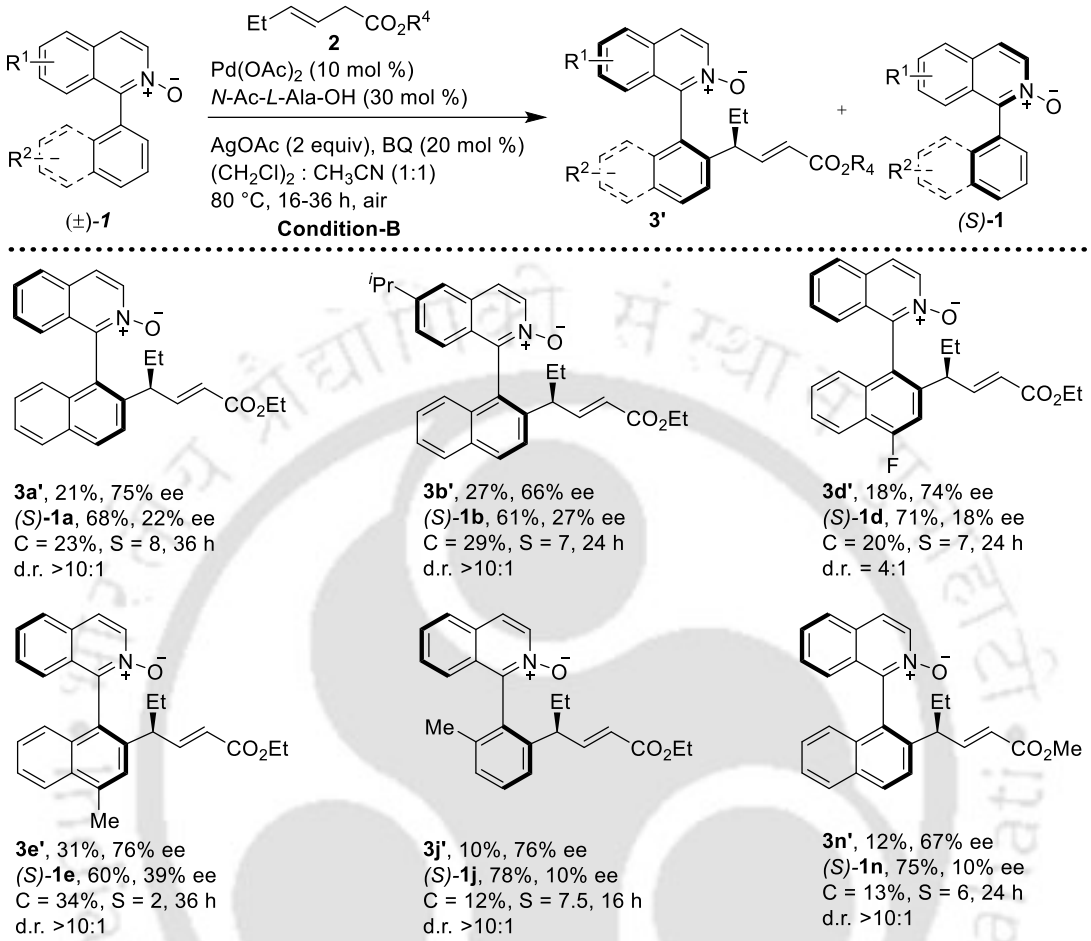
[a]Reaction conditions: *rac*-**1** (0.2 mmol), **2** (0.14 mmol), $Pd(TFA)_2$ (10 mol %), Ag_2CO_3 (2 equiv), *N*-Ac-*L*-Phe-OH (30 mol %), BQ (20 mol %), $(CH_2Cl)_2$: CH_3CN (1:1, 2 mL), 50 °C, 5-36 h, air. [b]Isolated yield. n.d. =not detected. BQ = *p*-Benzoquinone.

Table 3. Substrate Scope of *Trans*-3-hexenoates[a,b]



[a]Reaction conditions: *rac*-**1** (0.2 mmol), **2** (0.14 mmol), $Pd(TFA)_2$ (10 mol %), Ag_2CO_3 (2 equiv), *N*-Ac-*L*-Phe-OH (30 mol %), BQ (20 mol %), $(CH_2Cl)_2$: CH_3CN (1:1, 2 mL), 50 °C, 5-36 h, air. [b]Isolated yield. n.d. = not detected. BQ = *p*-Benzoquinone.

Table 4. Substrate Scope of Diastereomer-II[a,b]

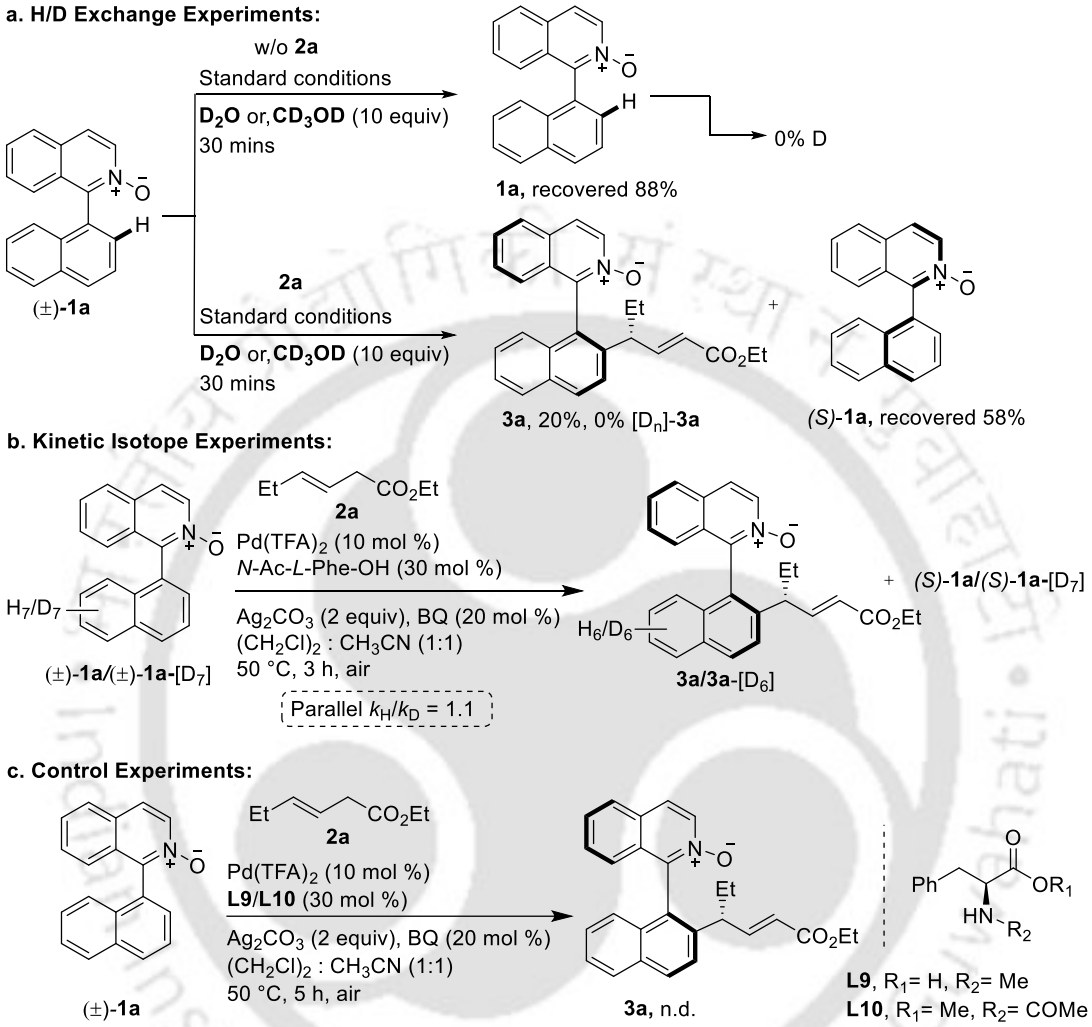


[a]Reaction conditions: *rac*-**1** (0.2 mmol), **2** (0.14 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (2 equiv), *N*-Ac-*L*-Ala-OH (30 mol %), BQ (20 mol %), $(CH_2Cl)_2$: CH_3CN (1:1, 2 mL), 80 °C, 16-36 h, air. [b]Isolated yield.

Furthermore, substituted Morita-Baylis-Hillman (MBH) acetate **2l** reacted to afford **3x** in 96% ee (30% yield) and the recovered (*S*)-**1a** was obtained in 46% ee (55% yield and S = 69). In contrast, the reaction of allyl acetate **2n** was unsuccessful.

The scope of diastereomer-II (**3′**) was further explored under conditions B (Table 4). The reaction of isoquinoline *N*-oxides with 6-*iso*-propyl **1b**, 4'-fluoro **1d**, 4′-methyl **1e** and 1-(2-methylphenyl) **1j** with *trans*-3-hexenoate **2b** was investigated as the representative substrates. The

allylation readily took place to produce **3b′-n′** in 66-76% ee (10-31% yields and S = 2-8) with d.r. ≥4:1, exhibiting the versatility of the stereochemical control strategy.

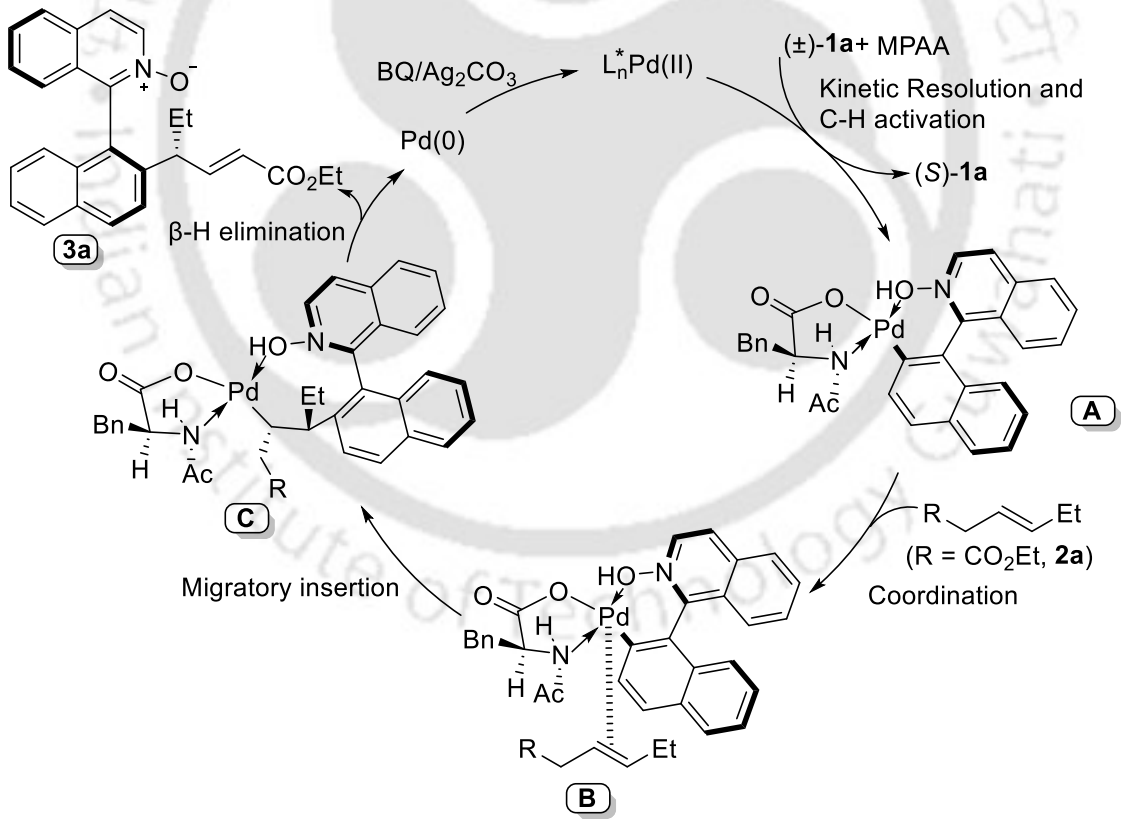


Scheme 6. Preliminary Mechanistic Investigations

To gain insight into the reaction pathway, H/D exchange experiments using D_2O or CD_3OD as co-solvent, were performed in the presence or absence of **2a**. The absence of deuterium incorporation indicates that C-H bond cleavage might be irreversible (Scheme 6). In addition, kinetic isotope experiments utilizing (±)-**1a** and (±)-**1a**-[D_7] with **2a** under condition-A for 3 h exhibited k_H/k_D = 1.1 for parallel, which indicate that C-H cleavage might be involved in the rate-limiting step. Furthermore, the loss of catalytic activity utilizing *N*-methylated phenylalanine **L9**

and *N*-Ac-*L*-phenylalanine methyl ester **L10** reveals the essential role of free carboxylic acid and amino protecting group (PG) for effective ligand chelation and alkene insertion.

Based on the experimental results and literature precedents,[6a,7b] a plausible catalytic cycle is proposed for diastereomer-I (Scheme 7). In the initial step, assistance from N-Ac-*L*-Phe-OH facilitates the formation of aryl-Pd complex **A** *via* C–H bond activation, concurrently leading to the recovery of (*S*)-**1a** *via* kinetic resolution. Coordination of complex **A** with **2a** can give **B**, which on stereoselective migratory insertion can produce **C** with a new stereocenter. Furthermore, *β*-hydride elimination of **C** may undergo a reductive elimination to furnish **3a**. Reoxidation of Pd(0) by BQ or Ag_2CO_3 can regenerate the active Pd-catalyst and complete the catalytic cycle. To demonstrate the practicability, scale-up of the reaction was performed in 2 mmol scale to furnish **3s** in 98% ee (23% yield and 157 mg) (Table 3). Moreover, the absolute configuration of **3s** has been assigned as *RR* by matching the CD experimental spectra with the computed ECD spectra.



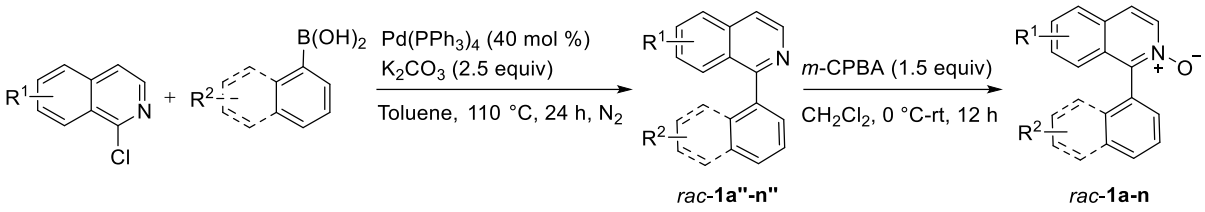
Scheme 7. Plausible Reaction Pathway

In conclusion, the Pd-catalyzed atroposelective C-H allylation of 1-naphthyl-isoquinoline *N*-oxide with *trans*-3-alkenoates has been accomplished. Merging axial and central chirality, kinetic resolution, stereo divergence and enantioselectivity highlight the notable practical aspects.

4.3 Experimental Section

General Information. $Pd(TFA)_2$ (97%), $Pd(OAc)_2$ (98%), $PdCl_2$ (99.99%), $Pd(PPh_3)_2Cl_2$ (98%), AgOAc (99%), Ag_2CO_3 (≥99.9%), 1,4-benzoquinone (BQ) (≥98%) were purchased from Aldrich and used as received. *N*-Ac-*L*-Val-OH (>98%), *N*-Ac-*L*-Leu-OH (>98%), *N*-Ac-*L*-Phe-OH (>98%), *N*-Ac-*L*-Ala-OH (>98%), *L*-Fmoc-Ala-OH (>98%), *L*-Boc-Ala-OH(>98%), *L-tert*-Leucine (>98%), *L-iso*-Leucine(>98%) were purchased from BLD pharma and *N*-Ac-*DL*-Phe-OH (>98%) were purchased from TCI chemicals and used as received. TFE, HFIP were received from TCI chemicals and used as received. $(CH_2Cl)_2$, CH_3CN, MeOH were dried prior as per the standard procedure. Silica gel-G/GF254 plates (Merck) were used for TLC analysis with a mixture of hexane and ethyl acetate as the eluent. Column chromatography was carried out using Rankem silica gel (60-120 mesh). Bruker Avance III 400, 500 and 600 MHz NMR spectrometers were used to record (^1H, ^{13}C and ^{19}F) NMR spectra using $CDCl_3$ as the solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) and spin-spin coupling constant (*J*) are reported in parts per million and hertz (Hz), respectively, and to describe peak patterns following abbreviations were used when appropriate: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Open capillary tubes were used for the measurements and are uncorrected. Mestrenova software was used throughout the spectral analysis. Q-Tof ESI-MS instrument was used for recording HRMS data. Infrared spectra were recorded on Perkin Elmer FT-IR instrument. Optical rotations were determined using Rudolph autopol I polarimeter. HPLC analysis was carried out using Waters-2489 with Daicel Chiralcel AD-H, AD, OD-H, OD column using *iso*-propanol and hexane as an eluent.

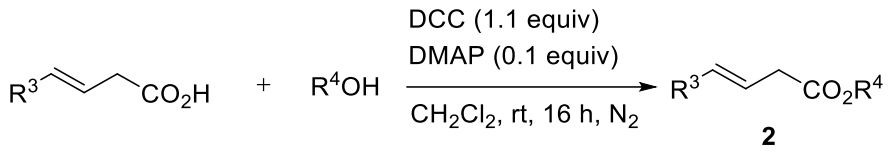
General Procedure for the Synthesis of 1-Arylisoquinoline *N*-oxides 1



Step-I: To a stirred solution of corresponding 1-chloroisoquinoline **(**3 mmol, 1 equiv**)** in toluene **(**20 mL**),** K_2CO_3 **(**7.5 mmol, 2.5 equiv, 1.1 g**)** and boronic acid (3.6 mmol, 1**.**2 equiv**)** were added followed by the addition of $Pd(PPh_3)_4$ (40 mol %, 0.12 mmol, 139 mg**).** The reaction mixture was stirred at 110 °C for 24 h under N_2. After completion of the reaction (monitored by TLC), the resultant mixture was cooled to room temperature, quenched with H_2O **(**30 mL**)** and extracted with ethyl acetate **(**3×30 mL**).** The combined organic solution was washed with brine (20 mL) and water (5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography (hexane/ethyl acetate = 8:2) to afford 1-aryl-isoquinoline *rac*-**1a''-n''**.

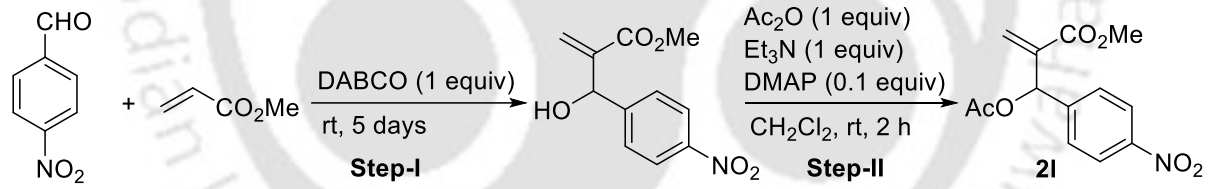
Step-II: To a stirred solution of the 1-arylisoquinoline (±)-**1a''-n''** (2.2 mmol, 1 equiv) in CH_2Cl_2 (20 mL), *m*-chloroperoxybenzoic acid (3.3 mmol, 1.5 equiv, 570 mg) was added at 0 °C . Then, the reaction mixture was stirred at room temperature for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with saturated Na_2CO_3 (15 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic solution was washed with brine (20 mL) and water (5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography (ethyl acetate /MeOH = 9:1) to afford 1-arylisoquinoline *N*-oxide (±)-**1a-n.**

General Procedure for the Synthesis of *Trans*-3-Alkenoates 2



To a stirred solution of carboxylic acid (5 mmol, 1 equiv) in CH_2Cl_2 (15 mL), corresponding alcohol (15 mmol, 1.5 equiv), DMAP (0.5 mmol, 0.1 equiv, 61 mg) were added, followed by the addition of DCC (5.5 mmol, 1.1 equiv, 1.1 g) at 0 ˚C. The reaction mixture was allowed to stir at room temperature for 16 h under N_2. After completion of the reaction (monitored by TLC), precipitated urea was filtered off through a pad of celite. Then the residue was quenched with saturated Na_2CO_3 (25 mL) and water (15 mL) and extracted with ethyl acetate (3×30 mL). The combined organic layer was washed with brine (10 mL) and water (5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography (ethyl acetate /hexane = 1:9) to afford the desired *trans*-3-alkenoates **2**.

General Procedure for the Synthesis of MBH Acetate 2l

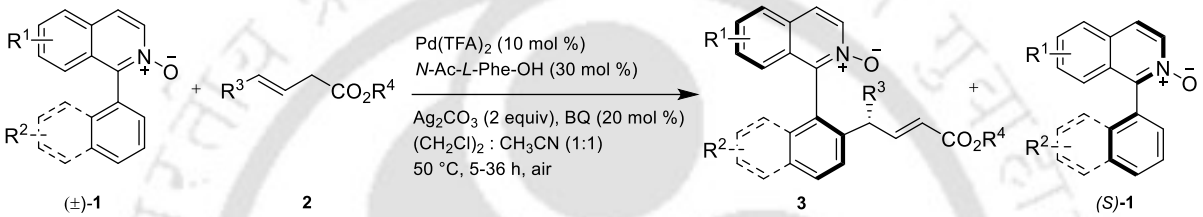


Step-I. 4-nitrobenzaldehyde (10 mmol, 1.0 equiv, 1 g), methyl acrylate (30 mmol, 2.5 equiv, 2.6 g) and DABCO (10 mmol, 1.0 equiv, 1.1 g) were stirred at room temperature for 5 days. After completion (monitored by TLC), the reaction mixture was diluted with ethyl acetate (20 mL) and washed with saturated $NaHCO_3$ (2 x 10 mL). The residue was extracted with ethyl acetate (3 x 10 mL). The combined organic part was washed with water (10 mL) and brine (5 mL). Drying Na_2SO_4 and evaporation of the solvent gave a residue that was purified on silica gel column chromatography (ethyl acetate /hexane = 1:4) to afford methyl 2-(hydroxy(4-nitrophenyl)methyl)acrylate in 55% (410 mg) yield.

Step-II. To a stirred solution of Methyl 2-(hydroxy(4-nitrophenyl)methyl)acrylate (1 mmol, 1.0 equiv, 237 mg) in CH_2Cl_2 (5 mL), Ac_2O (1 mmol, 1.0 equiv, 102 mg) DMAP (0.1 mmol, 0.1 equiv,

12 mg) and Et_3N (1 mmol, 1.0 equiv, 0.14 mL) were added. The resultant mixture was stirred at room temperature for 2 h. After completion (monitored by TLC), the reaction mixture was quenched with 2 M HCl and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic part was washed with water (10 mL). Drying Na_2SO_4 and evaporation of the solvent gave a residue that was purified on silica gel column chromatography (ethyl acetate /hexane = 1:9) to afford **2l** in 75% (190 mg) yield.

General procedure for Pd-catalyzed C-H Allylation of 1-Arylisoquinoline *N*-oxides 3 (Diastereomer-I)



To a stirred solution of *rac* 1-aryl isoquinoline *N*-oxide **1** (0.2 mmol, 1 equiv) in $(CH_2Cl)_2$: CH_3CN (1:1, 2 mL), *trans*-3-alkenoate **2** (0.14 mmol, 0.7 equiv), BQ (20 mol %, 0.04 mmol, 5 mg), *N*-Ac-*L*-Phe-OH (30 mol %, 0.06 mmol, 7 mg), Ag_2CO_3 (0.4 mmol, 2 equiv, 102 mg) and $Pd(TFA)_2$ (10 mol %, 0.02 mmol, 8 mg) were added. The reaction mixture was stirred at 50 °C for 5-36 h under air. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through a short pad of celite. Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate as eluent to afford **3** (Diastereomer-I) and recovered (*S*)-**1**.

Scale-up Synthesis of 3s. To a stirred solution of *rac*-1-(Naphthalen-1-yl)isoquinoline 2-oxide **1a** (2 mmol, 1 equiv, 500 mg) in $(CH_2Cl)_2$: CH_3CN (1:1, 20 mL), ethyl (*E*)-hex-3-enoate **2g** (1.4 mmol, 0.7 equiv, 305 mg), BQ (20 mol %, 0.4 mmol, 50 mg), *N*-Ac-*L*-Phe-OH (30 mol %, 0.6 mmol, 70 mg), Ag_2CO_3 (4 mmol, 2 equiv, 1.1 g), $Pd(TFA)_2$ (10 mol %, 0.2 mmol, 80 mg) were added. The reaction mixture was stirred at 50 °C for 5 h under air. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through pad of celite. Subsequent evaporation of the solvent gave a residue that was purified on silica gel column chromatography (ethyl acetate /hexane = 9:1) to afford **3s** in 23% (157 mg) yield with 99% ee and recovered (*S*)-**1a**.

Absolute Configuration Determination by ECD (Electronic Circular Dichroism)

For determination of the absolute configuration of synthesized **3s**, the computed ECD-spectrum of (*RR*)-**3s** and (*RS*)-**3s** was compared with the experimental spectrum (c = 10^{-4} M, CH_3CN). Geometry optimizations were performed using the B3LYP functional with Grimme's D3 dispersion correction with Becke–Johnson damping (B3LYP-D3BJ)[10]. 6-31G** basis set was used for the calculations.[11] Solvent effect has been implicitly implemented using cpcm solvent model.[12] Full Time Dependent Density Functional Theory (TDDFT) calculation has been carried out using same level of theory without considering the Tamm-Dancoff approximation (TDA) to evaluate the ECD spectrum.[13] the spectra were generated using Multiwfn 3.8 (dev).[14] By normalizing with the experimental data, we have found that *RR*-conformer of **3s** is best fitted with the experimental results.

Mechanistic Investigation

H/D Exchange Experiment of 1a with D_2O or CD_3OD in Absence of 2a. To a stirred solution of *rac*-**1a** (0.2 mmol, 1equiv, 50 mg) in $(CH_2Cl)_2$: CH_3CN (1:1, 2 mL), BQ (20 mol %, 0.04 mmol, 5 mg), *N*-Ac-*L*-Phe-OH (30 mol %, 0.06 mmol, 7 mg), Ag_2CO_3 (0.4 mmol, 2 equiv, 102 mg), $Pd(TFA)_2$ (10 mol %, 0.02 mmol, 8 mg) and D_2O or CD_3OD (2 mmol, 10 equiv, 0.01 mL) were added. The reaction mixture was stirred at 50 °C for 30 mins under air. After that, it was filtered through a short pad of celite. Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate as eluent to recover **1a**. No deuterium incorporation in **1a** was observed on the basis of 400 MHz ^1H NMR spectrum.

H/D Exchange Experiment of 1a with D_2O and CD_3OD in Presence of 2a. To a stirred solution of *rac*-**1a** (0.2 mmol, 1equiv, 50 mg) in $(CH_2Cl)_2$: CH_3CN (1:1, 2 mL), **2a** (0.14 mmol, 0.7 equiv, 20 mg), BQ (20 mol %, 0.04 mmol, 5 mg), *N*-Ac-*L*-Phe-OH (30 mol %, 0.06 mmol, 7 mg), Ag_2CO_3 (0.4 mmol, 2 equiv, 102 mg), $Pd(TFA)_2$ (10 mol %, 0.02 mmol, 8 mg) and D_2O or, CD_3OD (2 mmol, 10 equiv, 0.01 mL) were added. The reaction mixture was stirred at 50 °C for 30 mins under air. After that, it was filtered through a short pad of celite. Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate as eluent to afford **3a**. No deuterium incorporation in **3a** was observed on the basis of 400 MHz ^1H NMR spectrum.

Kinetic Isotope Effect Experiments

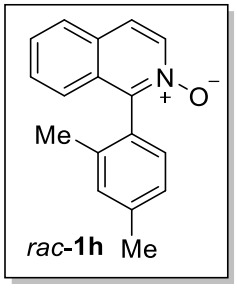
Parallel Reactions. Two round bottom flasks were charged with *rac*-**1a** (0.1 mmol, 0.5 equiv, 25 mg) or *rac*-**1a**-[D_7] (0.1 mmol, 0.5 equiv, 25 mg) in $(CH_2Cl)_2$: CH_3CN (1:1, 1 mL), **2a** (0.07 mmol, 0.7 equiv, 10 mg), BQ (20 mol %, 0.02 mmol, 3 mg), *N*-Ac-*L*-Phe-OH (30 mol %, 0.03 mmol, 3 mg), Ag_2CO_3 (0.2 mmol, 2 equiv, 51 mg), $Pd(TFA)_2$ (10 mol %, 0.01 mmol, 4 mg) were added. The reaction mixture was stirred at 50 °C for 3 h under air. Then both the reaction mixtures were combined and was filtered through a short pad of celite. Evaporation of the solvent gave a residue that was purified on silica gel column chromatography as described in the general procedure to afford **3a/3a**-[D_6] and a mixture of unreacted (*S*)-**1a**/(*S*)-**1a**-[D]$_7$. The KIE value was determined to be k_H/k_D = 5.66 on the basis of 400 MHz ^{1}H NMR analysis of the recovered substrate (*S*)-**1a**/(*S*)-**1a**-[D]$_7$.

Competitive Reactions. A mixture of *rac*-**1a** (0.1 mmol, 0.5 equiv, 25 mg) or *rac*-**1a**-[D_7] (0.1 mmol, 0.5 equiv, 25 mg) in $(CH_2Cl)_2$: CH_3CN (1:1, 2 mL), **2a** (0.14 mmol, 0.7 equiv, 20 mg), BQ (20 mol %, 0.04 mmol, 5 mg), *N*-Ac-*L*-Phe-OH (30 mol %, 0.06 mmol, 7 mg), Ag_2CO_3 (0.4 mmol, 2 equiv, 102 mg), $Pd(TFA)_2$ (10 mol %, 0.02 mmol, 8 mg) were added. The reaction mixture was stirred at 50 °C for 3 h under air. The reaction mixture was filtered through a short pad of celite. Evaporation of the solvent gave a residue that was purified on silica gel column chromatography as described in the general procedure to afford **3a/3a**-[D_6] and a mixture of unreacted (*S*)-**1a**/(*S*)-**1a**-[D]$_7$. The KIE value was determined to be k_H/k_D = 4.55 on the basis of 400 MHz ^{1}H NMR analysis of the recovered substrate (*S*)-**1a**/(*S*)-**1a**-[D]$_7$.

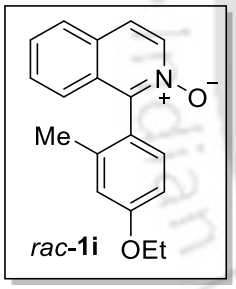
Control Experiment. To a stirred solution of *rac*-**1a** (0.2 mmol, 1 equiv, 50 mg) in $(CH_2Cl)_2$: CH_3CN (1:1, 2 mL), **2a** (0.14 mmol, 0.7 equiv, 20 mg), BQ (20 mol %, 0.04 mmol, 5 mg), **L9** or, **L10** (30 mol %, 0.06 mmol, 7 mg), Ag_2CO_3 (0.4 mmol, 2 equiv, 102 mg), $Pd(TFA)_2$ (10 mol %, 0.02 mmol, 8 mg) were added. The reaction mixtures were stirred at 50 °C for 5 h under air. Formation of **3a** was not observed and the starting materials were recovered intact.

4.4 Characterization data

Characterization Data of Newly Synthesized 1-Aryl isoquinoline *N*-oxide Adducts

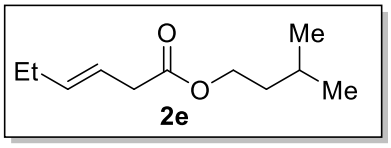


1-(2,4-Dimethylphenyl)isoquinoline 2-oxide 1h. Analytical TLC on silica gel, 9:1 ethyl acetate/methanol R_f = 0.35; yellow solid; yield 88% (172 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 7.2 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 7.2 Hz, 1H), 7.58-7.56 (m, 1H), 7.49-7.45 (m, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.23 (s, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 2.43 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.0, 139.7, 137.9, 137.5, 131.5, 129.9, 129.7, 129.2, 128.5, 127.8, 127.1, 127.0, 125.7, 123.4, 21.5, 19.4; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{16}NO$: 250.1226; Found 250.1222.



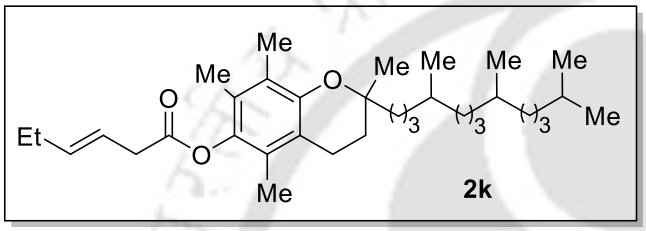
1-(4-Ethoxy-2-methylphenyl)isoquinoline 2-oxide 1i. Analytical TLC on silica gel, 9:1 ethyl acetate/methanol R_f = 0.30; yellow solid; yield 90% (180 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.2 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 7.2 Hz, 1H), 7.58-7.54 (m, 1H), 7.50-7.46 (m, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 6.95-6.94 (m, 1H), 6.91-6.88 (m, 1H), 4.10 (q, *J* = 7.2 Hz, 2H), 2.09 (s, 3H), 1.46 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1, 147.0, 139.8, 137.4, 131.1, 130.1, 129.2, 128.5, 127.0, 125.9, 123.4, 122.8, 116.7, 63.6, 19.8, 15.0; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{18}H_{18}NO_2$: 280.1332; Found 280.1336.

Characterization Data of Newly Synthesized *Trans*-3-hexenoate Adducts



2e

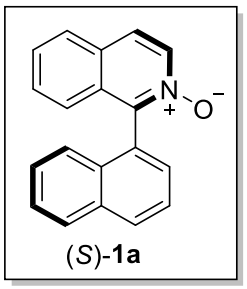
***Iso*pentyl (*E*)-hex-3-enoate 2e.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.64-5.57 (m, 1H), 5.55-5.48 (m, 1H), 4.11 (t, *J* = 6.8 Hz, 2H), 3.00 (d, *J* = 7.2 Hz, 2H), 2.05 (p, *J* = 7.2 Hz, 2H), 1.74-1.64 (m, 1H), 1.51 (q, *J* = 6.8 Hz, 2H), 0.99 (t, *J* = 7.6 Hz, 3H), 0.91 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 136.3, 120.8, 63.3, 38.2, 37.4, 25.6, 25.2, 22.5, 13.5; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{11}H_{21}O_2$: 185.1536; Found 185.1525.



2k

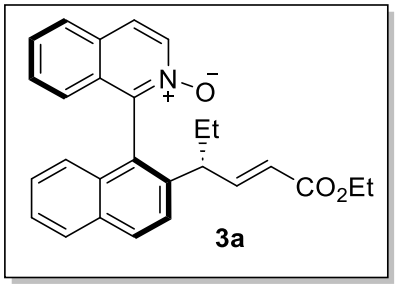
2,5,7,8-Tetramethyl-2-(4,8,12-trimethyl tridecyl)chroman-6-yl (*E*)-hex-3-enoate 2k. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80-5.65 (m, 2H), 3.29 (d, *J* = 6.8 Hz, 2H), 2.59 (t, *J* = 6.8 Hz, 2H), 2.14-2.09 (m, 5H), 2.01 (s, 3H), 1.97 (s, 3H), 1.85-1.72 (m, 2H), 1.55-1.50 (m, 2H), 1.44-1.36 (m, 2H), 1.29-1.24 (m, 13H), 1.17-1.09 (m, 6H), 1.03 (t, *J* = 7.6 Hz, 3H), 0.91-0.85 (m, 13H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 149.5, 140.6, 137.1, 126.8, 125.1, 123.1, 120.5, 117.5, 75.2, 39.5, 38.2, 37.6, 37.5, 37.4, 32.93, 32.91, 32.85, 32.83, 28.1, 25.7, 25.0, 24.9, 24.6, 22.9, 22.8, 21.2, 20.7, 19.9, 19.82, 19.7, 13.6, 13.1, 12.2, 11.9; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{35}H_{59}O_3$: 527.4459; Found 527.4425.

Characterization Data of the Products

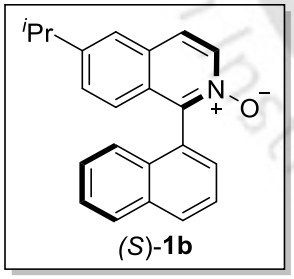


(*S*)-**1a**

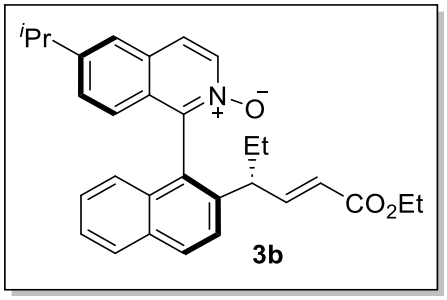
(*S*)-1-(Naphthalen-1-yl)isoquinoline 2-oxide (*S*)-**1a.** Analytical TLC on silica gel, 9:1 ethyl acetate/hexane R_f = 0.35; Yellow solid; yield 65% (35 mg); $[\alpha]_D^{25}$ = +105.0 (c = 0.1, CH_2Cl_2); HPLC: 34% ee [CHIRALCEL OD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 11.69 min (major), 14.62 min (minor)].



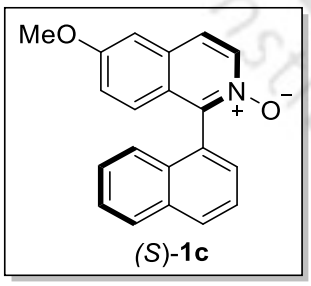
(*R*)-1-(2-((*R*,*E*)-6-Ethoxy-6-oxohex-4-en-3-yl)naphthalen-1-yl)isoquinoline 2-oxide 3a. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.30; yellow liquid; yield 25% (13 mg); major diastereomer (d.r. >10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 7.2 Hz, 1H), 8.05 (d, *J* = 8.8 Hz, 1H), 7.87 (dd, *J* = 17.6, 8.4 Hz, 2H), 7.82 (d, *J* = 7.2 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.35-7.29 (m, 2H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.85 (dd, *J* = 15.6, 8.4 Hz, 1H), 5.10 (d, *J* = 16.8 Hz, 1H), 4.06 (q, *J* = 7.2 Hz, 2H), 2.96-2.91 (m, 1H), 2.00-1.92 (m, 1H), 1.86-1.77 (m, 1H), 1.21 (t, *J* = 7.2 Hz, 3H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 150.0, 144.5, 139.9, 137.7, 132.8, 131.8, 130.6, 130.5, 129.4, 128.7, 128.6, 127.4, 127.3, 127.0, 126.3, 125.7, 125.0, 124.8, 124.1, 121.5, 60.3, 47.9, 27.9, 14.4, 12.4; FT-IR (neat) 2924, 1722, 1462, 1506, 1263 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{27}H_{26}NO_3$: 412.1907; Found 412.1922; $[\alpha]_D^{25}$ = -94.0 (c = 0.01, CH_2Cl_2); HPLC: 97% ee (major diastereomer) [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 6.35 min (major), 8.18 min (minor)].



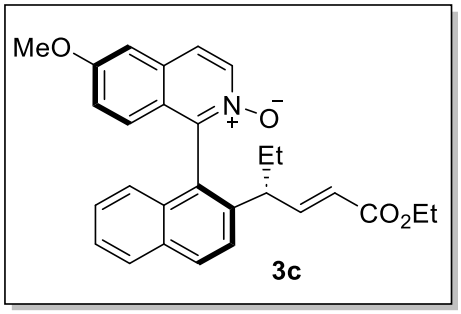
(*S*)-6-*Iso*propyl-1-(naphthalen-1-yl)isoquinoline 2-oxide 1b. Analytical TLC on silica gel, 9:1 ethyl acetate/hexane R_f = 0.30; colorless solid; yield 61% (31 mg); $[\alpha]_D^{25}$ = +20.0 (c = 0.04, CH_2Cl_2); HPLC: 38% ee [CHIRALCEL AD-H, hexane/^{i}PrOH = 90:10, flow rate: 1 mL/min, λ= 254 nm, t_R = 20.47 min (major), 29.72 min (minor)].



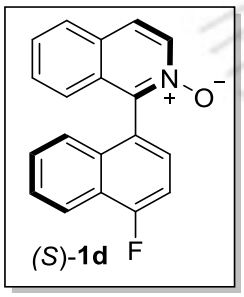
(*R*)-1-(2-((*R*,*E*)-6-Ethoxy-6-oxohex-4-en-3-yl)naphthalen-1-yl)-6-isopropylisoquinoline 2-oxide 3b. Analytical TLC on silica gel, 2:8 ethyl acetate/hexane R_f = 0.30; yellow liquid; yield 27% (9 mg); major diastereomer (d.r. = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 7.2 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 7.2 Hz, 1H), 7.67 (s, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.21 (d, *J* = 8.8 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.95-6.89 (m, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 5.09 (d, *J* = 15.6 Hz, 1H), 4.11-4.03 (m, 2H), 3.06-3.01 (m, 1H), 2.95-2.89 (m, 1H), 2.01-1.93 (m, 1H), 1.86-1.76 (m, 1H), 1.31 (s, 3H), 1.30 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H), 0.84 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 150.1, 150.0, 144.3, 139.8, 137.5, 132.8, 131.8, 130.6, 129.4, 129.0, 128.9, 128.5, 127.4, 126.2, 125.9, 125.1, 124.8, 123.9, 123.5, 121.6, 60.3, 47.9, 34.3, 28.0, 23.6, 14.3, 12.4; FT-IR (neat) ; FT-IR (neat) 2924, 1712, 1462, 1380, 1263, 1185 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{30}H_{32}NO_3$: 454.2377; Found 454.2384; $[\alpha]_D^{25}$ = -34.7 (c = 0.03, CH_2Cl_2); HPLC: 90% ee (major diastereomer) [CHIRALCEL AD-H, hexane/^{i}PrOH = 90:10, flow rate: 1 mL/min, λ= 254 nm, t_R = 6.35 min (major), 8.14 min (minor)].



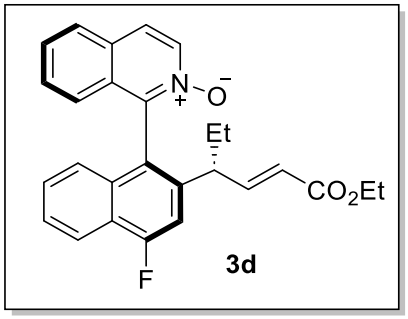
(*S*)-6-Methoxy-1-(naphthalen-1-yl)isoquinoline 2-oxide 1c. Analytical TLC on silica gel, 8:2 ethyl acetate/hexane R_f = 0.35; Yellow solid; yield 75% (30 mg); $[\alpha]_D^{25}$ = +4.0 (c = 0.05, CH_2Cl_2); HPLC: 10% ee [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 55.27 min (major), 44.73 min (minor)].



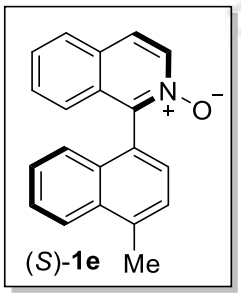
(*R*)-1-(2-((*R*,*E*)-6-Ethoxy-6-oxohex-4-en-3-yl)naphthalen-1-yl)-6-methoxyisoquinoline 2-oxide 3c. Analytical TLC on silica gel, 8:2 ethyl acetate/hexane R_f = 0.35; yellow liquid; yield 10% (12 mg); major diastereomer (d.r. >10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 7.0 Hz, 1H), 8.04 (d, *J* = 9.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 7.0 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.43 (t, *J* = 7.0 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.16 (s, 1H), 7.02 (d, *J* = 8.5 Hz, 1H), 6.95 (d, *J* = 9.0 Hz, 1H), 6.90-6.82 (m, 2H), 5.11 (d, *J* = 15.5 Hz, 1H), 4.06 (q, *J* = 7.0 Hz, 2H), 3.93 (s, 3H), 2.95 (q, *J* = 7.0 Hz, 1H), 2.01-1.95 (m, 1H), 1.84-1.79 (m, 1H), 1.21 (t, *J* = 7.0 Hz, 3H), 0.86 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 160.0, 150.0, 139.8, 137.9, 132.8, 131.9, 130.58, 130.56, 130.53, 128.5, 127.6, 127.5, 127.4, 126.2, 125.7, 125.1, 124.8, 123.0, 121.8, 121.6, 105.7, 60.3, 55.7, 47.9, 27.8, 14.3, 12.4; FT-IR (neat) 2923, 1709, 1582, 1460, 1354, 1264, 1236, 1112 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{28}H_{28}NO_4$: 442.2013; Found 442.2013; $[\alpha]_D^{25}$ = -7.1 (c = 0.05, CH_2Cl_2); HPLC: 87% ee (major diastereomer) [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 5.67 min (major), 8.0 min (minor)].



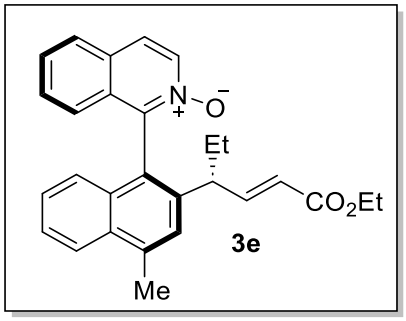
(*S*)-1-(4-Fluoronaphthalen-1-yl)isoquinoline 2-oxide 1d. Analytical TLC on silica gel, 9:1 ethyl acetate/hexane R_f = 0.30; Yellow solid; yield 73% (29 mg); $[\alpha]_D^{25}$ = +39.0 (c = 0.05, CH_2Cl_2); HPLC: 18% ee [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 9.65 min (major), 12.11 min (minor)].



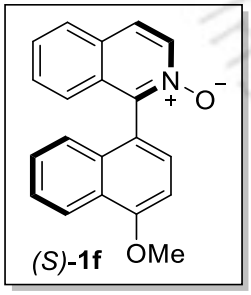
(*R*)-1-(2-((*R*,*E*)-6-Ethoxy-6-oxohex-4-en-3-yl)-4-fluoro-naphthalen-1-yl)isoquinoline 2-oxide 3d. Analytical TLC on silica gel, 2:8 ethyl acetate/hexane R_f = 0.40; yellow liquid; yield 15% (11 mg); major diastereomer (d.r. = 7:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 7.2 Hz, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 7.2 Hz, 1H), 7.57-7.50 (m, 2H), 7.39-7.33 (m, 2H), 7.27 (d, *J* = 11.6 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.79 (dd, *J* = 15.6, 8.0 Hz, 1H), 5.12 (d, *J* = 16.8 Hz, 1H), 4.07 (q, *J* = 6.8 Hz, 2H), 2.94 (q, *J* = 8.0 Hz, 1H), 1.98-1.91 (m, 1H), 1.81-1.74 (m, 1H), 1.21 (t, *J* = 6.8 Hz, 3H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 161.3 (J_{C-F} = 253.5 Hz), 149.2, 143.7, 141.0 (J_{C-F} = 7.3 Hz), 137.7, 133.3 (J_{C-F} = 5.4 Hz), 130.6, 129.6, 128.7, 128.6, 128.5, 127.1, 126.6, 125.6, 125.0, 124.3, 123.4, 123.3, 121.9, 121.3 (J_{C-F} = 4.9 Hz), 108.7 (J_{C-F} = 20.8 Hz), 60.4, 47.8, 27.8, 14.3, 12.3; ^{19}F NMR (375 MHz, $CDCl_3$) δ -119.7; FT-IR (neat) 2922, 1712, 1465, 1380, 1304, 1130 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{27}H_{25}FNO_3$:430.1813; Found 430.1819; $[\alpha]_D^{25}$ = -16.0 (c = 0.1, CH_2Cl_2); HPLC: 98% ee (major diastereomer) [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 5.70 min (major), 6.94 min (minor)].



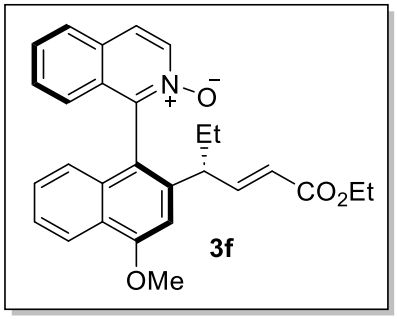
(*S*)-1-(4-Methylnaphthalen-1-yl)isoquinoline 2-oxide 1e. Analytical TLC on silica gel, 9:1 ethyl acetate/hexane R_f = 0.40; yellow solid; yield 60% (30 mg); $[\alpha]_D^{25}$ = +48.0 (c = 0.04, CH_2Cl_2); HPLC: 37% ee [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 8.97 min (major), 17.95 min (minor)].



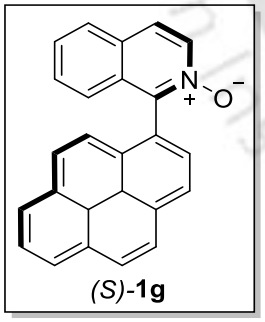
(*R*)-1-(2-((*R*,*E*)-6-Ethoxy-6-oxohex-4-en-3-yl)-4-methyl-naphthalen-1-yl)isoquinoline 2-oxide 3e. Analytical TLC on silica gel, 8:2 ethyl acetate/hexane R_f = 0.35; yellow liquid; yield 27% (15 mg); major diastereomer (d.r. >10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 6.8 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 7.2 Hz, 1H), 7.55-7.47 (m, 2H), 7.43 (s, 1H), 7.36-7.28 (m, 2H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.87 (dd, *J* = 15.6, 8.4 Hz, 1H), 5.11 (d, *J* = 16.4 Hz, 1H), 4.07 (q, *J* = 7.2 Hz, 2H), 2.88 (q, *J* = 7.6 Hz, 1H), 2.81 (s, 3H), 2.02-1.91 (m, 1H), 1.86-1.77 (m, 1H), 1.21 (t, *J* = 7.2 Hz, 3H), 0.85 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 150.1, 144.7, 139.5, 137.7, 137.24, 137.21, 132.1, 131.8, 130.6, 129.3, 128.6, 128.5, 127.1, 127.0, 126.1, 125.9, 125.6, 125.5, 124.8, 124.0, 121.5, 60.3, 47.9, 27.9, 20.0, 14.4, 12.4; FT-IR (neat) 2971, 1647, 1466, 1379, 1304, 1128 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{28}H_{28}NO_3$: 426.2064; Found 426.2074; $[\alpha]_D^{25}$ = -27.0 (c = 0.1, CH_2Cl_2); HPLC: 90% ee (major diastereomer) [CHIRALCEL OD, hexane/^{i}PrOH = 95:05, flow rate: 0.7 mL/min, λ= 254 nm, t_R = 66.81 min (major), 78.57 min (minor)].



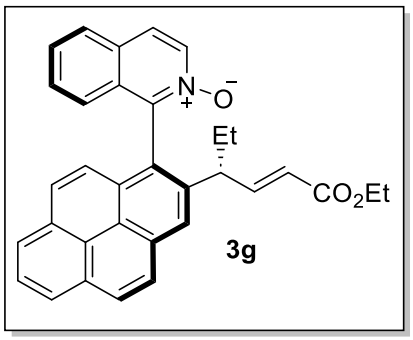
(*S*)-1-(4-Methoxynaphthalen-1-yl)isoquinoline 2-oxide 1f. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.35; Foamy solid; yield 64% (28 mg); $[\alpha]_D^{25}$ = + 67.0 (c = 0.09, CH_2Cl_2); HPLC: 30% ee [CHIRALCEL OD-H, hexane/^{i}PrOH = 80:20, flow rate: 1 mL/min, λ= 254 nm, t_R = 21.49 min (major), 36.91 min (minor)].



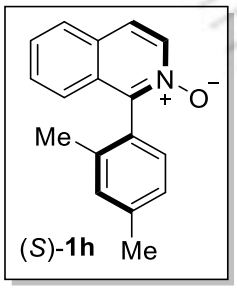
(*R*)-1-(2-((*R*,*E*)-6-Ethoxy-6-oxohex-4-en-3-yl)-4-methoxy-naphthalen-1-yl)isoquinoline 2-oxide 3f. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.35; Brown liquid; yield 22% (10 mg); major diastereomer (d.r. >10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 7.2 Hz, 1H), 8.31 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 7.2 Hz, 1H), 7.53 (t, *J* = 8.4 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.35-7.28 (m, 2H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.93-6.87 (m, 2H), 5.12 (d, *J* = 16.8 Hz, 1H), 4.10-4.05 (m, 5H), 2.92 (q, *J* = 8.0 Hz, 1H), 2.02-1.95 (m, 1H), 1.87-1.77 (m, 1H), 1.21 (t, *J* = 7.2 Hz, 3H), 0.86 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 157.3, 149.9, 144.8, 140.5, 137.7, 132.7, 130.9, 129.3, 128.6, 127.9, 127.0, 126.0, 125.6, 125.3, 124.8, 123.9, 122.7, 121.6, 119.5, 102.6, 60.3, 55.8, 48.2, 27.9, 14.4, 12.4; FT-IR (neat) 2924, 1709, 1585, 1460, 1354, 1264, 1236, 1112 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{28}H_{28}NO_4$: 442.2013; Found 442.2015; $[\alpha]_D^{25}$ = -31.0 (c = 0.08, CH_2Cl_2); HPLC: 97% ee (major diastereomer) [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 6.51 min (major), 7.57 min (minor)].



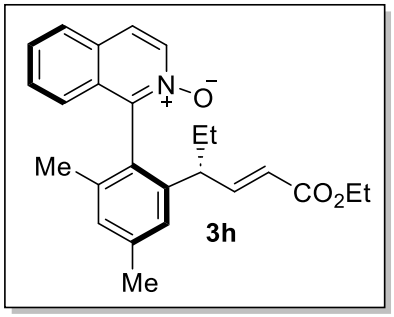
(*S*)-1-(3a^1, 5a^1-Dihydropyren-1-yl)isoquinoline 2-oxide 1g. Analytical TLC on silica gel, 8:2 ethyl acetate/hexane R_f = 0.40; Brown solid; yield 76% (36 mg); $[\alpha]_D^{25}$ = +3.0 (c = 0.05, CH_2Cl_2); HPLC: 16% ee [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 16.47 min (major), 26.68 min (minor)].



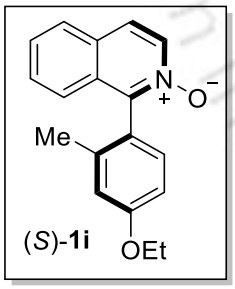
(*R*)-1-(2-((*R*,*E*)-6-Ethoxy-6-oxohex-4-en-3-yl)pyren-1-yl)-isoquinoline 2-oxide 3g. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.40; Brown liquid; yield 12% (8 mg); major diastereomer (d.r. >10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 7.2 Hz, 1H), 8.29 (s, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 8.17-8.13 (m, 4H), 8.00 (t, *J* = 7.6 Hz, 1H), 7.93-7.87 (m, 3H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.29-7.27 (m, 1H), 6.93 (dd, *J* = 15.6, 8.8 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 5.09 (d, *J* = 16.4 Hz, 1H), 4.03 (q, *J* = 7.2 Hz, 2H), 3.22 (q, *J* = 8.4 Hz, 1H), 2.21-2.14 (m, 1H), 2.05-1.95 (m, 1H), 1.19 (t, *J* = 7.2 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 150.6, 144.9, 139.9, 137.7, 132.8, 131.1, 131.0, 130.8, 130.2, 129.5, 129.1, 128.8, 128.7, 128.6, 127.4, 127.1, 126.3, 125.9, 125.86, 125.81, 125.3, 124.7, 124.32, 124.31, 124.1, 123.7, 121.4, 60.3, 48.0, 28.4, 14.3, 12.5; FT-IR (neat) 2956, 2923, 2853, 1712, 1599, 1461, 1265 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{33}H_{28}NO_3$: 486.2064; Found 486.2060; $[\alpha]_D^{25}$ = -13.1 (c = 0.13, CH_2Cl_2); HPLC: 98% ee (major diastereomer) [CHIRALCEL AD-H, hexane/^{i}PrOH = 80:20, flow rate: 1 mL/min, λ= 254 nm, t_R = 14.99 min (major), 34.53 min (minor)].



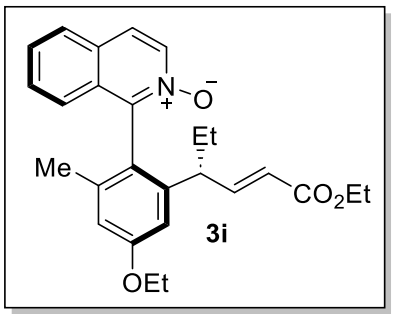
(*S*)-1-(2,4-Dimethylphenyl)isoquinoline 2-oxide 1h. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.35; Yellow solid; yield 68% (34 mg); $[\alpha]_D^{25}$ = +30.0 (c = 0.05, CH_2Cl_2); HPLC: 29% ee [CHIRALCEL AD-H, hexane/^{i}PrOH = 90:10, flow rate: 1 mL/min, λ= 254 nm, t_R = 24.39 min (major), 26.06 min (minor)].



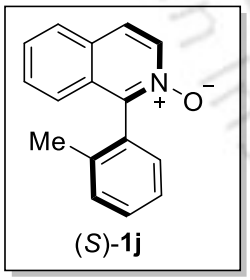
(*S*)-1-(2-((*R*,*E*)-6-Ethoxy-6-oxohex-4-en-3-yl)-4,6-di-methyl-phenyl)isoquinoline 2-oxide 3h. Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.30; yellow liquid; yield 22% (8 mg); major diastereomer (d.r. >10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.2 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 7.2 Hz, 1H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.09-7.08 (m, 3H), 6.72 (dd, *J* = 15.6, 8.4 Hz, 1H), 4.97 (d, *J* = 16.0 Hz, 1H), 4.04 (q, *J* = 7.2 Hz, 2H), 2.68 (q, *J* = 8.4 Hz, 1H), 2.41 (s, 3H), 1.92 (s, 3H), 1.89-1.83 (m, 1H), 1.70-1.63 (m, 1H), 1.20 (t, *J* = 6.8 Hz, 3H), 0.78 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 150.8, 145.8, 141.6, 139.9, 137.6, 137.4, 130.0, 129.3, 128.6, 127.5, 127.0, 125.6, 125.4, 123.7, 121.0, 60.2, 47.4, 28.0, 21.7, 19.7, 14.4, 12.3; FT-IR (neat) 2922, 1712, 1605, 1468, 1278, 1152 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{25}H_{28}NO_3$: 390.2064; Found 390.2067; $[\alpha]_D^{25}$ = -20.0 (c = 0.05, CH_2Cl_2); HPLC: 99% ee (major diastereomer) [CHIRALCEL OD-H, hexane/^{i}PrOH = 95:5, flow rate: 1 mL/min, λ= 254 nm, t_R = 25.99 min (major), 36.66 min (minor)].



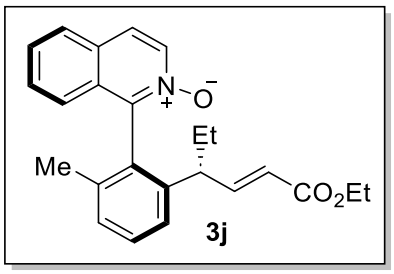
(*S*)-1-(4-Ethoxy-2-methylphenyl)isoquinoline 2-oxide 1i. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.40; Colorless solid; yield 77% (39 mg); $[\alpha]_D^{25}$ = +15.0 (c = 0.04, CH_2Cl_2); HPLC: 11% ee [CHIRALCEL AD-H, hexane/^{i}PrOH = 80:20, flow rate: 0.3 mL/min, λ= 254 nm, t_R = 57.39 min (major), 59.63 min (minor)].



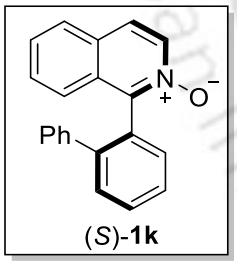
(*S*)-1-(4-Ethoxy-2-((*R*,*E*)-6-ethoxy-6-oxohex-4-en-3-yl)-6-methylphenyl)isoquinoline 2-oxide 3i. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.35; Brown liquid; yield 10% (10 mg); major diastereomer (d.r. = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.2 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 7.2 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 6.81 (s, 2H), 6.69 (dd, *J* = 16.0, 8.8 Hz, 1H), 4.98 (d, *J* = 15.6 Hz, 1H), 4.13-4.02 (m, 4H), 2.69 (q, *J* = 8.4 Hz, 1H), 1.93 (s, 3H), 1.88-1.81 (m, 1H), 1.69-1.62 (m, 1H), 1.46 (t, *J* = 7.2 Hz, 3H), 1.20 (t, *J* = 7.2 Hz, 3H), 0.79 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 160.2, 150.5, 145.7, 143.4, 139.4, 137.4, 130.3, 129.4, 128.7, 128.6, 127.0, 125.6, 123.7, 122.6, 121.2, 114.5, 111.6, 63.6, 60.2, 47.5, 28.0, 20.2, 15.1, 14.4, 12.3; FT-IR (neat) 2924, 1708, 1602, 1468, 1281, 1152, 1055 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{26}H_{30}NO_4$: 420.2169; Found 420.2172; $[\alpha]_D^{25}$ = -9.0 (c = 0.13, CH_2Cl_2); HPLC: 94% ee (major diastereomer) [CHIRALCEL AD-H, hexane/^{i}PrOH = 80:20, flow rate: 1 mL/min, λ= 254 nm, t_R = 7.47 min (major), 10.11 min (minor)].



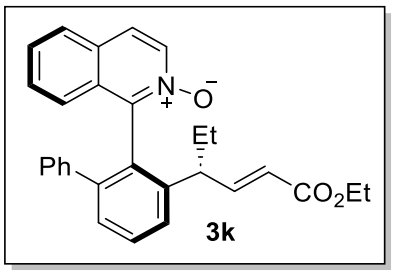
(*S*)-1-(*o*-Tolyl)isoquinoline 2-oxide 1j. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.40; Yellow solid; yield 74% (36 mg); $[\alpha]_D^{25}$ = +23.0 (c = 0.06, CH_2Cl_2); HPLC: 16% ee [CHIRALCEL OD-H, hexane/^{i}PrOH = 95:5, flow rate: 1 mL/min, λ= 254 nm, t_R = 57.01 min (major), 67.46 min (minor)].



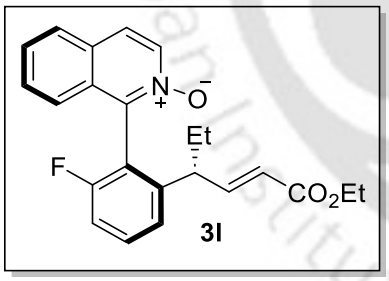
(*S*)-1-(2-((*R*,*E*)-6-Ethoxy-6-oxohex-4-en-3-yl)-6-methylphenyl)isoquinoline 2-oxide 3j. Analytical TLC on silica gel, 6:4 ethyl acetate/hexane R_f = 0.30; brown liquid; yield 13% (9 mg); major diastereomer (d.r. > 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.2 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 7.2 Hz, 1H), 7.54 (t, *J* = 8.4 Hz, 1H), 7.47-7.39 (m, 2H), 7.29 (t, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 1H), 6.71 (dd, *J* = 15.6, 8.4 Hz, 1H), 4.97 (d, *J* = 15.6 Hz, 1H), 4.03 (q, *J* = 7.2 Hz, 2H), 2.72 (q, *J* = 8.0 Hz, 1H), 1.96 (s, 3H), 1.90-1.83 (m, 1H), 1.72-1.64 (m, 1H), 1.20 (t, *J* = 6.8 Hz, 3H), 0.79 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 150.6, 145.5, 141.8, 137.9, 137.4, 130.5, 130.1, 129.8, 129.4, 129.0, 128.6, 128.5, 127.1, 125.3, 124.9, 123.8, 121.1, 60.2, 47.5, 28.0, 19.8, 14.3, 12.2; FT-IR (neat) 2923, 2853, 1703, 1602, 1463, 1268 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{24}H_{26}NO_3$: 376.1907; Found 376.1907; $[\alpha]_D^{25}$ = -9.1 (c = 0.13, CH_2Cl_2); HPLC: 97% ee (major diastereomer) [CHIRALCEL AD-H, hexane/^{i}PrOH = 80:20, flow rate: 1 mL/min, λ= 254 nm, t_R = 5.74 min (major), 7.31 min (minor)].



(*S*)-1-([1,1'-Biphenyl]-2-yl)isoquinoline 2-oxide 1k. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.30; Brown solid; yield 76% (38 mg); $[\alpha]_D^{25}$ = +8.0 (c = 0.05, CH_2Cl_2); HPLC: 16% ee [CHIRALCEL OD-H, hexane/^{i}PrOH = 80:20, flow rate: 1 mL/min, λ= 254 nm, t_R = 11.92 min (major), 19.89 min (minor)].

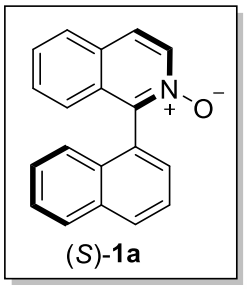


(*R*)-1-(3-((*R*,*E*)-6-Ethoxy-6-oxohex-4-en-3-yl)-[1,1'-bi-phenyl]-2-yl)isoquinoline 2-oxide 3k. Analytical TLC on silica gel, 3:2 Ethyl acetate/hexane R_f = 0.40; yellow liquid; yield 13% (9 mg); major diastereomer (dr >10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 7.2 Hz, 1H), 7.63 (t, *J* = 8.4 Hz, 1H), 7.60-7.55 (m, 2H), 7.50 (d, *J* = 9.2 Hz, 1H), 7.45-7.43 (m, 1H), 7.35-7.31 (m, 1H), 7.25-7.22 (m, 3H), 7.05-6.98 (m, 3H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.56 (dd, *J* = 15.6, 8.8 Hz, 1H), 4.77 (d, *J* = 15.6 Hz, 1H), 3.94 (q, *J* = 7.2 Hz, 2H), 2.93 (q, *J* = 8.4 Hz, 1H), 2.09-1.99 (m, 1H), 1.86-1.77 (m, 1H), 1.13 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 150.5, 145.9, 143.6, 142.3, 140.8, 136.6, 130.3, 129.9, 129.7, 128.9, 128.8, 128.3, 128.2, 128.1, 127.9, 127.2, 126.4, 126.3, 125.4, 123.9, 121.0, 60.1, 47.2, 34.1, 27.3, 14.3, 12.4; FT-IR (neat) 2923, 1716, 1555, 1463, 1264, 1183, 1028 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{29}H_{28}NO_3$: 438.2064; Found 438.2061; $[\alpha]_D^{25}$ = -18.0 (c = 0.04, CH_2Cl_2); HPLC: 98% ee (major diastereomer) [CHIRALCEL AD-H, hexane/^{i}PrOH = 80:20, flow rate: 1 mL/min, λ= 254 nm, t_R = 6.86 min (major), 8.29 min (minor)].

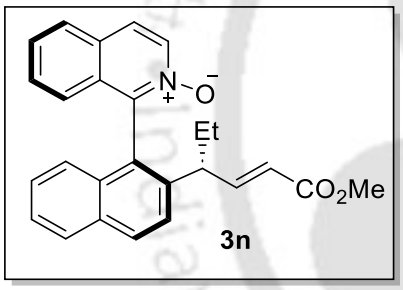


(*R*)-1-(2-((*R*,*E*)-6-Ethoxy-6-oxohex-4-en-3-yl)-6-fluoro-phenyl)isoquinoline 2-oxide 3l. Analytical TLC on silica gel, 7:3 Ethyl acetate/hexane R_f = 0.30; yellow liquid; yield 32% (18 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.2 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 6.8 Hz, 1H), 7.58-7.53 (m, 2H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.16 (t, *J* = 8.8 Hz, 2H), 6.70 (dd, *J* = 15.6, 8.8 Hz, 1H), 5.05 (d, *J* = 16.4 Hz, 1H), 4.02 (q, *J* = 6.8 Hz, 2H), 2.91 (q, *J* = 8.0 Hz, 1H), 1.95-1.88 (m, 1H), 1.75-1.68 (m, 1H), 1.19 (t, *J* = 7.2 Hz, 3H), 0.83 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 161.3 (J_{C-F} = 246.8 Hz), 149.8, 144.8, 140.7, 137.4, 131.9 (J_{C-F} = 8.5 Hz), 130.1, 129.6, 128.7, 128.6, 127.1, 125.0, 124.4, 123.1 (J_{C-F} = 3.0 Hz), 121.6, 119.1 (J_{C-F} = 16.4 Hz), 114.6 (J_{C-F} = 21.4 Hz), 60.3, 47.0, 27.7,

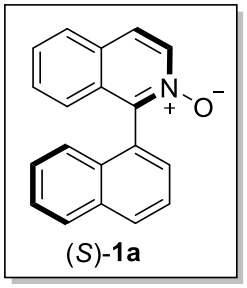
14.3, 12.1; ^{19}F NMR (375 MHz, $CDCl_3$) δ -111.9; FT-IR (neat) 2927, 1716, 1600, 1452, 1281, 1152, 1032 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{23}FNO_3$: 380.1656; Found 380.1658; $[\alpha]_D^{25}$ = -2.0 (c = 0.04, CH_2Cl_2); HPLC: 5% ee [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 5.38 min and 5.96 min].



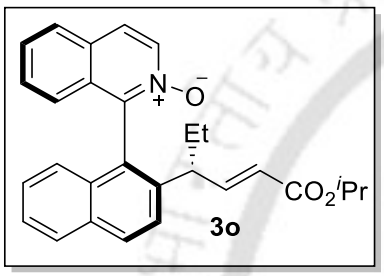
(*S*)-1-(Naphthalen-1-yl)isoquinoline 2-oxide (*S*)-1a. Analytical TLC on silica gel, 9:1 Ethyl acetate/hexane R_f = 0.35; Foamy solid; yield 58% (28 mg); $[\alpha]_D^{25}$ = +98.0 (c = 0.09, CH_2Cl_2); HPLC: 46% ee [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 8.14 min (major), 9.11 min (minor)].



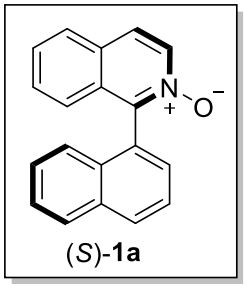
(*R*)-1-(2-((*R*,*E*)-6-methoxy-6-oxohex-4-en-3-yl)naphtha-len-1-yl)isoquinoline 2-oxide 3n. Analytical TLC on silica gel, 7:3 Ethyl acetate/hexane R_f = 0.30; Brown liquid; yield 30% (16 mg); major diastereomer (dr >10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 7.2 Hz, 1H), 8.04 (d, *J* = 8.8 Hz, 1H), 7.86 (dd, *J* = 17.2, 8.0 Hz, 2H), 7.81 (d, *J* = 6.8 Hz, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.35-7.29 (m, 2H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.94-6.88 (m, 2H), 5.11 (d, *J* = 15.6 Hz, 1H), 3.62 (s, 3H), 2.93 (q, *J* = 8.4 Hz, 1H), 2.00-1.94 (m, 1H), 1.84-1.76 (m, 1H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 150.4, 144.4, 139.9, 137.7, 132.8, 131.8, 130.6, 130.5, 129.5, 128.7, 128.6, 128.5, 127.4, 127.3, 127.0, 126.3, 125.7, 125.0, 124.7, 124.1, 121.1, 51.5, 47.9, 28.0, 12.3; FT-IR (neat) 2923, 2853, 1747, 1717, 1462, 1506, 1263 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}NO_3$: 398.1751; Found 398.1753; $[\alpha]_D^{25}$ = -13.1 (c = 0.08, CH_2Cl_2); HPLC: 98% ee (major diastereomer) [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 7.28 min (major), 8.20 min (minor)].



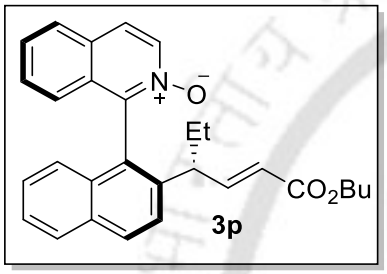
(*S*)-1-(Naphthalen-1-yl)isoquinoline 2-oxide (*S*)-1a. Analytical TLC on silica gel, 9:1 Ethyl acetate/hexane R_f = 0.35; Foamy solid; yield 65% (30 mg); $[\alpha]_D^{25}$ = +79.0 (c = 0.09, CH_2Cl_2); HPLC: 30% ee [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 8.09 min (major), 9.08 min (minor)].



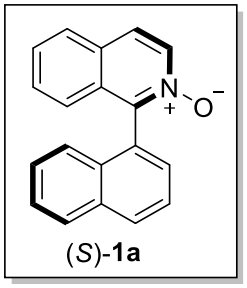
(*R*)-1-(2-((*R*,*E*)-6-*Iso*propoxy-6-oxohex-4-en-3-yl)naphthalen-1-yl)isoquinoline 2-oxide 3o. Analytical TLC on silica gel, 7:3 Ethyl acetate/hexane R_f = 0.35; yellow liquid; yield 23% (13 mg); major diastereomer (d.r. >10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 7.2 Hz, 1H), 8.05 (d, *J* = 8.8 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 7.2 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.53 (t, *J* = 8.4 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.30 (q, *J* = 7.2 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.82 (dd, *J* = 15.6, 8.0 Hz, 1H), 5.06 (d, *J* = 16.8 Hz, 1H), 4.93 (p, *J* = 6.4 Hz, 1H), 2.93 (q, *J* = 7.2 Hz, 1H), 2.00-1.93 (m, 1H), 1.85-1.77 (m, 1H), 1.16 (d, *J* = 6.4 Hz, 6H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 149.6, 144.5, 139.9, 137.6, 132.8, 131.8, 130.6, 130.5, 129.4, 128.7, 128.6, 127.4, 127.3, 127.0, 126.2, 125.8, 125.0, 124.8, 124.1, 122.0, 67.6, 47.8, 27.8, 22.0, 12.4; FT-IR (neat) 2951, 1745, 1641, 1462, 1506, 1263, 1214, 1162 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{28}H_{28}NO_3$: 426.2064; Found 426.2067; $[\alpha]_D^{25}$ = -7.0 (c = 0.08, CH_2Cl_2); HPLC: 97% ee (major diastereomer) [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 5.78 min (major), 7.76 min (minor)].



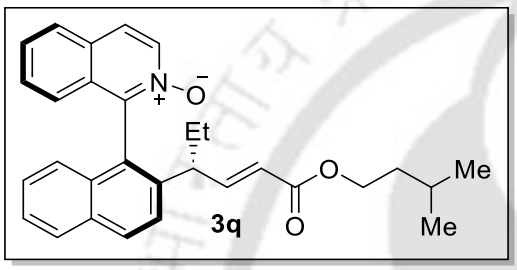
(*S*)-1-(Naphthalen-1-yl)isoquinoline 2-oxide (*S*)-1a. Analytical TLC on silica gel, 9:1 Ethyl acetate/hexane R_f = 0.35; Foamy solid; yield 68% (28 mg); $[\alpha]_D^{25}$ = +62.5 (c = 0.04, CH_2Cl_2); HPLC: 26% ee [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 8.81 min (major), 9.87 min (minor)].



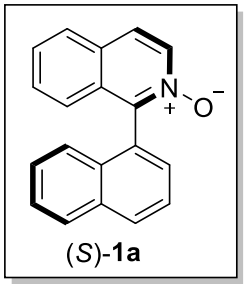
(*R*)-1-(2-((*R*,*E*)-6-Butoxy-6-oxohex-4-en-3-yl)naphthalen-1-yl)isoquinoline 2-oxide 3p. Analytical TLC on silica gel, 8:2 Ethyl acetate/hexane R_f = 0.40; Brown liquid; yield 20% (16 mg); major diastereomer (d.r. >10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 7.2 Hz, 1H), 8.05 (d, *J* = 8.8 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 6.8 Hz, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 6.8 Hz, 1H), 7.34-7.29 (m, 2H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.95-6.85 (m, 2H), 5.10 (d, *J* = 15.6 Hz, 1H), 4.01 (t, *J* = 7.2 Hz, 2H), 2.93 (q, *J* = 7.6 Hz, 1H), 2.00-1.93 (m, 1H), 1.87-1.77 (m, 1H), 1.59-1.52 (m, 2H), 1.37-1.28 (m, 2H), 0.91 (t, *J* = 7.6 Hz, 3H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.5, 150.0, 144.4, 139.9, 137.7, 132.8, 131.8, 130.6, 130.5, 129.4, 128.7, 128.6, 128.5, 127.4, 127.3, 127.0, 126.3, 125.7, 125.0, 124.8, 121.5, 64.2, 47.9, 30.8, 27.9, 19.2, 13.8, 12.4; FT-IR (neat) 2922, 1714, 1460, 1501, 1263 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{29}H_{30}NO_3$: 440.2220; Found 440.2223; $[\alpha]_D^{25}$ = -10.0 (c = 0.1, CH_2Cl_2); HPLC: 97% ee (major diastereomer) [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 6.023 min (major), 8.323 min (minor)].



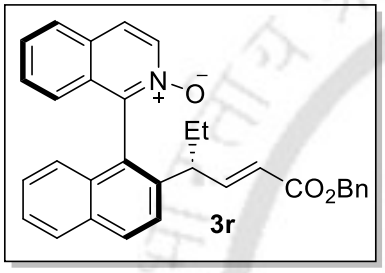
(*S*)-1-(Naphthalen-1-yl)isoquinoline 2-oxide (*S*)-1a. Analytical TLC on silica gel, 9:1 Ethyl acetate/hexane R_f = 0.35; Foamy solid; yield 61% (29 mg); $[\alpha]_D^{25}$ = +53.0 (c = 0.09, CH_2Cl_2); HPLC: 26% ee [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 8.14 min (major), 9.13 min (minor)].



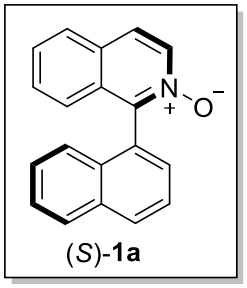
(*R*)-1-(2-((*R*,*E*)-6-(*Iso*pentyloxy)-6-oxohex-4-en-3-yl)naphthalen-1-yl)isoquinoline 2-oxide 3q. Analytical TLC on silica gel, 3:2 Ethyl acetate/hexane R_f = 0.35; yellow liquid; yield 23% (17 mg); major diastereomer (d.r. = 5:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 7.2 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 7.2 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.34-7.29 (m, 2H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.85 (dd, *J* = 15.6, 8.4 Hz, 1H), 5.10 (d, *J* = 16.8 Hz, 1H), 4.04 (t, *J* = 5.6 Hz, 1H), 2.93 (q, *J* = 7.6 Hz, 1H), 2.00-1.93 (m, 1H), 1.86-1.77 (m, 1H), 1.66-1.57 (m, 1H), 1.46 (q, *J* = 6.8 Hz, 2H), 0.89 (d, *J* = 6.4 Hz, 6H), 0.85 (t, *J* = 7.6 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 150.0, 144.5, 139.9, 137.7, 132.8, 131.8, 130.6, 130.5, 129.4, 128.7, 128.6, 127.4, 127.3, 127.0, 126.3, 125.8, 125.0, 124.8, 124.1, 121.5, 63.0, 47.9, 37.4, 27.9, 25.2, 22.6, 12.4; FT-IR (neat) 2920, 1722, 1458, 1502, 1265 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{30}H_{32}NO_3$: 454.2377; Found 454.2379; $[\alpha]_D^{25}$ = -13.3 (c = 0.09, CH_2Cl_2); HPLC: 99% ee (major diastereomer) [CHIRALCEL AD-H, hexane/^{i}PrOH = 90:10, flow rate: 1 mL/min, λ= 254 nm, t_R = 18.29 min (major), 34.45 min (minor)].



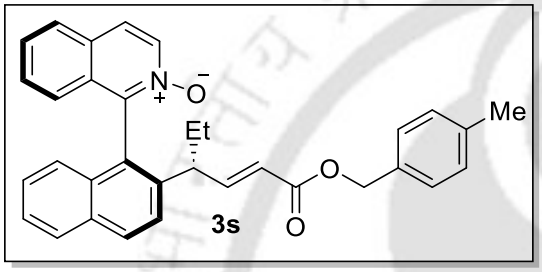
(*S*)-1-(Naphthalen-1-yl)isoquinoline 2-oxide (*S*)-1a. Analytical TLC on silica gel, 9:1 Ethyl acetate/hexane R_f = 0.35; Foamy solid; yield 74% (34 mg); $[\alpha]_D^{25}$ = +7.7 (c = 0.06, CH_2Cl_2); HPLC: 18% ee [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 8.14 min (major), 9.12 min (minor)].



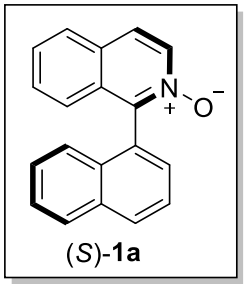
(*R*)-1-(2-((*R*,*E*)-6-(Benzyloxy)-6-oxohex-4-en-3-yl)naphthalen-1-yl)isoquinoline 2-oxide 3r. Analytical TLC on silica gel, 7:3 Ethyl acetate/hexane R_f = 0.30; Brown liquid; yield 15% (13 mg); major diastereomer (d.r. >10:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 7.2 Hz, 1H), 8.04 (d, *J* = 8.8 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.79 (dd, *J* = 14.4, 8.0 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 2H), 7.38-7.28 (m, 6H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.96-6.89 (m, 2H), 5.13 (d, *J* = 16.4 Hz, 1H), 5.09-5.02 (m, 2H), 2.94 (q, *J* = 7.2 Hz, 1H), 2.00-1.94 (m, 1H), 1.85-1.77 (m, 1H), 0.85 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 150.7, 144.4, 139.7, 137.6, 136.1, 132.8, 131.8, 130.7, 130.4, 129.4, 128.7, 128.6, 128.57, 128.55, 128.4, 127.4, 127.3, 127.0, 126.3, 125.7, 125.0, 124.7, 124.1, 121.1, 66.1, 47.9, 27.8, 12.4; FT-IR (neat) 2922, 1712, 1451, 1506, 1263 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{32}H_{28}NO_3$:474.2064; Found 474.2068; $[\alpha]_D^{25}$ = -9.5 (c = 0.08, CH_2Cl_2); HPLC: 96% ee (major diastereomer) [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 9.93 min (major), 16.42 min (minor)].



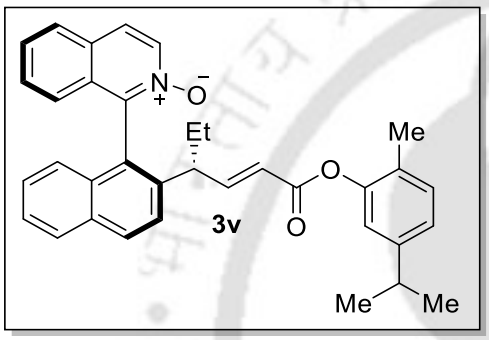
(*S*)-1-(Naphthalen-1-yl)isoquinoline 2-oxide (*S*)-1a. Analytical TLC on silica gel, 9:1 Ethyl acetate/hexane R_f = 0.35; Foamy solid; yield 65% (29 mg); $[\alpha]_D^{25}$ = +38.0 (c = 0.03, CH_2Cl_2); HPLC: 33% ee [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 8.77 min (major), 9.84 min (minor)].



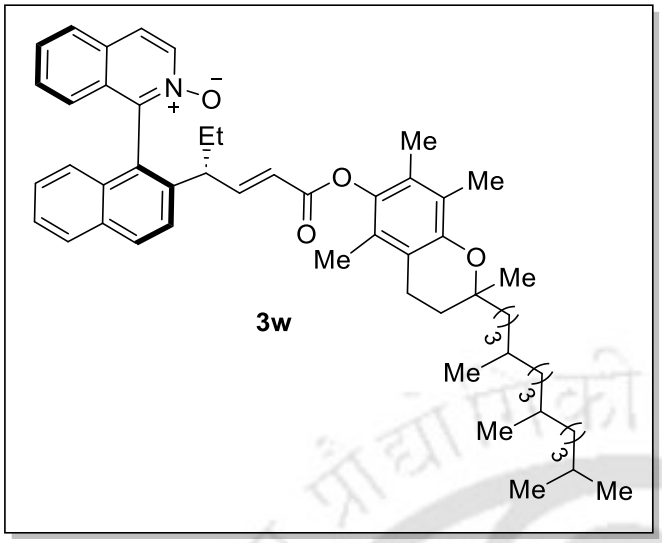
(*R*)-1-(2-((*R*,*E*)-6-((4-Methylbenzyl)oxy)-6-oxo-hex-4-en-3-yl)naphthalen-1-yl)isoquinoline 2-oxide 3s. Analytical TLC on silica gel, 8:2 Ethyl acetate/hexane R_f = 0.35; yellow liquid; yield 24% (14 mg); major diastereomer (d.r. >10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 7.2 Hz, 1H), 8.04 (d, *J* = 8.8 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.79 (dd, *J* = 16.8, 8.4 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.48-7.43 (m, 2H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.25-7.23 (m, 1H), 7.20-7.15 (m, 4H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.95-6.89 (m, 2H), 5.13 (d, *J* = 16.8 1H), 5.05-4.98 (m, 2H), 2.93 (q, *J* = 7.6 Hz, 1H), 2.35 (s, 3H), 2.00-1.93 (m, 1H), 1.86-1.77 (m, 1H), 0.85 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 150.5, 144.4, 139.8, 138.2, 137.6, 133.1, 132.8, 131.8, 130.6, 130.5, 129.4, 129.3, 128.7, 128.6, 128.5, 127.4, 127.3, 127.0, 126.3, 125.7, 125.0, 124.8, 124.1, 121.3, 66.1, 47.9, 27.8, 21.3, 12.3; FT-IR (neat) 2920, 1727, 1462, 1506, 1260 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{33}H_{30}NO_3$: 488.2220; Found 488.2191; $[\alpha]_D^{25}$ = -7.8 (c = 0.06, CH_2Cl_2); HPLC: 99% ee (major diastereomer) [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 9.26 min (major), 16.60 min (minor)].



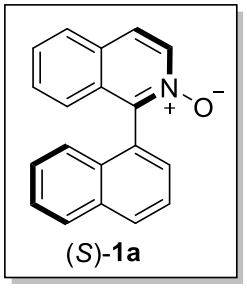
(*S*)-1-(Naphthalen-1-yl)isoquinoline 2-oxide (*S*)-1a. Analytical TLC on silica gel, 9:1 Ethyl acetate/hexane R_f = 0.35; Foamy solid; yield 65% (35 mg); $[\alpha]_D^{25}$ = +26.0 (c = 0.04, CH_2Cl_2); HPLC: 26% ee [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 8.14 min (major), 9.13 min (minor)].



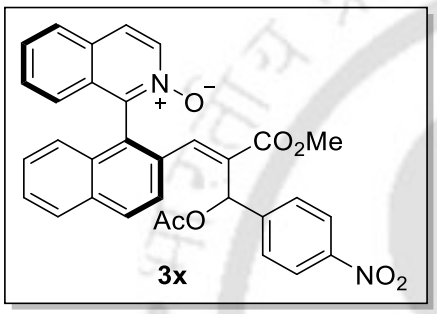
(*R*)-1-(2-((*R*, *E*)-6-(5-Isopropyl-2-methylphenoxy)-6-oxohex-4-en-3-yl)naphthalen-1-yl)isoquinoline 2-oxide 3v. Analytical TLC on silica gel, 3:2 Ethyl acetate/hexane R_f = 0.30; Brown liquid; yield 20% (12 mg); major diastereomer (d.r. >10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 7.2 Hz, 1H), 8.08 (d, *J* = 8.8 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 7.2 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.38-7.30 (m, 2H), 7.13-7.07 (m, 2H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 2H), 6.77 (s, 1H), 5.32 (d, *J* = 15.6 Hz, 1H), 3.03 (q, *J* = 7.6 Hz, 1H), 2.88-2.81 (m, 1H), 2.07-2.03 (m, 1H), 2.01 (s, 3H), 1.91-1.84 (m, 1H), 1.20 (d, *J* = 6.8 Hz, 6H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5, 152.2, 149.2, 148.1, 144.5, 139.6, 137.7, 132.9, 131.9, 130.9, 130.8, 130.5, 129.5, 128.8, 128.64, 128.62, 127.5, 127.4, 127.2, 127.1, 126.4, 125.8, 125.1, 124.7, 124.24, 124.21, 120.6, 119.8, 48.1, 33.7, 27.9, 24.0, 15.9, 12.4; FT-IR (neat) 2951, 1720, 1632, 1564, 1506, 1264, 1211, 1162 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{35}H_{34}NO_3$: 516.2533; Found 516.2531; $[\alpha]_D^{25}$ = -7.3 (c = 0.08, CH_2Cl_2); HPLC: 92% ee (major diastereomer) [CHIRALCEL OD-H, hexane/^{i}PrOH = 95:5, flow rate: 1 mL/min, λ= 254 nm, t_R = 58.28 min (major), 47.44 min (minor)].



(1*R*)-1-(2-((3*R*,*E*)-6-Oxo-6-((2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-yl)oxy)hex-4-en-3-yl)naph-thalen-1-yl)isoquinoline 2-oxide 3w. Analytical TLC on silica gel, 7:3 Ethyl acetate/hexane R_f = 0.35; yellow liquid; yield 27% (21 mg); major diastereomer (d.r. >10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 7.2 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 7.2 Hz, 1H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.32 (q, *J* = 7.6 Hz, 2H), 7.09 (dd, *J* = 15.6, 8.4 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 1H), 5.35 (d, *J* = 15.6 Hz, 1H), 3.03 (q, *J* = 7.2 Hz, 1H), 2.55 (t, *J* = 6.4 Hz, 2H), 2.06 (s, 3H), 2.03-1.97 (m, 1H), 1.88 (s, 3H), 1.84 (s, 3H), 1.81-1.72 (m, 2H), 1.49.55-1 (m, 3H), 1.41-1.34 (m, 2H), 1.27-1.22 (m, 13H), 1.16-1.12 (m, 3H), 1.07-1.03 (m, 3H), 0.91 (t, *J* = 7.2 Hz, 3H), 0.87-0.83 (m, 13H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 152.0, 149.5, 144.5, 140.4, 139.7, 137.7, 132.9, 131.9, 130.8, 130.5, 129.5, 128.8, 128.6, 127.5, 127.1, 126.8, 126.4, 125.8, 125.1, 125.0, 124.8, 124.2, 123.1, 120.6, 117.5, 75.2, 48.2, 39.5, 37.6, 37.56, 37.54, 37.50, 37.4, 32.94, 32.93, 32.8, 29.8, 28.13, 28.08, 25.0, 24.9, 24.6, 22.9, 22.77, 21.18, 21.17, 20.7, 19.9, 19.8, 13.1, 12.4, 12.3, 11.9; FT-IR (neat) 2919, 1717, 1452, 1448, 1110 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{54}H_{70}NO_4$:796.5299; Found 796.5265.

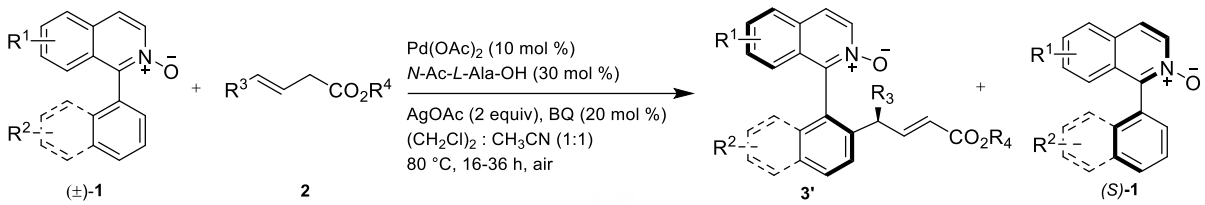


(*S*)-1-(Naphthalen-1-yl)isoquinoline 2-oxide (*S*)-1a. Analytical TLC on silica gel, 9:1 Ethyl acetate/hexane R_f = 0.35; Foamy solid; yield 55% (31 mg); $[\alpha]_D^{25}$ = +97.5 (c = 0.04, CH_2Cl_2); HPLC: 46% ee [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 8.15 min (major), 9.16 min (minor)].

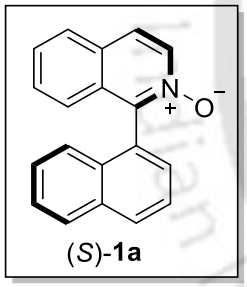


(1*R*)-1-(2-((*E*)-3-Acetoxy-2-(methoxycarbonyl)-3-(4-nitrophenyl)prop-1-en-1-yl)naphthalen-1-yl)isoquinoline 2-oxide 3x. Analytical TLC on silica gel, 7:3 Ethyl acetate/hexane R_f = 0.30; Brown liquid; yield 30% (16 mg); major diastereomer (d.r. >10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 7.2 Hz, 1H), 8.00-7.90 (m, 5H), 7.78 (d, *J* = 7.2 Hz, 1H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.52-7.48 (m, 2H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 6.8 Hz, 1H), 7.12-7.08 (m, 4H), 6.54 (s, 1H), 6.42 (s, 1H), 3.58 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 166.3, 147.6, 144.9, 143.7, 137.8, 137.5, 133.8, 133.7, 133.5, 131.3, 130.2, 129.71, 129.68, 128.8, 128.7, 128.6, 128.0, 127.7, 127.5, 127.1, 127.0, 125.9, 125.7, 125.1, 124.1, 123.7, 73.8, 52.1, 20.8; FT-IR (neat) 2922, 1729, 1628, 1560, 1502, 1234, 1214, 1162 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{32}H_{25}N_2O_7$: 549.1656; Found 549.1655; $[\alpha]_D^{25}$ = -17.6 (c = 0.05, CH_2Cl_2); HPLC: 96% ee (major diastereomer) [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 31.56 min (major), 29.24 min (minor)].

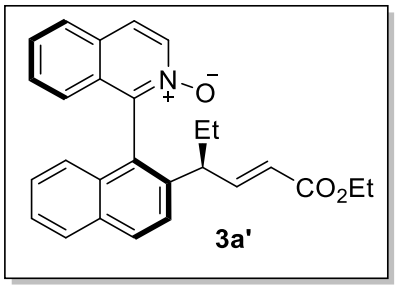
General procedure for Pd-catalyzed C-H allylation of 1-Arylisoquinoline *N*-oxides 3' (Diastereomer-II)



To a stirred solution of (±)-aryl isoquiniline *N*-oxide **1** (0.2 mmol, 1 equiv) in $(CH_2Cl)_2$: CH_3CN (1:1, 2 mL), *trans*-3-alkenoate **2** (0.14 mmol, 0.7 equiv), BQ (20 mol %, 0.04 mmol, 5 mg), *N*-Ac-*L*-Ala-OH (30 mol %, 0.06 mmol, 7 mg), AgOAc (2 equiv, 0.4 mmol, 63 mg) and $Pd(OAc)_2$ (10 mol %, 0.02 mmol, 6 mg) were added. The reaction mixture was stirred at 80 °C for 16-36 h under air. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through a short pad of celite. Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and Ethyl acetate as eluent to afford **3' (**Diastereomer-II) and recovered (*S*)-**1**.

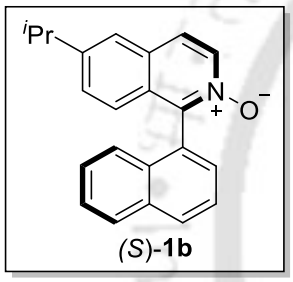


(*S*)-1-(Naphthalen-1-yl)isoquinoline 2-oxide (*S*)-1a. Analytical TLC on silica gel, 9:1 Ethyl acetate/hexane R_f = 0.35; Yellow solid; yield 68% (33 mg); $[\alpha]_D^{25}$ = +90.0 (c = 0.1, CH_2Cl_2); HPLC: 22% ee [CHIRALCEL OD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 12.70 min (major), 15.82 min (minor)].

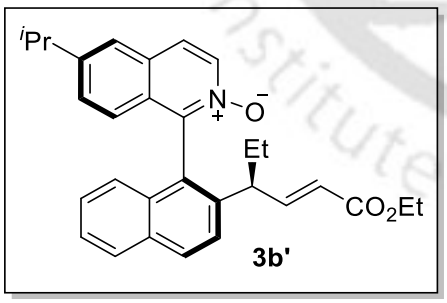


(*R*)-1-(2-((*S*,*E*)-6-Ethoxy-6-oxohex-4-en-3-yl)naphthalen-1-yl)isoquinoline 2-oxide 3a'. Analytical TLC on silica gel, 7:3 Ethyl acetate/hexane R_f = 0.30;

yellow liquid; yield 21% (9 mg); major diastereomer (d.r. >10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 7.2 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.87 (dd, *J* = 14.4, 8.0 Hz, 2H), 7.80 (d, *J* = 6.8 Hz, 1H), 7.57-7.53 (m, 2H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.12 (dd, *J* = 15.6, 6.4 Hz, 1H), 7.02 (t, *J* = 8.8 Hz, 2H), 5.80 (d, *J* = 16.8 Hz, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 2.97 (q, *J* = 7.2 Hz, 1H), 1.77-1.71 (m, 2H), 1.23 (t, *J* = 6.8 Hz, 3H), 0.56 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.9, 150.4, 144.4, 140.6, 137.8, 132.9, 132.0, 130.62, 130.6, 129.4, 128.6, 127.3, 127.14, 127.12, 126.2, 125.7, 125.2, 124.1, 121.9, 60.3, 47.1, 27.4, 14.4, 12.4; FT-IR (neat) 2924, 1722, 1462, 1506, 1263 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{27}H_{26}NO_3$: 412.1907; Found 412.1918; $[\alpha]_D^{25}$ = -50.0 (c = 0.03, CH_2Cl_2); HPLC: 75% ee (major diastereomer) [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 11.61 min (major), 8.74 min (minor)].

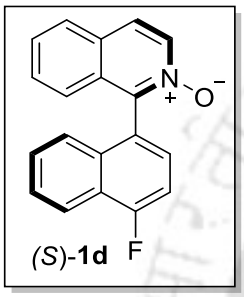


(*S*)-6-*Iso*propyl-1-(naphthalen-1-yl)isoquinoline 2-oxide 1b. Analytical TLC on silica gel, 9:1 Ethyl acetate/hexane R_f = 0.30; colorless solid; yield 61% (34 mg); $[\alpha]_D^{25}$ = +12.0 (c = 0.04, CH_2Cl_2); HPLC: 27% ee [CHIRALCEL OD-H, hexane/^{i}PrOH = 80:20, flow rate: 1 mL/min, λ= 254 nm, t_R = 17.63 min (major), 21.49 min (minor)].

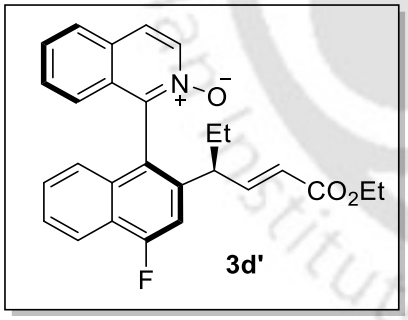


(*R*)-1-(2-((*S*,*E*)-6-ethoxy-6-oxohex-4-en-3-yl)naphtha-len-1-yl)-6-isopropylisoquinoline 2-oxide 3b'. Analytical TLC on silica gel, 2:8 Ethyl acetate/hexane R_f = 0.30; yellow liquid; yield 27% (13 mg); major diastereomer (d.r. >10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 7.0 Hz, 1H), 8.06-8.02 (m, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.77-7.74 (m, 1H), 7.67 (s, 1H), 7.61-7,52 (m, 1H), 7.44 (t, *J* = 7.0 Hz, 1H), 7.30-7.28 (m, 1H), 7.25-7.21 (m, 1H), 7.18-7.13 (m, 1H), 7.06-7.01 (m, 1H), 6.96-6.85 (m, 1H), 5.81 (d, *J* = 16 Hz, 1H), 4.11 (q, *J* = 7.0

Hz, 2H), 3.07-2.98 (m, 2H), 1.76-1.70 (m, 2H), 1.33-1.30 (m, 6H), 1.24-1.19 (m, 3H), 0.85 (t, J = 7.5 Hz, 1H), 0.57 (t, J = 7.0 Hz, 2H);^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 150.4, 149.6, 144.1, 140.5, 137.7, 132.9, 130.5, 129.3, 129.2, 128.9, 128.5, 127.4, 127.2, 126.1, 125.7, 125.3, 125.2, 123.8, 123.5, 121.9, 60.3, 47.0, 34.2, 27.4, 23.8, 23.6, 14.4, 12.4; FT-IR (neat) 2924, 1712, 1462, 1380, 1263, 1185 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{30}H_{32}NO_3$: 454.2377; Found 454.2382; $[\alpha]_D^{25}$ = -9.0 (c = 0.1, CH_2Cl_2); HPLC: 66% ee (major diastereomer) [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 11.87 min (major), 5.74 min (minor)].

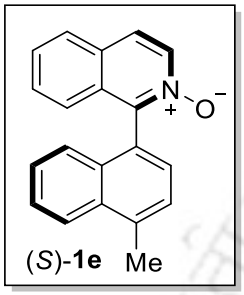


(*S*)-1-(4-Fluoronaphthalen-1-yl)isoquinoline 2-oxide 1d. Analytical TLC on silica gel, 9:1 Ethyl acetate/hexane R_f = 0.30; Yellow solid; yield 71% (30 mg); $[\alpha]_D^{25}$ = +41.0 (c = 0.05, CH_2Cl_2); HPLC: 18% ee [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 8.54 min (major), 10.86 min (minor)].

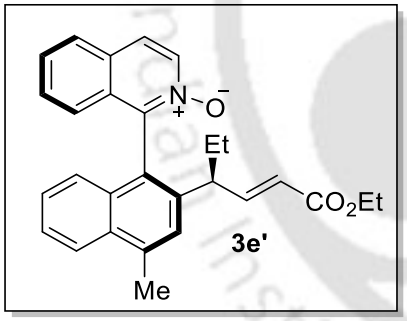


(*R*)-1-(2-((*S*,*E*)-6-Ethoxy-6-oxohex-4-en-3-yl)-4-fluoro-naphthalen-1-yl)isoquinoline 2-oxide 3d'. Analytical TLC on silica gel, 2:8 Ethyl acetate/hexane R_f = 0.40; yellow liquid; yield 18% (12 mg); major diastereomer (d.r. >10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 6.8 Hz, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 6.8 Hz, 1H), 7.56 (t, J = 7.2 Hz, 1H), 7.51(t, J = 7.6 Hz, 1H), 7.39 (t, J = 8.0 Hz, 1H), 7.34(t, J = 8.0 Hz, 1H), 7.20 (d, J = 11.6 Hz, 1H), 7.13-7.07 (m, 1H), 7.05-7.00 (m, 2H), 5.79 (d, J = 17.2 Hz, 1H), 4.12 (q, J = 7.2, 2H), 2.97 (q, J = 7.2 Hz, 1H), 1.77-1.67 (m, 2H), 1.24 (t, J = 6.8 Hz, 3H), 0.57 (t, J = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 149.6, 143.6, 141.6 (J_{C-F} = 7.4

Hz), 137.86, 137.84, 133.5 ($J_{C\text{-}F}$ = 5.3 Hz), 130.7, 129.5, 128.6, 128.5, 128.3, 127.2, 126.5, 125.4, 125.2, 125.1, 124.2, 122.3, 121.3 ($J_{C\text{-}F}$ = 4.9 Hz), 109.1 ($J_{C\text{-}F}$ = 20.6 Hz), 60.4, 47.0, 27.3, 14.4, 12.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ -119.8; FT-IR (neat) 2922, 1712, 1465, 1380, 1304, 1130 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{27}H_{25}FNO_3$:430.1813; Found 430.1822; $[\alpha]_D^{25}$ = -16.0 (c = 0.1, CH_2Cl_2); HPLC: 98% ee (major diastereomer) [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 6.50 min (major), 10.90 min (minor)].

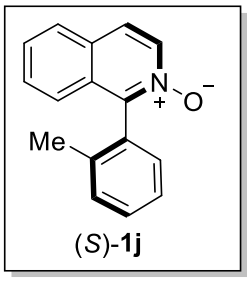


(*S*)-1-(4-Methylnaphthalen-1-yl)isoquinoline 2-oxide 1e. Analytical TLC on silica gel, 9:1 Ethyl acetate/hexane R_f = 0.40; yellow solid; yield 60% (28 mg); $[\alpha]_D^{25}$ = +55.0 (c = 0.04, CH_2Cl_2); HPLC: 40% ee [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 8.46 min (major), 17.86 min (minor)].



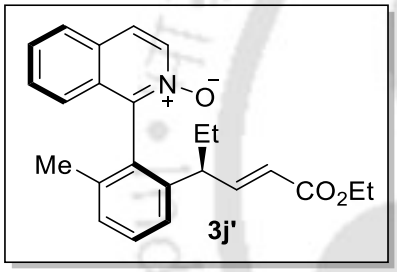
(*R*)-1-(2-((*S*,*E*)-6-Ethoxy-6-oxohex-4-en-3-yl)-4-methylnaphthalen-1-yl)isoquinoline 2-oxide 3e'. Analytical TLC on silica gel, 8:2 Ethyl acetate/hexane R_f = 0.35; yellow liquid; yield 31% (17 mg); major diastereomer (d.r. = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40-8.38 (m, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 7.2 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.50-7.43 (m, 1H), 7.38-7.34 (m, 2H), 7.32-7.28 (m, 1H), 7.12 (dd, *J* = 15.6, 6.8 Hz, 1H), 7.08-7.01 (m, 2H), 5.80 (d, *J* = 15.6 Hz, 1H), 4.15-4.05 (m, 2H), 2.96-2.91 (m, 1H), 2.79 (s, 3H), 1.76-1.71 (m, 2H), 1.24 (t, *J* = 7.2 Hz, 3H), 0.84 (t, *J* = 7.6 Hz, 1H), 0.55 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 150.5, 140.1, 137.9, 137.2, 132.2, 132.0, 130.8, 129.3, 128.5, 128.4, 127.1, 127.0, 126.0, 125.9, 125.8, 125.6, 125.5, 125.4, 124.8, 124.0, 121.8, 60.3, 47.1, 27.4, 20.0, 14.4, 12.4; FT-IR (neat) 2971, 1647, 1466, 1379, 1304, 1128

cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{28}H_{28}NO_3$: 426.2064; Found 426.2076; $[\alpha]_D^{25}$ = -28.4 (c = 0.01, CH_2Cl_2); HPLC: 68% ee (major diastereomer) [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 5.49 min (major), 10.30 min (minor)].



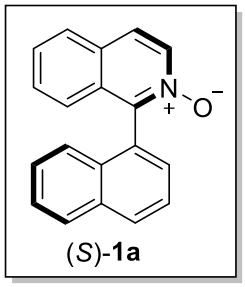
(*S*)-**1j**

(*S*)-1-(*o*-Tolyl)isoquinoline 2-oxide 1j. Analytical TLC on silica gel, 7:3 Ethyl acetate/hexane R_f = 0.40; Yellow solid; yield 78% (36 mg); $[\alpha]_D^{25}$ = +15.0 (c = 0.06, CH_2Cl_2); HPLC: 10% ee [CHIRALCEL OD-H, hexane/^{i}PrOH = 92:8, flow rate: 1 mL/min, λ= 254 nm, t_R = 34.61 min (major), 40.14 min (minor)].

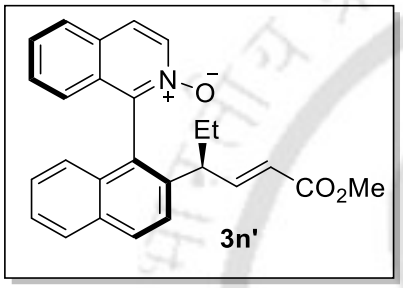


3j'

(*S*)-1-(2-((*S*,*E*)-6-Ethoxy-6-oxohex-4-en-3-yl)-6-methyl-phenyl)isoquinoline 2-oxide 3j'. Analytical TLC on silica gel, 6:4 Ethyl acetate/hexane R_f = 0.30; Brown liquid; yield 10% (8 mg); major diastereomer (d.r. >10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 7.2 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 7.2 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.50-7.42 (m, 2H), 7.28 (s, 1H), 7.24 (s, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 6.98 (dd, *J* = 16.0, 7.6 Hz, 1H), 5.64 (d, *J* = 16.8 Hz, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 2.74 (q, *J* = 8.4, 1H), 1.95 (s, 3H), 1.64-1.62 (m, 1H), 1.59-1.57 (m, 1H), 1.24 (t, *J* = 7.2 Hz, 3H), 0.53 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 150.8, 145.4, 142.3, 137.9, 137.6, 130.3, 130.1, 129.8, 129.4, 129.0, 128.5, 128.4, 127.2, 125.3, 125.0, 123.8, 121.3, 60.3, 46.8, 27.5, 20.0, 14.4, 12.3; FT-IR (neat) 2923, 2853, 1703, 1602, 1463, 1268 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{24}H_{26}NO_3$: 376.1907; Found 376.1907; $[\alpha]_D^{25}$ = -13.0 (c = 0.04, CH_2Cl_2); HPLC: 76% ee (major diastereomer) [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 5.40 min (major), 6.20 min (minor)].



(*S*)-1-(Naphthalen-1-yl)isoquinoline 2-oxide (*S*)-1a. Analytical TLC on silica gel, 9:1 Ethyl acetate/hexane R_f = 0.35; Yellow solid; yield 75% (37 mg); $[\alpha]_D^{25}$ = +4.0 (c = 0.06, CH_2Cl_2); HPLC: 8% ee [CHIRALCEL OD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 13.17 min (major), 16.53 min (minor)].



(*R*)-1-(2-((*S*,*E*)-6-Methoxy-6-oxohex-4-en-3-yl)naphtha-alen-1-yl)isoquinoline 2-oxide 3n'. Analytical TLC on silica gel, 7:3 Ethyl acetate/hexane R_f = 0.30; Brown liquid; yield 12% (10 mg); major diastereomer (d.r. >10:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.39 (d, *J* = 7.2 Hz, 1H), 8.02 (d, *J* = 9.0 Hz, 1H), 7.87 (dd, *J* = 18.0, 7.8 Hz, 2H), 7.80 (d, *J* = 7.2 Hz, 1H), 7.56-7.52 (m, 2H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.28 (t, *J* = 7.2 Hz, 1H), 7.15 (dd, *J* = 16.2, 6.6 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 5.82 (d, *J* = 15.6 Hz, 1H), 3.66 (s, 3H), 2.98 (q, *J* = 7.2 Hz, 1H), 1.78-1.72 (m, 2H), 0.56 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.3, 150.8, 144.4, 140.5, 137.8, 132.9, 132.0, 130.65, 130.61, 129.4, 128.55, 128.53, 127.3, 127.2, 127.1, 126.2, 125.7, 125.2, 125.1, 124.1, 121.4, 51.5, 47.1, 27.2, 12.4; FT-IR (neat) 2923, 2853, 1747, 1717, 1462, 1506, 1263 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}NO_3$: 398.1751; Found 398.1753; $[\alpha]_D^{25}$ = -37.0 (c = 0.08, CH_2Cl_2); HPLC: 67% ee (major diastereomer) [CHIRALCEL AD-H, hexane/^{i}PrOH = 70:30, flow rate: 1 mL/min, λ= 254 nm, t_R = 18.90 min (major), 10.28 min (minor)].

4.5 References

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Ghosh, S.; Dutta, S.; Guin, S.; Ghosh, A.; Ge, H.; Sunoj, R. B.; Maiti, D. *Angew. Chem. Int. Ed.* **2024**, *63*, e202310112.

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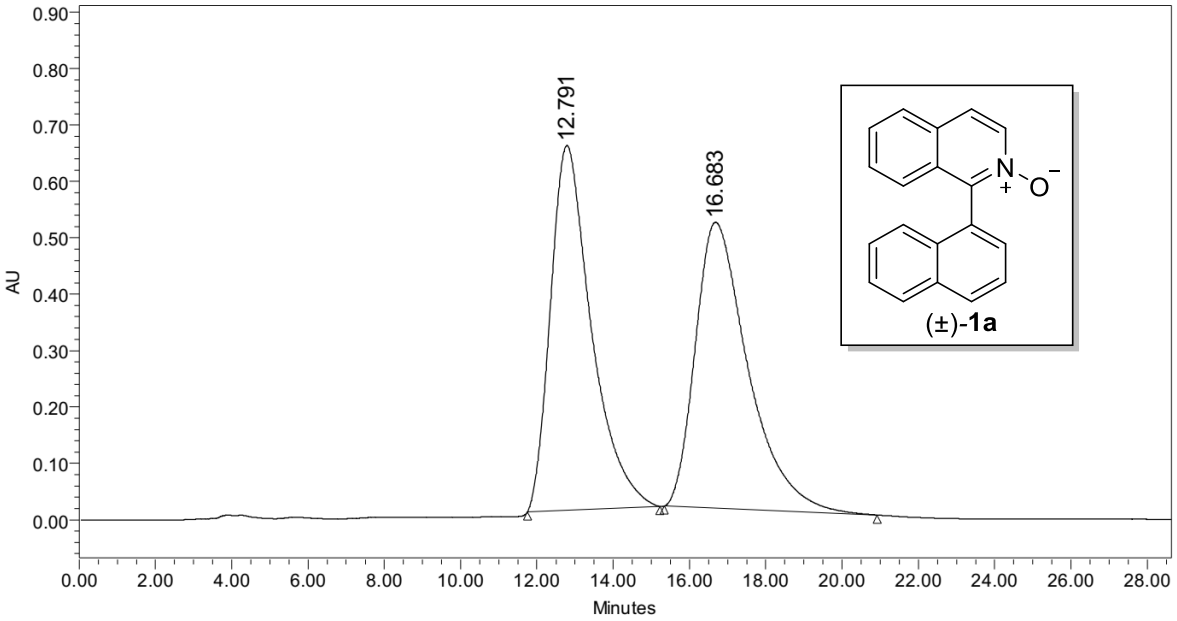
4.6 Selected HPLC Chromatograms of Diastereomer I:



	RT	Area	% Area	Height
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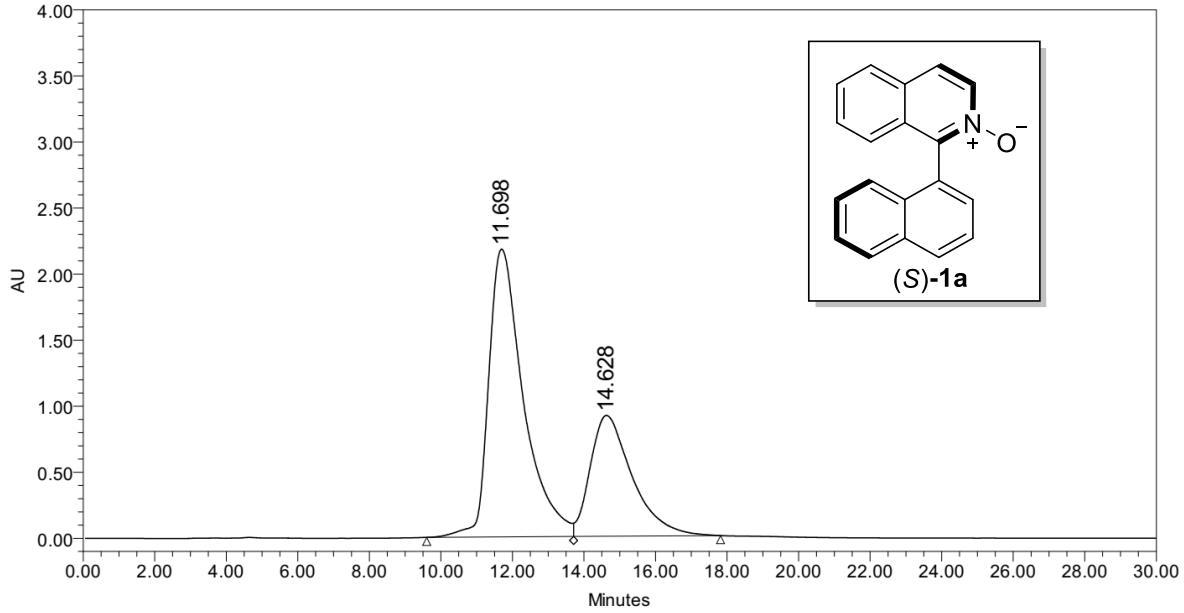
2	16.683	48688756	50.30	507297



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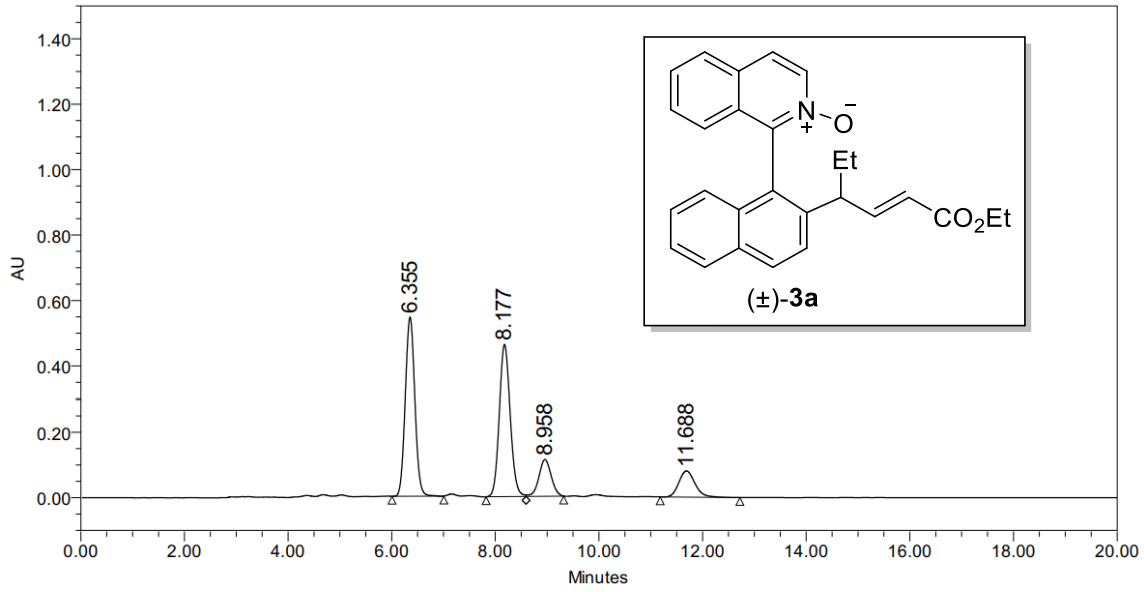
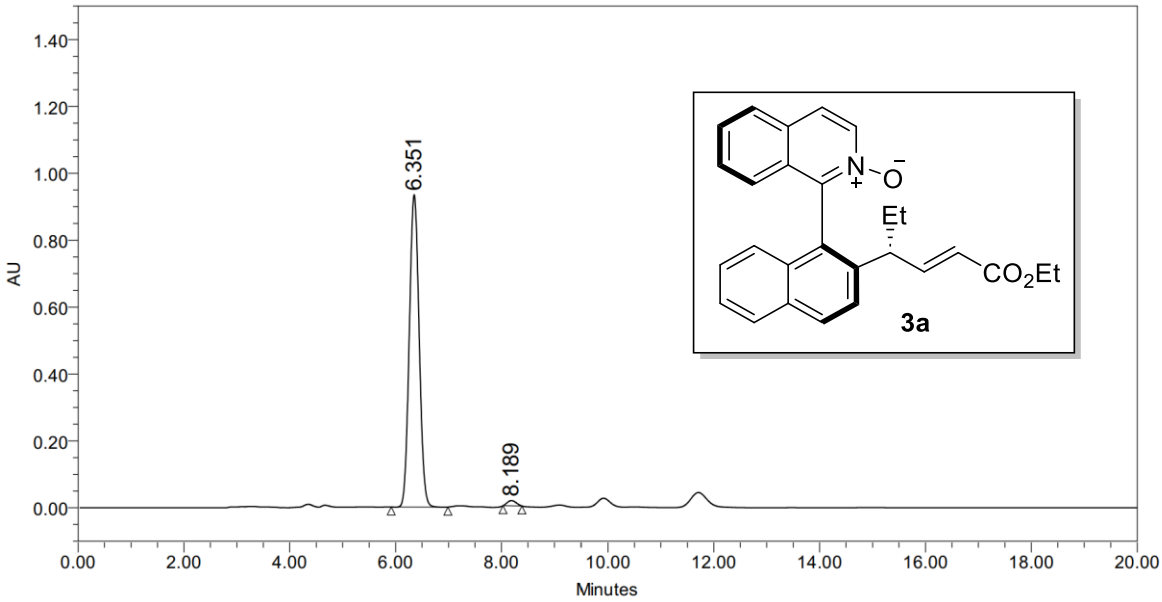
1	11.698	146959160	66.35	2178169
2	14.628	74547226	33.65	914808



	RT	Area	% Area	Height
1	6.355	7000328	40.37	544832
2	8.177	6765406	39.01	462157
3	8.958	1849242	10.66	112090
4	11.688	1726297	9.95	79904



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1	6.351	12038030	98.49	933689
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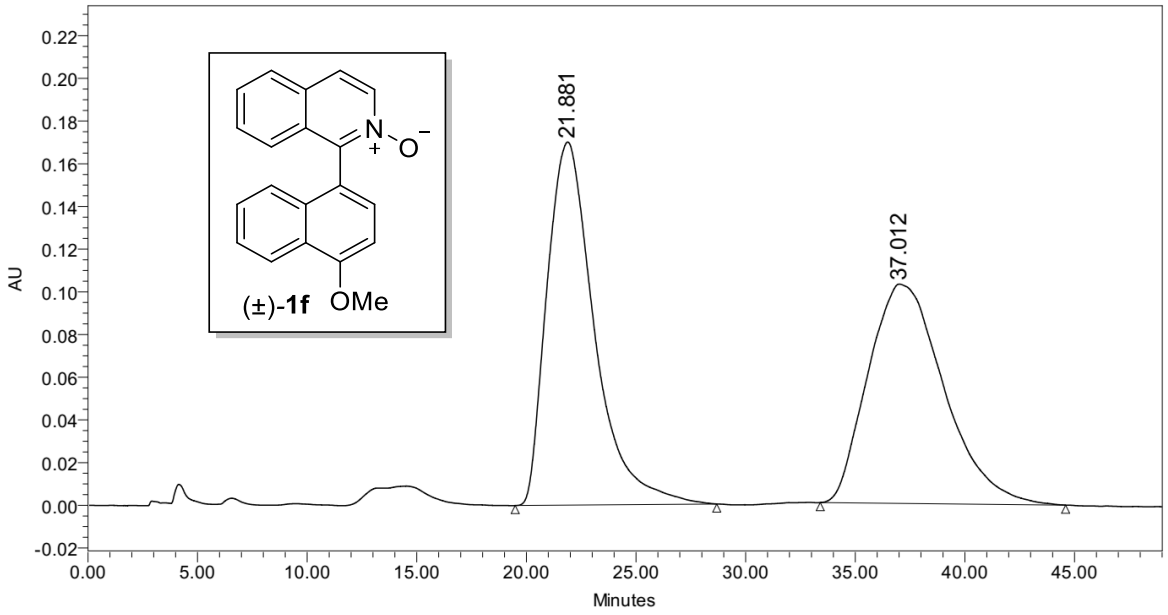

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1	21.881	25599433	50.86	170103
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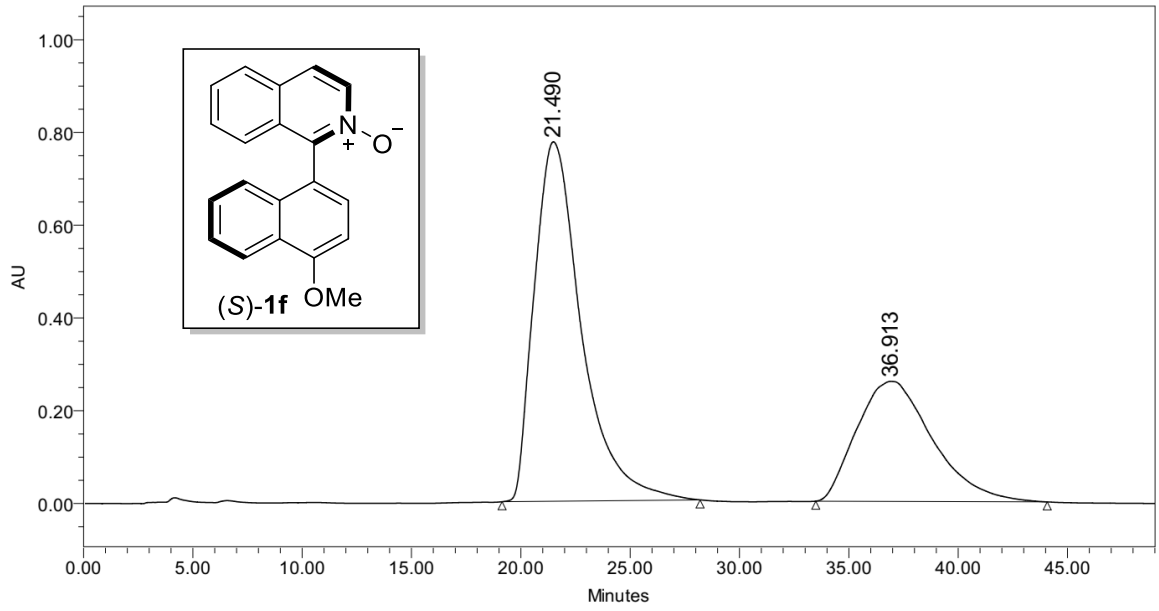

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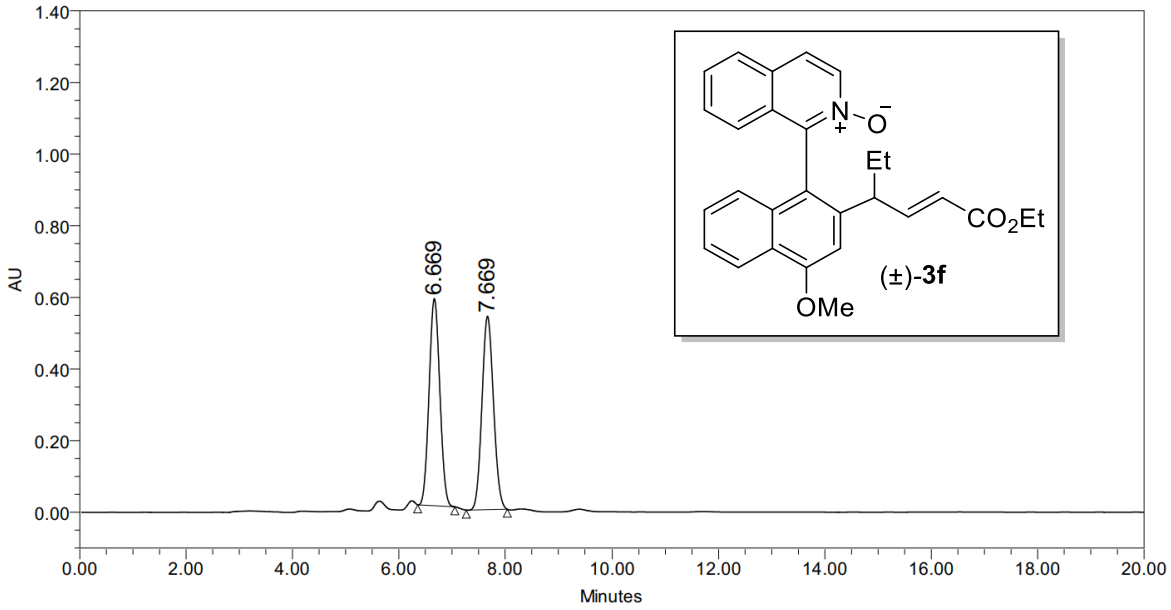

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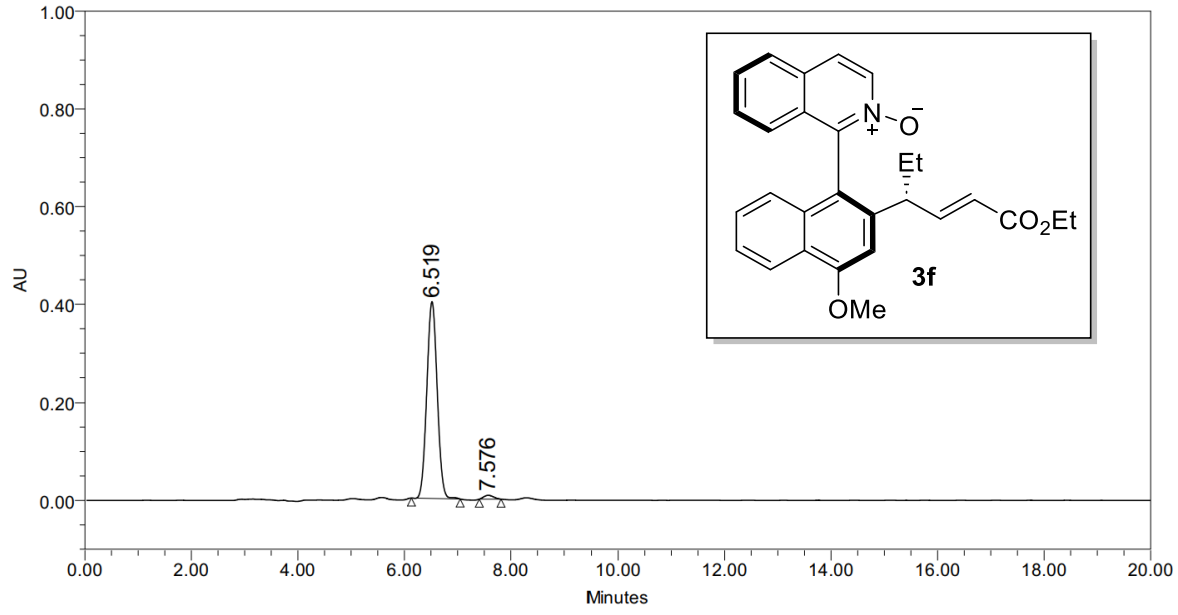

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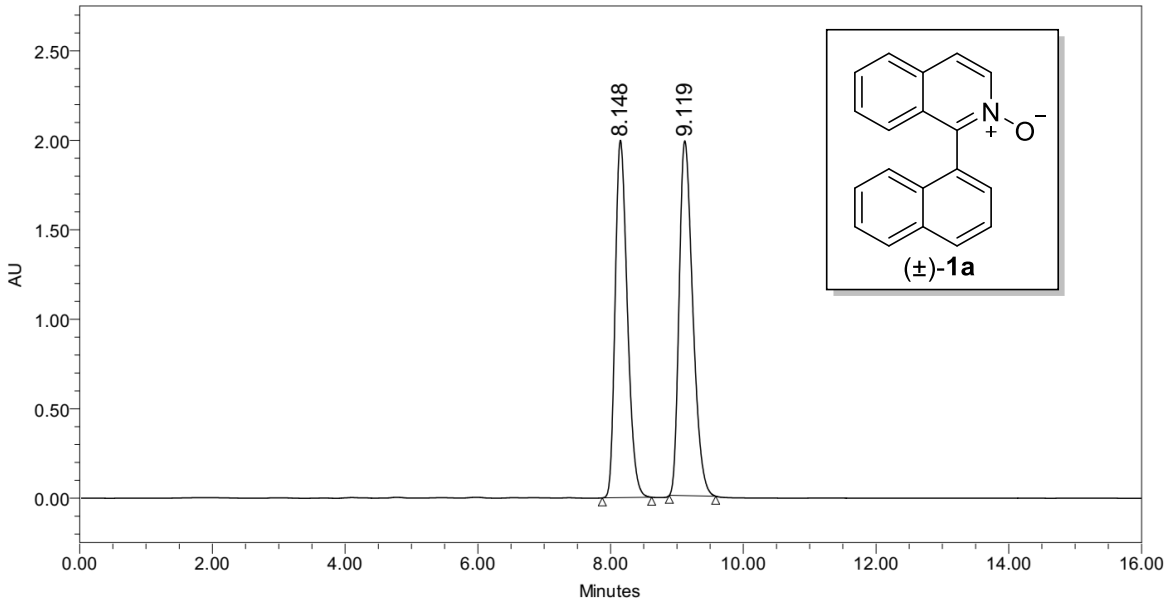

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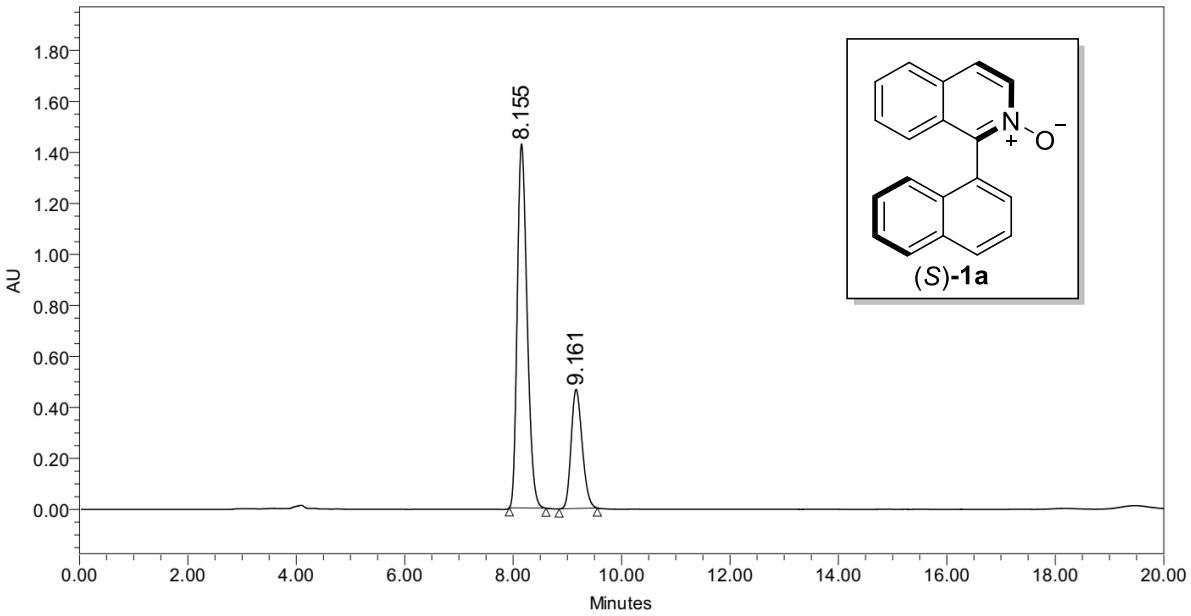

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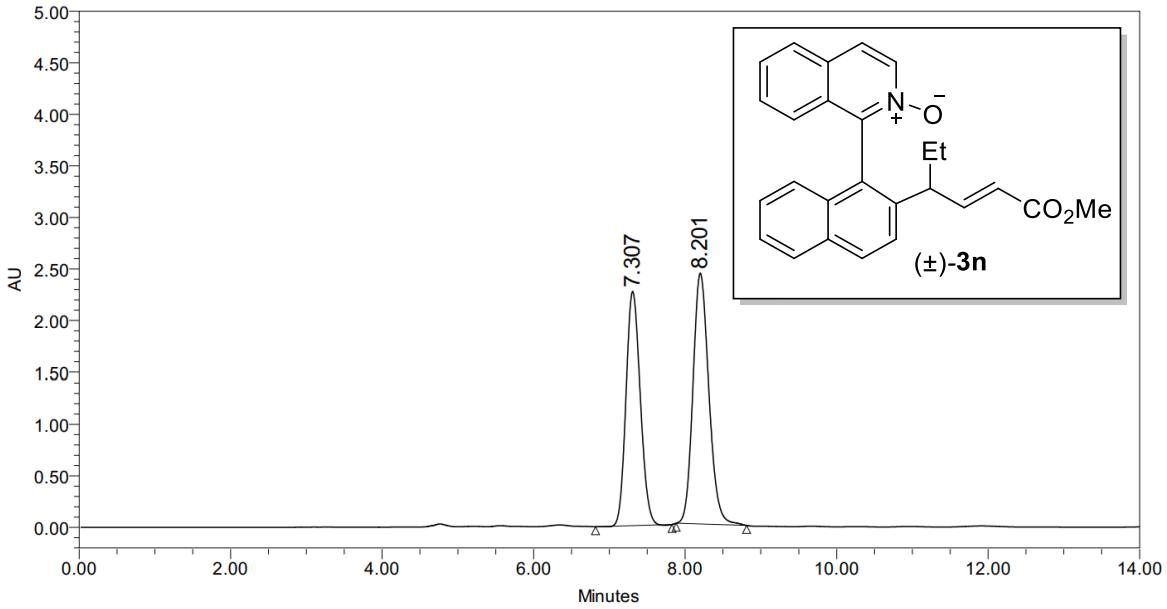

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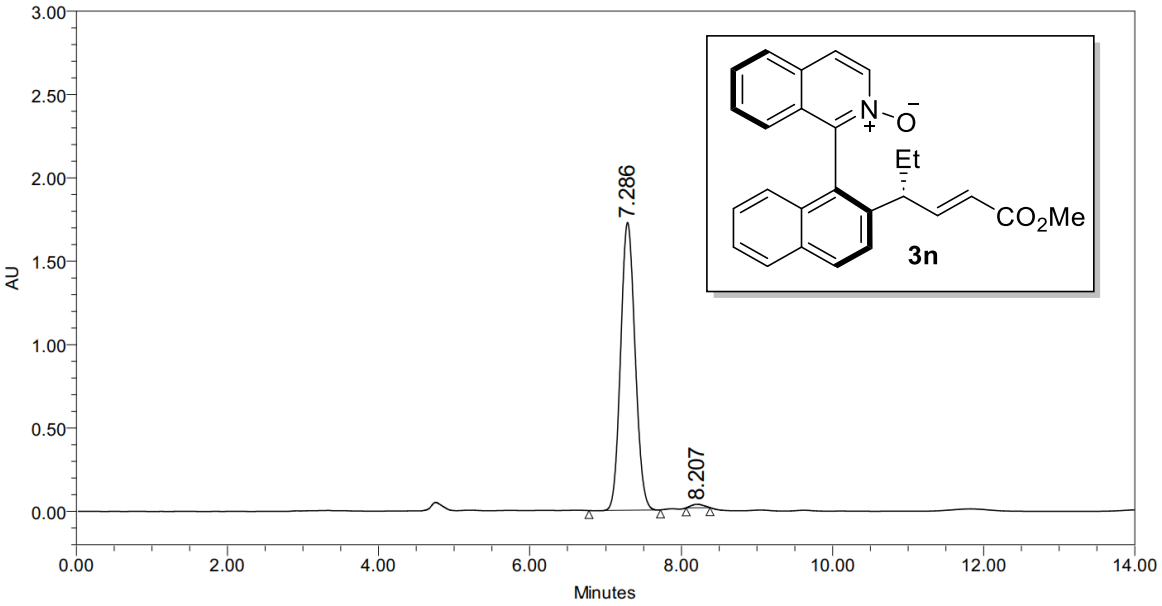

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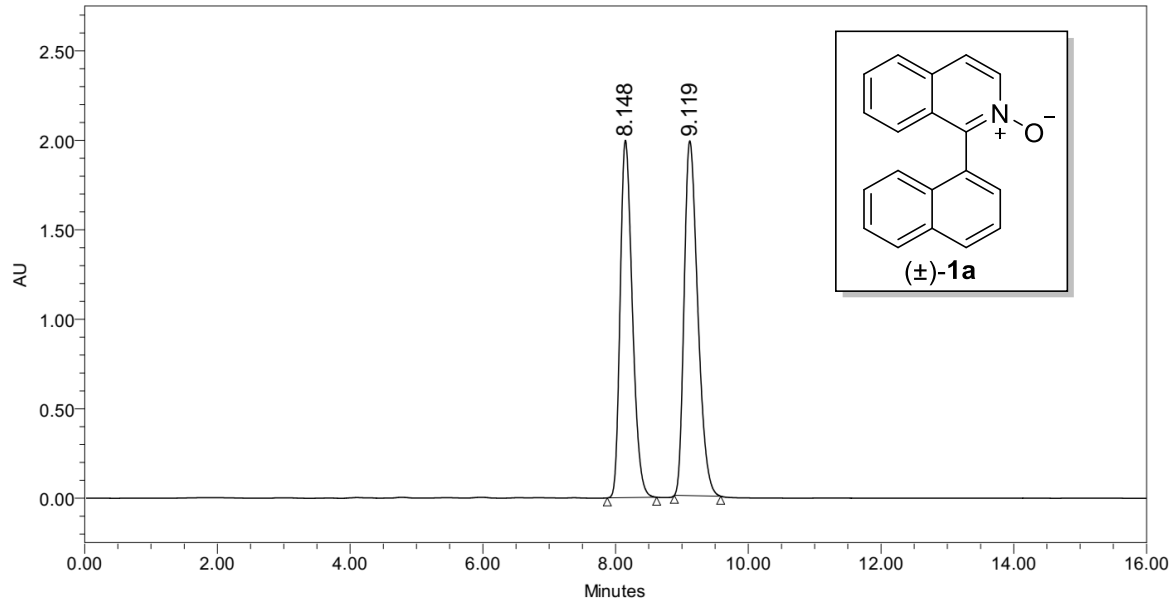

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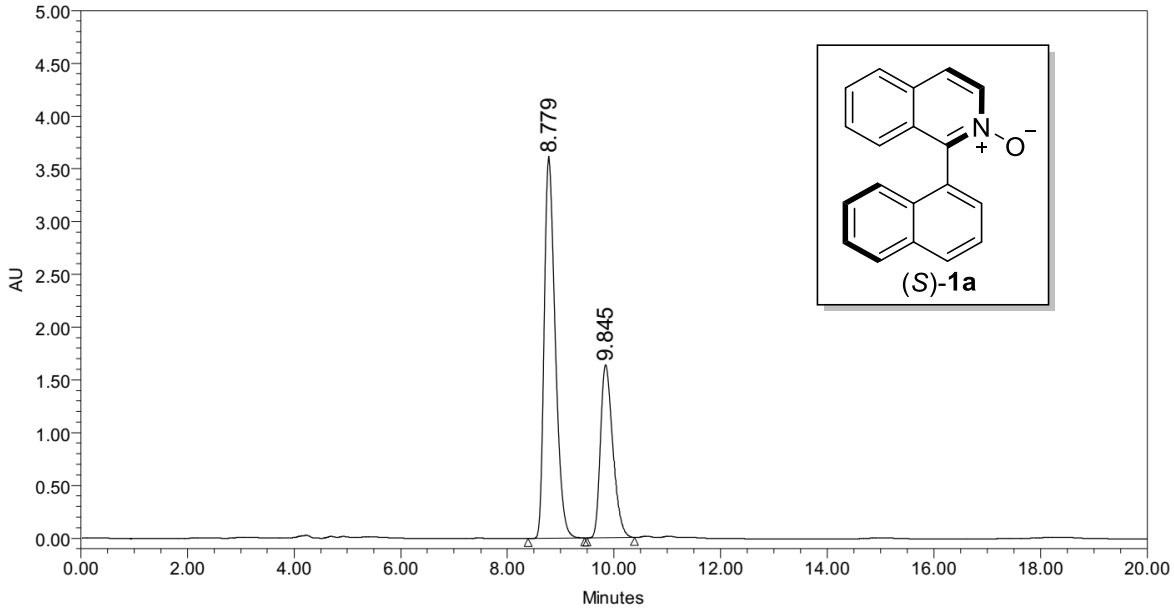
2	9.119	28245453	52.66	1982700



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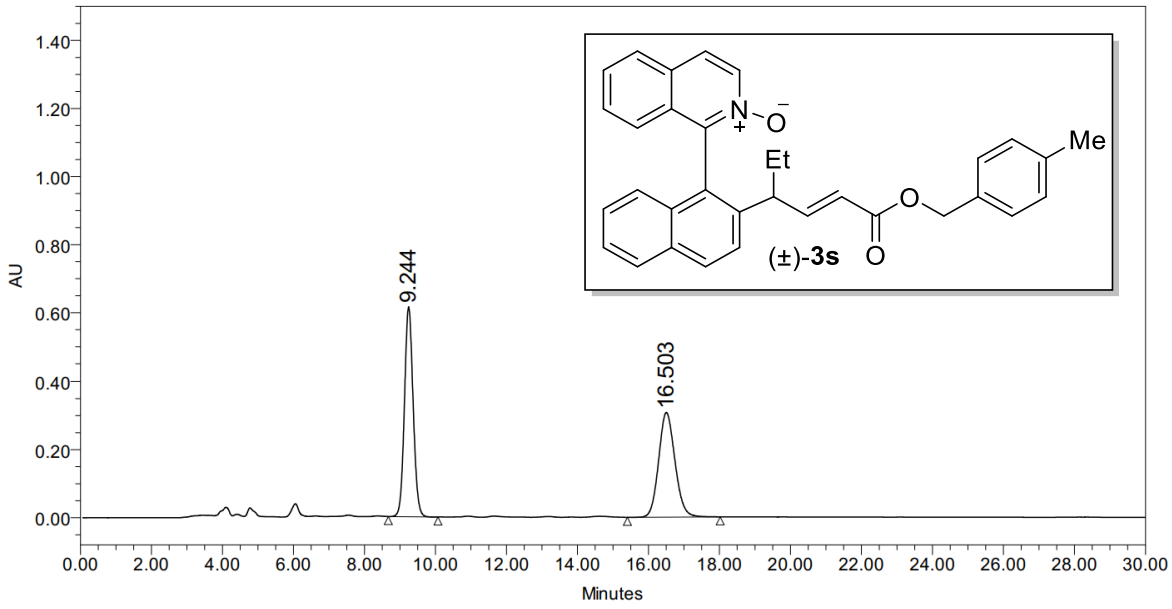
1	8.779	51869821	66.27	3617188
2	9.845	26400233	33.73	1638895



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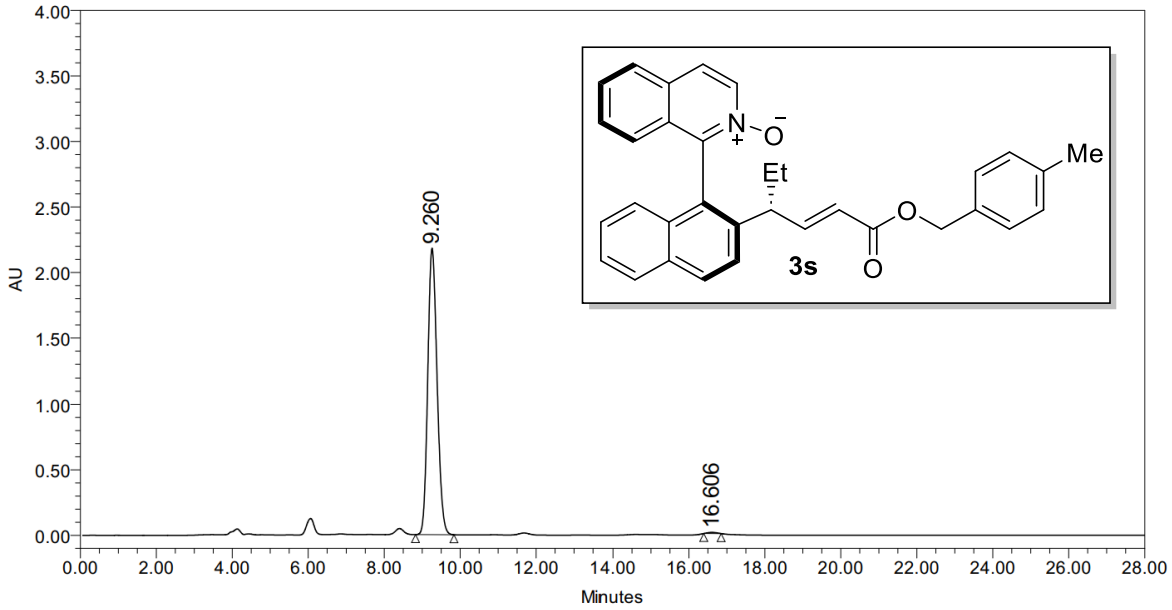
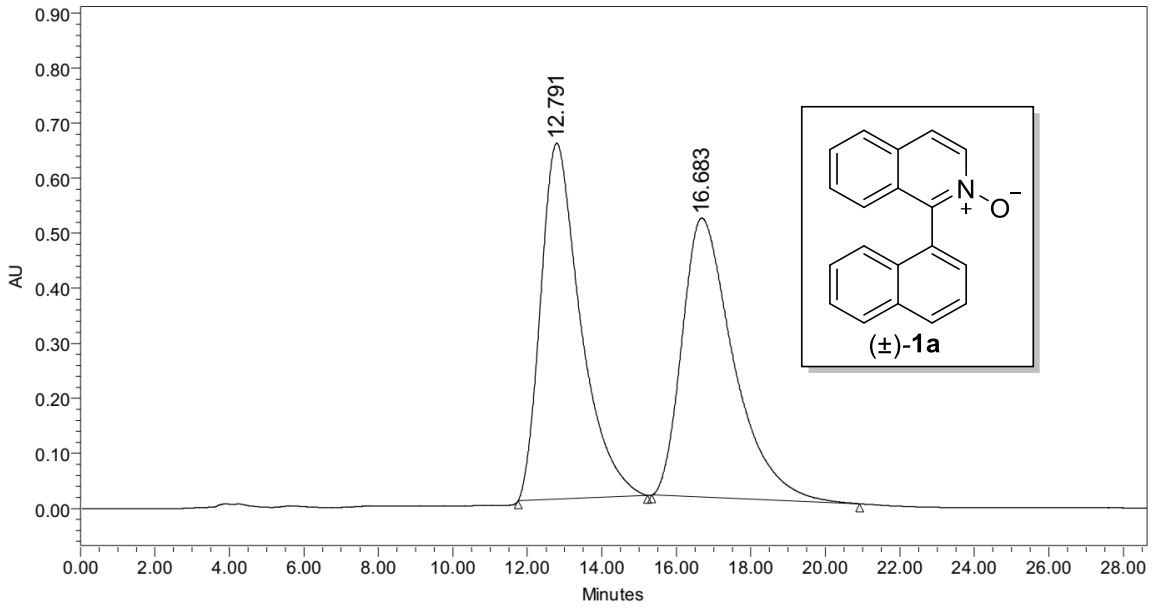
1	9.244	10449052	51.53	614379
2	16.503	9827764	48.47	307734

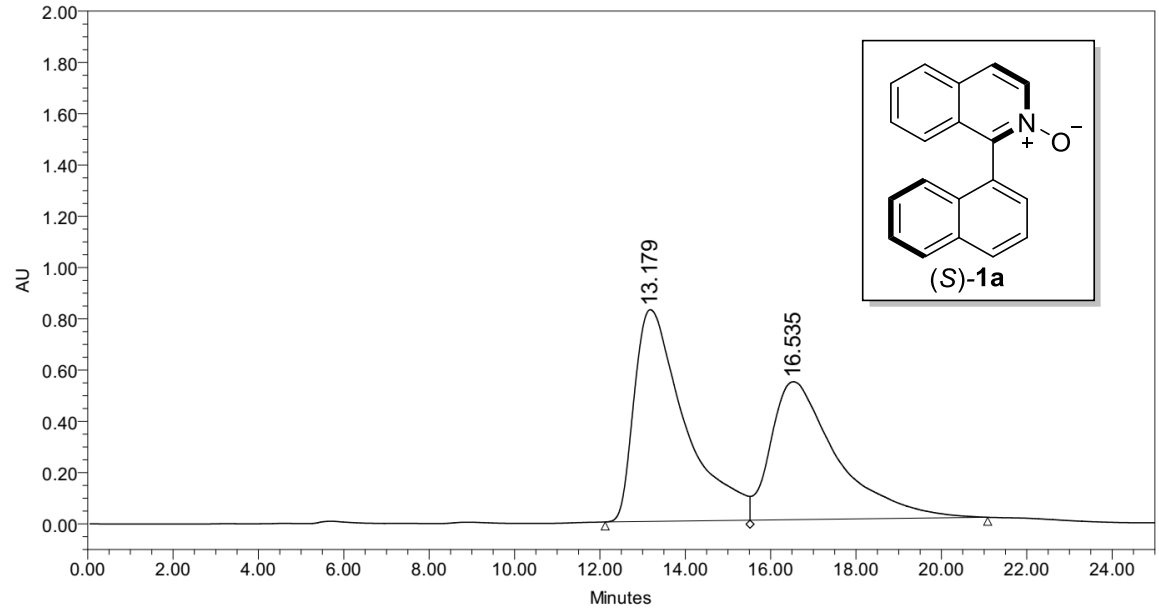


	RT	Area	% Area	Height
1	9.260	37173638	99.59	2180937
2	16.606	151179	0.41	8826

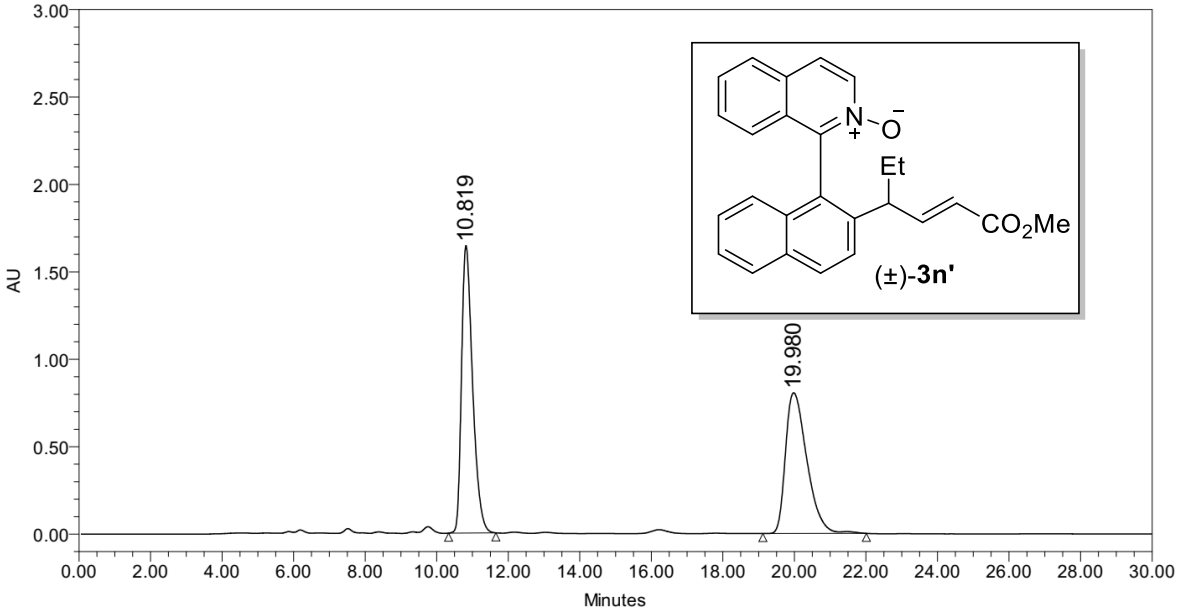
4.7 Selected HPLC Chromatograms of Diastereomer II:



	RT	Area	% Area	Height
1	12.791	48104894	49.70	647016
2	16.683	48688756	50.30	507297



	RT	Area	% Area	Height
1	13.179	68215066	54.16	825476
2	16.535	57728748	45.84	538006



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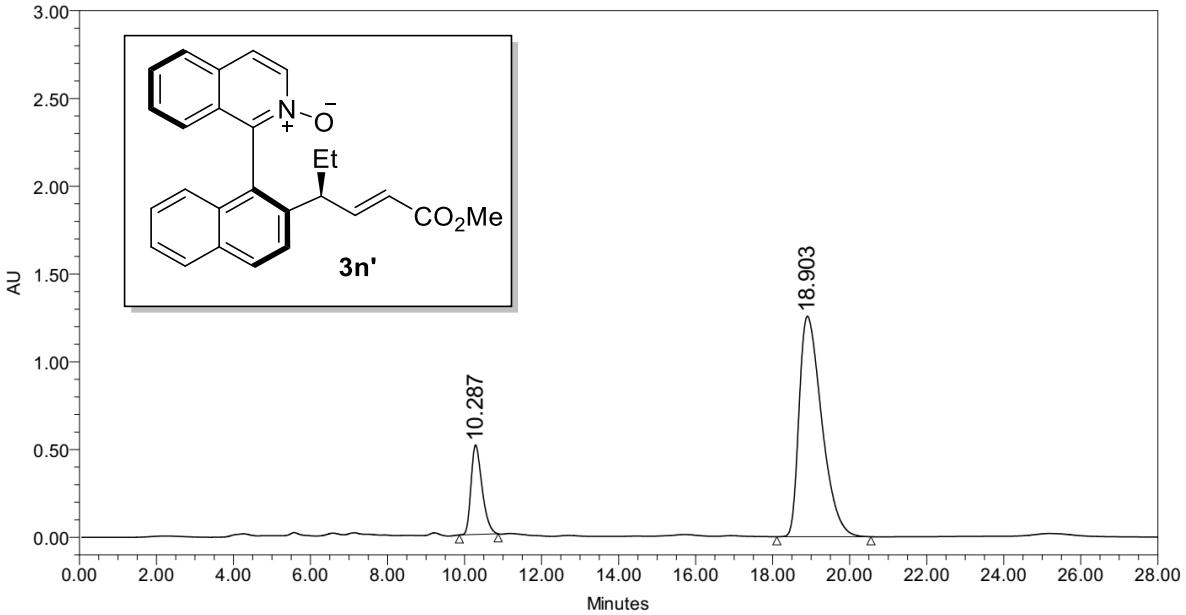
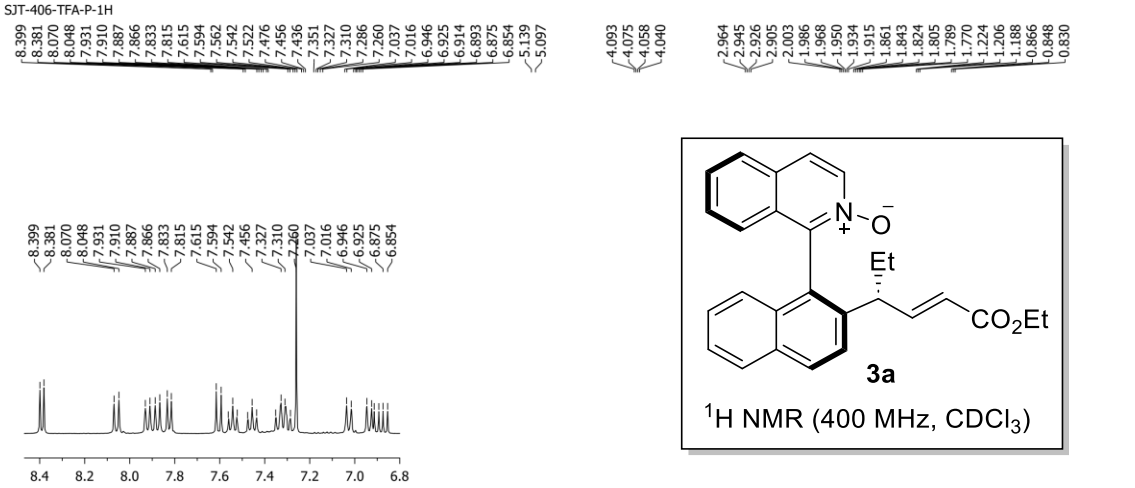
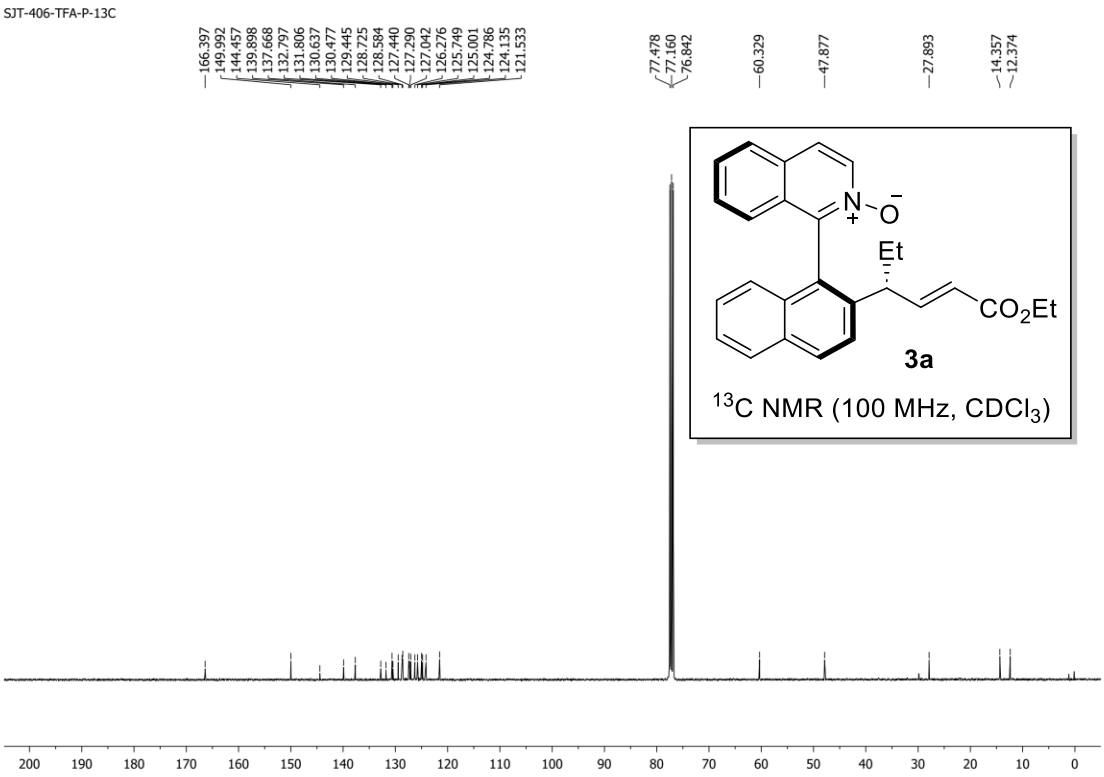
1	10.819	35339512	51.36	1644503
2	19.980	33474618	48.64	804672

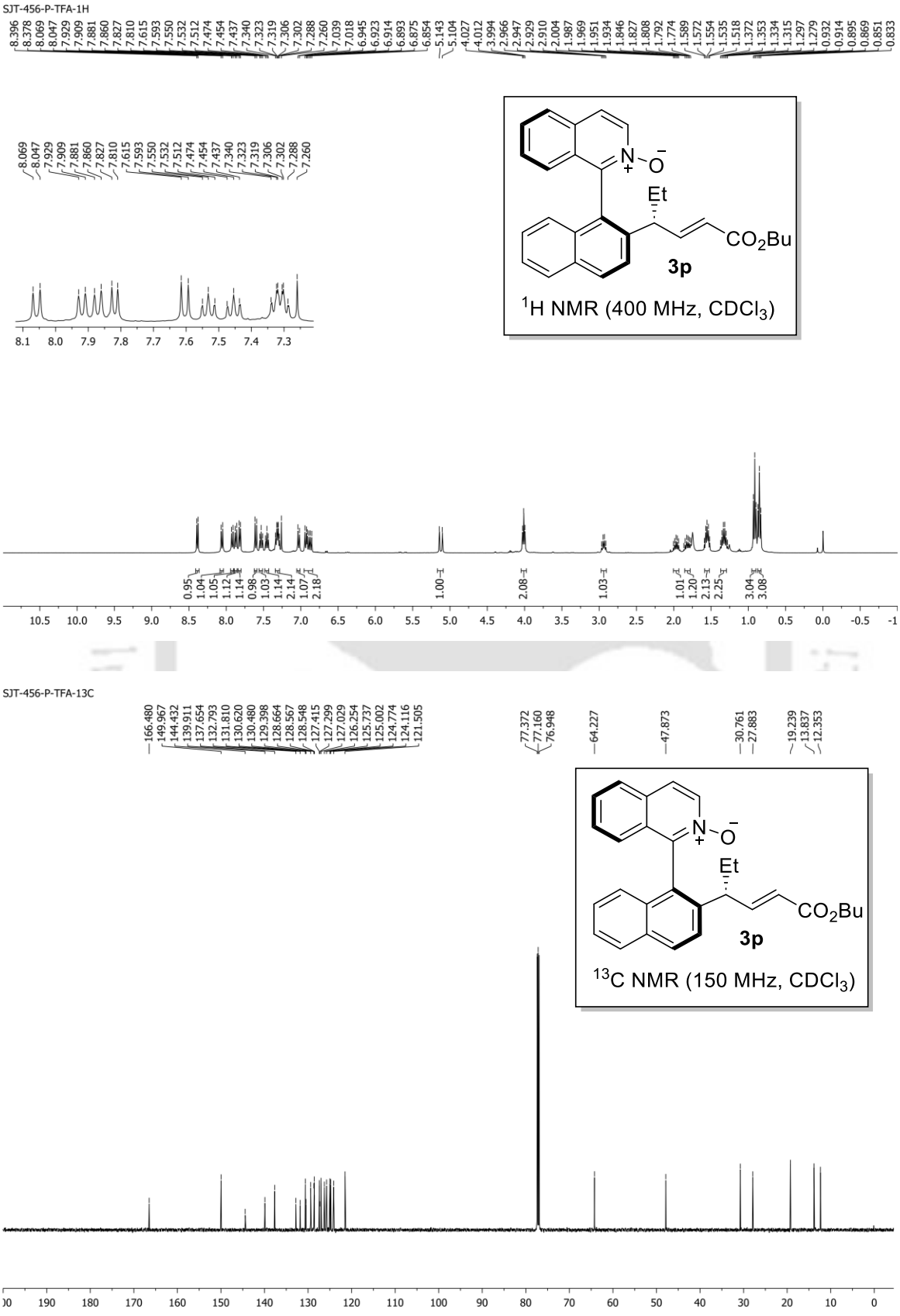


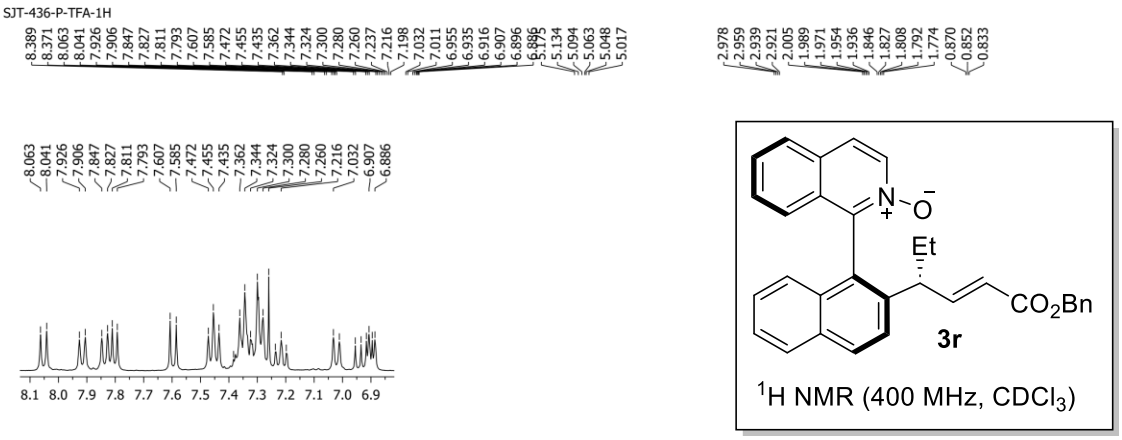
	RT	Area	% Area	Height
1	10.287	10163548	16.56	509907
2	18.903	51210954	83.44	1256639

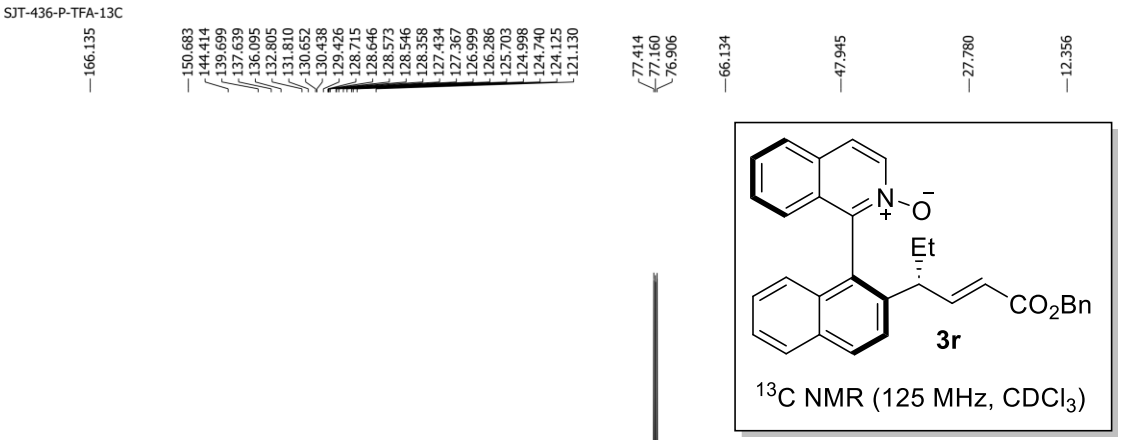
4.8 Selected NMR Spectra

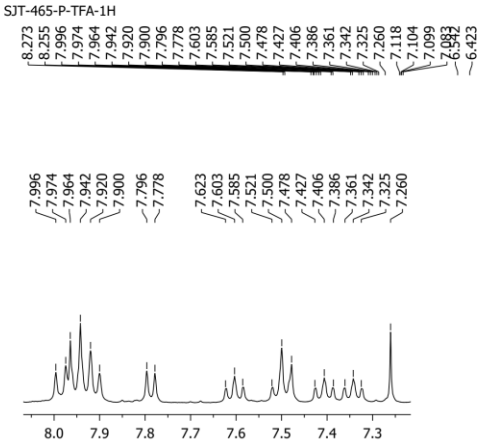


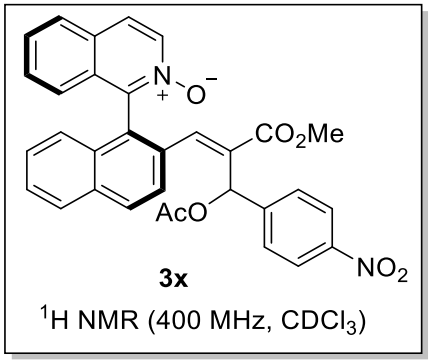


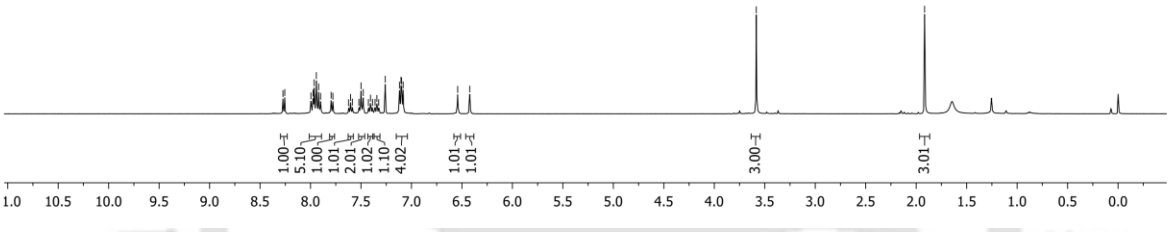


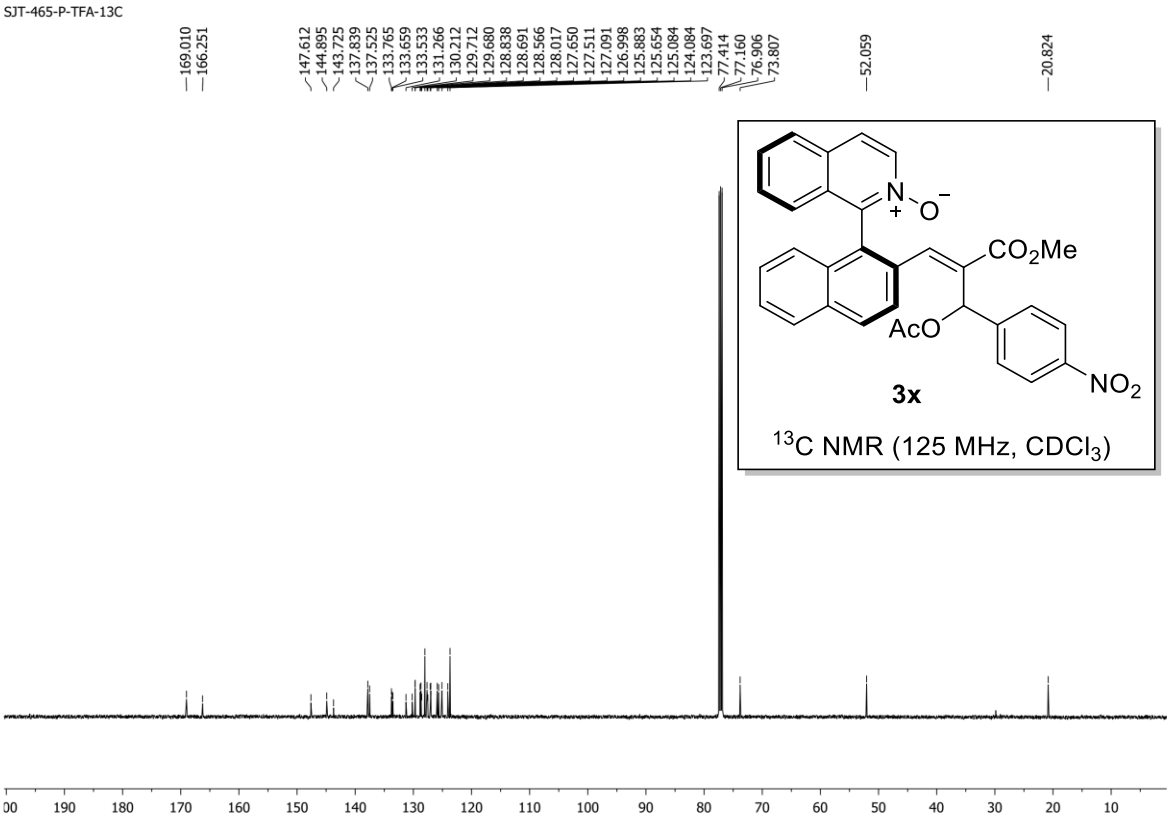












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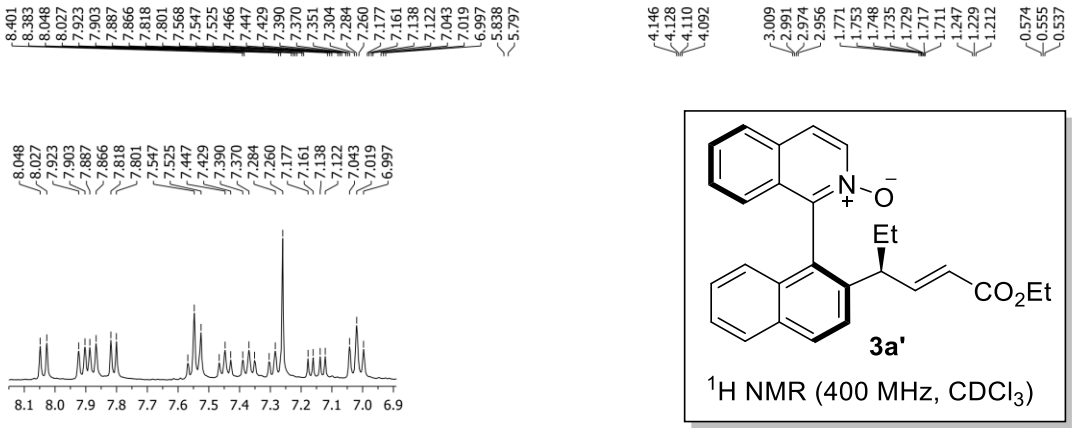

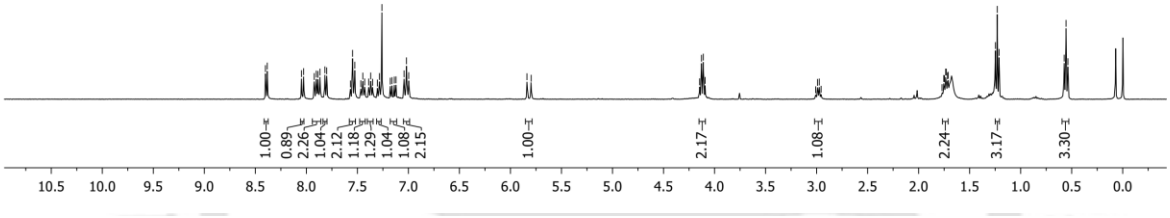

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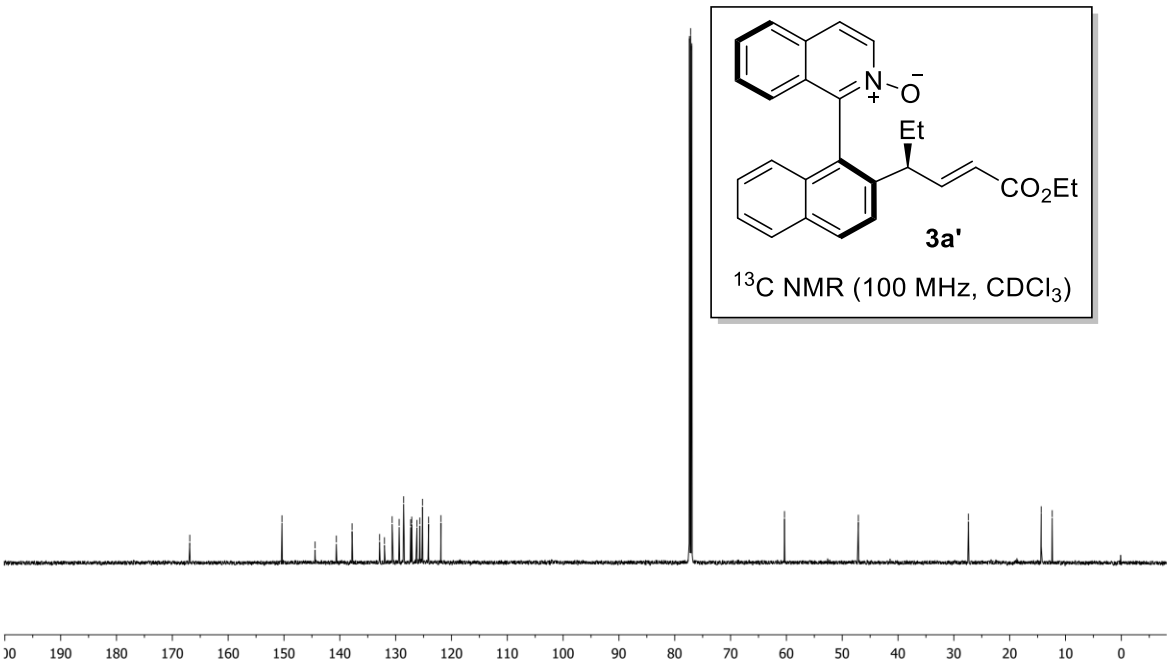
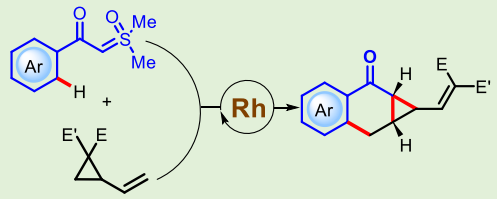


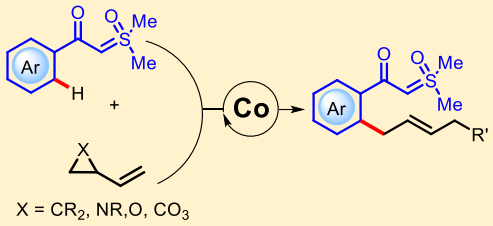
Thesis Overview

Chapter 1



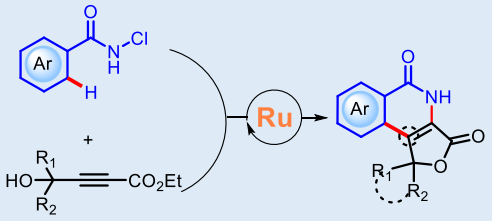
Org. Lett. **2023**, *25*, 3352.

Chapter 2



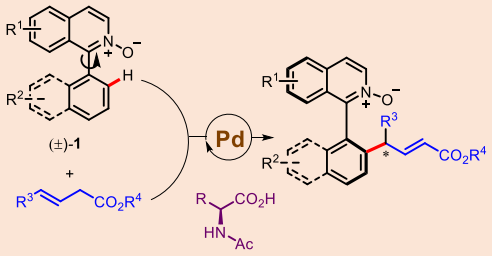
Chem. Commun. **2023**, *59*, 14173.

Chapter 3



J. Org. Chem. **2024**, *89*, 16850.

Chapter 4



Manuscript under preparation

Summary

Chapter 1 describes a Rh-catalyzed cascade C–H activation, ring scission and annulation of benzoyl sulfoxonium ylides with VCPs to afford cyclopropane-fused α-tetralone frameworks. The method employs traceless DG assistance, features step- and atom-economy and demonstrates substrate scope with synthetic utility in constructing structurally diverse architectures.

Chapter 2 focuses on a Co-catalyzed weak chelation-assisted C–H allylation of sulfoxonium ylides with strained vinyl systems such as VCPs, 2-vinyloxirane, 2-vinylaziridine and 4-vinyl-1,3-dioxolan-2-one to furnish allyl frameworks as valuable structural motifs. The method overcomes C(aryl)–H/C(olefinic)–H selectivity challenges, proceeds *via* sequential C–H and C–C/C–het bond activation and demonstrates substrate scope with step- and atom-economy. The use of earth-abundant cobalt-catalysis highlights the synthetic utility of sulfoxonium ylides as weak chelation-assisted DG in sustainable C–H allylation.

Chapter 3 covers a Ru-catalyzed C–H activation/annulation of *N*-chlorobenzamides with heteroatom-functionalized unsymmetrical alkynes such as 4-hydroxy-2-alkynoates, alkynyl sulfones and sulfonyl-based ynamides in water under oxidant-free conditions. The reaction delivers regioselective furanone-fused isoquinolones *via* cascade C–H activation/annulation with in situ lactonization, while also affording versatile isoquinolone handlers. The method offers substrate scope, operational simplicity, sustainability and synthetic utility for downstream diversification.

Chapter 4 deals with a Pd-catalyzed, weakly DG-assisted atroposelective C–H allylation of 1-arylisoquinoline *N*-oxides with *trans*-3-alkenoates *via* kinetic resolution using *N*-Ac-*L*-Phe-OH as chiral ligand, affording allylated scaffolds with concurrent axial and central chirality. The protocol overcomes styrenyl selectivity and stereoisomer control challenges to deliver excellent enantio-/diastereoselectivity. The method offers substrate scope and functional group tolerance for atroposelective C–H functionalization

List of Publications

From thesis:

1. **Saha, S**.; Debnath, B.; Talukdar, K.; Karjee, P.; Mandal, S.; Punniyamurthy, T. Cascade C-H Activation/Annulation of Sulfoxonium Ylides with Vinyl Cyclopropanes: Access to Cyclopropane-Fused *α*-Tetralones. *Org. Lett.* **2023**, *25*, 3352.
2. **Saha, S**.; Bhattacharyya, H.; Karjee, P.; Debnath, B.; Verma, K.; Punniyamurthy, T. Expedient C-H Allylation of Sulfoxonium Ylides: Merging C-H and C-C/C-Het Bond Activation. *Chem. Commun.* **2023**, *59*, 14173.
3. **Saha, S**.; Bhattacharyya, H.; Dolai, S.; Samantaray, S.; Verma, K.; Punniyamurthy, T. Ru-Catalyzed Redox-Neutral Coupling of *N*-Chlorobenzamides with Unsymmetrical Alkynes in Water. *J. Org. Chem.* **2024**, *89*, 16850.
4. **Saha, S**.; Bhattacharyya, H.; Samantaray, S.; Bhowmik, S.; Punniyamurthy, T. Atroposelective C-H allylation: access to concurrent axial and central enantio-induction of heterobiaryls (manuscript is under preparation).

From others:

5. Mandal, S.; Karjee, P.; **Saha, S.**; Punniyamurthy, T. Directed C8-H Allylation of Quinoline *N*-Oxides with Vinylcyclopropanes *via* Sequential C-H/C-C Activation. *Chem. Commun.* **2023**, *59*, 2823.
6. Bhattacharyya, H.; **Saha, S**.; Verma, K.; Punniyamurthy, T. Redox-Neutral Site-Selective C-H Allylation and Iodolactonization of Benzoic Acids Using Morita-Baylis-Hillman Adducts in Water. *Org. Lett.* **2023**, *25*, 6830.
7. Verma, K.; Mishra, M.; Maharana, P. K.; Bhattacharyya, H.; **Saha, S**.; Punniyamurthy, T. $Sc(OTf)_3$-Catalyzed Domino C-C/C-N Bond Formation of Aziridines with Quinones *via* Radical Pathway. *Org. Lett.* **2023**, *25*, 7933.
8. Samantaray, S.; Maharana, P. K.; Kar, S.; **Saha, S**.; Punniyamurthy, T. Redox-Neutral Zinc-Catalyzed Cascade [1,4]-H Shift/Annulation of Diaziridines with Donor-Acceptor Aziridines. *Chem. Commun.* **2024**, *60*, 3441.

9. Karjee, P.; Debnath, B.; Mandal, S.; **Saha, S.**; Punniyamurthy, T. One-Pot C-N/C-C Bond Formation and Oxidation of Donor-Acceptor Cyclopropanes with Tetrahydroisoquinolines: Access to Benzo-Fused Indolizines. *Chem. Commun.* **2024**, *60*, 4068.

10. Verma, K.; Bhattacharyya, H.; **Saha, S.;** Punniyamurthy, T. Expedient (3+3)-Annulation of Carbonyl Ylides with Azaoxyallyl Cations: Formal Access to Oxa-Benzo[*c*]Azepin-3-Ones. *Chem. Commun.* **2024**, *60*, 13368.

11. Bhattacharyya, H.; **Saha, S**.; Verma, K.; Punniyamurthy, T. Palladium-Catalyzed Substrate-Switchable C–H Alkenylation and Alkylation of Benzoic Acids Using MBH Alcohols. *Chem. Commun.* **2025**, *61*, 4200.

12. Debnath, B.; Mandal, S.; **Saha, S**.; Karjee, P.; Punniyamurthy, T. Rh-Catalyzed [3+3]-Annulation of Quinolines with Cyclopropenones: Access to Functionalized 2-Quinolones. *Chem. Commun.* **2025**, *61*, 7875.

13. Roy, S.; **Saha, S**.; Bhattacharyya, H.; Punniyamurthy, T. Cascade C-H Functionalization/Annulation of 2-Aryl-1,3-Dicarbonyls with Morita-Baylis-Hillman Adducts: Access to *α-Iso*-/Benzochromenyl Acrylates. *Chem. Commun.* **2025**, *61*, 9095.

14. Roy, S.; **Saha, S**.; Bhattacharyya, H.; Punniyamurthy, T. Pd-Catalyzed C-H Functionalization/Annulation of 2-Aryl-1,3-Dicarbonyls with Vinylcyclopropanes: Merging C-H and C-C Activation. *Org. Lett.* **2025**, *27*, 7898.

15. Samantaray, S.; **Saha, S.**; Punniyamurthy, T. Rh-Catalyzed Chemodivergent [4+1]-Annulation/Allylation of Sulfoxonium Ylides with *α*-Methylene-*β*-Lactones: Access to *α*-Indanonyl/*α*-Benzyl Acrylates. *Chem. Commun.* **2026**, 62, 874.

Conferences Attended

1. **Sharajit Saha** and Tharmalingam Punniyamurthy, "Cascade C-H Activation/Annulation of Sulfoxonium Ylides with Vinyl cyclopropanes: Access to Cyclopropane Fused α-Tetralones." **32nd CRSI National Symposium in Chemistry**, February 2024, Department of Chemistry, BITS Pilani, Rajasthan.
2. **Sharajit Saha**, Hemanga Bhattacharyya and Tharmalingam Punniyamurthy, "Ru-Catalyzed Redox-Neutral Coupling of *N*-Chlorobenzamides with Unsymmetrical Alkynes in Water." **FICS-2024**, Indian Institute of Technology Guwahati, Assam.
3. **Sharajit Saha**, Hemanga Bhattacharyya, Bijoy Debnath and Tharmalingam Punniyamurthy, "Expedient C-H Allylation and Annulation of Sulfoxonium Ylides with Vinyl cyclopropanes." **ISCHA-2024**, Indian Institute of Technology Bombay, Maharashtra.

   (Best Poster Award)