Site-Selective C–H Functionalization of Aryl Carboxylic Acids and Ketones Using Morita-Baylis-Hillman Adducts

A Thesis Submitted

in Partial Fulfilment of the Requirements

for the Degree of

Doctor of Philosophy in Chemistry

By

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Dedicated To

My Parents and Teachers

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
September 2025

Hemanga Bhattacharyya

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CERTIFICATE

This is to certify that Mr. Hemanga Bhattacharyya has been working under my supervision since September 2020. I am forwarding his thesis entitled "*Site-Selective C–H Functionalization of Aryl Carboxylic Acids and Ketones Using Morita-Baylis-Hillman Adducts*" 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
September 2025

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.

Hemanga Bhattacharyya

List of Abbreviations

Ar	aryl
Ac	acetyl
AIBN	azobisisobutyronitrile
AcOH	acetic acid
Ac-Ile-OH	*N*-acetyl-*L*-isoleucine
Å	angstrom (10^{-10} m)
Ac-*t*-Leu-OH	*N*-acetyl-*L*-leucine
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 wthdrawing group
FT-IR	Fourier transform infrared spectroscopy
FG	functional group

GC	gas chromatography
g	gram
HFIP	hexafluoroisopropanol
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

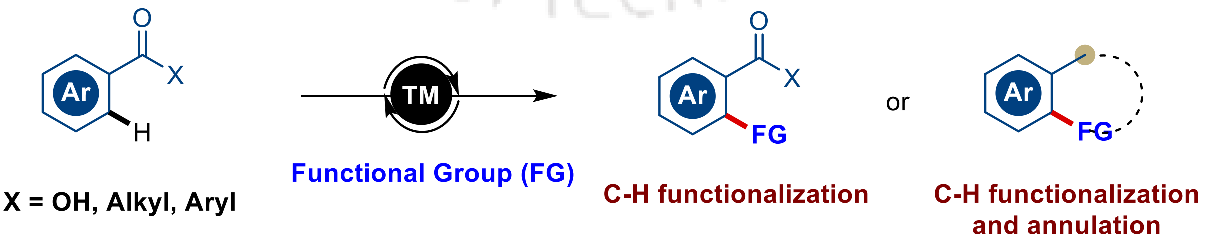
TMS	trimethylsilyl
VCP	vinylcyclopropane
μm	micrometre
μL	microlitre

Abstract

The thesis is organized into four chapters. The first chapter presents advances in weakly chelating carboxylate and ketone directed site-selective C–H functionalization and annulation strategies for benzoic acids and aryl ketones. The second chapter explores redox-neutral, site-selective C–H allylation and iodolactonization of benzoic acids using Morita-Baylis-Hillman (MBH) adducts in water. The third chapter demonstrates a Pd-catalyzed substrate-switchable C–H alkenylation and alkylation of benzoic acids using MBH alcohols. The fourth chapter details a Ru-catalyzed weak-chelation-assisted C–H allylation of aryl ketones using MBH alcohols.

Chapter 1. Site-Selective C–H Functionalization and Annulation Strategies for Aryl Carboxylic Acids and Ketones

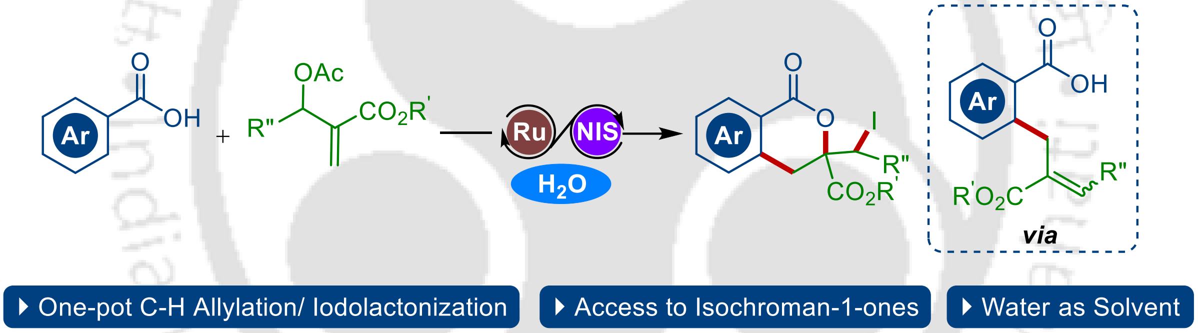
Selective C–H functionalization is a key strategy in modern organic synthesis, but reliance on exogenous directing groups (DGs), which adds extra steps and reduces overall efficiency. To overcome this, recent advances in C–H functionalization reactions focus on native functional groups such as carboxylic acids and ketones, which are abundant, biologically relevant, and capable of weak coordination with transition metals to enable C–H activation and functionalization. This approach improves step and atom economy, particularly when combined with one-pot or post-synthetic annulation strategies, providing an efficient platform for constructing diverse and medicinally important molecular architectures. This chapter highlights reported methods on native carboxylate- and ketone-directed C–H functionalization and annulation strategies of arenes (Scheme 1).



Scheme 1. C–H Functionalization/Annulation Strategies for Benzoic Acids and Ketones

Chapter 2. Site-Selective C–H Allylation and Iodolactonization of Benzoic Acids Using Morita-Baylis-Hillman Adducts

Recent advances in C–H functionalization increasingly utilize native functional groups as directing groups, with carboxylates emerging as powerful handles for site-selective transformations of benzoic acids. While oxidative alkenylation/ alkynylation and annulation strategies have enabled access to benzolactone frameworks, however methods for incorporating allyl fragments remain underexplored. To address this gap, a redox-neutral Ru(II)-catalyzed C–H allylation and iodolactonization of benzoic acids with MBH adducts in water has been developed, providing isochroman-1-ones, core units of benzolactone scaffolds (Scheme 2). The method offers key advantages such as water as reaction medium, avoids external oxidants, and exhibits broad substrate scope, scalability, and functional group tolerance. Moreover, its successful application to late-stage modification of natural products and drug molecules highlights its potential utility in medicinal chemistry and drug discovery.

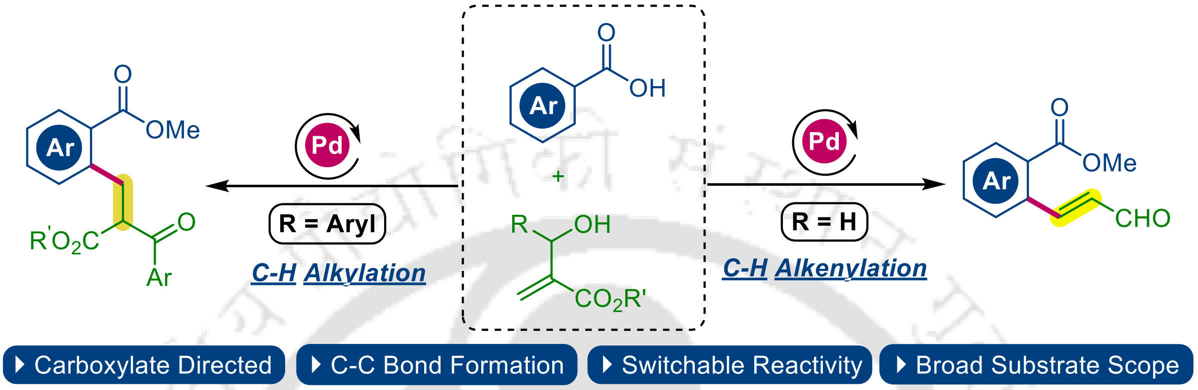


Org. Lett. **2023**, *25*, 6830.

Scheme 2. C–H Allylation and Iodolactonization of Benzoic Acids with MBH Adducts

Chapter 3. Substrate-Switchable C–H Alkenylation and Alkylation of Benzoic Acids Using Morita-Baylis-Hillman Alcohols

C–H functionalization offers a powerful route for directly converting inert C–H bonds into valuable functionalities. Allylic alcohols are versatile partners for C–H functionalization reactions, enabling alkenylation or alkylation *via* β-hydride elimination to access carbonyl products. Increasingly, simple native directing groups such as carboxylic acids are being utilized to simplify synthetic routes and improve efficiency. In this context, a Pd(II)-catalyzed *ortho*-selective, carboxylate-directed C–H functionalization of arenes with MBH alcohols, a class of allylic alcohol, has been developed. The reaction outcome is dependent on the substitution pattern of the MBH alcohol: unsubstituted MBH alcohols afford aryl acrylaldehydes, whereas aryl-substituted MBH alcohols yield *α*-benzyl *β*-ketoesters (Scheme 3). The methodology demonstrates broad substrate scope, functional group tolerance, scalability, and switchable reactivity, highlighting its synthetic utility.

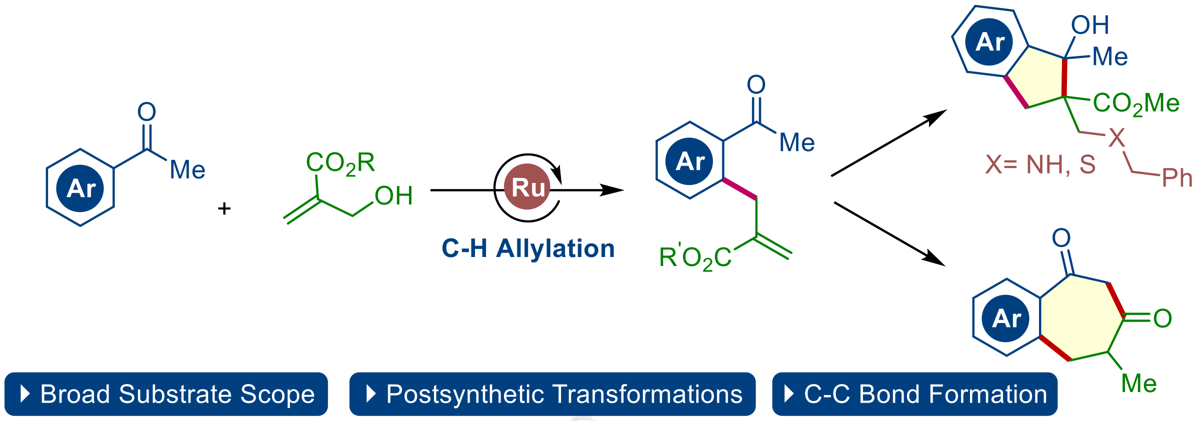


Chem. Commun. **2025**, *61*, 4200.

Scheme 3. Substrate-Switchable C–H Alkenylation and Alkylation of Benzoic Acids

Chapter 4. Weak-Chelation-Assisted C–H Allylation of Aryl Ketones Using Morita-Baylis-Hillman Alcohols

Ketone-directed C–H functionalization represents a powerful strategy for site-selective bond formation. While C–H allylation typically employs pre-activated allyl electrophiles, the direct use of allyl alcohols is more atom- and step-economical but challenged by the poor leaving ability of hydroxyl groups and competing *β*-hydride elimination. In particular, ketone-directed C–H allylation with allyl alcohols remains largely unexplored. MBH alcohols, a class of allylic alcohol, are valuable synthetic intermediates in organic synthesis. Here, a Ru(II)-catalyzed, keto-directed *ortho*-selective C–H allylation of aryl ketones with MBH alcohols is disclosed, delivering *α*-benzyl acrylates. The resulting allylated products undergo diverse post-synthetic transformations to form bioactive scaffolds such as multi-substituted indanes and benzo-fused seven-membered cyclic *β*-diketones (Scheme 4). The methodology features broad substrate scope, functional group tolerance, and post-synthetic versatility, establishing MBH alcohols as unique and underexplored coupling partners in ketone-directed C–H allylation.



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Scheme 4. Ru(II)-Catalyzed C–H Allylation of Aryl Ketones Using MBH Alcohols

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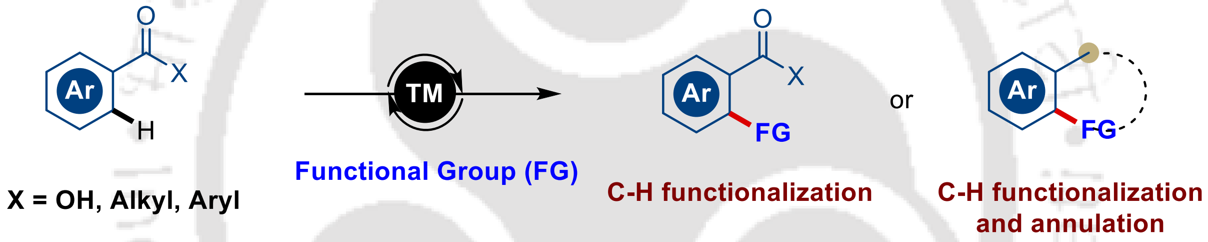
Chapter 1

Site-Selective C–H Functionalization and Annulation Strategies for Aryl Carboxylic Acids and Ketones



Site-Selective C–H Functionalization and Annulation Strategies for Aryl Carboxylic Acids and Ketones

The selective functionalization of C–H bond represents a pivotal strategy in modern organic synthesis, as it exploits the most abundant bonds within a molecule for streamlined structural diversification. Although remarkable progress has been achieved over the past decade, a major limitation has been the reliance on stoichiometric installation and removal of exogenous directing groups (DGs), which adds extra steps and reduces overall efficiency.[1] To address this challenge, recent attention has shifted toward the use of native functional groups as inherent DGs, eliminating the need for additional synthetic manipulations (Figure 1).[2] In particular, carboxylic acids and ketones have emerged as highly attractive alternatives, mainly because of their natural abundance, prevalence in bioactive molecules, and ability to engage in weak coordination with transition metals through the formation of thermodynamically less stable metallacycles, which enable efficient C–H activation without external modification.[3] This strategy not only simplifies reaction design but also enhances step and atom economy, making especially valuable for the synthesis of complex and medicinally relevant molecules.

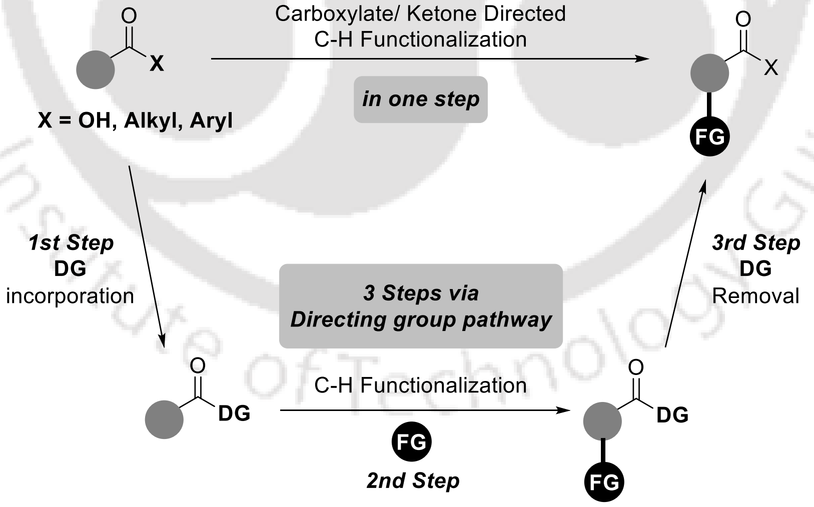


Figure 1. Efficiency of Native Carboxylate/ Ketone Directed C–H Functionalization.

Carboxylic acid-directed C–H functionalization encompasses a diverse range of reactions that enable the selective modification of aromatic carboxylic acids. Key transformations include arylation,[10] alkenylation,[22] alkynylation,[11] allylation,[13] and acylation[8] primarily occurring at proximal *ortho* C(sp^2)–H positions. These reactions involve C–O bond formations such as hydroxylation[7] and intramolecular lactonization,[14-25] as well as C–N [9] and C–X (halogenation)[6] bond formations. Advances have been made in both catalytic systems and ligand design to achieve regioselectivity with broad substrate scope, often under mild and environmentally friendly conditions, making carboxylate-directed C–H functionalization a powerful tool for the synthesis of biologically important benzo-fused lactones, such as isocoumarins, isochromanes and phthalides. These benzolactones are prevalent in many natural products and bioactive molecules with diverse pharmacological properties (Figure 2).[4]

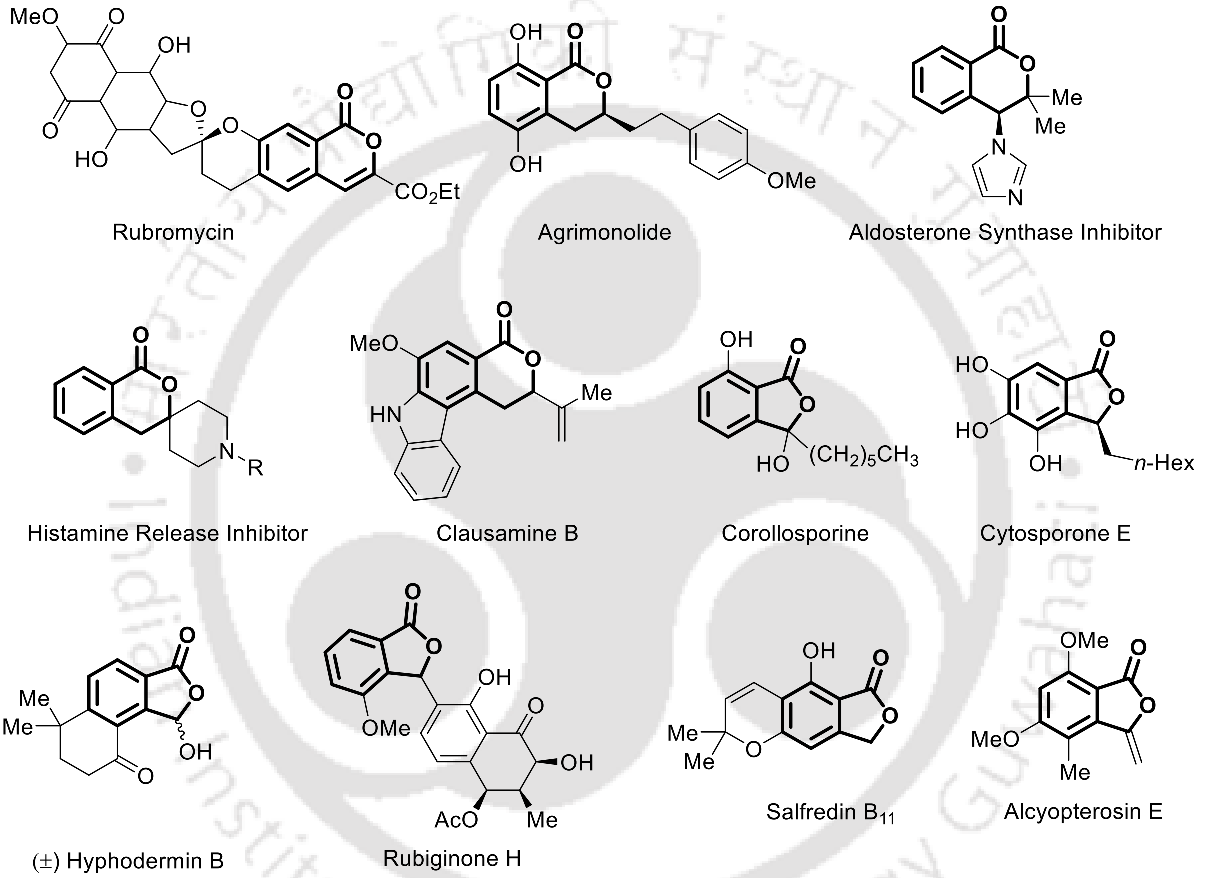


Figure 2. Biologically Important Benzolactones

Ketone-directed C–H functionalization encompasses a variety of reaction types primarily focused on modifying aromatic ketones through transition metal catalysis. Ketone-directed C–H functionalization reactions enable diverse site-selective modifications such as alkylation,[26] allylation,[31] alkenylation,[30] hydroxylation,[27] halogenation[28] and amidation[29] expanding synthetic possibilities with abundant ketone-containing molecules as substrates or intermediates. These diverse reaction types, often enabled by Ru, Rh, Pd, Co and Ir catalysts, expand the synthetic utility of ketones as versatile substrates in organic synthesis. Additionally, ketone-directed C–H functionalization and subsequent annulation has been employed *via* a transition metal catalyzed direct functionalization of *ortho* C–H bonds on aromatic ketones coupled with intramolecular cyclization sequences to build indene frameworks,[34-37] which are key structures in various natural products and pharmaceutically relevant compounds (Figure 3).[5]

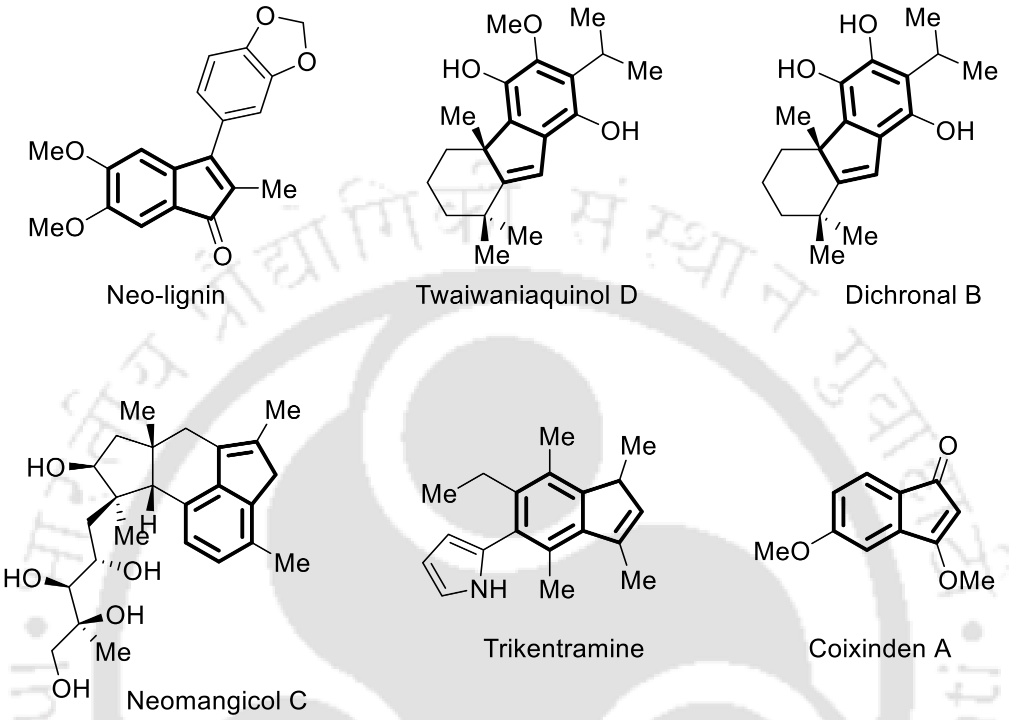


Figure 3. Biologically Important Indenes

Therefore, development of such carboxylate and ketone DG guided C–H functionalization strategies is of tremendous research interest. In addition, one-pot C–H functionalization and subsequent annulation reaction has emerged as an increasingly effective and attractive strategy to meet the increasing demand for affording diverse carbocycles and heterocycles of synthetic importance in a step- and atom-economic manner.

1.1 Literature

As previously mentioned, utilization of native carboxylic acid and ketone functional group directed C–H functionalization of arenes, particularly when integrated with annulation strategies, has emerged as a powerful platform for the efficient construction of structurally diverse and biologically relevant molecular architectures (Figure 4). In this chapter, the reported methods for the native carboxylate and ketone directed site-selective C–H functionalization as well as annulation strategies of arenes are discussed.

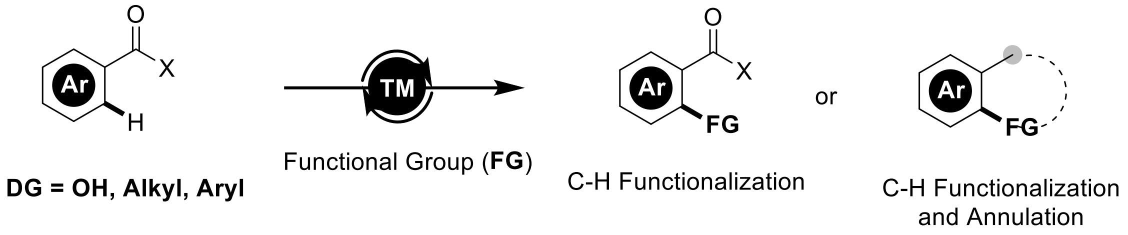
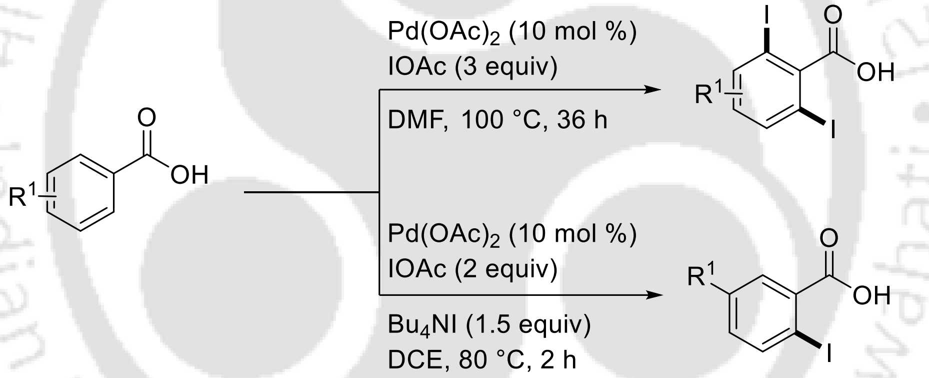


Figure 4. C–H Functionalization and Annulation Strategies for Aryl Carboxylic Acids and Ketones

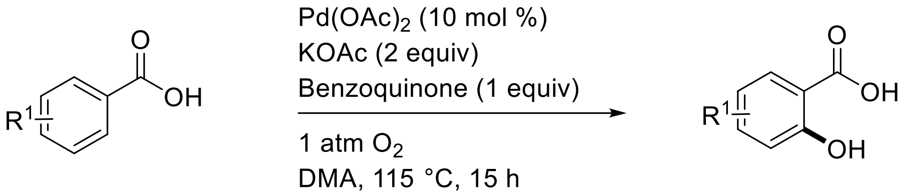
1.1.1 C(sp^2)-H Functionalization of Aryl Carboxylic Acids

Yu and co-workers achieved a Pd(II)-catalyzed *ortho* halogenation of benzoic acids using IOAc for C–I bond formation (Scheme 1).[6] When DMF was employed as the solvent, diiodinated products were predominantly obtained. However, in the presence of a bulky counterion such as tetrabutylammonium, monoiodinated products were formed for *meta*-substituted benzoic acids.



Scheme 1. Pd(II)-Catalyzed *Ortho* Halogenation of Benzoic Acids

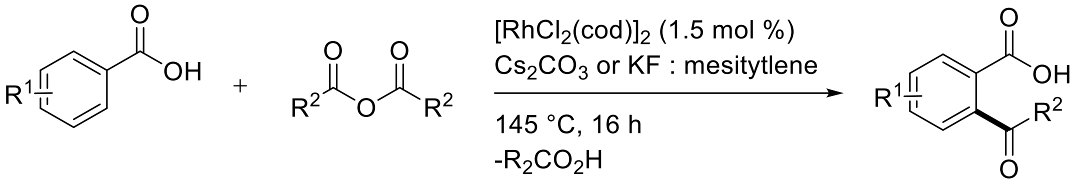
They further reported a Pd(II)-catalyzed *ortho* hydroxylation of benzoic acids using molecular oxygen (Scheme 2).[7] The reaction proceeds efficiently with potassium salts as bases and tolerates a wide range of functional groups.



Scheme 2. Pd(II)-Catalyzed *Ortho* Hydroxylation of Benzoic Acids

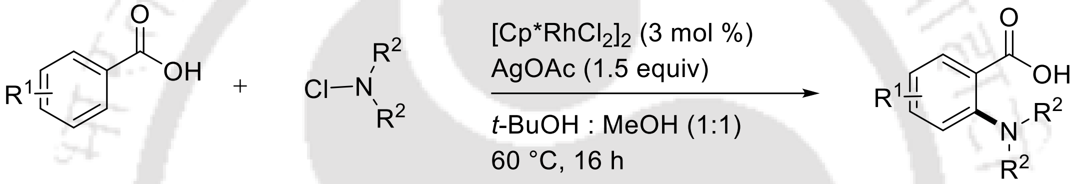
Gooßen group developed a Rh(III)-catalyzed acylation of aromatic carboxylic acids using aliphatic anhydrides, achieving selective functionalization at the *ortho* position (Scheme

3).[8] The protocol tolerates a broad range of substrates and provides access to valuable 2-acylbenzoic acids, complementary to traditional Friedel-Crafts acylation.



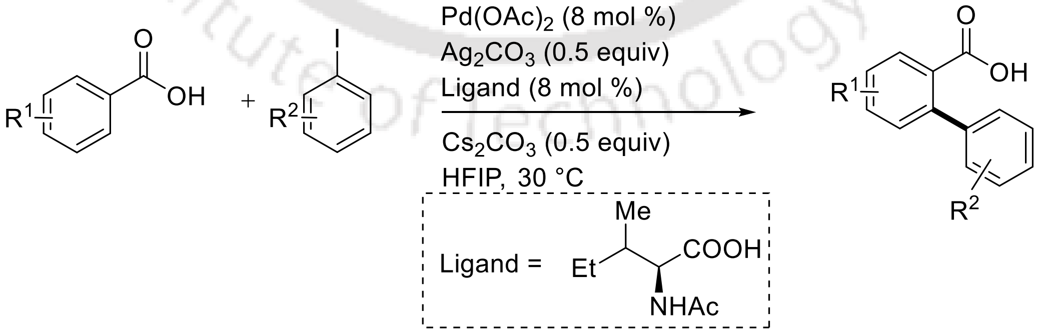
Scheme 3. Rh(III)-Catalyzed *Ortho* Acylation of Benzoic Acids

Yu and co-workers developed a Rh(III)-catalyzed direct C–H amination of benzoic acids using chloramines (Scheme 4).[9] The method provides functionalized anthranilic acids with high *ortho* selectivity and good yields under mild conditions, tolerating various functional groups.



Scheme 4. Rh(III)-Catalyzed Direct *Ortho* Amination of Benzoic Acids with Chloramines

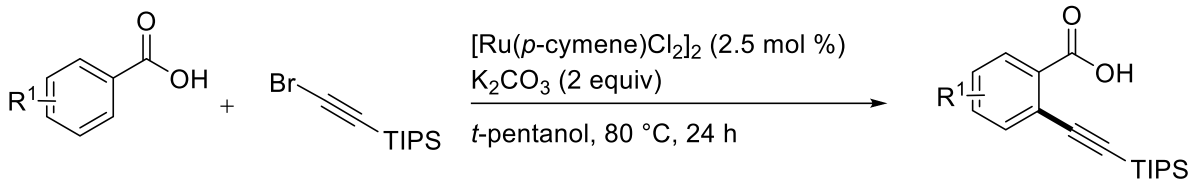
Su group reported an ambient-temperature *ortho* C–H arylation of electron-deficient benzoic acids with aryl iodides using a Pd catalyst supported by Ac-Ile-OH ligand (Scheme 5).[10] The ligand played a key role in accelerating the C–H activation process and extending catalyst lifetime, enabling a wide scope of benzoic acids and aryl iodides to undergo cross-coupling in moderate to excellent yields.



Scheme 5. Pd(II)-Catalyzed Arylation of Benzoic Acids with Aryl Iodides

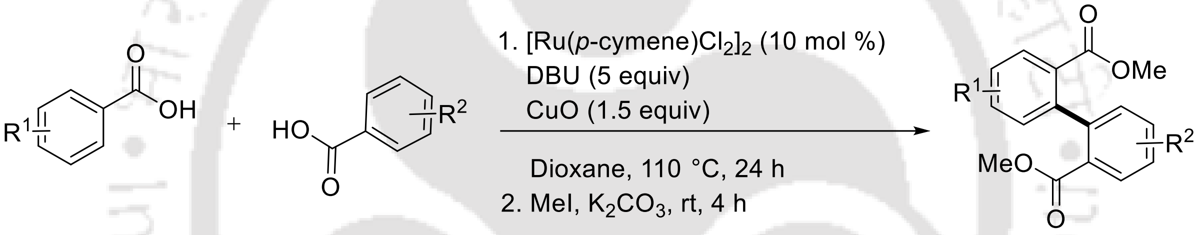
Zeng and co-workers reported a Ru(II)-catalyzed *ortho* alkynylation of benzoic acids, using a weakly coordinating carboxyl group with (bromoethynyl)triisopropylsilanes (Scheme 6).[11]

The method enabled direct C–H alkynylation under mild conditions, displayed broad substrate scope, including electron-rich and multisubstituted benzoic acids.



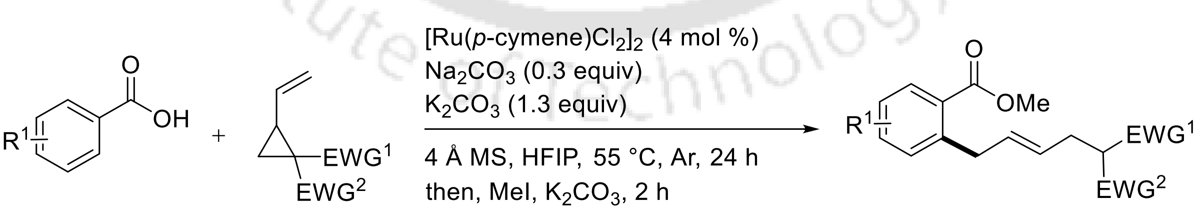
Scheme 6. Ru(II)-Catalyzed *Ortho* Alkynylation of Benzoic Acids

Baidya group developed a Ru(II)-catalyzed cross-dehydrogenative coupling of arene carboxylic acids to synthesize 2,2′-biaryl acid scaffolds, including both homodimerized and cross-dimerized products (Scheme 7).[12] The protocol features a key role of the organic base DBU, which stabilizes reactive intermediates through noncovalent interactions, lowering the activation barrier for the challenging second C–H metalation step.



Scheme 7. Ru(II)-Catalyzed Cross-Dehydrogenative Coupling of Arene Carboxylic Acids

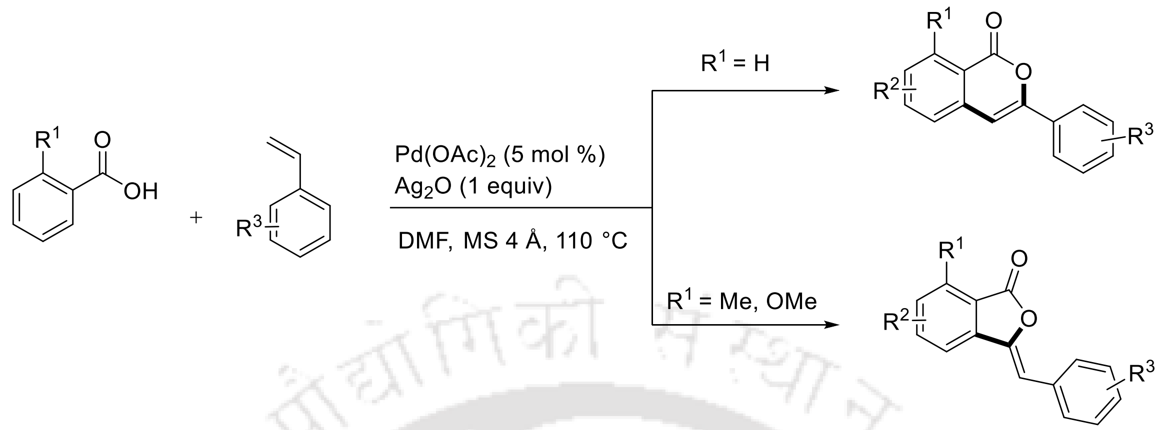
Gooßen group reported a Ru(II)-catalyzed *ortho* C–H allylation of benzoic acids using vinylcyclopropanes (VCPs) as allyl sources under mild redox-neutral conditions (Scheme 8).[13] The reaction proceeds *via* selective cleavage of both C–H and C–C bonds, delivering a broad range of allylarenes.



Scheme 8. Ru(II)-Catalyzed *Ortho* C–H Allylation of Benzoic Acids Using VCPs

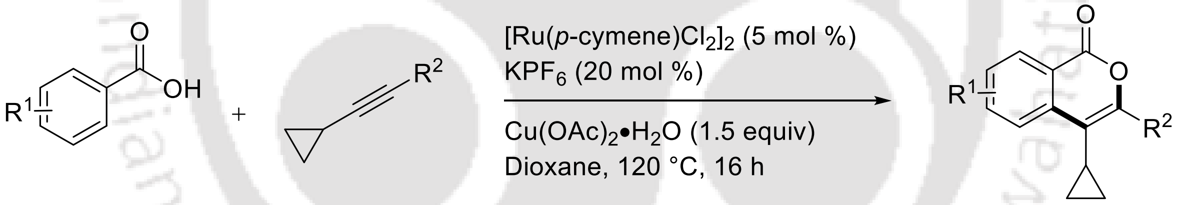
1.1.2 C(sp^2)-H Functionalization and Annulation of Aryl Carboxylic Acids

Lee and co-workers developed a Pd(II)-catalyzed oxidative coupling of benzoic acids with vinylarenes to synthesize isocoumarins and 3-benzylidenephthalides (Scheme 9).[14] Electron-donating groups improved the yields, and regioselectivity can be controlled by benzoic acid substitution, providing a practical, step-economical approach for lactone synthesis.



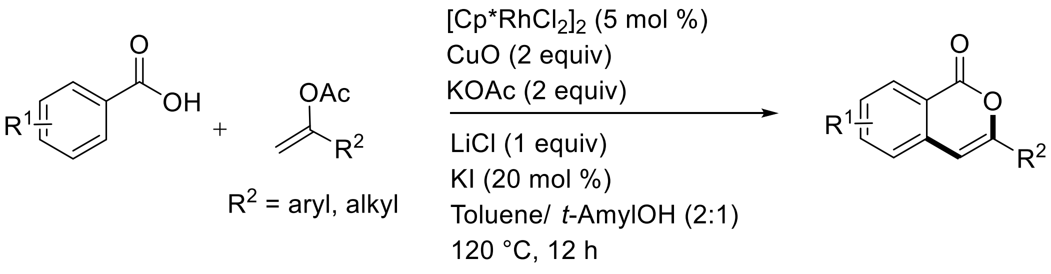
Scheme 9. Pd(II)-Catalyzed Oxidative Coupling of Benzoic Acids with Vinylarenes

Ackermann group developed a Ru(II)-catalyzed oxidative annulations of cyclopropyl-substituted alkynes with benzoic acids *via* C–H/O–H bond activation (Scheme 10).[15] These reactions proceed with high regioselectivity and complete retention of the cyclopropane motif, yielding cyclopropyl-substituted isocoumarins.



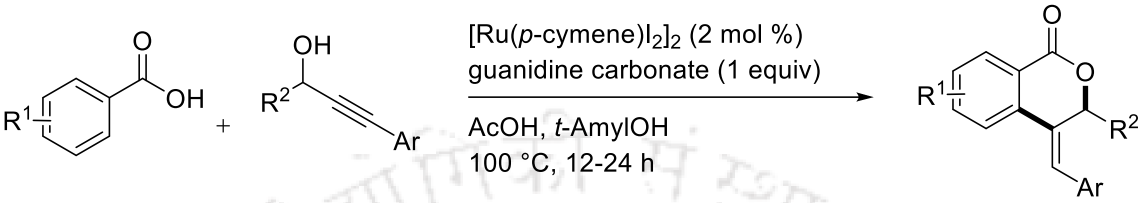
Scheme 10. Ru(II)-Catalyzed Oxidative Annulation of Alkynes with Benzoic Acids

Wen and co-workers developed a Rh(III)-catalyzed oxidative coupling of benzoic acids with electron-rich geminal-substituted vinyl acetates to synthesize 3-substituted isocoumarins (Scheme 11).[16] The method tolerates a broad range of benzoic acids and vinyl acetates, producing 3-aryl and 3-alkyl substituted isocoumarins regioselectively.



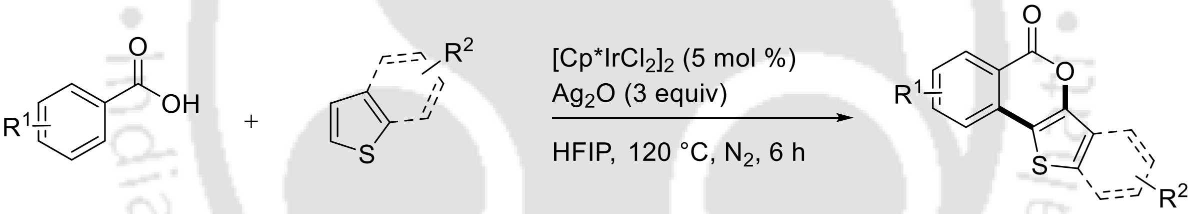
Scheme 11. Rh(III)-Catalyzed Annulation of Benzoic Acids with Vinyl Acetates

Gooßen group achieved regioselective C–H hydroarylation of internal alkynes with aryl carboxylic acids as DGs under Ru(II) catalysis (Scheme 12).[17] This method is applicable to a broad range of electron-rich/-poor benzoic acids, in combination with functionalized alkynes and propargylic alcohols, which undergo intramolecular lactonization to give γ-alkylidene-δ-lactones.



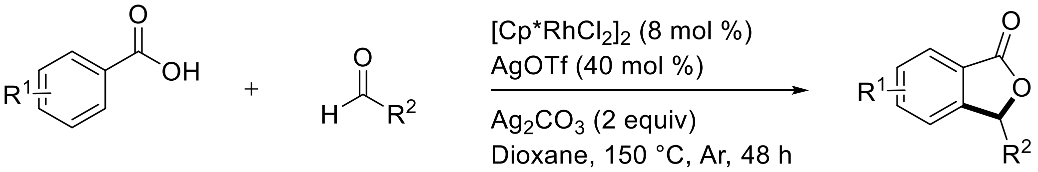
Scheme 12. Ru(II) C–H Hydroarylation of Propargyl Alcohols with Benzoic Acids

You and co-workers developed an Ir(III)-catalyzed annulation of (benzo)thiophenes with (hetero)aromatic carboxylic acids to synthesize thiophene-fused coumarin frameworks (Scheme 13).[18] This practical method enables efficient, step- and atom-economic synthesis of thiophene-containing polyheterocycles relevant to pharmaceutical and materials chemistry.



Scheme 13. Ir(III)-Catalyzed Annulation of (Benzo)Thiophenes with Benzoic Acids

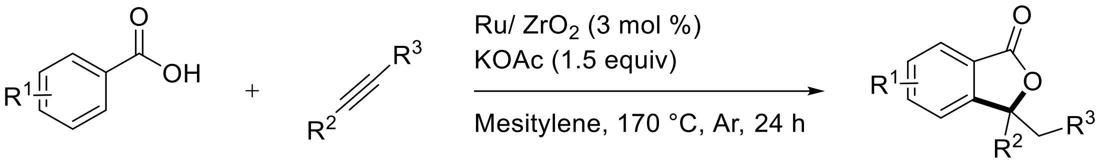
Li and co-workers developed a Rh(III)-catalyzed cascade cyclization for the direct synthesis of 3-substituted phthalides from aromatic carboxylic acids with aldehydes (Scheme 14).[19] Electron-rich benzoic acids and electron-deficient aldehydes are preferred substrates, providing an atom-economical route to bioactive lactones with water as the only by-product.



Scheme 14. Rh(III)-Catalyzed Cascade Cyclization of Benzoic Acids and Aldehydes

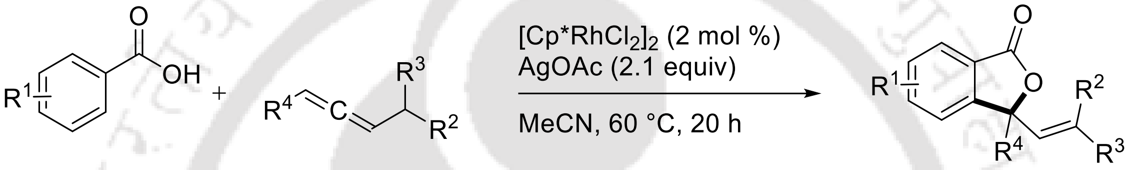
Shishido group developed a supported Ru(II)-catalyzed coupling of aromatic carboxylic acids with internal alkynes to selectively synthesize multi-substituted phthalide derivatives

(Scheme 15).[20] Ru/ZrO_2 showed high activity, excellent regioselectivity, and recyclability for at least five cycles without loss of efficiency.



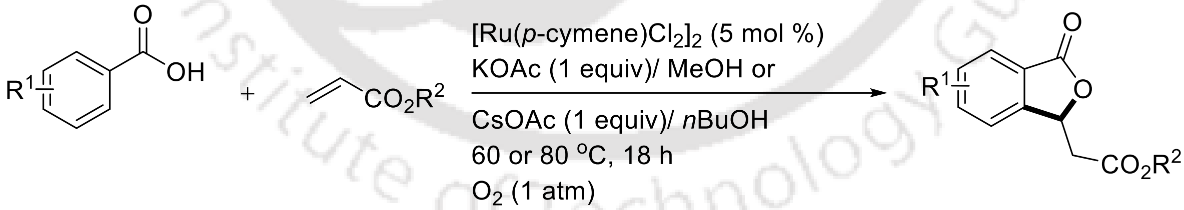
Scheme 15. Ru(II)-Catalyzed Annulation of Benzoic Acids with Internal Alkynes

Cheng group developed a Rh(III)-catalyzed (4+1) annulation of aryl carboxylic acids with allenes to synthesize 3,3-disubstituted phthalides (Scheme 16).[21] The reaction proceeds through carboxylate-assisted *ortho* C–H activation with functional group tolerance and regioselectivity.

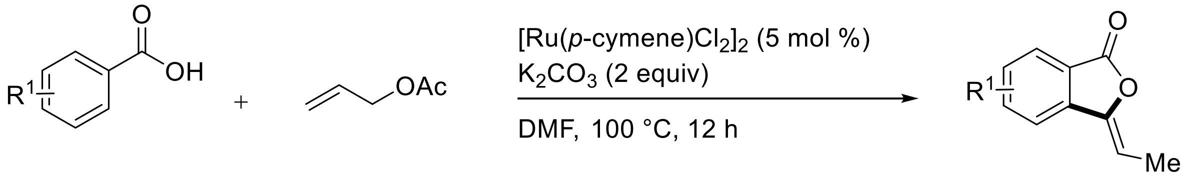


Scheme 16. Rh(III)-Catalyzed [4+1] Annulation of Aryl Carboxylic Acids with Allenes

Ackermann group developed a Ru(II)-catalyzed site-selective C–H alkenylation of benzoic acids with acrylates using ambient oxygen as the sole oxidant (Scheme 17).[22] This aerobic oxidase catalysis demonstrated broad substrate scope, enabling synthesis of phthalides. The process is sustainable, producing water as the only by-product, and operates under ambient pressure and moderate temperatures.

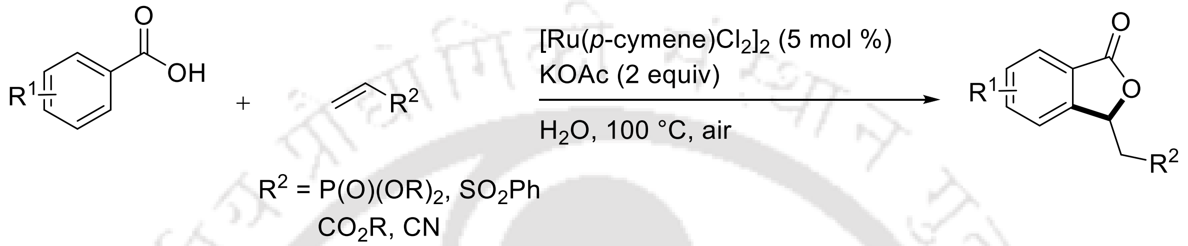


Scheme 17. Ru(II)-Catalyzed C–H Alkenylation of Benzoic Acids with Acrylates



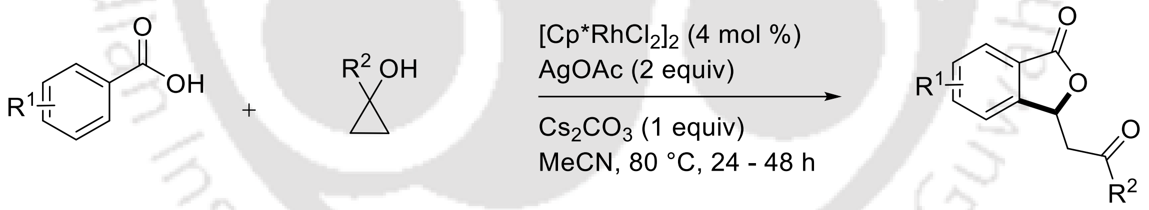
Scheme 18. Ru(II)-Catalyzed Cyclization of Benzoic Acids with Allylic Acetates

Jeganmohan and co-workers reported a Ru(II)-catalyzed redox-free cyclization of aromatic carboxylic acids with allylic acetates *via* two-fold aromatic and allylic C–H activations to synthesize (Z)-3-ylidenephthalides (Scheme 18).[23] The reaction proceeds with Z-selectivity. In addition, Baidya group developed a Ru(II)-catalyzed cross-dehydrogenative annulation of arene carboxylic acids with alkenes in water using air as the oxidant, yielding phthalide derivatives (Scheme 19).[24] The method features mild, green conditions and broad functional group tolerance, enabling efficient C–H activation without stoichiometric metallic oxidants.



Scheme 19. Ru(II)-Catalyzed Annulation of Benzoic Acids with Alkenes in Water

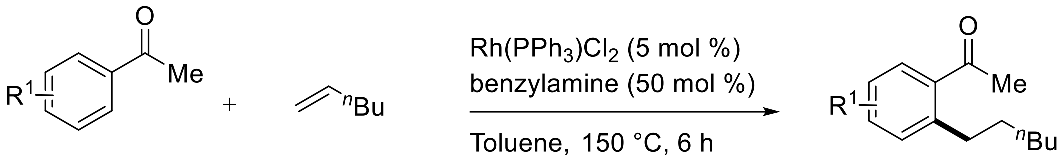
Yang group developed a Rh(III)-catalyzed cascade reaction combining C–H activation, ring-opening C–C cleavage, and cyclization of aromatic carboxylic acids with cyclopropanols to synthesize 3-substituted phthalides (Scheme 20).[25] This method operates with excellent functional group tolerance and includes late-stage functionalization of bioactive compounds.



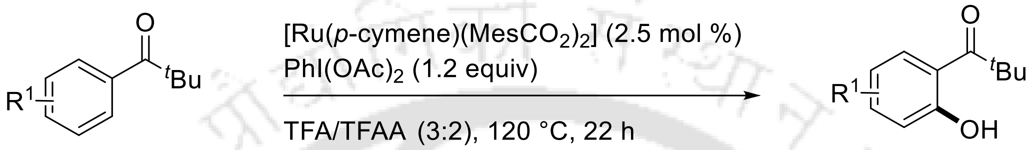
Scheme 20. Rh(III)-Catalyzed Cyclization of Benzoic Acids with Cyclopropanols

1.1.3 C(sp^2)-H Functionalization of Aryl Ketones

Jun and co-workers developed a Rh(I)-catalyzed *ortho* alkylation of aromatic ketones using olefins *via* chelation-assisted C–H activation (Scheme 21).[26] This method achieves high regioselectivity and broad substrate scope, including various olefins such as dienes, and internal olefins. Benzylamine acts as an effective cocatalyst enabling direct ketone functionalization, providing a versatile approach to monoalkylated aromatic ketones. Further, Ackermann group reported a Ru(II)-catalyzed C(sp^2)–H bond oxygenation of aromatic ketones using weakly coordinating ketone DGs (Scheme 22).[27] The reaction employs inexpensive Ru complexes with oxidants such as $PhI(OAc)_2$ under mild conditions, achieving site-selective hydroxylation. This method enables direct oxygenation of diverse ketone substrates, favoring electron-rich arenes, and demonstrates high chemoselectivity.

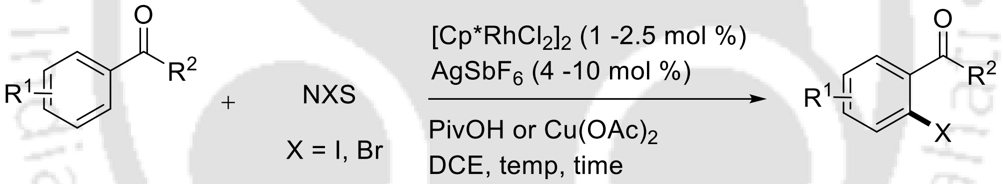


Scheme 21. Rh(I)-Catalyzed *Ortho* Alkylation of Aromatic Ketones Using Olefins



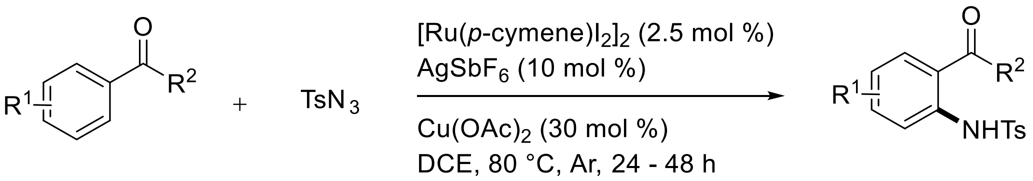
Scheme 22. Ru(II)-Catalyzed C–H Bond Oxygenation of Aromatic Ketones

Glorius group showed a versatile Rh(III)-catalyzed *ortho* bromination and iodination of aryl ketones *via* C–H bond activation (Scheme 23).[28] The reaction employs *N*-halosuccinimide reagents under mild conditions with aromatic ketones to afford *ortho* halogenated products.



Scheme 23. Rh(III)-Catalyzed for *Ortho* C–H Halogenation of Aromatic Ketones

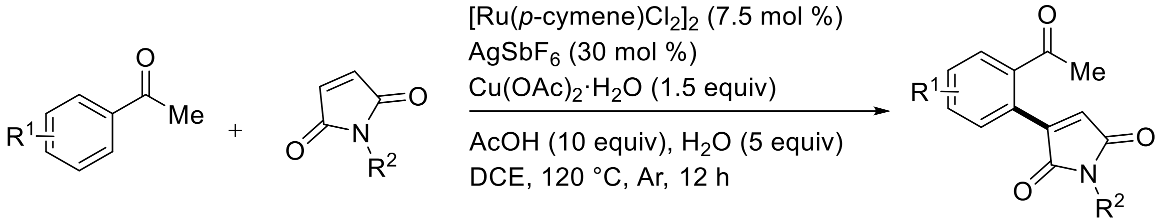
Jiao and co-workers accomplished a Ru(II)-catalyzed intermolecular C–H amidation of weakly coordinating aromatic ketones with sulfonyl azides (Scheme 24).[29] This method provides a practical approach for *ortho* C–N bond formation, furnishing *ortho* amino aryl ketones in moderate to good yields.



Scheme 24. Ru(II)-Catalyzed C–H Amidation of Aromatic Ketones with Sulfonyl Azides

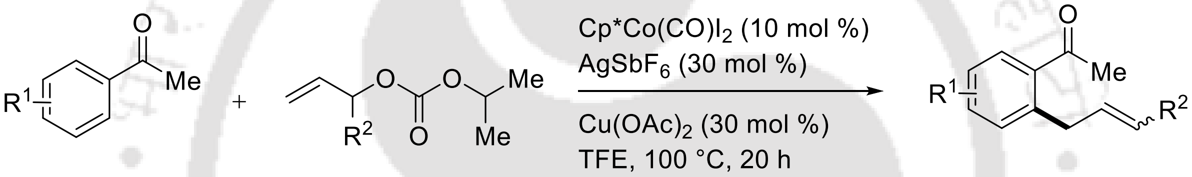
Prabhu group reported a Ru(II)-catalyzed ketone-directed *ortho* alkenylation of aromatic ketones with maleimides to form pharmaceutically valuable 3-arylated succinimides (Scheme

25).[30] This method offers an efficient route to succinimide derivatives from simple ketones and maleimides through selective C–H functionalization.



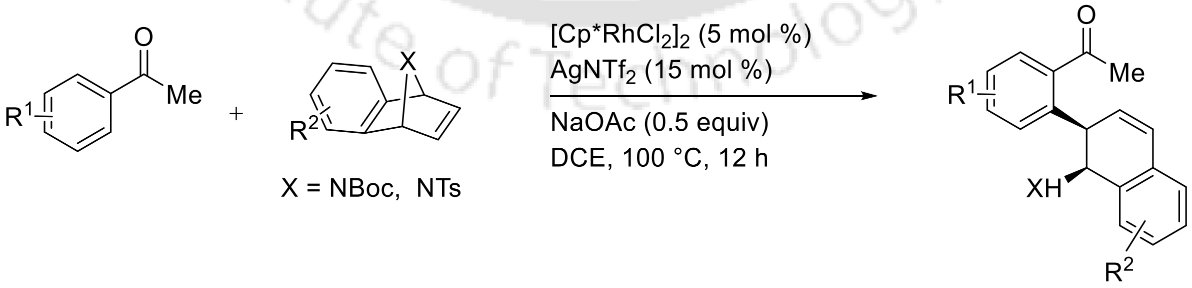
Scheme 25. Ru(II)-Catalyzed C–H Alkenylation of Aromatic Ketones with Maleimides

Maji group developed a weakly coordinating, ketone-directed Co(III)-catalyzed *ortho* C–H allylation of arenes using allyl carbonates (Scheme 26).[31] This method offers exclusive monoallylation with high regioselectivity across a broad substrate scope, including electron-rich/-deficient ketones.



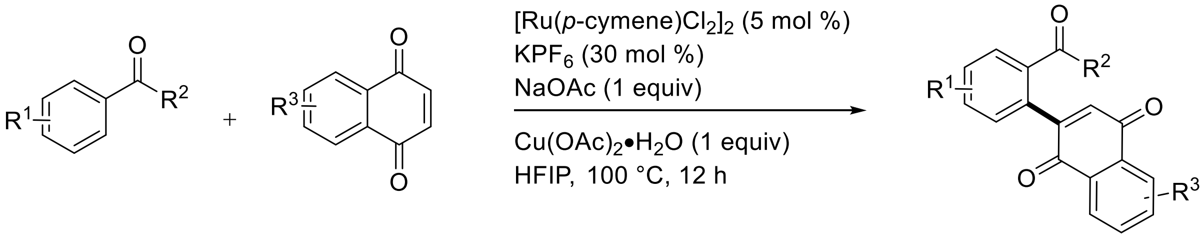
Scheme 26. Co(III)-Catalyzed C–H Allylation of Aryl Ketones Using Allyl Carbonates

Fan group showed a Rh(III)-catalyzed ketone directed ring-opening, addition and hydroarylation of azabenzonorbornadienes with arenes (Scheme 27).[32] Aryl ketones underwent stereoselective ring-opening and addition with bicyclic alkenes to provide *cis*-isomer. The reaction tolerated a broad substrate scope including substituted aryl ketones and bicyclic alkenes, offering a mild and versatile route to substituted polycyclic aromatic compounds.



Scheme 27. Rh(III)-Catalyzed Ketone Directed Ring-Opening Addition and Hydroarylation

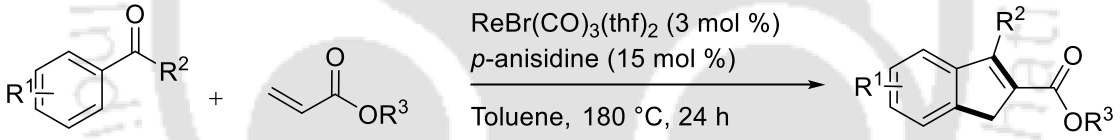
Volla group achieved a Ru(II)-catalyzed ketone-directed arylation of naphthoquinones using acetophenones (Scheme 28).[33] This approach provides an efficient route to access diverse arylated naphthoquinone derivatives, accommodating a broad range of functional groups on both acetophenones and naphthoquinones.



Scheme 28. Ru(II)-Catalyzed Ketone-Directed Arylation of Naphthoquinones

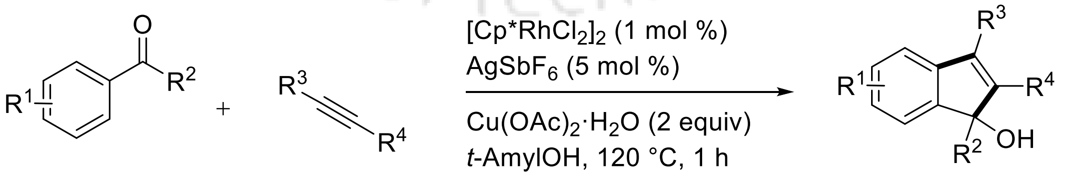
1.1.4 C(sp^2)-H Functionalization and Annulation of Aryl Ketones

Takai and co-workers developed a Re-catalyzed annulation of aromatic ketones with *α*,*β*-unsaturated esters (Scheme 29).[34] The reaction proceeds *via* in situ formation of a ketimine DG, followed by Re-catalyzed C–H activation and conjugate addition, culminating in cyclization and elimination of aniline. The protocol is atom-economical, producing only water as a byproduct, and shows good tolerance for various substituted acetophenones and different acrylate esters, delivering indene products in moderate to high yields.



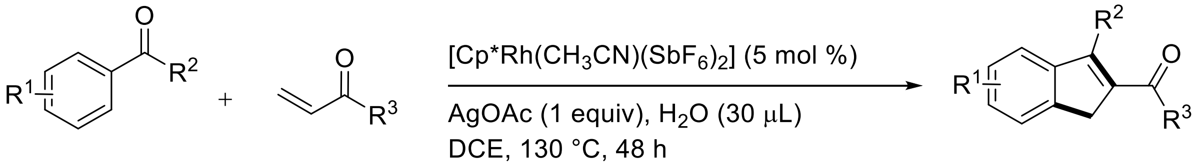
Scheme 29. Re-Catalyzed Annulation of Aromatic Ketones with α,β-Unsaturated Esters

Cheng group developed a Rh(III)-catalyzed regioselective synthesis of substituted indenols *via* C–H activation and carbocyclization of aryl ketones with alkynes (Scheme 30).[35] The method tolerates functional groups on both ketones and alkynes and provides an efficient route to valuable indenol derivatives.



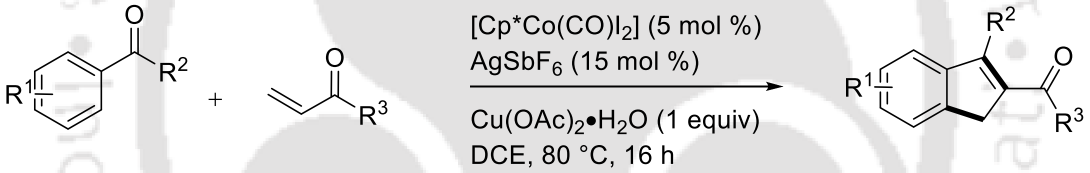
Scheme 30. Rh(III)-Catalyzed Regioselective Synthesis of Substituted Indenols

Li group reported a Rh(III)-catalyzed cascade cyclization of aromatic ketones with *α*,*β*-unsaturated ketones to synthesize indene derivatives *via* direct *ortho* C–H functionalization-initiated cyclization (Scheme 31).[36] The reaction proceeds through conjugate addition followed by intramolecular aldol condensation. The method offers an atom-economical and simple route to structurally diverse indenes in moderate to good yields, tolerating various functional groups on both aryl ketones and *α*,*β*-unsaturated ketones.



Scheme 31. Rh(III)-Catalyzed Cyclization of Aromatic Ketones with *α*,*β*-Unsaturated Ketones

Dethe group developed a Co(III)-catalyzed ketone-directed *ortho* C–H activation of aromatic ketones with *α*,*β*-unsaturated ketones to synthesize indene derivatives (Scheme 32).[37] The reaction involves Co-mediated C–H activation, followed by 1,4-conjugate addition to the olefin and intramolecular aldol condensation. This approach provides a sustainable method to access indenes with excellent functional group tolerance, utilizing earth-abundant cobalt catalysis.



Scheme 32. Co(III)-Catalyzed Cyclization of Aromatic Ketones with *α*,*β*-Unsaturated Ketones

1.2 Objective of the Thesis

Transition-metal-catalyzed site-selective C–H functionalization of aryl carboxylic acids and aryl ketones has emerged as a rapidly expanding field of research. In this chapter, a concise review of the literature on C–H functionalization and annulation strategies employing these native functional groups is presented. Despite significant progress, several synthetic challenges and knowledge gaps remain, offering opportunities for further exploration in this evolving area.

The following objectives of the thesis are listed below,

- To explore the use of native functional groups, such as carboxylic acids and ketones, as DGs for achieving diverse C–H functionalization reactions.

- To investigate the relatively less explored Morita-Baylis-Hillman (MBH) adducts in combination with native functional groups as DGs to achieve diverse C–H functionalization reactions.
- To develop one-pot or post-synthetic annulation strategies for the construction of biologically important core motifs.

1.3 References

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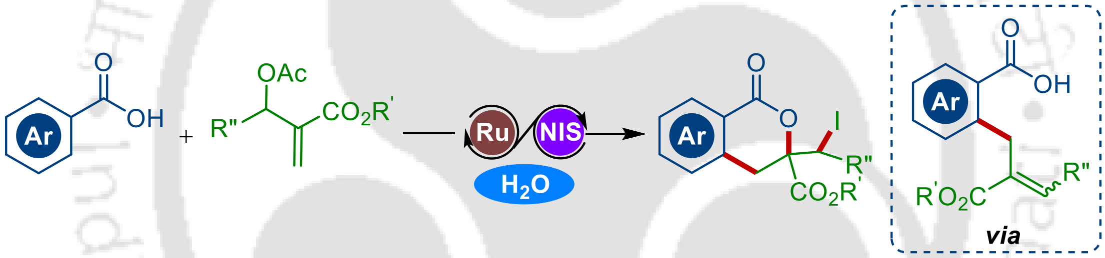
Chapter 2

Site-Selective C–H Allylation and Iodolactonization of Benzoic Acids Using Morita-Baylis-Hillman Adducts

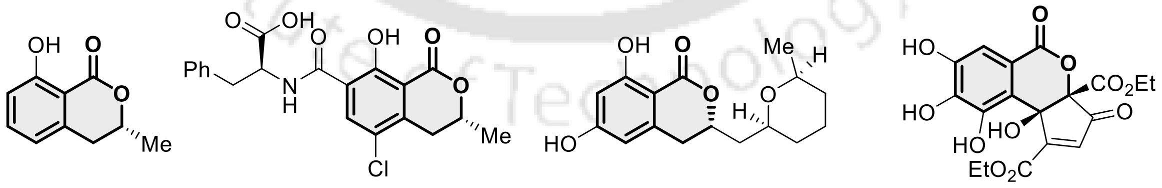


- One-pot C-H Allylation/ Iodolactonization
- Access to Isochroman-1-ones
- Water as Solvent

Org. Lett. **2023**, *25*, 6830.

Site-Selective C–H Allylation and Iodolactonization of Benzoic Acids Using Morita-Baylis-Hillman Adducts

Transition-metal-catalyzed C–H functionalization has become an essential strategy in modern synthetic organic chemistry, offering a highly efficient approach for the formation of valuable C–C and C–heteroatom bonds in both a step- and atom-economical fashion.[1] Recently, emphasis in this area has shifted towards exploiting simple and weakly coordinating functional groups as directing groups (DGs).[2] Among these, employing carboxylate groups to achieve site-selective C–H activation of benzoic acids is particularly appealing,[3] since this methodology enables the synthesis of benzolactones, key motifs of significant interest in medicinal and pharmaceutical research (Figure 1).[4] Benzoic acids are commonly utilized in building bioactive molecular structures because they are inexpensive and naturally abundant. These reactions typically proceed *via* a cascade carboxylate directed intermolecular oxidative C–H alkenylation[7,8] or alkynylation[6] followed by annulation and generally requires the presence of stoichiometric amount of oxidants. Developing robust synthetic methods for the incorporation of allyl fragments would be valuable as the allyl products can be explored for the formation of diverse organic structural frameworks. In particular, Morita-Baylis-Hillman (MBH) adducts are versatile synthetic building blocks[5] that can couple to yield allyl esters, which can be potential structural units in combination with carboxylate functional group for the construction of benzolactone frameworks.



Mellein
(antibacterial, fungicidal)

Ochratoxin A
(fungal toxin)

Cladosporin
(antibacterial, antifungal, insecticidal, and anti-inflammatory)

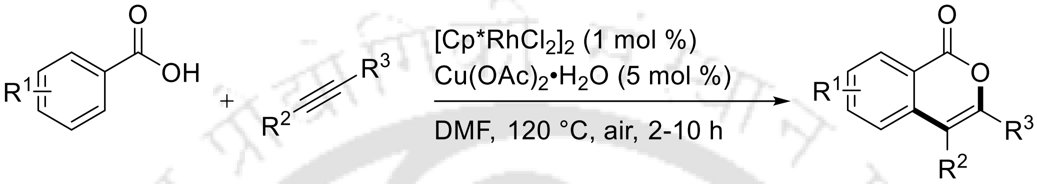
Tibetana A
(natural product)

Figure 1. Biologically Important Isochroman-1-one Moieties

2.1 Literature

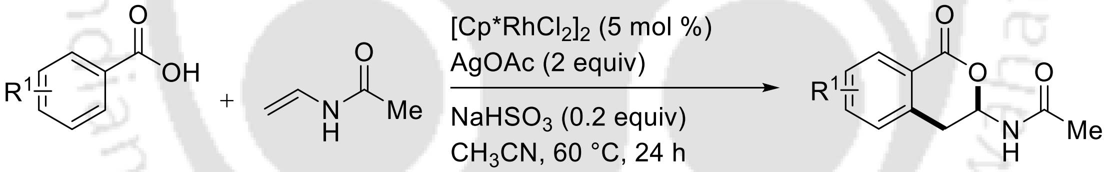
2.1.1 Carboxylate Directed C–H Functionalization and Annulation

Satoh and co-workers developed a method for the direct oxidative coupling of benzoic acids with internal alkynes *via* carboxylate-assisted C–H activation, employing [Cp*$RhCl_2$]$_2$ as the catalyst and $Cu(OAc)_2·H_2O$ as the oxidant, enabling the synthesis of 3,4-disubstituted isocoumarins (Scheme 1).[6]

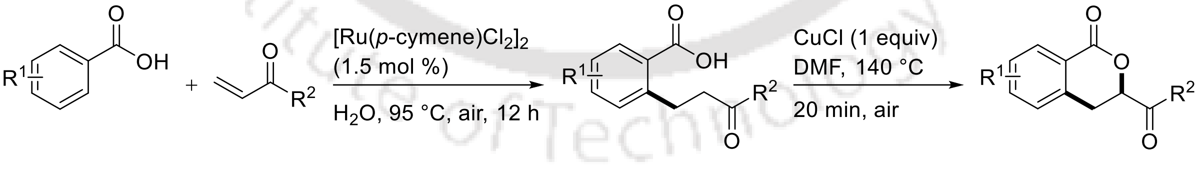


Scheme 1. Rh(III)-Catalyzed Annulation of Benzoic Acids with Internal Alkynes

Fu and co-workers described a Rh(III)-catalyzed annulation of benzoic acids with *N*-vinyl acetamide, leading to the synthesis of 3-acylamino isocoumarins (Scheme 2).[7] The reaction proceeds *via* a distinctive mechanism: it involves a sequence of *β*-hydride elimination, reductive elimination, and subsequent cyclization to deliver the final isocoumarin derivatives.

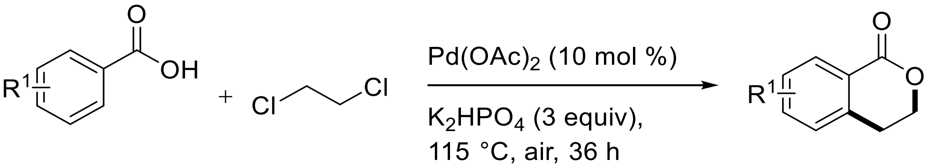


Scheme 2. Rh(III)-Catalyzed Annulation of Benzoic Acids with *N*-Vinyl Acetamide



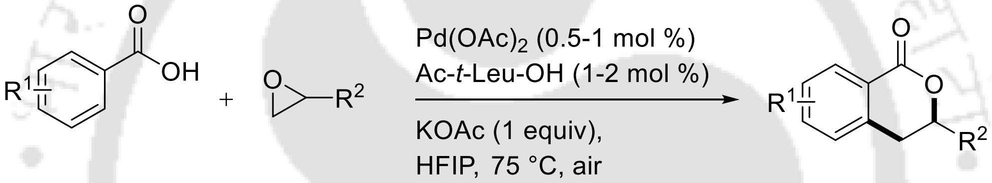
Scheme 3. Alkylation and Annulation of Benzoic Acids with *α*, *β*-Unsaturated Ketones

Shi group demonstrated a Ru(II)-catalyzed conjugate addition with *α*,*β*-unsaturated ketones, enabling the synthesis of *ortho*-alkylated benzoic acids (Scheme 3).[8] This transformation is notable for proceeding in neat water without any additives, underscoring its environmental friendliness and operational simplicity. The resulting *ortho*-alkylated benzoic acid intermediates can then undergo further conversion into 3-acyl 3,4-dihydroisocoumarin. Further, Yu group developed a Pd(II)-catalyzed methodology for the *ortho*-alkylation of benzoic acids with alkyl halides (Scheme 4).[9] The obtained alkylation product underwent an S_N2 reaction to deliver 3,4-dihydroisocoumarin.



Scheme 4. Pd(II) Catalyzed Alkylation and Annulation of Benzoic Acids with Haloalkanes

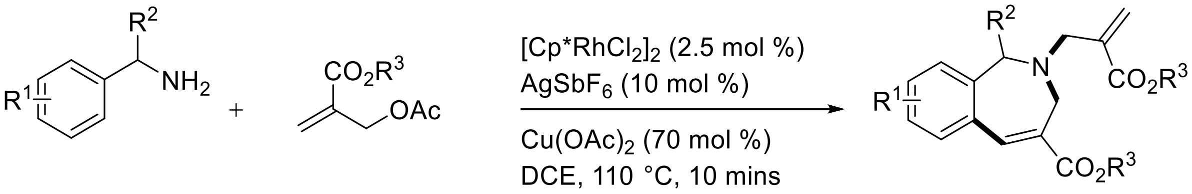
The same group demonstrated that ethylene oxide can serve as an effective coupling partner in the Pd(II)-catalyzed oxidative cyclization of benzoic acids, facilitating the synthesis of 3,4-dihydroisocoumarin derivatives (Scheme 5).[10] This transformation is significantly aided by the use of monoprotected amino acid (MPAA) ligands, which accelerate the C–H activation process and enable efficient coupling even at very low catalyst loadings.



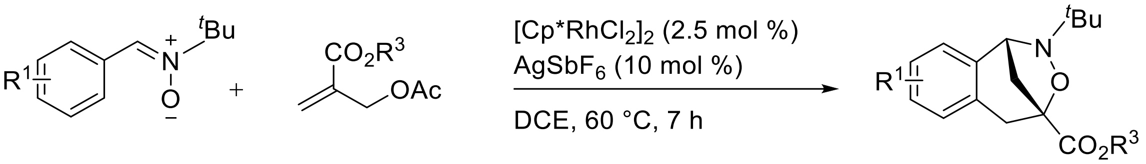
Scheme 5. Pd(II)-Catalyzed 3,4-Dihroisocoumarins Synthesis with Ethylene Oxide

2.1.2 MBH Adducts in C–H Functionalization and Annulation

Hong and co-workers reported a Rh(III)-catalyzed cross-coupling reaction between benzylamines and Morita-Baylis-Hillman (MBH) adducts to afford a variety of 2-benzazepine derivatives (Scheme 6).[11] This protocol has been applied to a wide range of substrates, and typically proceeds with excellent levels of chemoselectivity as well as with high functional group tolerance. They further disclosed the unique reactivity of MBH adducts in the C–H functionalization of (hetero)aryl nitrones under Rh(III) catalysis (Scheme 7).[12] This protocol provides a facile route for the formation of bridged benzoxazepines in moderate to high yields.

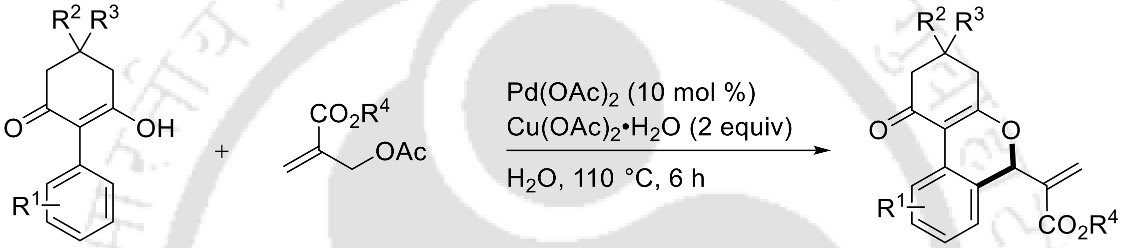


Scheme 6. Rh(III)-Catalyzed C–H Functionalization of Benzylamines with MBH Adducts



Scheme 7. Rh(III)-Catalyzed C–H Functionalization of Aryl Nitrones with MBH Adducts

Our group has reported a Pd-catalyzed site-selective C–H functionalization and annulation of 2-aryl-1,3-dicarbonyls with MBH adducts, leading to the formation of *α*-isochromenyl acrylates. This cascade reaction features the formation of both C–C and C–O bonds in a single operation, demonstrating good substrate scope, water as solvent and functional group tolerance (Scheme 8).[13]



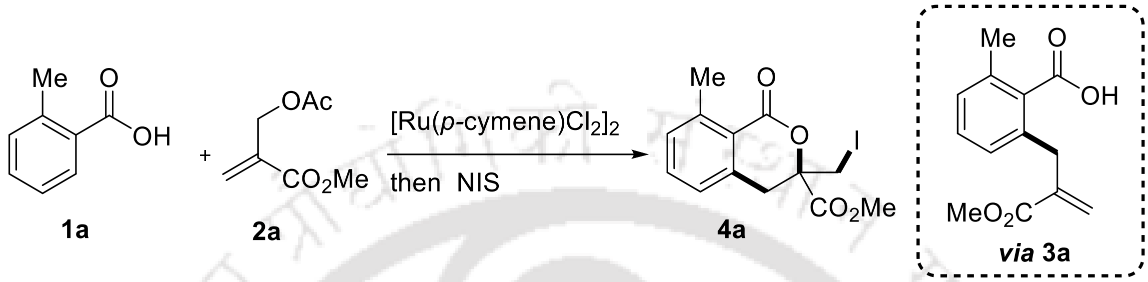
Scheme 8. C–H Functionalization/ Annulation of 2-Aryl-1,3-Dicarbonyls

2.2 Present Study

Herein, we report a redox-neutral Ru(II)-catalyzed C–H allylation followed by iodolactonization of benzoic acids with Morita-Baylis-Hillman (MBH) adducts in water,[2c] furnishing isochroman-1-ones, that are core unit of naturally occurring benzolactone scaffolds (Figure 1). In these transformations, both the carboxylic acids and MBH adducts are sparingly soluble in water, which were reacted to deliver benzolactones bearing iodo and ester functionalities. This methodology offers several notable advantages, including the use of water as the reaction medium, redox-neutral Ru-catalysis, substrate scope, scalability, functional group tolerance and applicability to the late-stage modification of natural products and drug molecules.

We optimized the reaction conditions to envision the C–H allylation and iodolactonization of **1a** and **2a** as the model substrates with [Ru(*p*-cymene)Cl_2]$_2$ as a catalyst and NIS as iodo source (Table 1). To our delight, the reaction occurred to produce isochroman-1-one **4a** in 91% yield when the substrates **1a** and **2a** were stirred with 5 mol % [Ru(*p*-cymene)Cl_2]$_2$ and 2 equiv CsOAc in water at 100 °C for 12 h followed by stirring with 2 equiv NIS for 3 h at room temperature. In a set of bases screened, NaOAc, KOAc, AgOAc and CsOAc, the latter gave the best results. Water was found to be the solvent of choice, while TFE, TCE, MeOH, HFIP and $(CH_2Cl)_2$ gave inferior yields. Lowering the reaction temperature to 80 °C or reducing the base loading to 1.5 equiv resulted in a decrease in yield. Control experiments confirmed that the combination of the Ru-catalyst and base is essential for achieving the transformation.

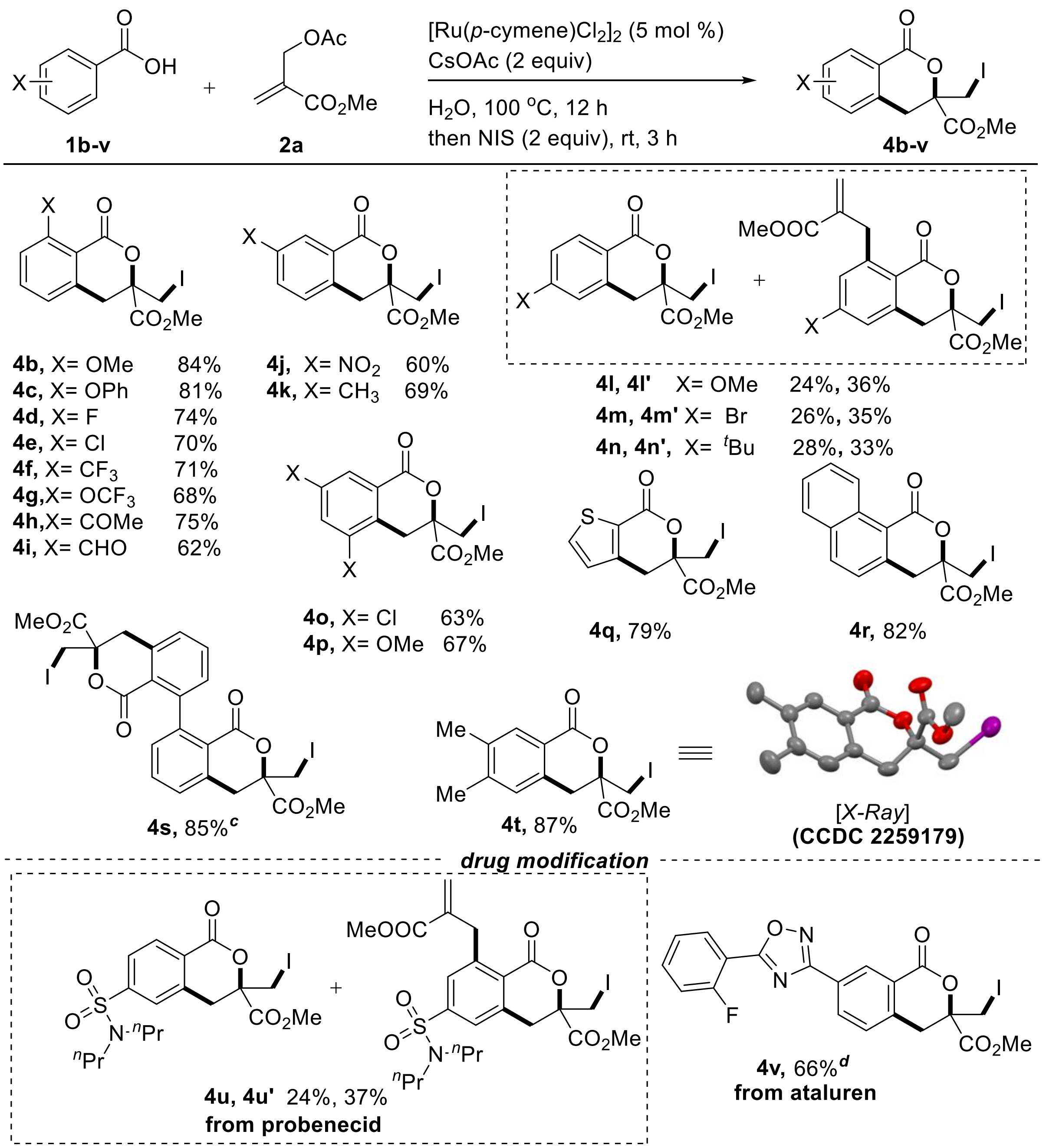
Table 1. Optimization of the Reaction Condition[a]



Entry	Base	Solvent	**4a** (Yield, %)[b]
1	NaOAc	H_2O	36
2	KOAc	H_2O	42
3	AgOAc	H_2O	30
4	**CsOAc**	**H_2O**	**91**
5	CsOAc	MeOH	45
6	CsOAc	TFE	81
7	CsOAc	TCE	56
8	CsOAc	HFIP	47
9	CsOAc	$(CH_2Cl)_2$	32
10[c]	CsOAc	H_2O	66
11[d]	CsOAc	H_2O	58
12[e]	CsOAc	H_2O	n.d.
13	-	H_2O	n.d.

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.11 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %), base (0.2 mmol), solvent (1 mL), 12 h, 100 °C; then NIS (0.2 mmol), rt, 3 h. [b]Isolated yield. [c]At 80 °C. [d]CsOAc (0.15 mmol) used. [e]In absence of Ru-catalyst. n.d. = not detected.

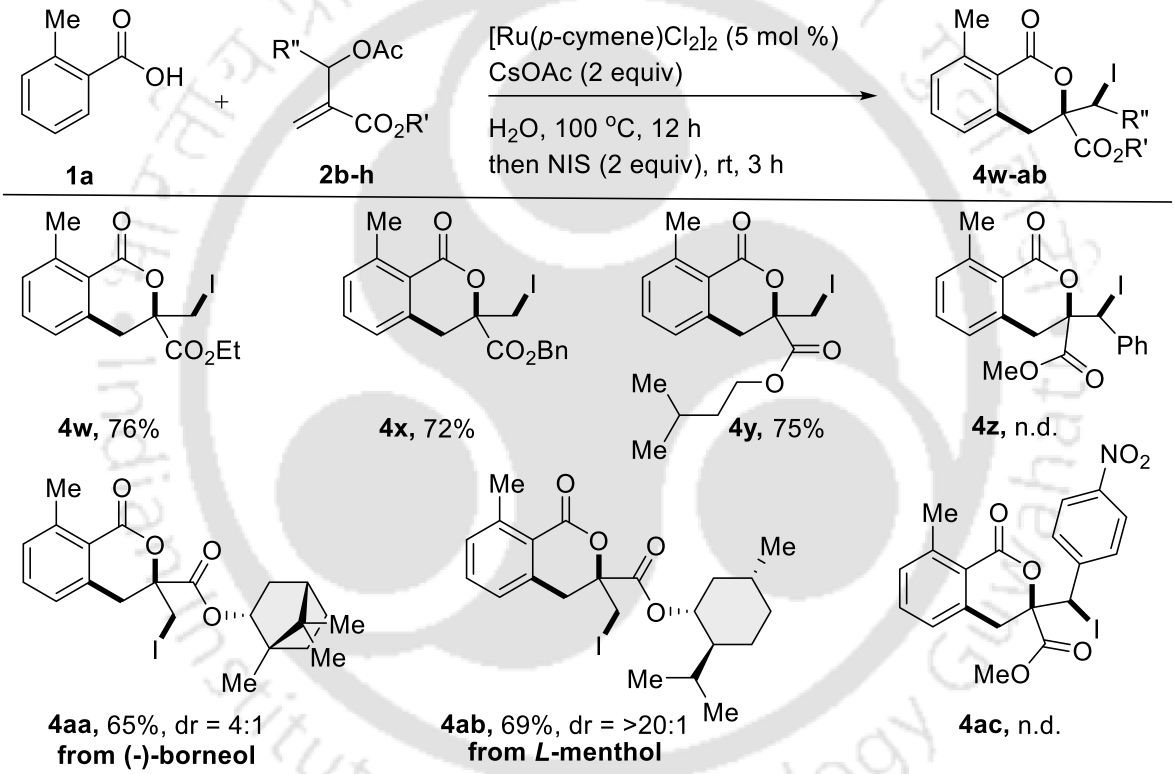
Table 2. Substrate Scope of Carboxylic Acids[a,b]



[a]Reaction conditions: **1 b-v** (0.1 mmol), **2a** (0.11 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %), CsOAc (0.2 mmol), H_2O (1 mL), 100 °C, 12 h, then NIS (0.2 mmol), rt, 3 h. [b]Isolated yield. [c]**2a** (0.22mmol) used. [d]H_2O/TFE (1:1).

Having optimized the reaction conditions, the substrate scope was explored by coupling a series of substituted carboxylic acids **1b-v** with MBH adduct **2a** as the standard coupling partner (Table 2). Substrates bearing substitution at 2-position of the aryl ring with methoxy **1b**, phenoxy **1c**, fluoro **1d**, chloro **1e**, trifluoromethyl **1f**, trifluoromethoxy **1g**, acetyl **1h** and formyl **1i** groups reacted to give benzolactones **4b-i** in 62-84% yields. Similar results were observed with carboxylic acids having substitution at the 3-position of the aryl ring with nitro **1j** and methyl **1k** groups, giving **4j** and **4k** in 60% and 69% yields, respectively. In case of the carboxylic acids having substitution at the 4-position of the aryl ring with methoxy **1l**, bromo

Table 3. Substrate Scope of MBH Adducts[a,b]

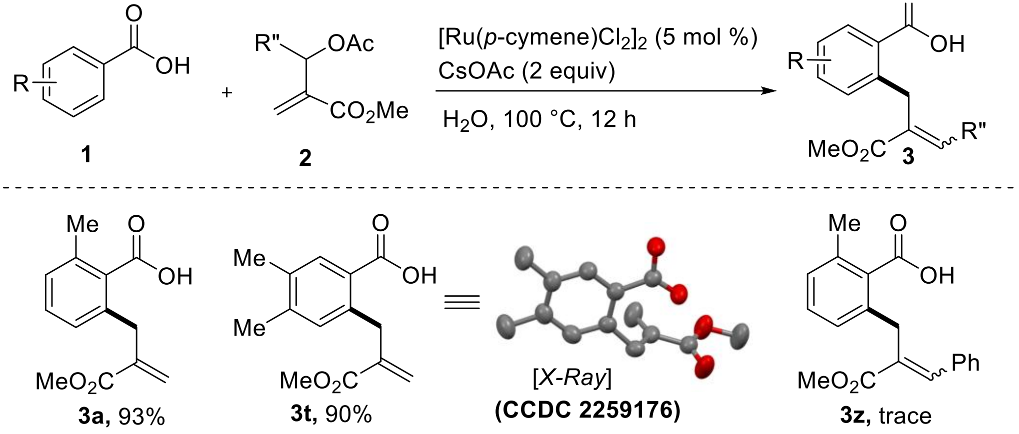


[a]Reaction conditions: **1a** (0.1 mmol), **2b-h** (0.11 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %), CsOAc (0.2 mmol), H_2O (1 mL), 100 °C, 12 h, then NIS (0.2 mmol), rt, 3 h. [b]Isolated yield.

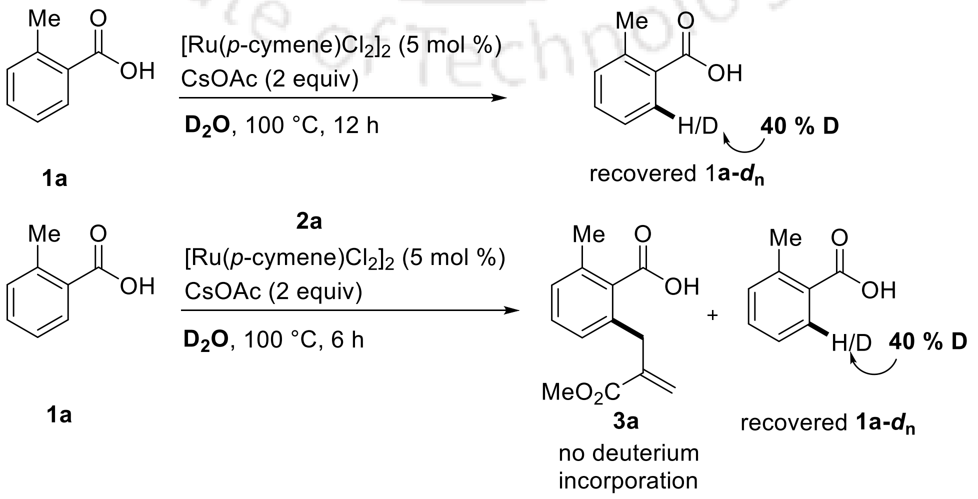
1m and *tert*-butyl **1n** groups, a separable mixture of mono and diallylated products **4l-l′**, **4m-m′** and **4n-n′** were formed. However, the carboxylic acids with 3,5-dichloro **1o** and 3,5-dimethoxy **1p** groups at the aryl ring furnished benzolactones **4o** and **4p** in 63% and 67% yields, respectively. Further, thiophene-2-carboxylic acid **1q** and *α*-naphthoic acid **1r** reacted to provide **4q** and **4r** in 79 and 82% yields, respectively, whereas diphenic acid **1s** underwent reaction with 2.2 equiv of MBH adduct to give **4s** in 85% yield. Moreover, the reaction of the carboxylic acid bearing 3,4-dimethyl groups in the aryl ring **1t** afforded **4t** in 87% yield, whose structure was determined by *X*-ray analysis (CCDC 2259179). In addition, drug molecule like probenecid **1u** underwent reaction to give a separable mixture of mono- and di-substituted benzolactones **4u** and **4u′**, whereas the reaction of ataluren **1v**, used for the treatment of muscular dystrophy, furnished **4v** in 66% yield.

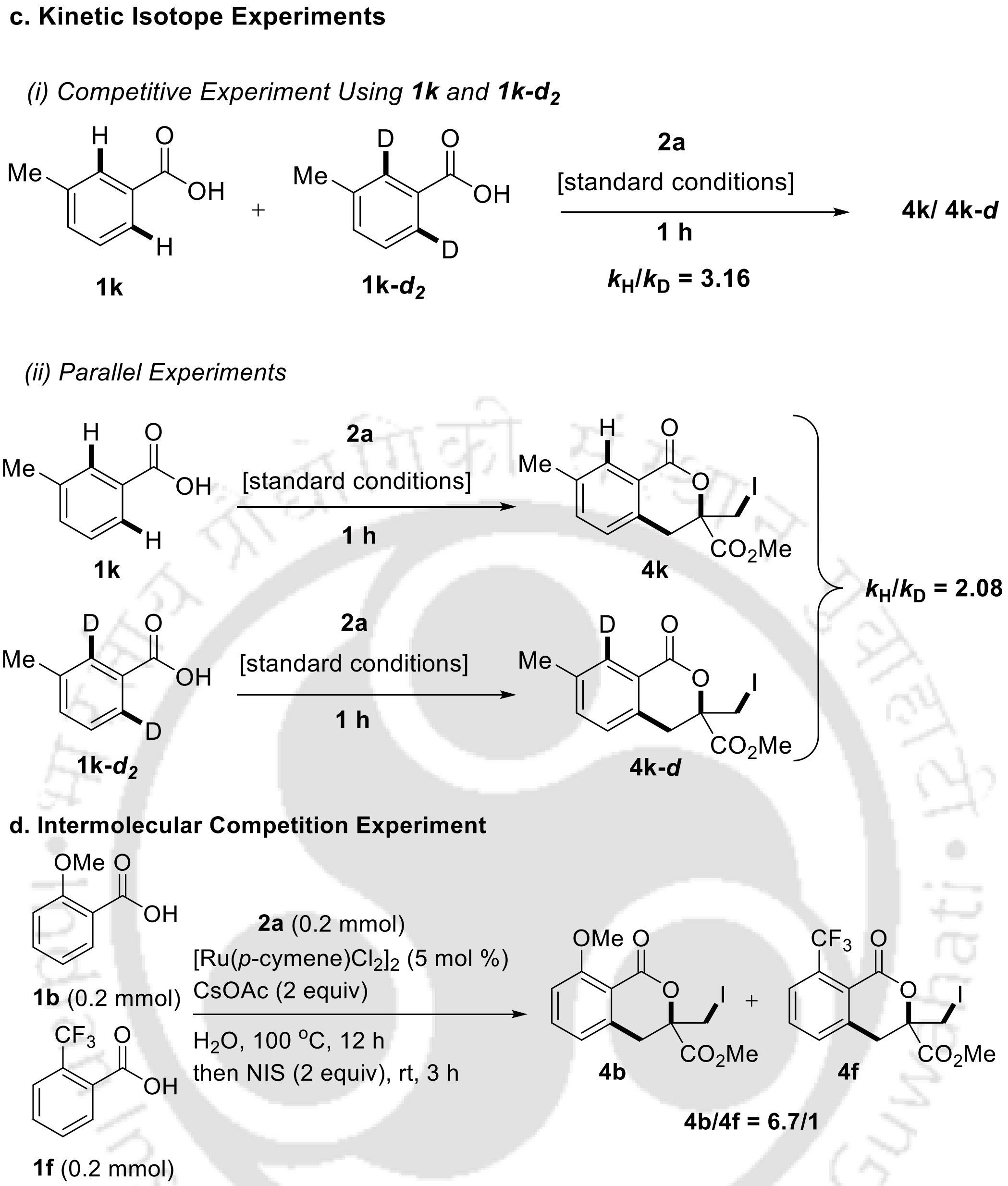
The scope of the procedure was extended to the coupling of a series of MBH adducts **2b-h** with **1a** as the standard substrate (Table 3). The reaction of the MBH adducts tethered with ethyl **2b** and benzyl **2c** groups afforded **4w** and **4x** in 76% and 72% yields, respectively. In addition, the substrate tethered with isoamyl **2d** reacted to give **4y** in 75% yield, whereas phenyl-substituted **2e** and *p*-nitro phenyl substituted **2h** were unsuccessful substrates, which may be due to the steric hindrance. In addition, the reaction of the MBH adducts tethered with (-)-borneol **2f** and *L*-menthol **2g** delivered **4aa** and **4ab** in 65% and 69% yields, respectively. These results suggest that the methodology is applicable for the lactonization of a wide range of (hetero)aromatic carboxylic acids and MBH adducts.

a. Isolation of Allylated Intermediates



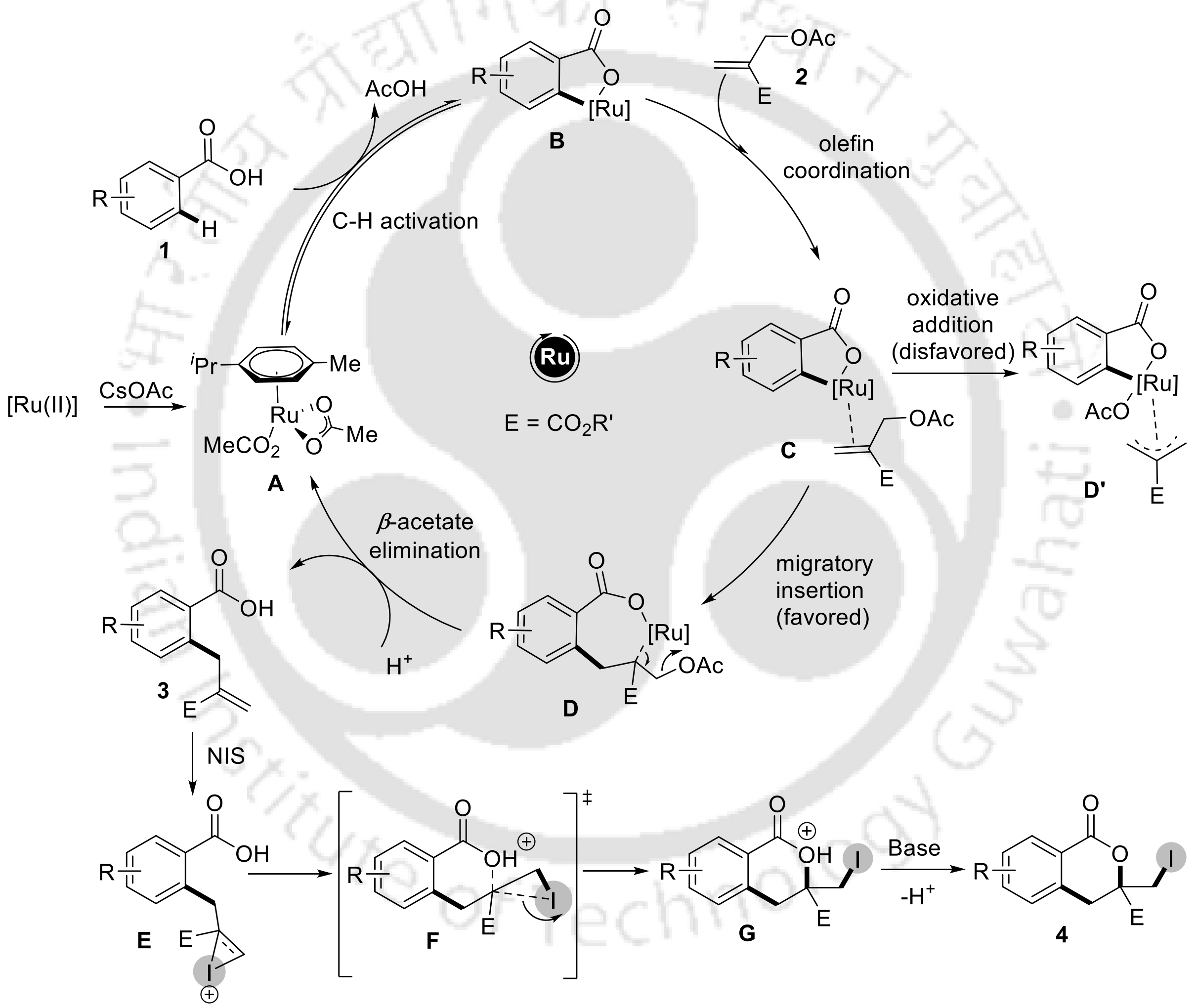
b. H/D Exchange Experiments





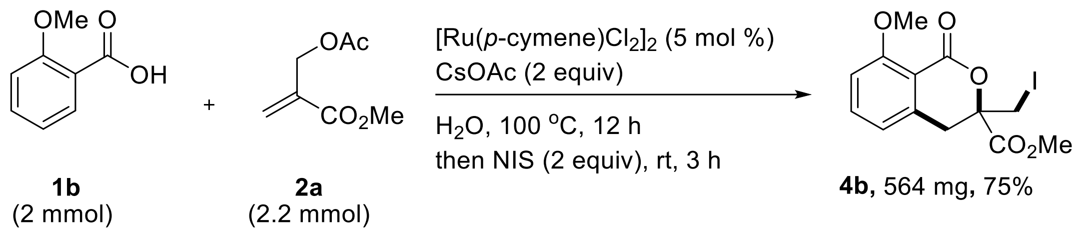
Scheme 9. Preliminary Mechanistic Investigation

To gain insight into the reaction pathway, the allylation was examined in the absence of NIS (Scheme 9a). For example, carboxylic acids **1a** and **1t** reacted with **2a** to produce **3a** and **3t** in 93% and 90% yields, respectively. The structure of the latter was determined using the single crystal *X*-ray analysis (CCDC 2259176), whereas the phenyl-substituted MBH adduct **2e** was less reactive, affording **3z** in only trace amount, which may be due to the steric hindrance. Further, H/D exchange experiments were performed using D_2O as the solvent in the absence and presence of **2a**. A 40% deuterium incorporation at the *ortho*-position of the recovered **1a** was observed (Scheme 9b), indicating that the C–H activation step might be reversible. In contrast, in the H/D exchange experiment conducted in the presence of **2a**, no deuterium incorporation was detected at the allyl residue of **3a**, thereby ruling out the involvement of a π-allyl Ru-complex. Further, intermolecular kinetic isotope effect studies using **1k** and **1k**-d_2 with **2a** revealed $k_H/k_D = 2.08$ (parallel) and $k_H/k_D = 3.16$ (competitive) (Scheme 9c), suggesting that C–H bond cleavage is likely involved in the rate-determining step. Additionally, intermolecular competitive experiment between benzoic acids bearing electron donating 2-methoxy **1b** and electron withdrawing 2-trifluoromethyl **1f** generated **4b** and **4f** in a ratio of 6.7/1, determined by ^{1}H-NMR (Scheme 9d). This result highlights the pronounced influence of electronic effects of benzoic acids.

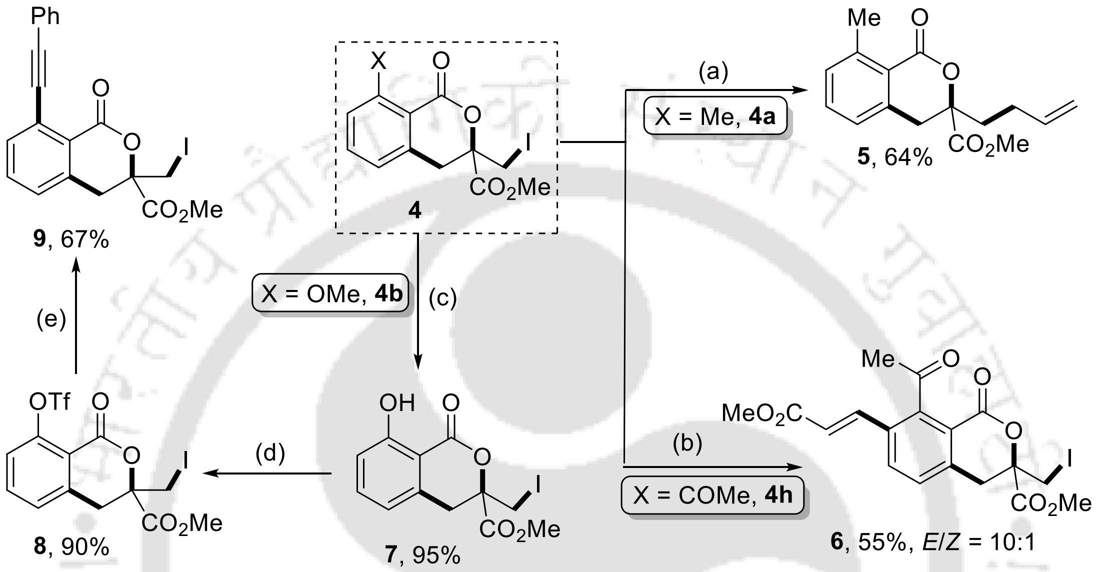


Scheme 10. Plausible Reaction Pathway

Based on these experimental observations and literature precedents,[14] a plausible mechanism is proposed in Scheme 10. The Ru-complex with CsOAc can form active Ru(II) species **A**, which can lead to the carboxylate directed site-selective C–H activation to afford ruthenacycle **B**. Subsequent chelation with the double bond of the MBH adduct affords **C**,



Scheme 11. Scale-up Synthesis



[a]Reaction conditions: (a) **4a** (0.1 mmol), allylSnBu$_3$ (0.4 mmol), AIBN (10 mol %), toluene (1 mL), 80 °C, 4 h. (b) **4h** (0.1 mmol), methyl acrylate (0.12 mmol), [Ru(*p*-cymene)Cl$_2$]$_2$ (5 mol %), AgSbF$_6$ (0.02 mmol), Cu(OAc)$_2$·H$_2$O (0.1 mmol), (CH$_2$Cl)$_2$ (2 mL), 100 °C, air, 8 h. (c) **4b** (0.1 mmol), BCl$_3$ in 1 M CH$_2$Cl$_2$ (0.2 mmol), CH$_2$Cl$_2$ (0.5 mL), -78 °C– 0 °C , 1.5 h. (d) **7** (0.1 mmol), Tf$_2$O (0.15 mmol), Et$_3$N (0.15 mmol), CH$_2$Cl$_2$ (1.5 mL), -78 °C– rt, N$_2$, 2 h. (e) **8** (0.05 mmol), phenyl acetylene (0.15 mmol), [Pd(PPh$_3$)$_2$Cl$_2$] (10 mol %), CuBr (5 mol %), DIPEA (0.15 mmol), DMF (1 mL), 80 °C, N$_2$, 4 h.

Scheme 12. Post-Synthetic Transformations

which undergoes migratory insertion to form **D**. Intramolecular *β*-acetate elimination then furnishes the carboxylic acids **3,** accompanied by regeneration of the catalyst **A**. The allylic double bond with NIS can yield the iodonium ion **E**, which can undergo intramolecular carboxylation to furnish **G** *via* **F**. Deprotonation of **G** can produce the iodolactones **4**. Alternatively, the allylation may proceed via the oxidative addition of the allyl electrophile, which would generate a π-allyl Ru-complex **D′**. However, this pathway is less likely, as supported by the H/D exchange experiments with **2a** (Scheme 9b).

To reveal the scalability, the reaction of **1b** with **2a** was investigated as the representative substrates (Scheme 11). The reaction afforded **4b** in 75% (564 mg) yield. In addition, the allylation of **4a** with allylSnBu$_3$ furnished **5** in 64% yield (Scheme 12a), whereas the Ru-catalyzed iterative-alkenylation of **4h** with methyl acrylate delivered **6** in 55% yield (Scheme 12b). Further, the demethylation of **4b** with BCl$_3$ in 1M CH$_2$Cl$_2$ afforded 8-hydroxy isochroman-1-one **7** (Scheme 12c). Moreover, the isochroman-1-one **7** was converted to **8** (Scheme 12d) that was subjected to Sonogashira coupling with phenylacetylene to give C–C coupled **9** in 67% yield (Scheme 12e).

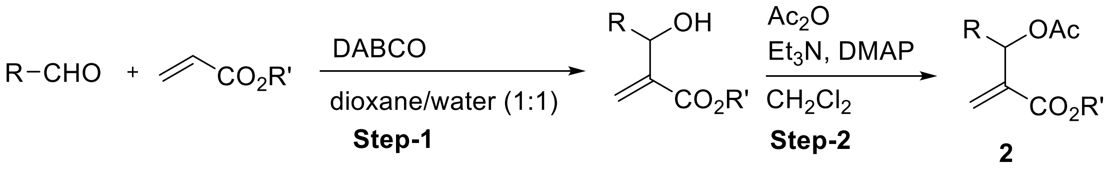
In summary, we have developed a cascade Ru-catalyzed, weak carboxylate-directed C–H allylation followed by iodolactonization of benzoic acids, employing readily accessible MBH adducts as versatile coupling partners in water. The methodology features practical advantages, including the use of water as solvent, substrate scope, excellent functional group tolerance, redox-neutral Ru catalysis, and successful application to the modification of natural products and drug molecules.

2.3 Experimental Section

General Information. [Ru(*p*-cymene)Cl$_2$]$_2$ (97%), NaOAc (98%), KOAc (98%), CsOAc (98%), AgOAc (≥99.99%) 2,2,2-trifluoroethanol, 2,2,2-trichloroethanol, 1,1,1,3,3,3-hexafluoroisopropanol, *N*-iodosuccinimide and carboxylic acids of Aldrich and TCI chemicals were used as received. MeOH, CH$_2$Cl$_2$ and (CH$_2$Cl)$_2$ 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 EtOAc 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 (^{1}H, ^{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/K*α* radiation and the structure was solved by direct method using SHELXL-16 (Göttingen, Germany).

General Procedure for the Preparation of MBH adducts 2.



Step-1: To a stirred solution of aldehyde (2 mmol) in dioxane/water (1:1) (5 mL), acrylate (6 mmol) and DABCO (2 mmol) was added at room temperature. After completion (monitored by TLC), the reaction mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layer was washed with brine (1 x 10 mL) and water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford the MBH product.

Step 2: To a stirred solution of the MBH product (1 mmol) and Ac_2O (1 mmol) in CH_2Cl_2 (5 mL), DMAP (0.1 mmol) and Et_3N (1 mmol) were added and the resultant mixture was stirred at room temperature for 2 h. After completion (monitored by TLC), the reaction mixture was poured into an aqueous 2M HCl and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure to give the residue that was purified by silica gel column chromatography using n-hexane and EtOAc as an eluent to afford the MBH acetate **2**.

General Procedure for the Carboxylate Directed Cascade *sp*^{2} C−H Allylation and Iodolactonization. Carboxylic acid **1** (0.2 mmol), MBH adduct **2** (0.22 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %, 0.01 mmol, 6 mg) and CsOAc (0.4 mmol, 77 mg) were stirred in H_2O (1 mL) at 100 °C (in a pre-heated oil bath) for 12 h. The reaction mixture was cooled to room temperature, *N*-iodosuccinimide (0.4 mmol, 90 mg) was added to the reaction mixture and the stirring continued at room temperature for 3 h. After completion, (monitored by TLC), the reaction mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layer was washed with saturated $Na_2S_2O_3{\cdot}5H_2O$ (1 x 10 mL) and water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford **4a** in 91% yield.

Scale-up Synthesis of 4b. Carboxylic acid **1b** (2 mmol, 752 mg), MBH adduct **2a** (2.2 mmol, 348 mg), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %, 0.1 mmol, 61 mg), CsOAc (4 mmol, 768 mg) were stirred in H_2O (10 mL) at 100 °C in a pre-heated oil bath for 12 h. The reaction mixture was cooled to room temperature, *N*-iodosuccinimide (4 mmol, 900 mg) was added and the stirring was continued for 3 h. After completion (monitored by TLC), the reaction mixture was extracted with EtOAc (3 x 20 mL) and the combined organic layer was washed with saturated $Na_2S_2O_3 \cdot 5H_2O$ (1 x 10 mL) and water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using n-hexane and EtOAc as an eluent to afford **4b** in 75% (564 mg) yield.

Post-synthetic Transformations

Synthesis of 5. Methyl 3-(iodomethyl)-8-methyl-1-oxoisochromane-3-carboxylate **4a** (0.15 mmol, 54 mg), allylSnBu_3 (0.60 mmol, 186 µL) and AIBN (0.01 mmol, 2.4 mg) were stirred in toluene at 80 °C for 4 h under nitrogen atmosphere. After completion (monitored by TLC), the reaction mixture was cooled to room temperature and was filtered through a short pad of silica. The solvent was removed under reduced pressure to give a residue that was purified by silica gel column chromatography using n-hexane and EtOAc as an eluent to afford **5** in 64% yield

Synthesis of 6. Methyl 8-acetyl-3-(iodomethyl)-1-oxoisochromane-3-carboxylate **4h** (0.1 mmol, 39 mg), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %, 0.01 mmol, 3 mg), $AgSbF_6$ (10 mol %, 0.02 mmol, 6.8 mg), $Cu(OAc)_2 \cdot H_2O$ (0.1 mmol, 20 mg) and methyl acrylate (0.12 mmol, 10.3 mg) were stirred in $(CH_2Cl)_2$ (2 mL) at 100 °C in a sealed tube for 12 h. After completion (monitored by TLC), the reaction mixture was cooled to room temperature and diluted with CH_2Cl_2 (10 mL) and passed through a short pad of celite. The solvent was removed under reduced pressure to provide a residue that was purified by silica gel column chromatography using n-hexane and EtOAc as an eluent to afford **6** in 55% yield.

Synthesis of 7. To a stirred solution of methyl 3-(iodomethyl)-8-methoxy-1-oxoisochromane-3-carboxylate **4b** (0.1 mmol, 40 mg) in CH_2Cl_2 (0.5 mL), BCl_3 (1 M in CH_2Cl_2, 0.2 mL) was added dropwise at -78 °C. After stirring for 1.5 h at 0 °C, the reaction was quenched with aqueous NH_4Cl and extracted with CH_2Cl_2 (3 x 10 mL). The organic phase was washed with brine (1 x 10 mL) and water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent yielded a residue that was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford **7** in 95% yield.

Synthesis of 8. To a stirred solution of methyl 8-hydroxy-3-(iodomethyl)-1-oxoisochromane-3-carboxylate **7** (0.1 mmol, 38 mg,) and Et_3N (0.15 mmol, 15.2 mg,) in CH_2Cl_2 (1.5 mL), triflic anhydride (0.15 mmol, 25 µL) was added dropwise at -78 °C. The reaction mixture was stirred at room temperature for 2 h. The resultant mixture was diluted with EtOAc (5 mL) and treated 10% aqueous HCl. The organic phase was washed with aqueous $NaHCO_3$ (1 x 5 mL), brine (1 x 5 mL) and water (1 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent produced a residue that was purified by silica gel column chromatography using n-hexane and EtOAc as an eluent to afford **8** in 90% yield.

Synthesis of 9. To stirred a solution of methyl 3-(iodomethyl)-1-oxo-8-(((trifluoromethyl)-sulfonyl)oxy)isochromane-3-carboxylate **8** (0.05 mmol, 25 mg) and phenylacetylene (0.15 mmol, 15.3 mg) in DMF (1 mL), $Pd(PPh_3)_2Cl_2$ (10 mol %, 0.005 mmol, 3.5 mg), CuBr (5 mol %, 0.0025 mmol, 0.36 mg) and DIPEA (0.15 mmol, 19.4 mg) were added. The reaction mixture was stirred at 80 °C for 4 h under nitrogen atmosphere. After completion (monitored by TLC), the reaction mixture was cooled to room temperature and diluted with EtOAc (10 mL). The organic phase was washed with brine (1 x 10 mL) and water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford **9** in 67 % yield.

Mechanistic Investigations

Preparation of Allylated Intermediate 3. Carboxylic acid **1** (0.2 mmol), MBH adduct **2** (0.22 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %, 0.01 mmol, 6 mg) and CsOAc (0.4 mmol, 77 mg) were stirred in H_2O (1 mL) at 100 °C in a pre-heated oil bath for 12 h. After completion (monitored by TLC), the reaction mixture was cooled to room temperature and extracted with EtOAc (2 x 10 mL) and the combined organic layer was washed with brine (1 x 10 mL) and water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford **3**.

H/D Exchange Experiment of 1a with D_2O in Absence of 2a. 2-Methylbenzoic acid **1a** (0.2 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %, 0.01 mmol, 6 mg) and CsOAc (0.4 mmol, 77 mg) were stirred in D_2O (1 mL) at 100 °C in a pre-heated oil bath for 12 h. The reaction mixture was cooled to room temperature and extracted with EtOAc (2 x 10 mL) and the combined organic layer was washed with brine (1 x 10 mL) and water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford **1a-*d*n**. The deuterium incorporation was calculated as 40% at C2-H of **1a-*d*n** based on 400 MHz ^{1}H NMR spectrum.

H/D Exchange Experiment of 1a with D_2O in Presence of 2a. 2-Methylbenzoic acid **1a** (0.2 mmol), methyl 2-(acetoxymethyl)acrylate **2a** (0.22 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %, 0.01 mmol, 6 mg) and CsOAc (0.4 mmol, 77 mg) were stirred in D_2O (1 mL) at 100 °C in a pre-heated oil bath for 6 h. The reaction mixture was cooled to room temperature and extracted with EtOAc (2 x 10 mL) and the combined organic layer was washed with brine (1 x 10 mL) and water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford **3a** and recovered **1a-*d*n**. The deuterium incorporation was calculated as 40% in **1a-*d*n** and no deuterium incorporation in the allylated product **3a** was observed from 400 MHz ^{1}H NMR spectrum.

Preparation of 3-Methylbenzoic–2,6-*d*$_2$ acid 1k-*d*$_2$.[15] 3-Methylbenzoic acid **1k** (0.50 mmol, 68 mg), [Ru(O_2CAd)$_2$(*p*-cymene)] (5 mol %, 14.9 mg) and D_2O (5 mmol, 90 μL) were stirred in 1,4-dioxane (1 mL) 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 and all the volatiles were removed under reduced pressure and the residue was purified using silica gel column chromatography with n-hexane and EtOAc as an eluent to afford **1k-*d*$_2$** [91% D].

Kinetic Isotope Effect Experiments

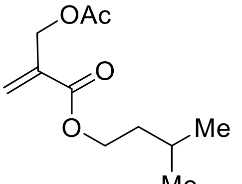
Parallel. 3-Methylbenzoic acid (**1k** or **1k-*d*$_2$**, 0.2 mmol), methyl 2-(acetoxymethyl)acrylate **2a** (0.22 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %, 0.01 mmol, 6 mg) and CsOAc (0.4 mmol, 77 mg) were stirred in H_2O (1 mL) at 100 °C for 1 h. The reaction mixture was cooled to room temperature, *N*-Iodosuccinimide (NIS) (0.4 mmol, 90 mg) was added and the stirring was continued for an additional 1 h at room temperature. The reaction mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layer was washed with saturated $Na_2S_2O_3 \cdot 5H_2O$ (1 x 10 mL) and water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue whose 400 MHz ^{1}H NMR recorded in $CDCl_3$ (1 mL) using $(CH_2Cl)_2$ (0.2 mmol, 16 μL) as internal standard gave the yields of **4k** and **4k-*d*** as 48% and 23% respectively, resulting in a k_H/k_D of 2.08.

Competitive. 3-Methylbenzoic acid **1k** (0.20 mmol, 27.2 mg) and 3-methylbenzoiC–2,6-*d*$_2$ acid **1k-*d*$_2$** (0.20 mmol, 27.6 mg) [91% D], methyl 2-(acetoxymethyl)acrylate **2a** (0.22 mmol), [Ru(*p*-cymene)Cl$_2$]$_2$ (5 mol %, 0.01 mmol, 6 mg) and CsOAc (0.4 mmol, 77 mg) were stirred in H_2O (2 mL) at 100 °C for 1 h. The reaction mixture was cooled to room temperature, then *N*-iodosuccinimide (NIS) (0.4 mmol, 90 mg) was added and stirring was continued for an additional 1 h at room temperature. The reaction mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layer was washed with saturated $Na_2S_2O_3 \cdot 5H_2O$ (1 x 10 mL) and water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue **4k/4k-*d*** whose 400 MHz ^{1}H NMR was measured in $CDCl_3$ with $(CH_2Cl)_2$ (0.20 mmol, 16 µL,) as an internal standard. The k_H/k_D was found to be 3.16.

Intermolecular Competition Experiment between Benzoic acids 1b and 1f. Carboxylic acid **1b** (0.2 mmol, 30.4 mg), **1f** (0.2 mmol, 38 mg) and MBH adduct **2a** (0.22 mmol, 31.6 mg), [Ru(*p*-cymene)Cl$_2$]$_2$ (5 mol %, 0.01 mmol, 6 mg), CsOAc (0.4 mmol, 77 mg) were stirred in H_2O (1 mL) at 100 °C in a pre-heated oil bath for 12 h. The reaction mixture was cooled to room temperature, *N*-iodosuccinimide (0.4 mmol, 90 mg) was added and the stirring was continued for 3 h. The reaction mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layer was washed with saturated $Na_2S_2O_3 \cdot 5H_2O$ (1 x 10 mL) and water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a mixture of **4b** and **4f** in 6.7:1, calculated from 400 MHz ^{1}H NMR spectroscopy.

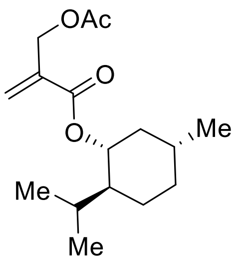
2.4 Characterization data

Characterization Data of Newly Synthesized MBH adducts



2d

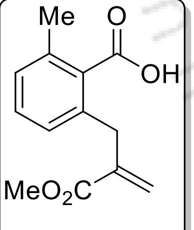
Isopentyl 2-(acetoxymethyl)acrylate 2d. Analytical TLC on silica gel, 1:20 EtOAc/hexane R_f = 0.47; colorless liquid; yield 81% (173 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.34 (s, 1H), 5.81 (s, 1H), 4.79 (s, 2H), 4.20 (t, *J* = 7 Hz, 2H), 2.09 (s, 3H), 1.73-1.66 (m, 1H), 1.57 (q, *J* = 6.5 Hz, 2H), 0.92 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 165.4, 135.7, 127.4, 63.8, 62.6, 37.4, 25.2, 22.6, 21.0; FT-IR (KBr) 1720, 1640, 1369, 1309, 1273, 1227, 1198, 1153, 1049, 990, 833 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{11}H_{18}O_4Na$ 237.1097; Found 237.1094.



2g

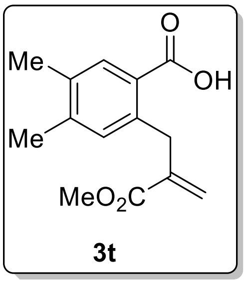
(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 2-(acetoxymethyl)-acrylate 2g. Analytical TLC on silica gel, 1:20 EtOAc/hexane $R_f = 0.41$; colorless liquid; yield 79% (223 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.33 (s, 1H), 5.80 (s, 1H), 4.83-4.75 (m, 3H), 2.09 (s, 3H), 2.04-2.00 (m, 1H), 1.89-1.83 (m, 1H), 1.71-1.67 (m, 2H), 1.54-1.47 (m, 1H), 1.46-1.40 (m, 1H), 1.12-0.97 (m, 2H), 0.91-0.87 (m, 7H), 0.76 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 164.9, 136.0, 127.2, 75.1, 62.8, 47.2, 40.9, 34.3, 31.5, 26.5, 23.6, 22.1, 21.0, 20.9, 16.5; FT-IR (KBr) 1732, 1641, 1469, 1273, 1227, 1197, 1153, 1049, 1011, 834 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{16}H_{27}O_4$ 283.1904; Found 283.1909.

Characterization Data of the Products

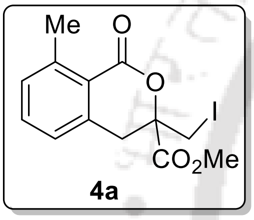


3a

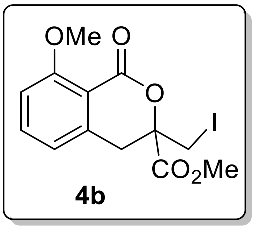
2-(2-(Methoxycarbonyl)allyl)-6-methylbenzoic acid 3a. Analytical TLC on silica gel, 3:7 EtOAc/hexane $R_f = 0.34$; colorless liquid; yield 93% (44 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.24 (m, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 1H), 6.29 (s, 1H), 5.55 (s, 1H), 3.76 (s, 2H), 3.73 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.6, 167.9, 139.0, 136.1, 135.7, 133.2, 130.0, 129.0, 127.7, 127.5, 52.4, 35.9, 20.4.; FT-IR (KBr) 2954, 1694, 1631, 1594, 1438, 1256, 1207, 1137, 1072, cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{13}H_{14}O_4Na$ 257.0784; Found 257.0784.


3t

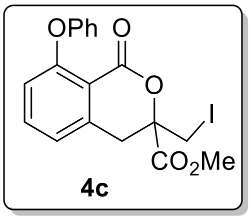
2-(2-(Methoxycarbonyl)allyl)-4,5-dimethylbenzoic acid 3t. Analytical TLC on silica gel, 3:7 EtOAc/hexane $R_f = 0.28$; colorless solid; mp 118-119 ºC; yield 90% (45 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.01 (s, 1H), 6.20 (s, 1H), 5.26 (s, 1H), 4.00 (s, 2H), 3.77 (s, 3H), 2.28 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.5, 167.9, 142.6, 140.3, 138.5, 135.3, 133.1, 133.0, 126.2, 126.0, 52.2, 35.7, 20.0, 19.4; FT-IR (KBr) 2951, 1721, 1687, 1632, 1562, 1504, 1439, 1271, 1198, 1138 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{16}O_4Na$ 271.0941; Found 271.0945.


4a

Methyl 3-(iodomethyl)-8-methyl-1-oxoisochromane-3-carboxylate 4a. Analytical TLC on silica gel, 2:8 EtOAc/hexane $R_f = 0.35$; colorless solid; mp 118-119 ºC; yield 91% (65.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (t, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 3.67 (d, *J* = 10.8 Hz, 1H), 3.64 (s, 3H), 3.58 (d, *J* = 10.4 Hz, 1H), 3.44-3.34 (m, 2H), 2.68 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.2, 162.7, 143.3, 136.3, 133.4, 131.9, 125.6, 123.0, 82.2, 53.6, 37.1, 22.4, 7.7; FT-IR (KBr) 2962, 1735, 1596, 1471, 1435, 1202, 1135, 1102, 1058 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{14}IO_4$ 360.9931; Found 360.9931.

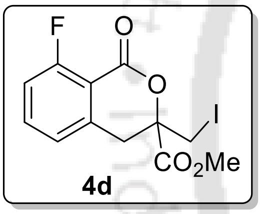

4b

Methyl 3-(iodomethyl)-8-methoxy-1-oxoisochromane-3-carboxylate 4b. Analytical TLC on silica gel, 3:7 EtOAc/hexane $R_f = 0.38$; colorless solid; mp 128-129 ºC; yield 84% (63 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 (t, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 9.0 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 3.94 (s, 3H), 3.66-3.64 (m, 4H), 3.59 (d, *J* = 10.8 Hz, 1H), 3.41-3.35 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.1, 161.3, 160.0, 138.2, 135.3, 119.6, 112.8, 111.8, 82.0, 56.4, 53.5, 36.9, 7.5; FT-IR (KBr) 2920, 1738, 1598, 1477, 1438, 1282, 1252, 1204, 1135, 1053 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{13}H_{13}IO_5Na$ 398.9700 Found 398.9703.



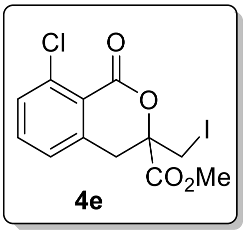
4c

Methyl 3-(iodomethyl)-1-oxo-8-phenoxyisochromane-3-carboxylate 4c. Analytical TLC on silica gel, 3:7 EtOAc/hexane R_f = 0.40; colorless solid; mp 120-121 °C; yield 81% (71 mg); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.41 (t, *J* = 7.5 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 7.5 Hz, 2H), 6.94 (d, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 1H), 3.69-3.67 (m, 4H), 3.60 (d, *J* = 11 Hz, 1H), 3.44 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 169.1, 159.3, 159.0, 156.6, 138.1, 135.0, 129.9, 124.1, 122.3, 119.6, 119.5, 115.6, 82.2, 53.6, 36.9, 7.5; FT-IR (KBr) 2917, 1743, 1602, 1580, 1465, 1258, 1204, 1136, 1091, 1044, 1002 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{18}H_{16}IO_5$ 439.0037; Found 439.0039.



4d

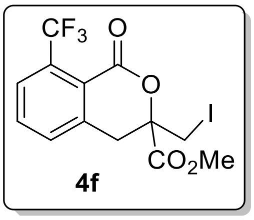
Methyl 8-fluoro-3-(iodomethyl)-1-oxoisochromane-3-carboxylate 4d. Analytical TLC on silica gel, 3:7 EtOAc/hexane R_f = 0.42; colorless solid; mp 131-132 °C; yield 74% (54 mg); ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.54-7.50 (m, 1H), 7.11 (t, *J* = 9.6 Hz, 1H), 7.03 (d, *J* = 7.8 Hz, 1H), 3.70-3.68 (m, 4H), 3.61 (d, *J* = 10.8 Hz, 1H), 3.46-3.40 (m, 2H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 168.8, 163.8 ($J_{C–F}$ = 265.3 Hz), 158.8 ($J_{C–F}$ = 4.7 Hz), 138.0, 135.9 ($J_{C–F}$ = 9.9 Hz), 123.5 ($J_{C–F}$ = 3.9 Hz), 117.1 ($J_{C–F}$ = 21.3 Hz), 113.0 ($J_{C–F}$ = 7.3 Hz), 82.6, 53.8, 36.4, 7.3; ^{19}F NMR (470 MHz, CDCl$_3$) δ -107.62; FT-IR (KBr) 2959, 1748, 1615, 1472, 1267, 1207, 1089, 1042, 1000 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{12}H_{10}FIO_4Na$ 386.9500; Found 386.9506.



4e

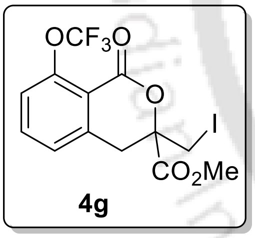
Methyl 8-chloro-3-(iodomethyl)-1-oxoisochromane-3-carboxylate 4e. Analytical TLC on silica gel, 3:7 EtOAc/hexane R_f = 0.43; colorless solid; mp 145-146 °C;

yield 70% (53 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45-7.40 (m, 2H), 7.14 (d, *J* = 7.2 Hz, 1H), 3.68-3.66 (m, 4H), 3.60 (d, *J* = 10.8 Hz, 1H), 3.46-3.39 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.7, 159.7, 138.2, 137.0, 134.0, 131.9, 126.4, 122.4, 82.2, 53.7, 37.2, 7.1; FT-IR (KBr) 2920, 1745, 1593, 1454, 1288, 1257, 1208, 1096, 1058 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{11}ClIO_4$ 380.9385; Found 380.9391.



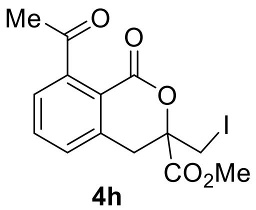
4f

Methyl 3-(iodomethyl)-1-oxo-8-(trifluoromethyl)isochromane-3-carboxylate 4f. Analytical TLC on silica gel, 3:7 EtOAc/hexane R_f = 0.45; colorless solid; mp 136-137 °C; yield 71% (59 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 3.70 (d, *J* = 11.0 Hz, 1H), 3.63-3.61 (m, 4H), 3.51-3.43 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.8, 159.4, 137.9, 133.4, 131.6, 131.4, 127.8 ($J_{C–F}$ = 6.1 Hz), 123.8, 122.0, 82.4, 53.7, 37.6, 6.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ -59.86; FT-IR (KBr) 2959, 1753, 1599, 1435, 1272, 1208, 1143, 1102, 1060 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{11}F_3IO_4$ 414.9649; Found 414.9641.



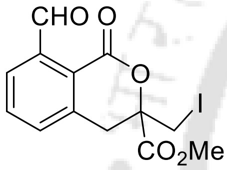
4g

Methyl 3-(iodomethyl)-1-oxo-8-(trifluoromethoxy)isochromane-3-carboxylate 4g. Analytical TLC on silica gel, 2:7 EtOAc/hexane R_f = 0.38; colorless solid; mp 115-116 °C; yield 68% (58.5 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (t, *J* = 7.8 Hz, 1H), 7.31-7.30 (m, 1H), 7.22 (d, *J* = 7.2 Hz, 1H), 3.69 (d, *J* = 11.4 Hz, 1H), 3.63 (s, 3H), 3.60 (d, *J* = 10.8 Hz, 1H), 3.47-3.42 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.9, 158.4, 149.1, 138.4, 135.0, 126.7, 123.0, 121.2 ($J_{C–F}$ = 257.3 Hz), 118.6, 82.5, 53.6, 36.9, 7.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ -57.51; FT-IR (KBr) 2959, 1752, 1610, 1471, 1258, 1210, 1163, 1097, 1061, 1047 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{11}F_3IO_5$ 430.9598; Found 430.9595.



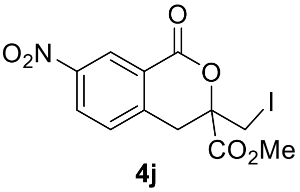
4h

Methyl 8-acetyl-3-(iodomethyl)-1-oxoisochromane-3-carboxylate 4h. Analytical TLC on silica gel, 3:7 EtOAc/hexane $R_f = 0.47$; colorless solid; mp 167-168 °C; yield 75% (56 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (t, $J = 8$ Hz, 1H), 7.27 (d, $J = 7.5$ Hz, 1H), 7.23 (d, $J = 7.5$ Hz, 1H), 3.72 (d, $J = 11.0$ Hz, 1H), 3.69 (s, 3H), 3.62 (d, $J = 11.0$ Hz, 1H), 3.49-3.40 (m, 2H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.7, 168.9, 162.2, 145.6, 136.0, 134.3, 128.8, 126.3, 121.9, 82.9, 53.8, 36.7, 30.6, 7.0; FT-IR (KBr) 2920, 1735, 1707, 1585, 1466, 1277, 1208, 1105, 1061, 1036 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{13}IO_5Na$ 410.9700; Found 410.9705.



4i

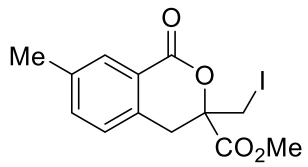
Methyl 8-formyl-3-(iodomethyl)-1-oxoisochromane-3-carboxylate 4i. Analytical TLC on silica gel, 2:8 EtOAc/hexane $R_f = 0.46$; sticky yellow liquid; yield 62% (46.4 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.77 (s, 1H), 7.87 (d, $J = 7.5$ Hz, 1H), 7.66 (t, $J = 8$ Hz, 1H), 7.45 (d, $J = 8$ Hz, 1H), 3.74 (d, $J = 11.0$ Hz, 1H), 3.68 (s, 3H), 3.64 (d, $J = 11.0$ Hz, 1H), 3.54-3.44 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.9, 168.7, 161.7, 138.7, 136.5, 134.1, 132.1, 128.5, 125.1, 82.9, 53.9, 36.8, 6.9; FT-IR (KBr) 2956, 1730, 1691, 1588, 1438, 1278, 1206, 1101, 1061, 1038 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{12}IO_5$ 374.9724; Found 374.9725.



4j

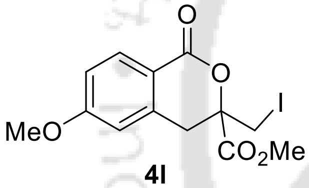
Methyl 3-(iodomethyl)-7-nitro-1-oxoisochromane-3-carboxylate 4j. Analytical TLC on silica gel, 3:7 EtOAc/hexane $R_f = 0.35$; yellow sticky liquid; yield 60% (47 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.39 (d, $J = 8.4$ Hz, 1H), 7.47 (d, $J = 8.4$ Hz, 1H), 3.74 (d, $J = 10.8$ Hz, 1H), 3.69-3.66 (m, 4H), 3.60-3.52 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.4, 161.3, 148.1, 141.9, 129.3, 128.6, 125.9, 125.5, 82.8, 54.1, 36.3, 7.1; FT-IR

(KBr) 2925, 1743, 1615, 1530, 1434, 1348, 1273, 1207, 1114, 1034 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{12}H_{10}INO_6Na$ 413.9445; Found 413.9442.



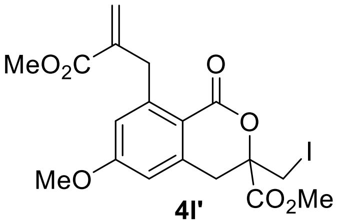
4k

Methyl 3-(iodomethyl)-7-methyl-1-oxoisochromane-3-carboxylate 4k. Analytical TLC on silica gel, 2:8 EtOAc/hexane $R_f = 0.41$; colorless solid; mp 125-126 °C; yield 69% (50 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 7.8 Hz, 1H), 3.70 (d, *J* = 10.8 Hz, 1H), 3.66 (s, 3H), 3.61 (d, *J* = 10.8 Hz, 1H), 3.43-3.35 (m, 2H), 2.38 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.3, 163.6, 138.6, 135.3, 132.4, 130.6, 127.5, 124.2, 82.9, 53.7, 35.8, 21.2, 7.7; FT-IR (KBr) 2920, 1738, 1618, 1505, 1438, 1288, 1180, 1141, 1077, 1038 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{13}H_{13}IO_4Na$ 382.9751; Found 382.9754.



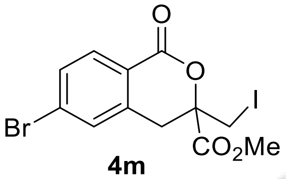
4l

Methyl 3-(iodomethyl)-6-methoxy-1-oxoisochromane-3-carboxylate 4l. Analytical TLC on silica gel, 2:8 EtOAc/hexane $R_f = 0.29$; colorless solid; mp 102-103 °C; yield 24% (18 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.5 Hz, 1H), 6.88 (d, *J* = 9.0 Hz, 1H), 6.68 (s, 1H), 3.86 (s, 3H), 3.70-3.68 (m, 4H), 3.60 (d, *J* = 11.0 Hz, 1H), 3.44-3.36 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.2, 164.4, 163.2, 138.0, 132.8, 116.8, 114.3, 112.5, 82.6, 55.8, 53.7, 36.3, 7.9; FT-IR (KBr) 2922, 1731, 1607, 1499, 1438, 1270, 1213, 1131, 1076, 1029 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{14}IO_5$ 376.9880; Found 376.9890.



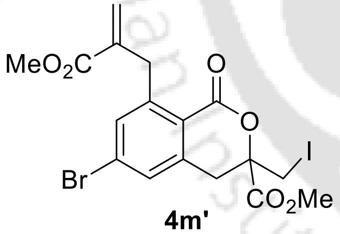
4l'

Methyl 3-(iodomethyl)-6-methoxy-8 (2(methoxycarbonyl)-allyl)-1-oxoisochromane-3-carboxylate 4l′. Analytical TLC on silica gel, 2:8 EtOAc/hexane $R_f = 0.25$; colorless liquid; yield 36% (19 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74-6.73 (m, 1H), 6.58-6.57 (m, 1H), 6.21 (s, 1H), 5.33 (s, 1H), 4.32 (d, J = 16.0 Hz, 1H), 3.92 (d, J = 16.0 Hz, 1H), 3.83 (s, 3H), 3.74 (s, 3H), 3.66-3.64 (m, 4H), 3.56 (d, J = 10.5 Hz, 1H), 3.40-3.32 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 167.5, 163.1, 162.0, 146.1, 139.5, 139.4, 126.2, 117.4, 115.5, 111.3, 81.8, 55.6, 53.5, 52.1, 37.6, 36.2, 7.6; FT-IR (KBr) 2952, 1722, 1604, 1580, 1437, 1273, 1201, 1150, 1077, 1040 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{20}IO_7$ 475.0248; Found 475.0249.



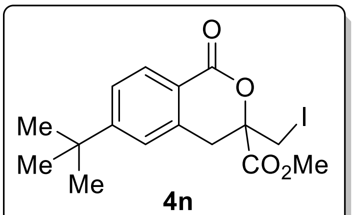
4m

Methyl 6-bromo-3-(iodomethyl)-1-oxoisochromane-3-carboxylate 4m. Analytical TLC on silica gel, 3:7 EtOAc/hexane R_f = 0.31; colorless solid; mp 154-155 °C; yield 26% (22 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, J = 8.5 Hz, 1H), 7.54 (d, J = 9.0 Hz, 1H), 7.40 (s, 1H), 3.72-3.69 (m, 4H), 3.61 (d, J = 11.0 Hz, 1H), 3.45 (d, J = 16.5 Hz, 1H), 3.35 (d, J = 16.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 162.7, 137.2, 132.1, 131.9, 130.7, 129.5, 123.3, 82.8, 53.9, 35.8, 7.4; FT-IR (KBr) 2919, 1739, 1595, 1280, 1214, 1138, 1085, 747 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{11}BrIO_4$ 424.8880; Found 424.8882.



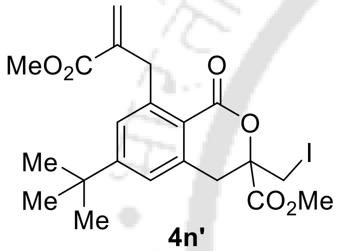
4m'

Methyl 6-bromo-3-(iodomethyl)-8-(2 (methoxycarbonyl)-allyl)-1-oxoisochromane-3-carboxylate 4m′. Analytical TLC on silica gel, 3:7 EtOAc/hexane R_f = 0.25; colorless liquid; yield 35% (20 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.28 (s, 1H), 6.27 (s, 1H), 5.39 (s, 1H), 4.32 (d, J = 16.0 Hz, 1H), 3.93 (d, J = 16.0 Hz, 1H), 3.75 (s, 3H), 3.68-3.66 (m, 4H), 3.57 (d, J = 11.0 Hz, 1H), 3.40 (d, J = 15.5 Hz, 1H), 3.32 (d, J = 16.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.8, 167.1, 161.6, 145.5, 138.7, 138.5, 134.7, 129.5, 128.5, 127.0, 122.0, 82.0, 53.7, 52.2, 37.0, 35.7, 7.2; FT-IR (KBr) 2923, 1733, 1632, 1580, 1436, 1267, 1202, 1138, 1069 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{17}H_{16}BrIO_6Na$ 544.9067; Found 544.9067.



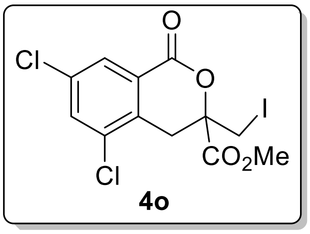
4n

Methyl 6-(*tert*-butyl)-3-(iodomethyl)-1-oxoisochromane-3-carboxylate 4n. Analytical TLC on silica gel, 2:8 EtOAc/hexane R*f* = 0.45; colorless solid; mp 172-173 ºC; yield 28% (22.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 9.6 Hz, 1H), 7.19 (s, 1H), 3.70 (d, *J* = 10.8 Hz, 1H), 3.68 (s, 3H), 3.61 (d, *J* = 10.8 Hz, 1H), 3.48-3.38 (m, 2H), 1.32 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 163.4, 158.6, 135.3, 130.3, 125.9, 124.5, 121.6, 82.8, 53.7, 36.4, 35.4, 31.1, 8.0; FT-IR (KBr) 2962, 1738, 1610, 1435, 1288, 1215, 1141, 1113, 1063 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{20}IO_4$ 403.0401; Found 403.0415.



4n'

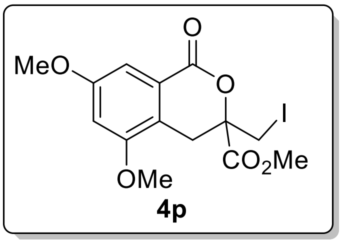
Methyl 6-(*tert*-butyl)-3-(iodomethyl)-8-(2 (methoxycarbonyl)-allyl)-1-oxoisochromane-3-carboxylate 4n′. Analytical TLC on silica gel, 3:7 EtOAc/hexane R*f* = 0.39; colorless solid; mp 117-118 ºC; yield 33% (18.2 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 1H), 7.08 (s, 1H), 6.19 (s, 1H), 5.25 (s, 1H), 4.34 (d, *J* = 16.0 Hz, 1H), 3.94 (d, *J* = 16.0 Hz, 1H), 3.75 (s, 3H), 3.66 (d, *J* = 10.8 Hz, 1H), 3.64 (s, 3H), 3.57 (d, *J* = 10.8 Hz, 1H), 3.44-3.35 (m, 2H), 1.30 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 167.6, 162.2, 157.4, 142.9, 139.8, 136.8, 129.4, 125.8, 123.4, 120.2, 82.1, 53.5, 52.0, 37.5, 36.2, 35.2, 31.0, 7.8; FT-IR (KBr) 2917, 1736, 1604, 1366, 1274, 1208, 1138, 1061 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{26}IO_6$ 501.0769; Found 501.0778.



4o

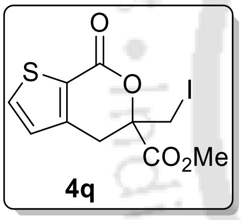
Methyl 5,7-dichloro-3-(iodomethyl)-1-oxoisochromane-3-carboxylate 4o. Analytical TLC on silica gel, 3:7 EtOAc/hexane R*f* = 0.35; colorless solid; mp 153 ºC; yield 63% (52 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.61 (s, 1H), 3.73 (d, *J* = 10.8 Hz, 1H), 3.71 (s, 3H), 3.69-3.64 (m, 2H), 3.27 (d, *J* = 16.8 Hz, 1H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 168.5, 161.4, 134.9, 134.4, 133.9, 132.0, 128.9, 127.3, 82.4, 54.1, 33.4, 7.2; FT-IR (KBr) 2954, 1749, 1596, 1565, 1456, 1282, 1222, 1186, 1131, 1085, 1034 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{12}H_9Cl_2IO_4Na$ 436.8815; Found 436.8814.



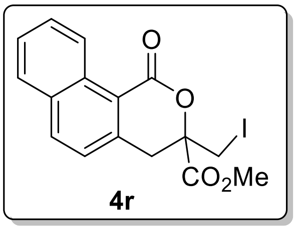
4p

Methyl 3-(iodomethyl)-5,7-dimethoxy-1-oxoisochromane-3-carboxylate 4p. Analytical TLC on silica gel, 3:7 EtOAc/hexane R_f = 0.29; light brown solid; mp 177-178 °C; yield 67% (54.4 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (s, 1H), 6.63 (s, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.71 (d, *J* = 11.0 Hz, 1H), 3.69 (s, 3H), 3.61 (d, *J* = 11 Hz, 1H), 3.55 (d, *J* = 16.5 Hz, 1H), 3.05 (d, *J* = 17.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 163.6, 160.2, 157.0, 125.7, 117.2, 104.7, 103.5, 82.9, 56.0, 55.9, 53.7, 29.8, 8.0; HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{14}H_{15}IO_6Na$ 428.9806; Found 428.9809.



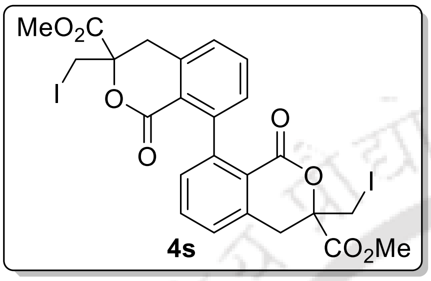
4q

Methyl 5-(iodomethyl)-7-oxo-4,7-dihydro-5H-thieno[2,3-c]pyran-5-carboxylate 4q. Analytical TLC on silica gel, 3:7 EtOAc/hexane R_f = 0.49; colorless solid; mp 139-140 °C; yield 79% (55.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 5.0 Hz, 1H), 6.95 (d, *J* = 5.0 Hz, 1H), 3.73-3.70 (m, 4H), 3.63 (d, *J* = 11.0 Hz, 1H), 3.55 (d, *J* = 16.5 Hz, 1H), 3.32 (d, *J* = 16.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 159.0, 143.9, 135.5, 126.6, 126.1, 84.4, 53.9, 33.6, 7.5; FT-IR (KBr) 2920, 1729, 1435, 1307, 1285, 1227, 1198, 1052 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{10}H_9IO_4SNa$ 374.9158; Found 374.9158.



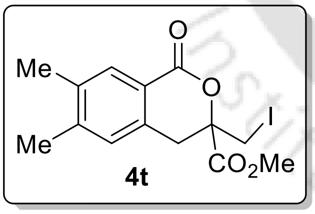
4r

Methyl 3-(iodomethyl)-1-oxo-3,4-dihydro-1H-benzo[h]isochromene-3-carboxylate 4r. Analytical TLC on silica gel, 2:8 EtOAc/hexane R_f = 0.37; colorless solid; mp 188-189 °C; yield 82% (65 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.23 (d, *J* = 8.5 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.56 (t, *J* = 7.0 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 1H), 3.73 (d, *J* = 11.0 Hz, 1H), 3.65 (d, *J* = 11.0 Hz, 1H), 3.64-3.60 (m, 4H), 3.54 (d, *J* = 16.5 Hz, 1H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 169.3, 162.4, 137.3, 135.5, 133.6, 131.7, 129.4, 128.7, 126.9, 126.4, 124.9, 119.6, 81.9, 53.6, 37.5, 7.5; FT-IR (KBr) 2956, 1729, 1510, 1435, 1274, 1193, 1120, 1044cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{16}H_{13}IO_4Na$ 418.9751; Found 418.9751.



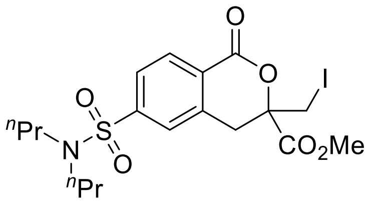
4s

Dimethyl 3,3'-bis(iodomethyl)-1,1'-dioxo-[8,8'-biisochromane]-3,3'-dicarboxylate 4s. Analytical TLC on silica gel, 3:7 EtOAc/hexane R$_f$ = 0.26; colorless solid; mp >250 °C; yield 85% (117 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.57-7.52 (m, 2H), 7.28-7.25 (m, 2H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.70-3.67 (m, 1H), 3.64-3.58 (m, 3H), 3.55-3.43 (m, 4H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.1, 162.1, 161.1, 144.8, 144.7, 136.7, 135.6, 133.5, 133.0, 130.5, 129.6, 127.5, 127.2, 122.4, 122.3, 82.5, 82.2, 54.2, 53.5, 36.8, 36.0, 8.6, 6.6; FT-IR (KBr) 2920, 1737, 1588, 1441, 1263, 1207, 1141, 1097, 1052 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{24}H_{21}I_2O_8$ 690.9320; Found 690.9318.



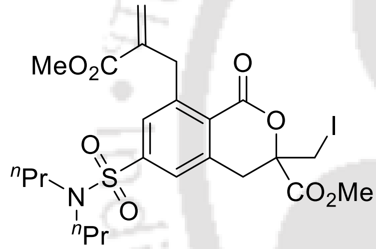
4t

Methyl 3-(iodomethyl)-6,7-dimethyl-1-oxoisochromane-3-carboxylate 4t. Analytical TLC on silica gel, 2:8 EtOAc/hexane R$_f$ = 0.40; light yellow solid; mp 161-162 °C; yield 87% (65 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.84 (s, 1H), 6.97 (s, 1H), 3.71-3.67 (m, 4H), 3.59 (d, *J* = 10.8 Hz, 1H), 3.40-3.31 (m, 2H), 2.29-2.27 (m, 6H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 169.4, 163.8, 144.5, 137.3, 132.9, 131.0, 128.7, 121.7, 82.9, 53.7, 35.6, 20.3, 19.6, 7.9; FT-IR (KBr) 2920, 1735, 1618, 1458, 1408, 1269, 1205, 1132, 1042 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{14}H_{15}IO_4Na$ 396.9907; Found 396.9910.



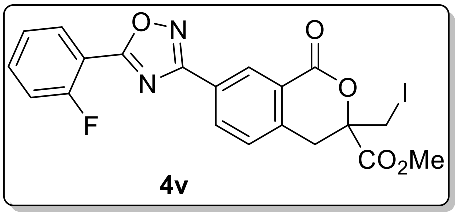
4u

Methyl 6-(*N*,*N*-dipropylsulfamoyl)-3-(iodomethyl)-1-oxo-isochromane-3-carboxylate 4u. Analytical TLC on silica gel, 3:7 EtOAc/hexane $R_f = 0.40$; colorless solid; mp 144-145 °C; yield 24% (24.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.5 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.68 (s, 1H), 3.72 (d, *J* = 11.0 Hz, 1H), 3.66-3.64 (m, 4H), 3.53 (d, *J* = 16.5 Hz, 1H), 3.43 (d, *J* = 16.5 Hz, 1H), 3.11-3.07 (m, 4H), 1.57-1.50 (m, 4H), 0.86 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 162.0, 145.8, 136.4, 131.2, 127.6, 126.7, 126.2, 82.8, 53.9, 50.0, 36.2, 22.0, 11.3, 7.2; FT-IR (KBr) 2923, 1746, 1604, 1457, 1341, 1283, 1208, 1153, 1097, 1061, 994 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{25}INO_6S$ 510.0442; Found 510.0446.



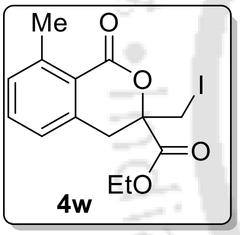
4u'

Methyl 6-(*N*,*N*-dipropylsulfamoyl)-3-(iodomethyl)-8-(2-(methoxycarbonyl)allyl)-1-oxoisochromane-3-carboxylate 4u′. Analytical TLC on silica gel, 3:7 EtOAc/hexane $R_f = 0.36$; colorless liquid; yield 37% (25 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.55 (s, 1H), 6.28 (s, 1H), 5.41 (s, 1H), 4.39 (d, *J* = 16.0 Hz, 1H), 4.02 (d, *J* = 16.0 Hz, 1H), 3.73 (s, 3H), 3.68 (d, *J* = 11.0 Hz, 1H), 3.63 (s, 3H), 3.59 (d, *J* = 11.0 Hz, 1H), 3.51-3.41 (m, 2H), 3.14-3.04 (m, 4H), 1.55-1.48 (m, 4H), 0.85 (t, *J* = 7.5 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.5, 167.0, 161.2, 144.9, 144.7, 138.5, 137.8, 129.5, 127.4, 126.3, 124.6, 82.3, 53.7, 52.1, 49.9, 37.5, 36.1, 21.9, 11.3, 7.0; FT-IR (KBr) 2964, 1740, 1630, 1591, 1438, 1269, 1341, 1202, 1151, 1066, 996 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{23}H_{30}INO_8SNa$ 630.0629; Found 630.0628.



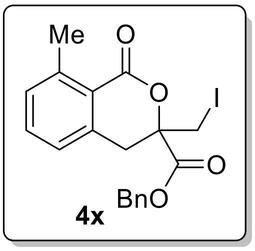
4v

Methyl 7-(5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl)-3-(iodomethyl)-1-oxoisochromane-3-carboxylate 4v. Analytical TLC on silica gel, 3:7 EtOAc/hexane R$_f$ = 0.29; yellow solid; mp 201-202 °C; yield 66% (67 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.35 (d, J = 7.5 Hz, 1H), 8.24 (t, J = 7.0 Hz, 1H), 7.65-7.61 (m, 1H), 7.41-7.29 (m, 3H), 3.74 (d, J = 11.0 Hz, 1H), 3.68-3.66 (m, 4H), 3.54 (d, J = 16.0 Hz, 1H), 3.48 (d, J = 16.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4 ($J_{C\text{–}F}$ = 4.3 Hz), 168.9, 167.7, 162.6, 162.0 ($J_{C\text{–}F}$ = 259.3 Hz), 138.3, 135.0 ($J_{C\text{–}F}$ = 8.5 Hz), 132.9, 131.1, 129.7, 128.5, 127.7, 125.3, 125.0 ($J_{C\text{–}F}$ = 3.6 Hz), 117.5 ($J_{C\text{–}F}$ = 20.8 Hz), 112.8 ($J_{C\text{–}F}$ = 11.4 Hz), 82.8, 53.9, 36.3, 7.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ -108.08; FT-IR (KBr) 2915, 1746, 1621, 1591, 1468, 1413, 1344, 1272, 1208, 1141, 1082, 1035 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{15}FIN_2O_5$ 509.0004; Found 509.0004.



4w

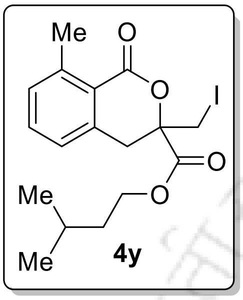
Ethyl 3-(iodomethyl)-8-methyl-1-oxoisochromane-3-carboxylate 4w. Analytical TLC on silica gel, 2:8 EtOAc/hexane R$_f$ = 0.51; yellow solid; mp 83-84 °C; yield 76% (57 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (t, J = 7.5 Hz, 1H), 7.19 (d, J = 7.5 Hz, 1H), 7.03 (d, J = 7.5 Hz, 1H), 4.14 – 4.01 (m, 2H), 3.68 (d, J =10.5 Hz, 1H), 3.58 (d, J = 11 Hz, 1H), 3.40 (d, J = 15.5 Hz, 1H), 3.32 (d, J = 15.5 Hz, 1H), 2.67 (s, 3H), 1.04 (t, J = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.7, 162.8, 143.1, 136.3, 133.2, 131.8, 125.6, 123.3, 82.0, 62.7, 37.5, 22.2, 14.0, 7.6; FT-IR (KBr) 2923, 1736, 1594, 1470, 1264, 1200, 1138, 1102, 1060 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{15}IO_4Na$ 396.9907; Found 396.9907.



4x

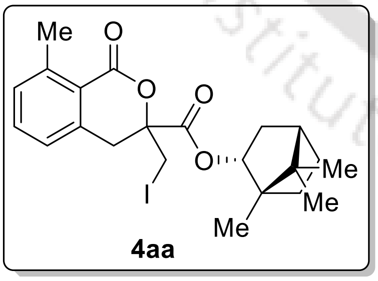
Benzyl 3-(iodomethyl)-8-methyl-1-oxoisochromane-3-carboxylate 4x. Analytical TLC on silica gel, 2:8 EtOAc/hexane R$_f$ = 0.46; yellow liquid; yield 72% (63 mg);

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.25-7.16 (m, 4H), 7.06 (d, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 7.5 Hz, 2H), 6.89 (d, *J* = 7.5 Hz, 1H), 5.04 (d, *J* = 12.0 Hz, 1H), 4.89 (d, *J* = 12.0 Hz, 1H), 3.63 (d, *J* = 10.5 Hz, 1H), 3.52 (d, *J* = 10.5 Hz, 1H), 3.32 (d, *J* = 15.5 Hz, 1H), 3.25 (d, *J* = 16.0 Hz, 1H), 2.49 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 168.7, 162.7, 143.2, 136.1, 134.6, 133.2, 131.9, 128.7, 128.4, 125.5, 123.2, 82.1, 68.3, 37.5, 22.2, 7.7; FT-IR (KBr) 2965, 1735, 1597, 1470, 1264, 1200, 1136, 1059 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{19}H_{18}IO_4$ 437.0244; Found 437.0251.



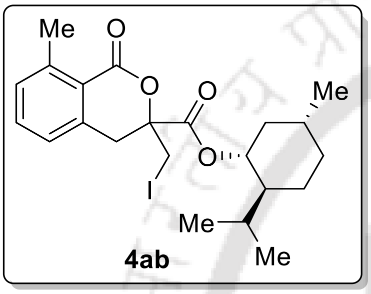
4y

Isopentyl 3-(iodomethyl)-8-methyl-1-oxoisochromane-3-carboxylate 4y. Analytical TLC on silica gel, 2:8 EtOAc/hexane R$_f$ = 0.50; colorless liquid; yield 75% (62 mg); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.37 (t, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 4.11-3.99 (m, 2H), 3.69 (d, *J* = 11.0 Hz, 1H), 3.58 (d, *J* = 11.0 Hz, 1H), 3.39 (d, *J* = 15.5 Hz, 1H), 3.32 (d, *J* = 16.0 Hz, 1H), 2.67 (s, 3H), 1.43-1.36 (m, 1H), 1.34-1.28 (m, 2H), 0.79 (d, *J* = 6.5 Hz, 3H), 0.75 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 168.9, 162.8, 143.2, 136.4, 133.2, 131.9, 125.6, 123.2, 82.1, 65.2, 37.4, 37.1, 24.6, 22.4, 22.3, 22.2, 7.9; FT-IR (KBr) 2960, 1736, 1597, 1470, 1264, 1201, 1137, 1103, 1059 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{17}H_{22}IO_4$ 417.0557; Found 417.0565.



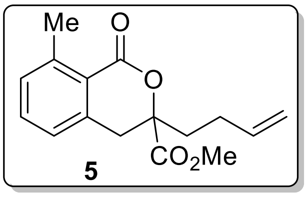
4aa

(1S,2R,4S)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 3-(iodomethyl)-8-methyl-1-oxoisochromane-3-carboxylate 4aa. Analytical TLC on silica gel, 3:7 EtOAc/hexane R$_f$ = 0.45; colorless liquid; yield 65% (63 mg); 4:1 mixture of diastereomers; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.50 (t, *J* = 7.5 Hz, 0.22H, minor), 7.37 (t, *J* = 7.5 Hz, 1H, major), 7.22-7.19 (m, 1.24H, major + minor), 7.06-7.03 (m, 1.23H, major + minor) 4.96-4.90 (m, 0.23H, minor), 4.74-4.71 (m, 1H, major), 3.73 (d, *J* = 11.0 Hz, 1.23H, major + minor), 3.61-3.58 (m, 1.23H, major + minor), 3.41-3.33 (m, 2.46H, major + minor), 2.69 (s, 3H, major), 2.67 (s, 0.69H, minor), 2.22-2.18 (m, 0.24H, minor), 2.12-2.06 (m, 1H, major), 1.78-1.73 (m, 1.27H, major + minor), 1.69-1.64 (m, 1.25H, major + minor), 1.53 (t, *J* = 4.5 Hz, 1H, major), 1.33-1.28 (m, 1.26H, major + minor), 0.93-0.86 (m, 2.48H, major + minor), 0.81-0.78 (m, 7.39H, major + minor), 0.74 (s, 3H, major), 0.46 (s, 0.46H, minor), 0.28-0.25 (m, 1H, major). ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.3, 169.1, 162.7, 142.9, 136.2, 133.7, 133.2, 133.1, 131.9, 131.8, 125.5, 123.4, 83.0, 82.9, 82.2, 81.9, 48.7, 48.6, 47.9, 47.8, 44.7, 44.6, 37.8, 37.4, 36.2, 36.1, 27.8, 27.2, 27.1, 22.2, 19.6, 18.8, 18.7, 13.2, 12.8, 7.8; FT-IR (KBr) 2956, 2926, 1739, 1592, 1472, 1263, 1201, 1063, 1102, 1042 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{22}H_{27}IO_4$ Na 505.0846; Found 505.0850.



4ab

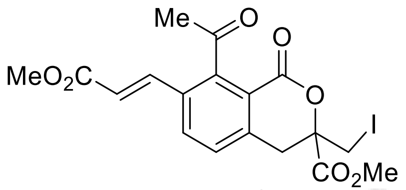
(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 3-(iodomethyl)-8-methyl-1-oxoisochromane-3-carboxylate 4ab. Analytical TLC on silica gel, 3:7 EtOAc/hexane R$_f$ = 0.48; colorless liquid; yield 69% (67 mg); >20:1 mixture of diastereomers; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.35 (t, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 4.56-4.50 (m, 1H), 3.69 (d, *J* = 10.8 Hz, 1H), 3.57 (d, *J* = 10.8 Hz, 1H), 3.39 (d, *J* = 15.6 Hz, 1H), 3.30 (d, *J* = 15.6 Hz, 1H), 2.67 (s, 3H), 1.63-1.59 (m, 2H), 1.52-1.47 (m, 1H), 1.33-1.25 (m, 2H), 0.96-0.85 (m, 2H), 0.81 (d, *J* = 6.8 Hz, 3H), 0.78 (d, *J* = 6.4 Hz, 3H), 0.75-0.58 (m, 2H), 0.48 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.3, 163.0, 143.0, 136.3, 133.0, 131.7, 125.5, 123.8, 82.2, 77.3, 46.9, 40.2, 37.9, 34.1, 31.3, 25.9, 23.0, 22.2, 22.0, 20.9, 15.9, 7.6; FT-IR (KBr) 2956, 2926, 1741, 1597, 1469, 1263, 1200, 1060, 1102, 955 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{22}H_{29}IO_4Na$ 507.1003; Found 507.1007.



5

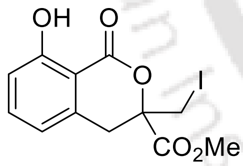
Methyl 3-(but-3-en-1-yl)-8-methyl-1-oxoisochromane-3-carboxylate 5. Analytical TLC on silica gel, 2:8 EtOAc/hexane R$_f$ = 0.40; colorless liquid; yield 64% (26 mg); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.34 (t, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 5.85-5.75 (m, 1H), 5.09-4.99 (m, 2H), 3.56 (s, 3H), 3.29-3.21

(m, 2H), 2.67 (s, 3H), 2.49-2.39 (m, 1H), 2.17-2.04 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 163.7, 143.0, 137.1, 137.0, 133.0, 131.6, 125.5, 123.5, 115.7, 83.7, 52.9, 37.5, 37.2, 27.6, 22.3; FT-IR (KBr) 2927, 1732, 1642, 1598, 1471, 1440, 1254, 1205, 1062, 1106, 916 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{16}H_{18}O_4Na$ 297.1097; Found 297.1099.



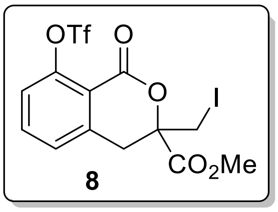
6

Methyl (*E*)-8-acetyl-3-(iodomethyl)-7-(3-methoxy-3-oxoprop-1-en-1-yl)-1-oxoisochromane-3-carboxylate 6. Analytical TLC on silica gel, 3:7 EtOAc/hexane R_f = 0.28; colorless solid; mp 168-169 °C; yield 55% (26 mg); E/Z = 10:1 mixture of diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 16.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 6.37 (d, *J* = 16.0 Hz, 1H), 3.79 (s, 3H), 3.74-3.69 (m, 4H), 3.65-3.62 (m, 1H), 3.52-3.41 (m, 2H), 2.54 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.4, 168.6, 166.3, 161.9, 145.2, 139.0, 137.5, 132.2, 131.4, 128.6, 122.6, 122.0, 82.8, 54.0, 52.1, 36.6, 32.2, 6.9; FT-IR (KBr) 2917, 1732, 1713, 1640, 1596, 1436, 1317, 1210, 1175, 1144, 1108, 1040 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{18}H_{17}IO_7Na$ 494.9911; Found 494.9912.



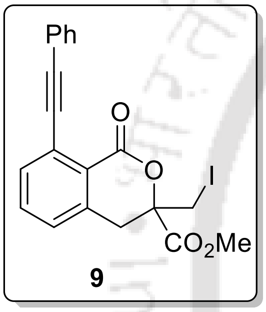
7

Methyl 8-hydroxy-3-(iodomethyl)-1-oxoisochromane-3-carboxylate 7. Analytical TLC on silica gel, 3:7 EtOAc/hexane R_f = 0.28; colorless solid; mp 131-132 °C; yield 95% (35 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.74 (s, 1H), 7.42 (t, *J* = 7.2 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 3.73-3.71 (m, 4H), 3.61 (d, *J* = 11.4 Hz, 1H), 3.45-3.37 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.6, 167.9, 162.2, 136.9, 135.7, 118.4, 117.3, 107.8, 83.5, 53.9, 35.9, 7.3; FT-IR (KBr) 2917, 1752, 1690, 1618, 1463, 1252, 1205, 1135, 1102, 1041 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{12}IO_5$ 362.9724; Found 362.9722.



8

Methyl 3-(iodomethyl)-1-oxo-8-(((trifluoromethyl)sulfonyl)oxy)isochromane-3-carboxylate 8. Analytical TLC on silica gel, 3:7 EtOAc/hexane R_f = 0.34; colorless liquid; yield 90% (44 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (t, *J* = 8.0 Hz, 1H), 7.32-7.28 (m, 2H), 3.70 (d, *J* = 11.0 Hz, 1H), 3.67 (s, 3H), 3.61 (d, *J* = 11.0 Hz, 1H), 3.52-3.46 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.6, 158.8, 149.2, 139.0, 135.4, 128.2, 123.1, 119.9 ($J_{C\text{–}F}$ = 330.0 Hz), 118.3, 82.7, 53.8, 36.6, 6.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ -73.26; FT-IR (KBr) 2959, 1742, 1613, 1464, 1427, 1208, 1137, 1101, 984, 841 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{13}H_{10}F_3IO_7SNa$ 516.9036; Found 516.9039.



9

Methyl 3-(iodomethyl)-1-oxo-8-(phenylethynyl)isochromane-3-carboxy-0late 9. Analytical TLC on silica gel, 3:7 EtOAc/hexane R_f = 0.44; brown thick liquid; yield 67% (15 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66-7.64 (m, 2H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.2 Hz, 1H), 7.37-7.35 (m, 3H), 7.17 (d, *J* = 7.8 Hz, 1H), 3.69 (d, *J* = 10.8 Hz, 1H), 3.67 (s, 3H), 3.61 (d, *J* = 10.8 Hz, 1H), 3.46-3.41 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.1, 160.9, 136.6, 134.2, 133.1, 132.3, 128.9, 128.5, 127.3, 126.0, 124.9, 123.3, 96.9, 87.9, 82.2, 53.7, 36.8, 7.4; FT-IR (KBr) 2924, 2210, 1743, 1583, 1492, 1465, 1441, 1259, 1205, 1095, 1055, 758, 691 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{16}IO_4$ 447.0088; Found 447.0088.

Sample Preparation for Crystal Growth. The compound **4t** was dissolved in minimum volume of CH_2Cl_2 and $CHCl_3$ and kept at room temperature for slow evaporation (2 days). Block shaped crystals were formed. The single crystal was subjected to X-ray diffraction.

Crystal Data and Structure Refinement for 4t.

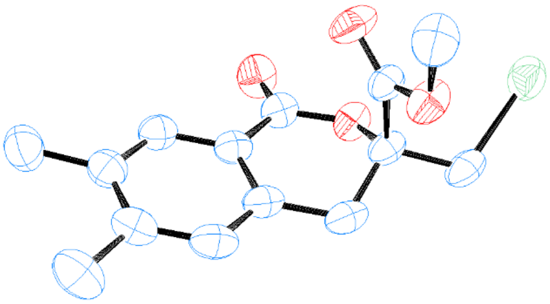


Figure 2. ORTEP diagram of methyl 3-(iodomethyl)-6,7-dimethyl-1-oxoisochromane-3-carboxylate **4t** (CCDC No 2259179) with 50% ellipsoid. H-Atoms are omitted for clarity.

CCDC	**2259179**
Identification code	**4t**
Empirical formula	$C_{14}H_{15}IO_4$
Formula weight	374.16
Crystal habit, colour	Block, Colorless
Temperature, *T*/K	298 K
Wavelength, λ/Å	0.71073 Å
Crystal system	Monoclinic
Space group	P 21/n
Unit cell dimensions	a = 8.2502(7) Å b = 11.0361(10) Å c = 16.2546(14) Å α = 90

	$\beta = 104.269(2)$ $\gamma = 90$
Volume, V/Å^3	1434.3
Z	4
Calculated density, Mg·m^{-3}	1.733
Absorption coefficient, μ/mm^{-1}	2.239
F(000)	736
θ range for data collection	2.25 to 26.35
Limiting indices	$-10 \leq h \leq 10$, $-13 \leq k \leq 13$, $-20 \leq l \leq 20$
Reflection collected /unique	2927/2645
Completeness to θ	99.6%
Absorption correction	Multi-scan
Refinement method	SHELXL-2019/1 (Sheldrick, 2019)
Data/restraints/parameters	2927/0/175
Goodness–of–fit on F^2	1.136
Final R indices [I >2sigma(I)]	R1 = 0.0359, wR2 = 0.0879
R indices (all data)	R1 = 0.0393, wR2 = 0.0922

Sample Preparation for Crystal Growth. The compound **3t** was dissolved in minimum volume of CH_2Cl_2 and $CHCl_3$ and kept at room temperature for slow evaporation (2 days). Block shaped crystals were formed. The single crystal was subjected to X-ray diffraction.

Crystal Data and Structure Refinement for 3t.

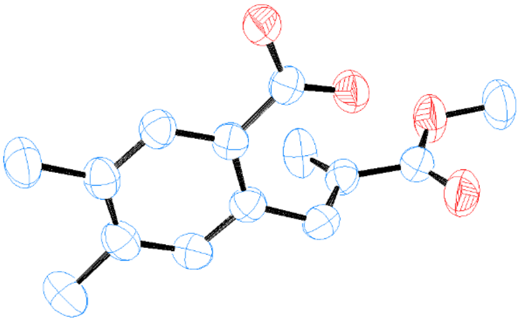


Figure 3. ORTEP diagram of 2-(2-(methoxycarbonyl)allyl)-4,5-dimethylbenzoic acid **3t** (CCDC No 2259176) with 50% ellipsoid. H-Atoms are omitted for clarity.

CCDC	**2259176**
Identification code	**3t**
Empirical formula	$C_{14}H_{16}O_4$
Formula weight	248.27
Crystal habit, colour	Block, Colourless
Temperature, *T*/K	298 K
Wavelength, λ/Å	0.71073 Å
Crystal system	Triclinic
Space group	P -1
Unit cell dimensions	a = 8.0608(3) Å b = 9.2659(4) Å c = 9.5041(4) Å α= 70.757(10) β= 78.506(10) γ = 82.627(10)

Volume, $V/\text{Å}^3$	655.26
Z	2
Calculated density, Mg·m^{-3}	1.258
Absorption coefficient, μ/mm^{-1}	0.092
$F(000)$	264
θ range for data collection	2.302 to 26.358
Limiting indices	$-10 \leq h \leq 10, -11 \leq k \leq 11, -11 \leq l \leq 11$
Reflection collected / unique	2657/ 2142
Completeness to θ	99.4%
Absorption correction	Multi-scan
Refinement method	SHELXL-2019/1 (Sheldrick, 2019)
Data / restraints / parameters	2657 / 0 / 169
Goodness–of–fit on F^2	1.136
Final R indices [$I > 2\text{sigma}(I)$]	R1 = 0.0654, wR2 = 0.1612
R indices (all data)	R1 = 0.0741, wR2 = 0.1686

2.5 References

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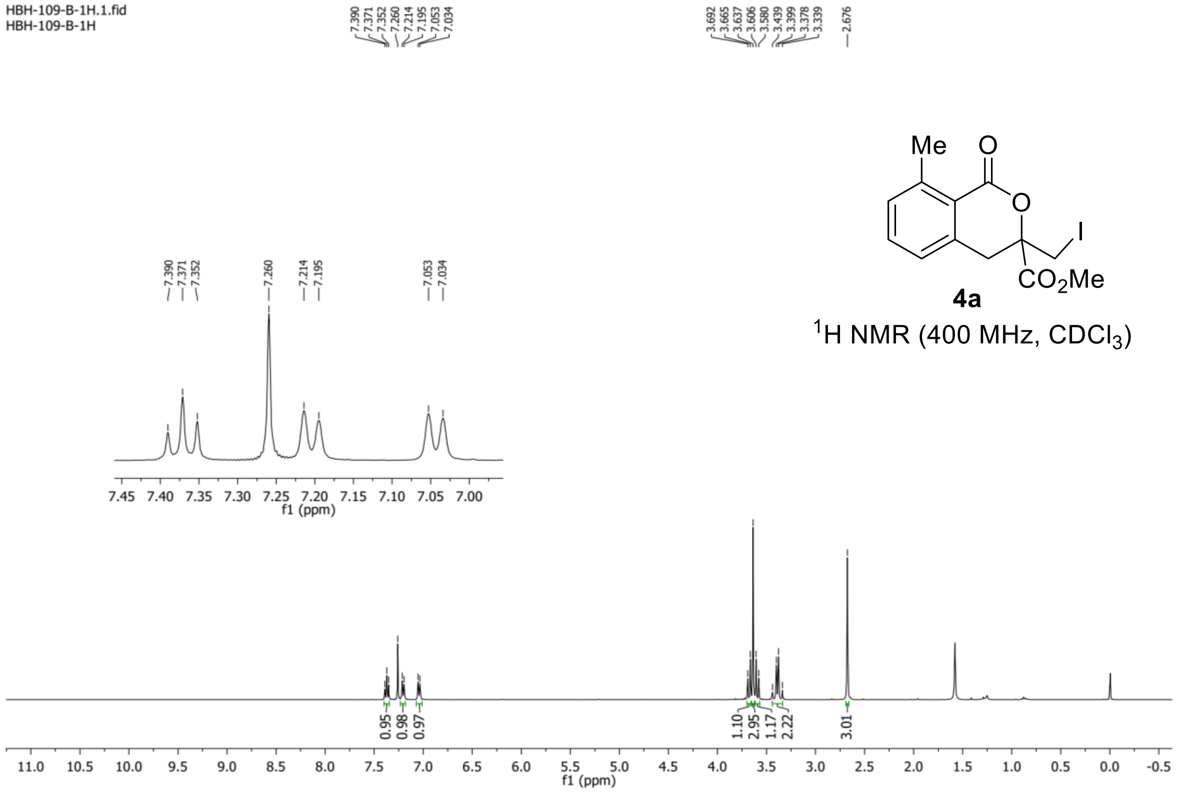
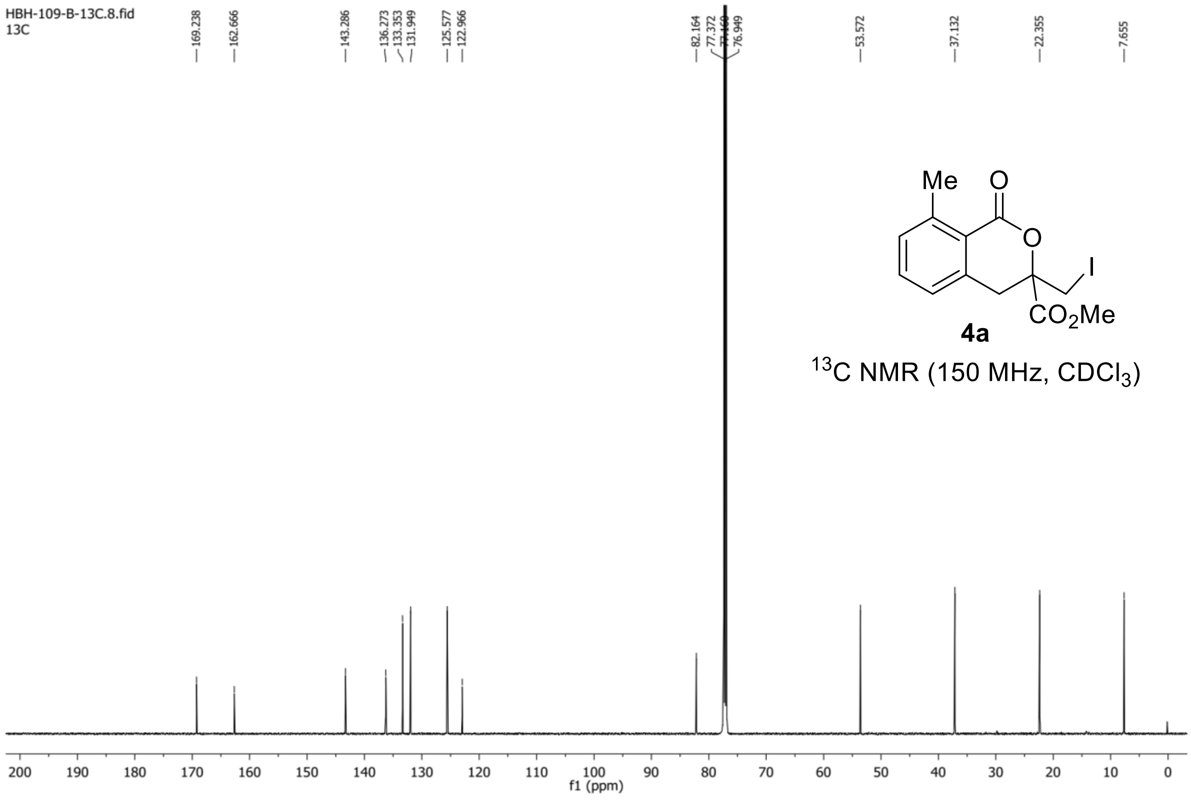
2.6 Selected NMR Spectra



4a

^{1}H NMR (400 MHz, $CDCl_3$)



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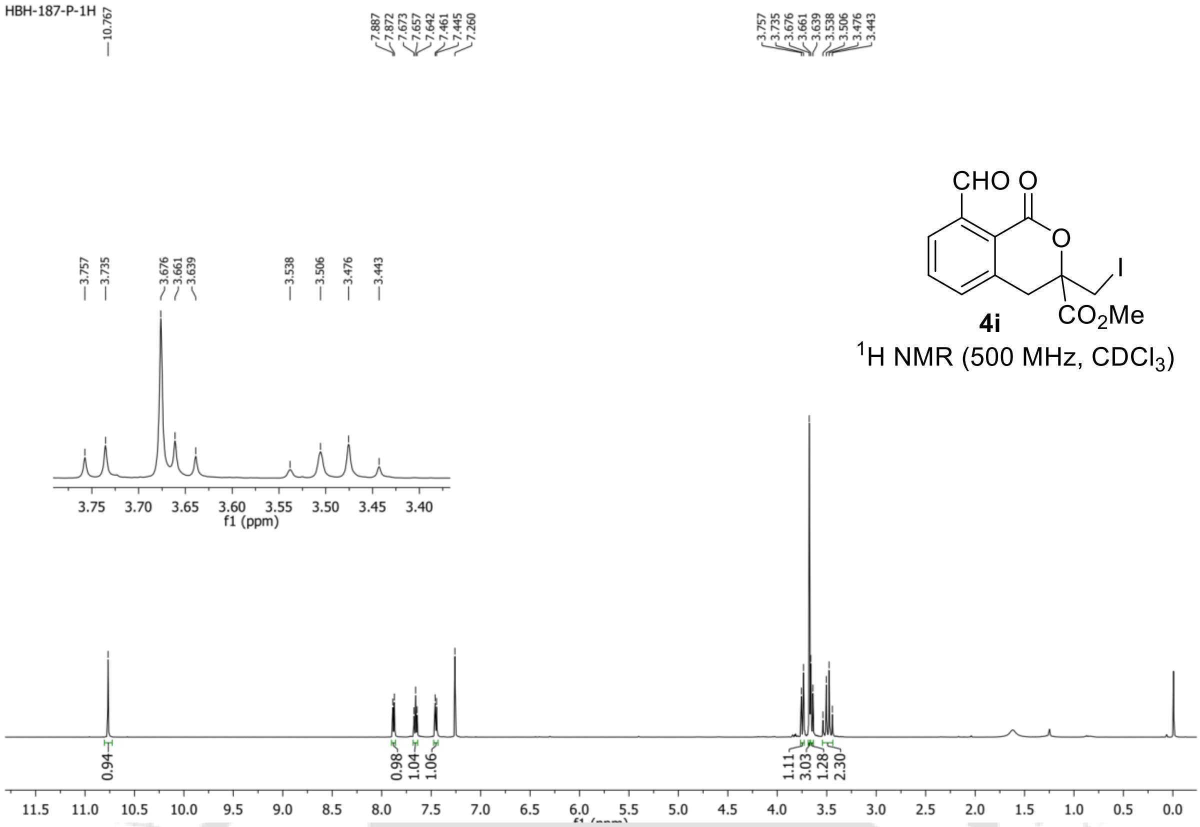

4i

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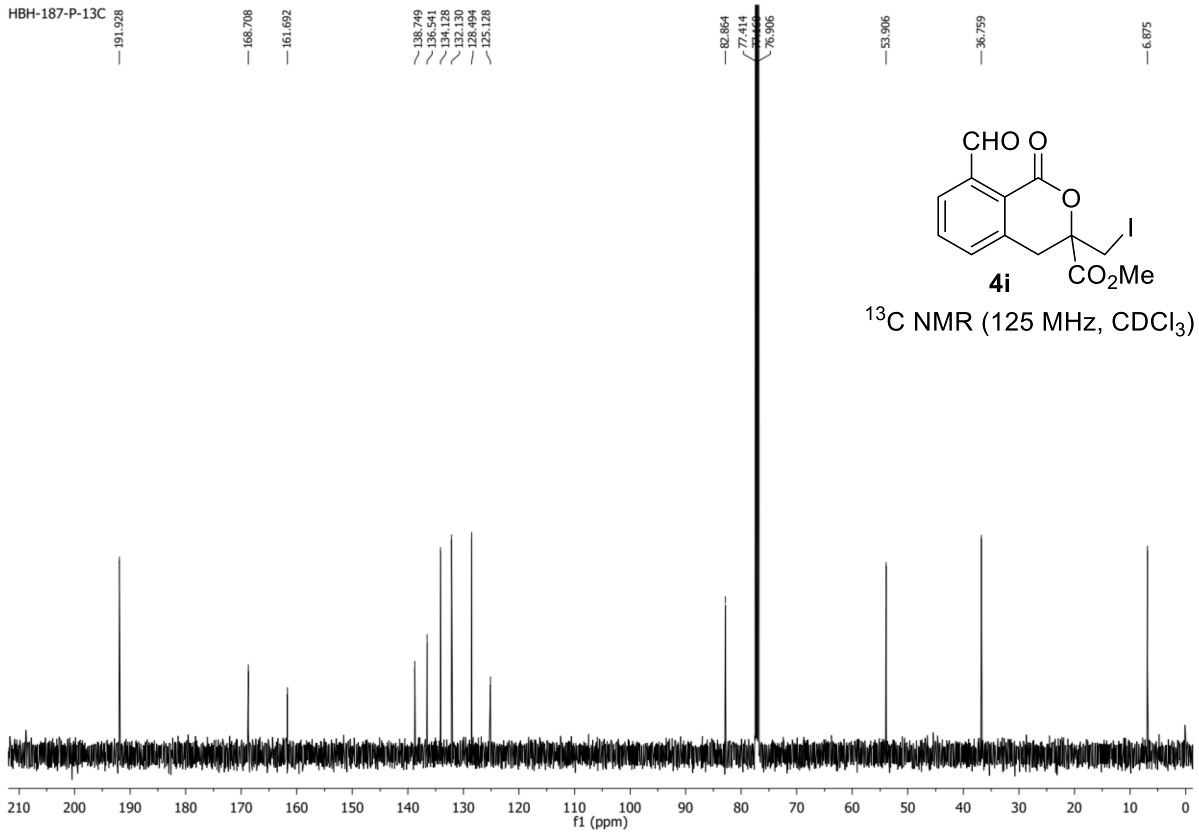

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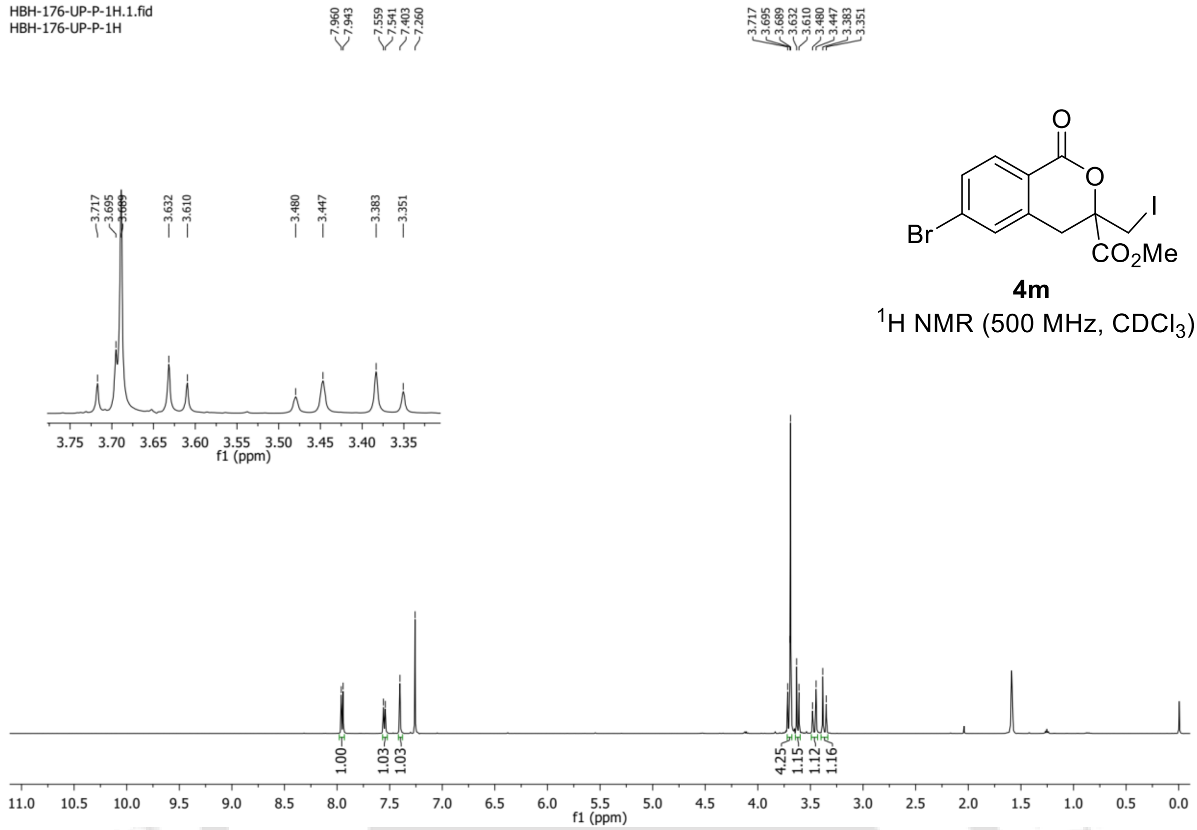

4m

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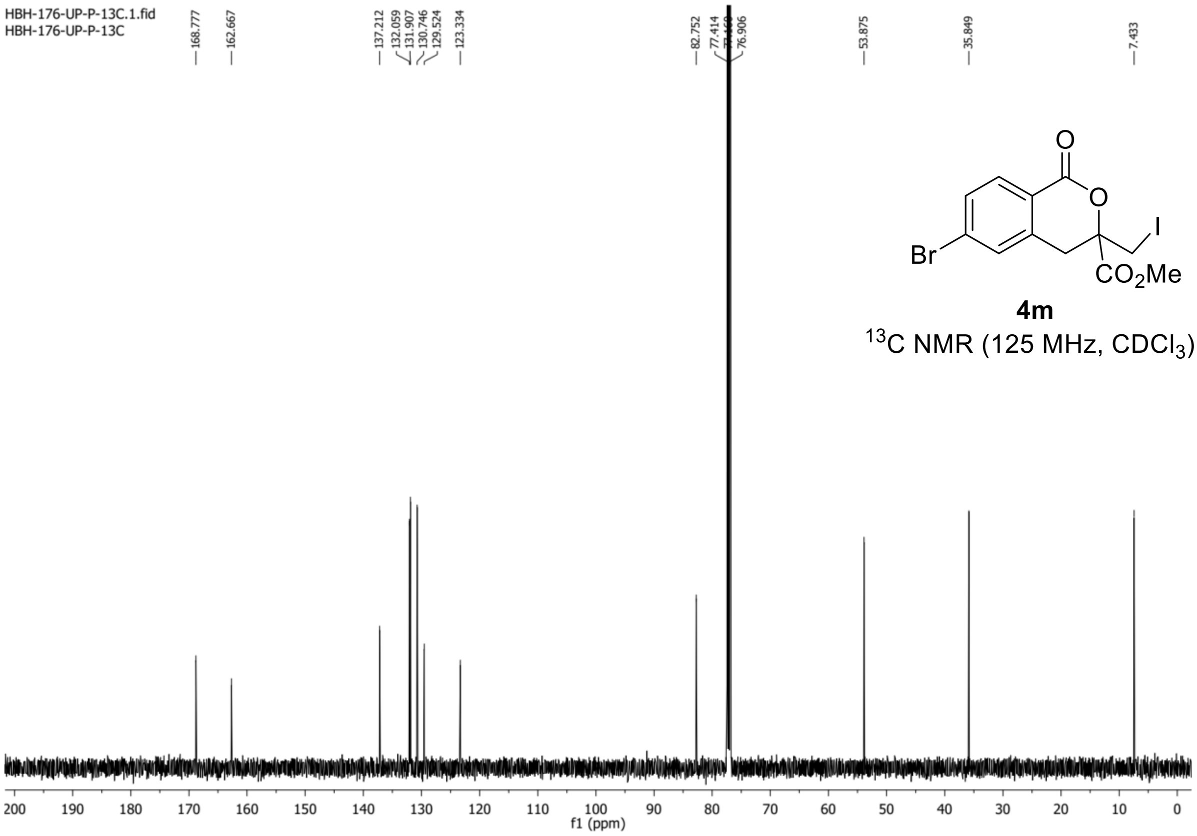

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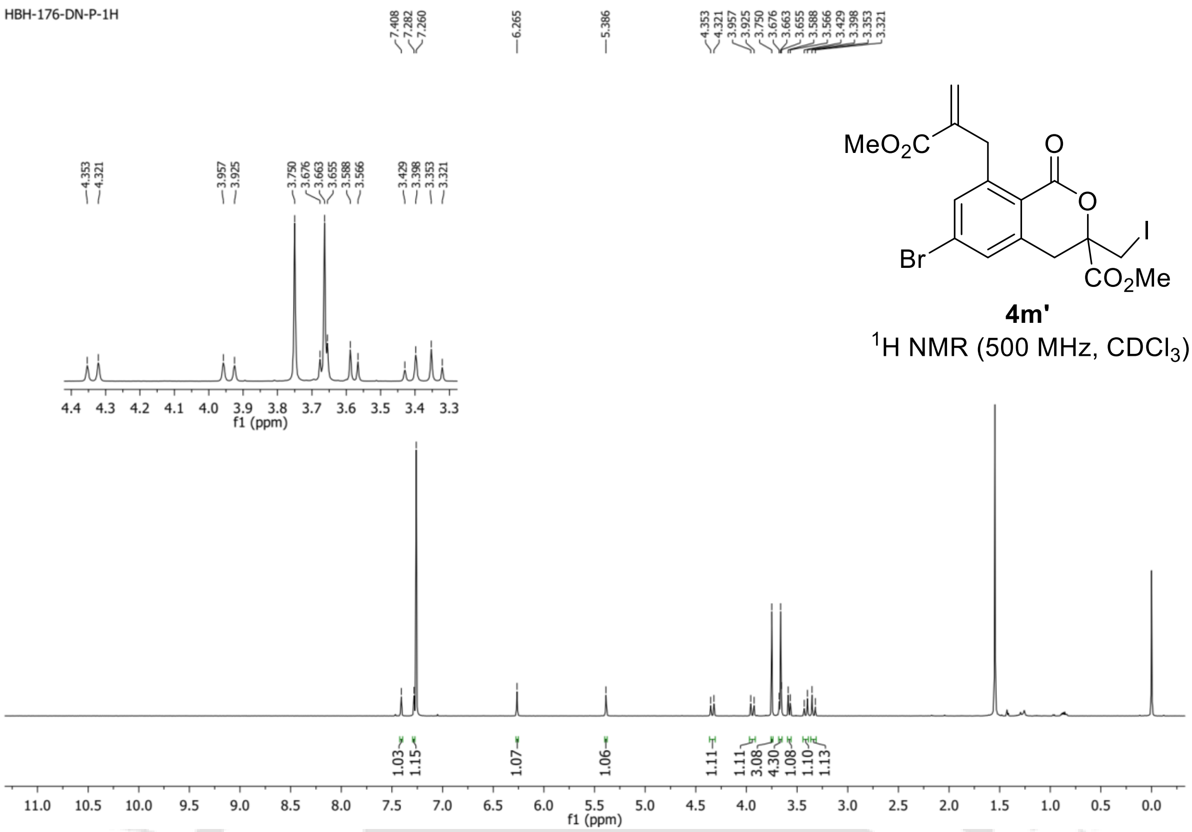

4m'

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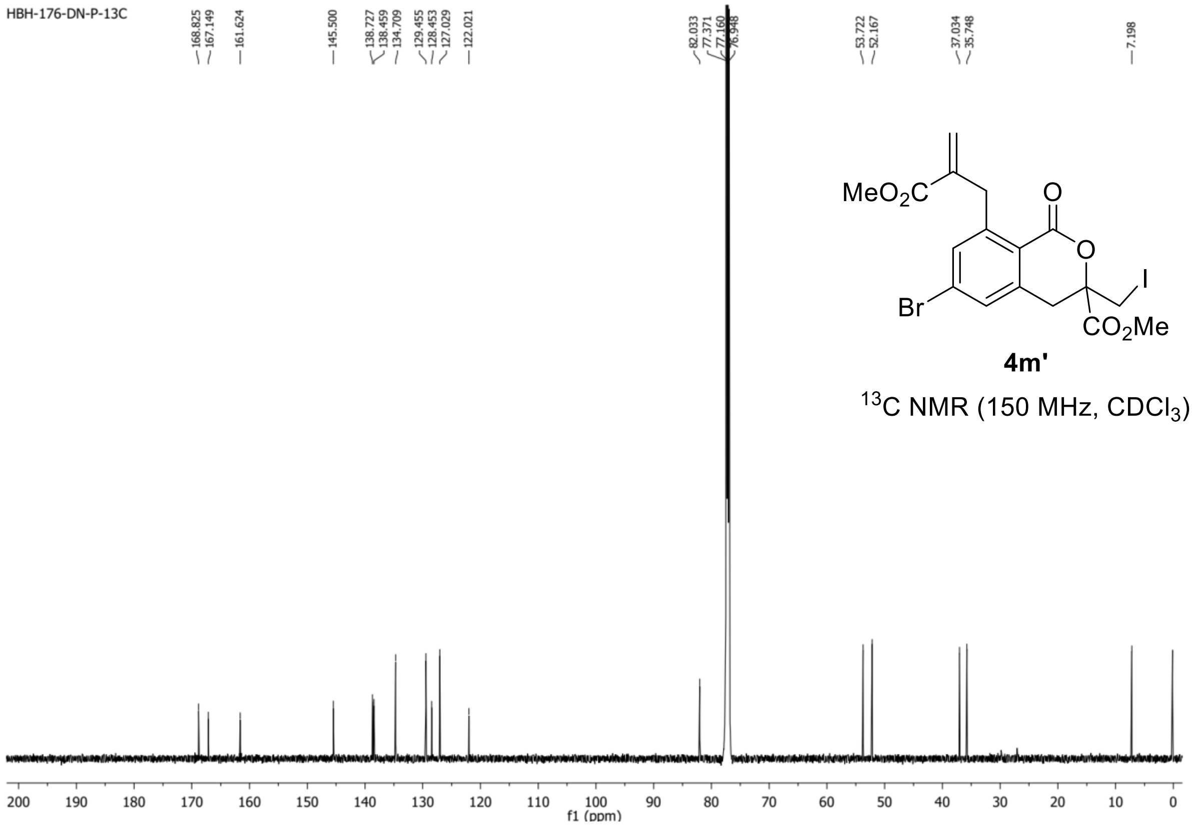

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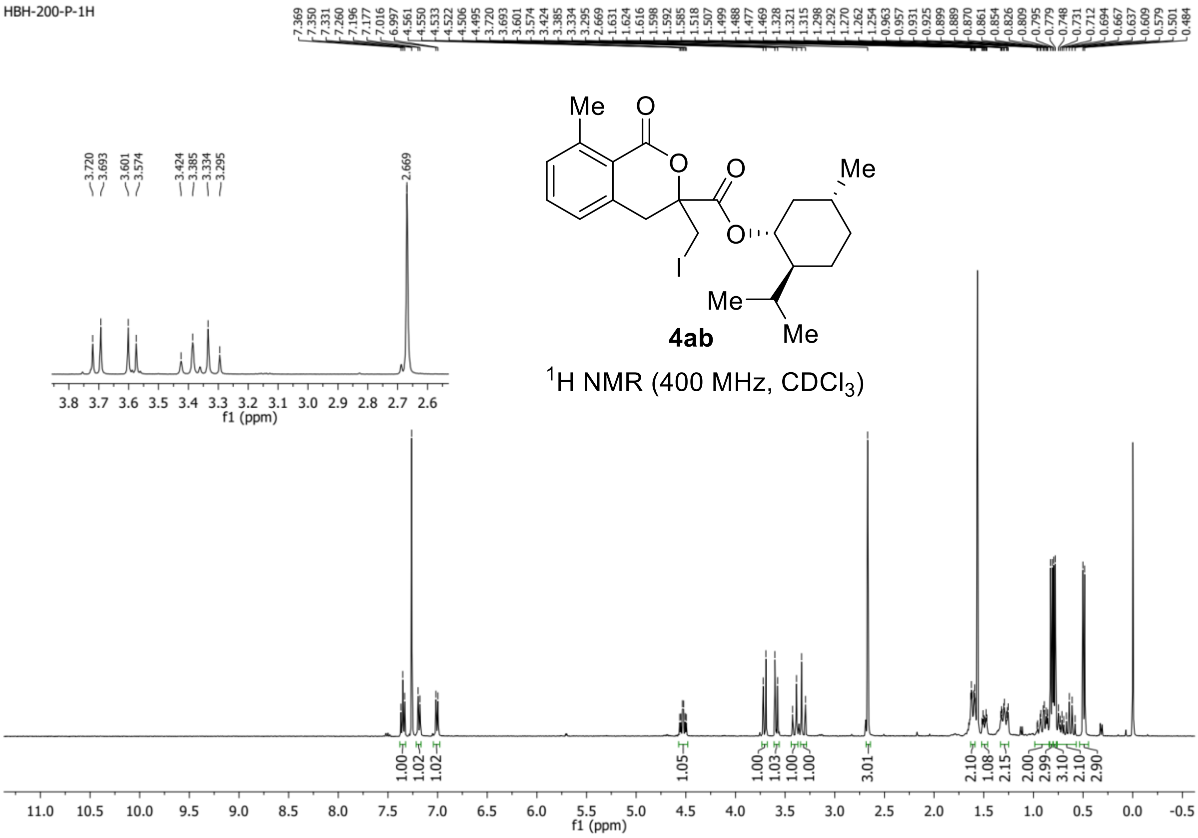

4ab

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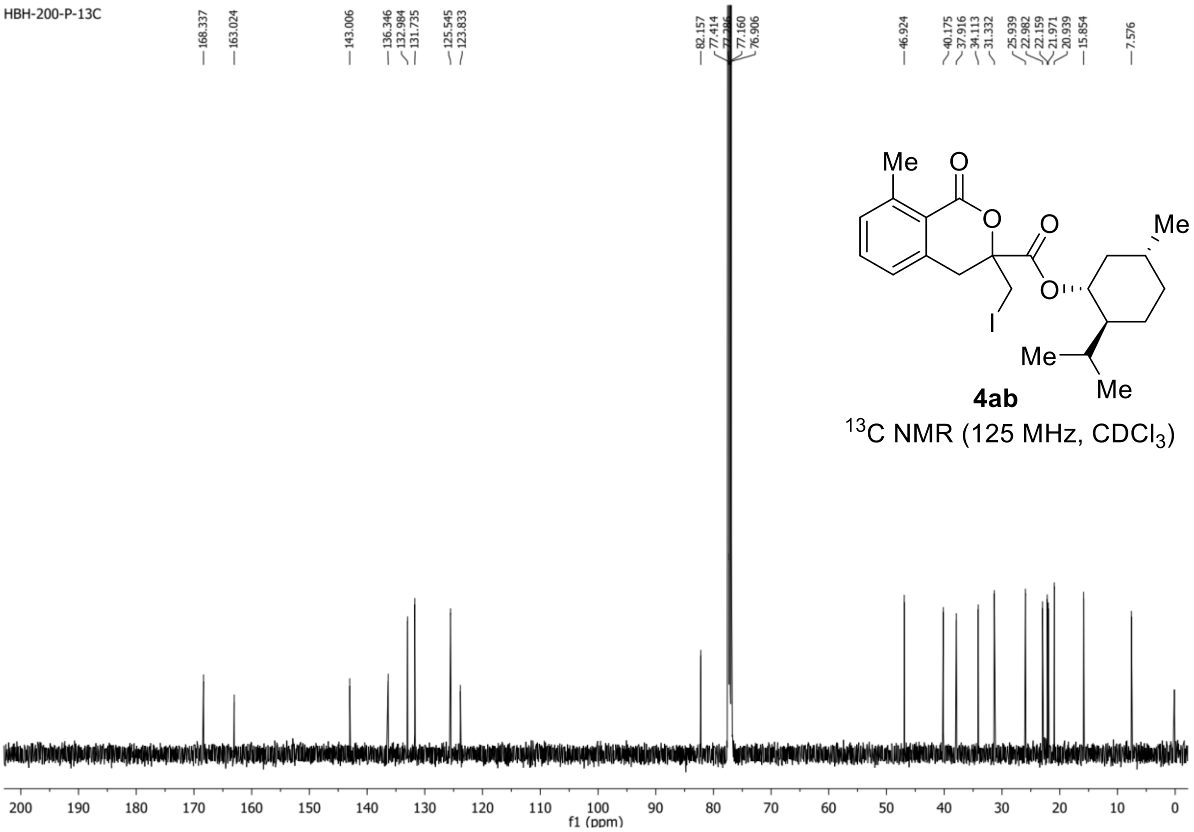

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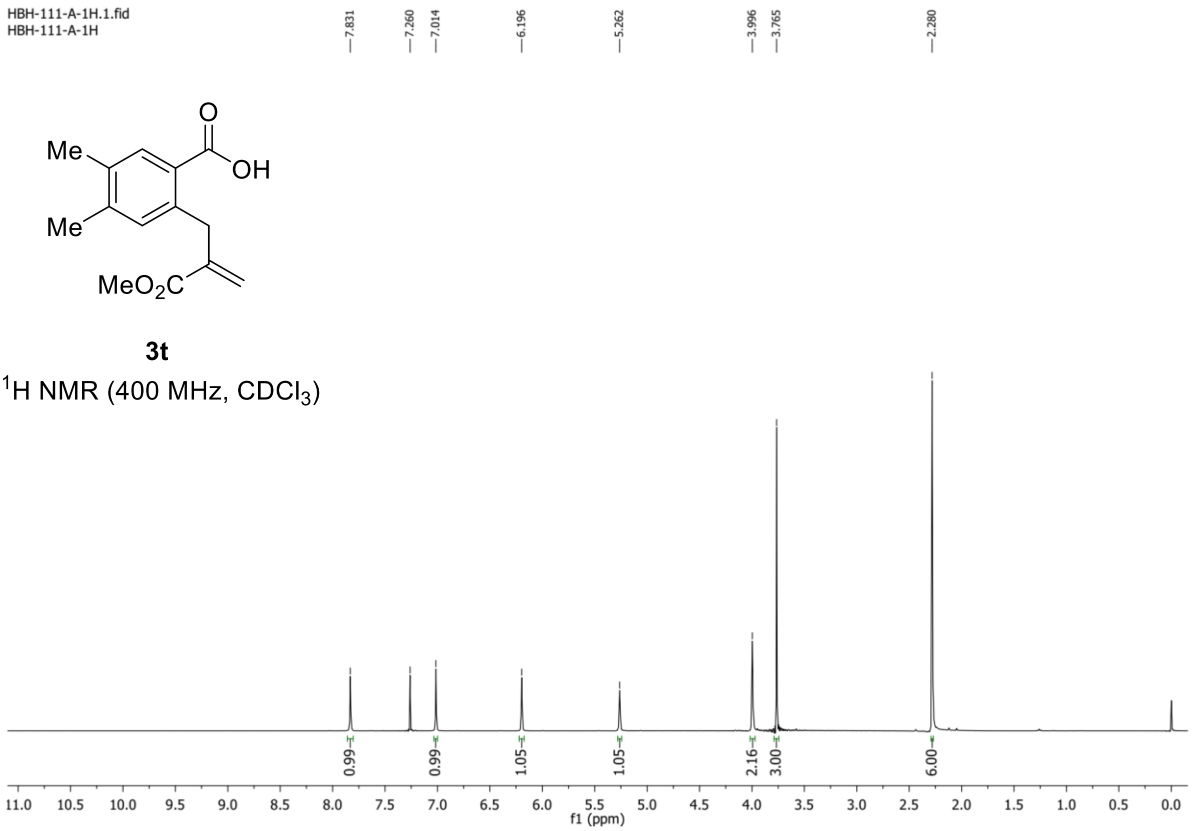

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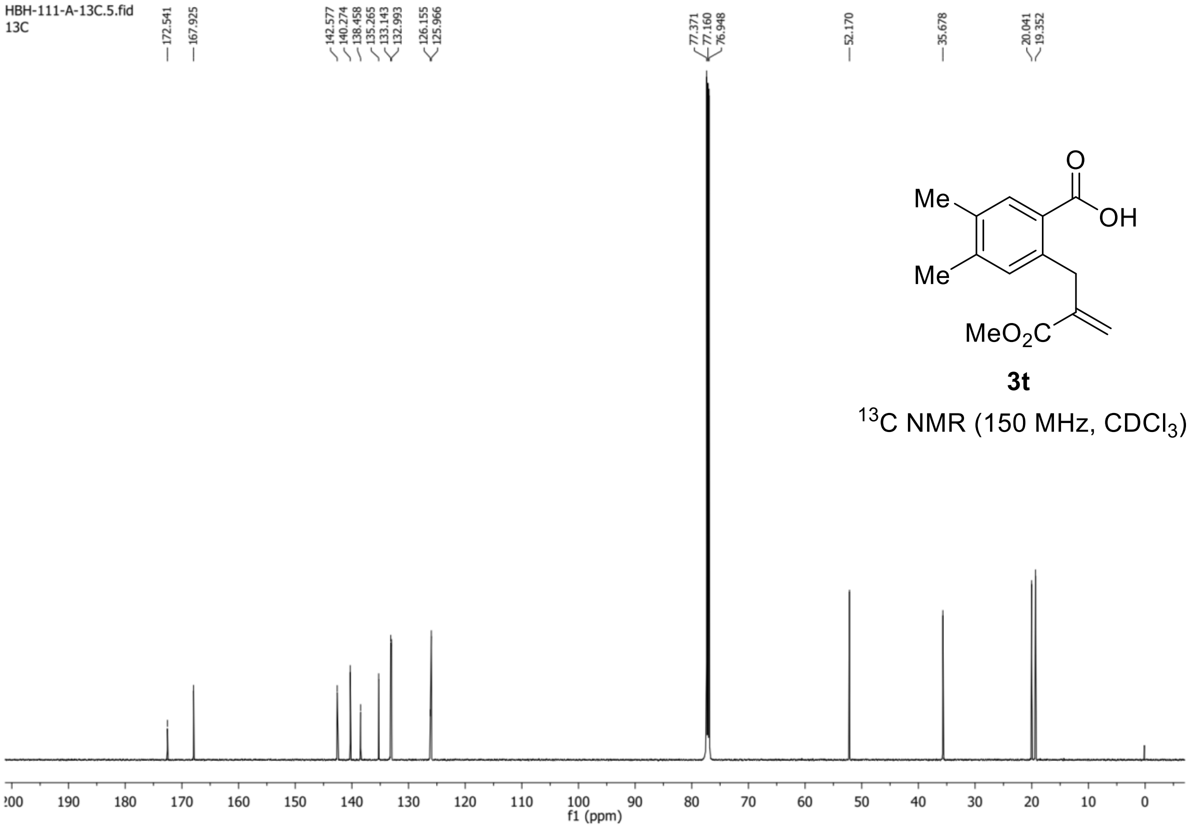

3t

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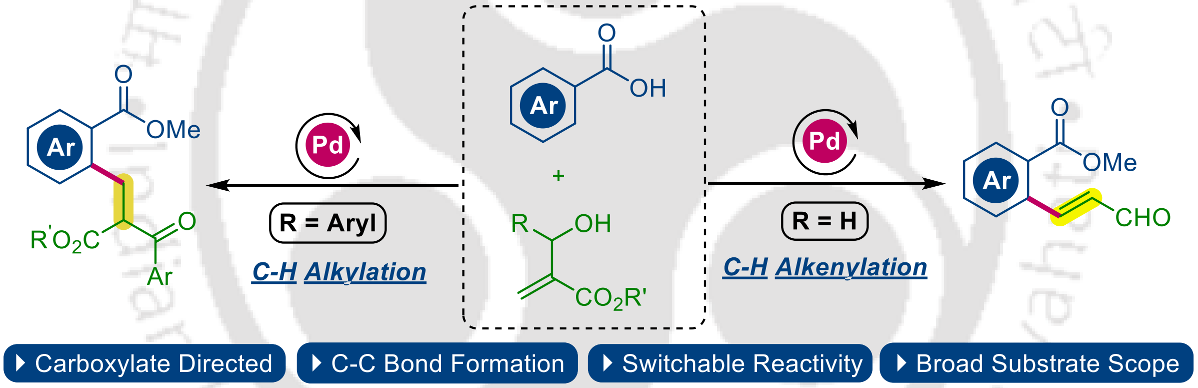
Chapter 3

Substrate-Switchable C–H Alkenylation and Alkylation of Benzoic Acids Using Morita-Baylis-Hillman Alcohols



Chem. Commun. **2025**, *61*, 4200.

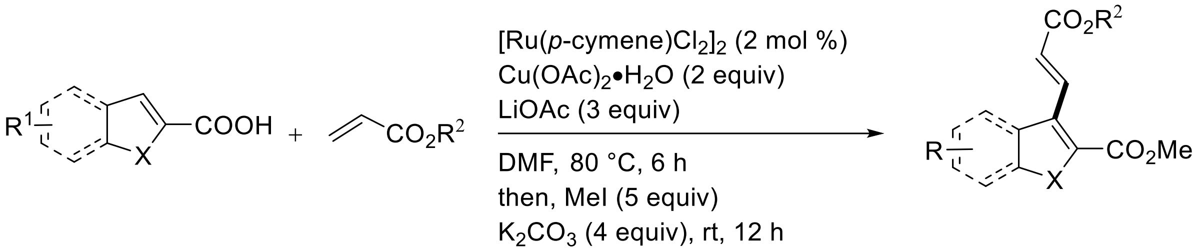
Substrate-Switchable C–H Alkenylation and Alkylation of Benzoic Acids Using Morita-Baylis-Hillman Alcohols

C–H functionalization has emerged as a powerful strategy in modern organic synthesis, enabling the direct transformation of inert C–H bonds into valuable functional groups.[1] Allylic alcohols have emerged as versatile coupling partners in C–H functionalization. In particular, their use in C–H alkenylation and C–H alkylation has attracted considerable attention, as they enable direct incorporation of alkyl fragments into complex molecular frameworks.[2] A defining mechanistic aspect of these transformations is β-hydride elimination, which governs the selectivity between alkenylated and alkylated pathways, ultimately delivering carbonyl-containing products in both cases. Presently, the focus in the field of C–H activation is pivoting towards the use of simple and abundant functional DGs like carboxylic acids.[3] Carboxylate group exhibit moderate coordinating ability and by directly accessing C–H bonds, this strategy minimizes the need for pre-functionalization steps and streamlines synthetic routes, leading to efficient and sustainable synthesis of functionalized molecules. Carboxylic acid-directed C–H functionalization has found wide applications in organic synthesis, enabling the construction of functionalized molecules. Morita-Baylis-Hillman (MBH) adducts are versatile motifs, known for their structural diversity and synthetic utilities.[4] MBH acetate and carbonates has been studied in transition-metal-catalyzed C–H functionalization, resulting exclusively in allyl products.[5] However, the application of MBH alcohols, a class of allylic alcohols, in C–H functionalization remains limited. In this work, we envision to use MBH alcohols with benzoic acids to access carbonyl compounds through C–H alkylation or alkenylation.

3.1 Literature

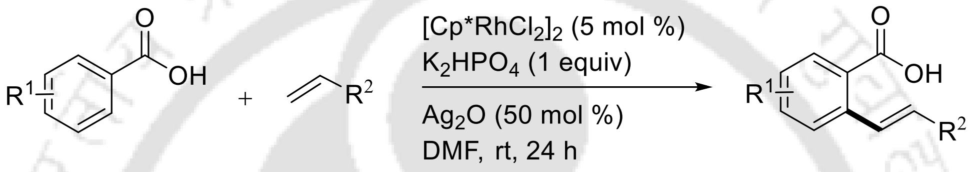
3.1.1 Carboxylate Directed C–H Alkenylation and Alkylation

Satoh reported a Ru(II)-catalyzed oxidative vinylation of thiophene-2-carboxylic acids with alkenes to afford 3-vinylated products. This C–H alkenylation applies to benzothiophene-, benzofuran-, pyrrole-, and indolecarboxylic acids, enabling their selective vinylation (Scheme 1).[6]



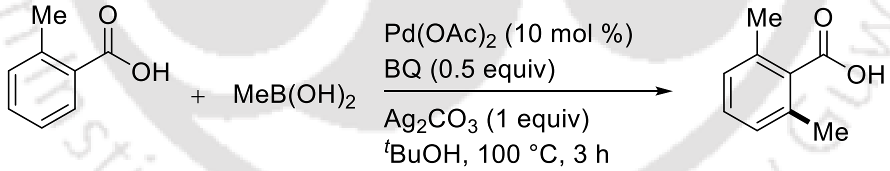
Scheme 1. Ru(II)-Catalyzed Carboxylate Directed Oxidative Alkenylation

Jeganmohan group reported a Rh(III)-catalyzed carboxylate-directed C–H alkenylation of aromatic acids with unactivated alkenes at room temperature, allowing for the efficient synthesis of *ortho*-alkenylated aromatic acids (Scheme 2).[7]



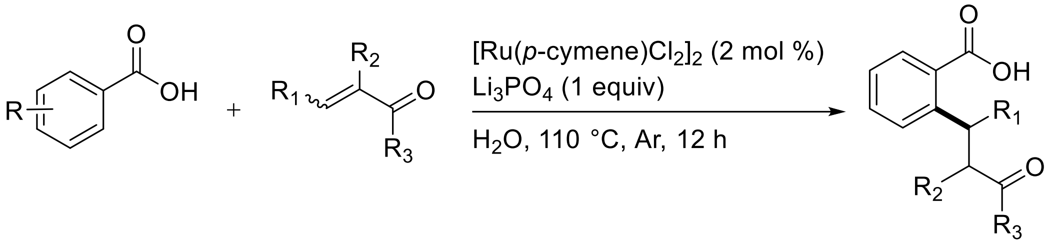
Scheme 2. Carboxylate-Directed C–H Alkenylation with Unactivated Alkenes

Yu showed a Pd(II) catalyzed *ortho*-methylation of benzoic acids using methyl boronic acid (Scheme 3).[8] The protocol describes the direct use of the native carboxyl group as a weakly coordinating DG to achieve regioselective activation of C(sp^2)–H bonds, enabling methylation at the *ortho*-position without external directing auxiliaries.



Scheme 3. Pd(II) Catalyzed *ortho*-Methylation of Benzoic Acids Using Methyl Boronic Acid

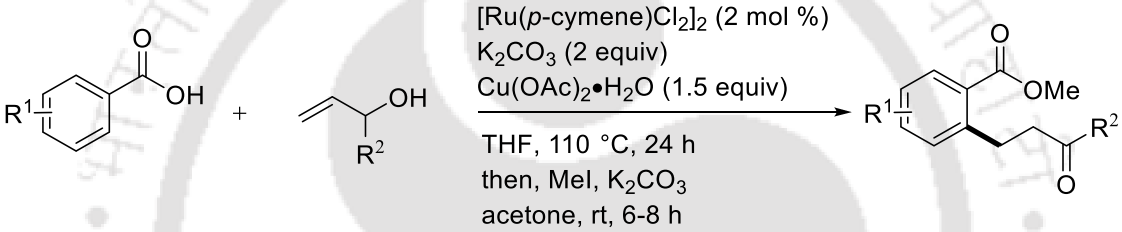
Gooßen group developed a Ru(II)-catalyzed C–H alkylation of benzoic acids with olefins in water, enabling the synthesis of 2-alkylbenzoic acids (Scheme 4).[9] This transformation is applicable for diversely substituted electron-rich/-deficient benzoic acids and accommodates a range of *α,β*-unsaturated olefins, including unprotected acrylic acid.



Scheme 4. Ru(II)-Catalyzed C–H Alkylation of Benzoic Acids with Olefins in Water

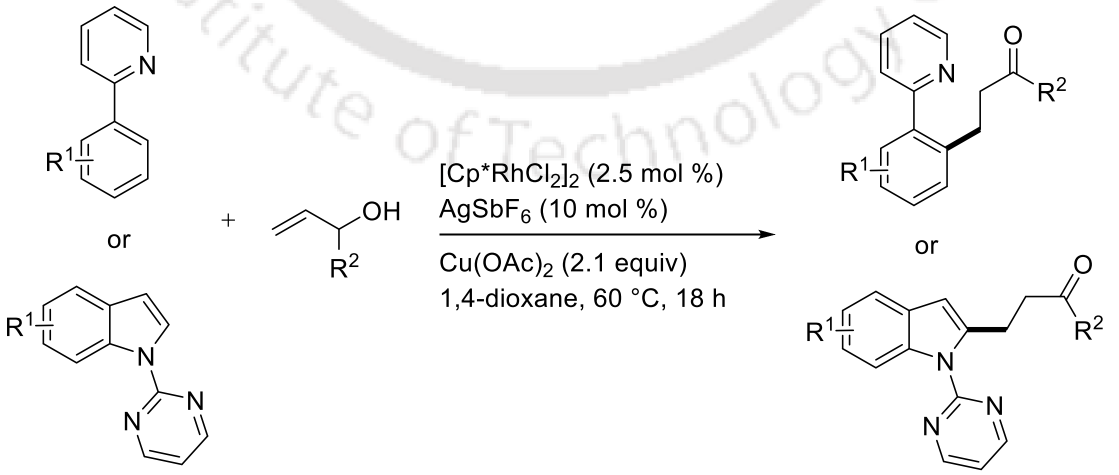
3.1.2 C–H Alkylation and Alkenylation Using Allylic Alcohols

Kapur and co-workers reported a Ru(II)-catalyzed *ortho* C–H alkylation of benzoic acids with allyl alcohols (Scheme 5).[10] The methodology uses Ru-catalysis to achieve selective *ortho*-functionalization of benzoic acids, providing access to 2-alkylated benzoic acid derivatives.



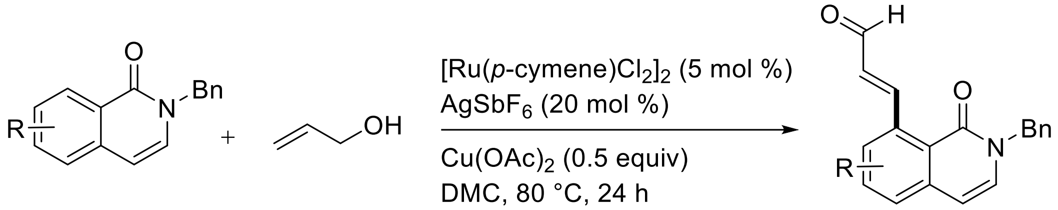
Scheme 5. Ru(II)-Catalyzed *ortho* C–H Alkylation of Benzoic Acids with Allyl Alcohols

Glorius group showed a Rh(III)-catalyzed dehydrogenative alkylation of (hetero)arenes with allylic alcohols (Scheme 6).[11] This transformation enables the coupling of different classes of heteroarenes, including 2-phenylpyridines and indoles with allylic alcohols to produce alkylated products.



Scheme 6. Rh(III)-Catalyzed Alkylation of (Hetero)Arenes with Allylic Alcohols

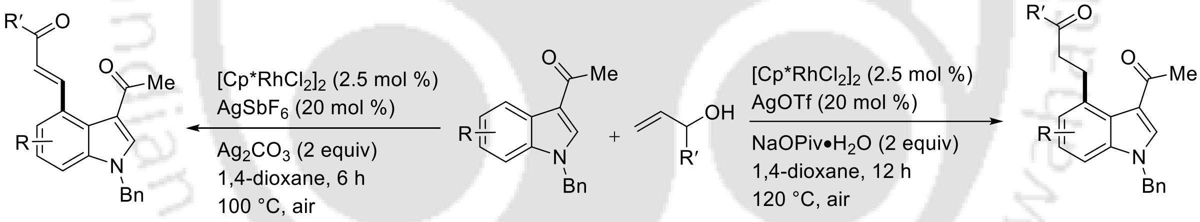
Sharma group reported a Ru(II)-catalyzed alkenylation of isoquinolones with allyl alcohols, producing aldehyde-functionalized isoquinolones (Scheme 7).[12] This protocol notably utilizes dimethyl carbonate (DMC) which makes this method environment-friendly.



Scheme 7. Ru(II)-Catalyzed Alkenylation of Isoquinolones with Allyl Alcohols

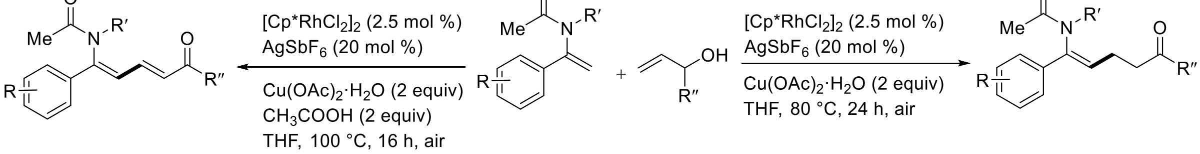
3.1.3 Switchable C–H Alkylation and Alkenylation Using Allylic Alcohol

Our group developed a Rh(III) catalyzed weak carbonyl coordination facilitated switchable C(sp^2)–H alkenylation and alkylation of indoles at the C4 position using allylic alcohols by switching the additives. (Scheme 9).[13] This versatile transformation accommodates a broad range of substrates, proceeding with excellent regioselectivity while exhibiting good functional group tolerance.



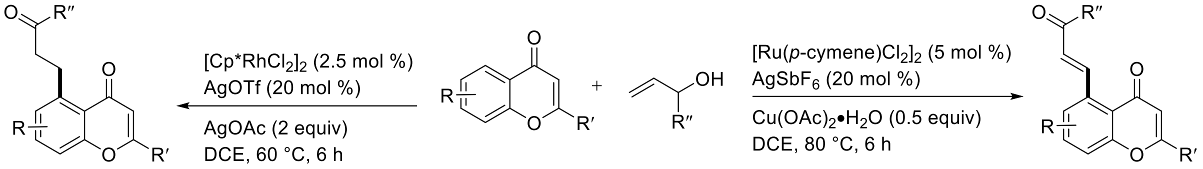
Scheme 8. Rh(III) Catalyzed C-4 Alkenylation and Alkylation of Indoles

Lou and co-workers reported a Rh(III) catalyzed *β*-C(sp^2)–H alkenylation and alkylation of enamides using allylic alcohols. This tunable transformation has been applied to a wide range of substrates and proceeded with excellent regioselectivity and stereoselectivity as well as with good functional group tolerance. (Scheme 10).[14]



Scheme 9. Rh(III) Catalyzed *β*-C–H Alkenylation and Alkylation of Enamides

Zhao and co-workers described two distinct types of C5-functionalization reactions of chromones with allyl alcohols. When employing Rh(III) catalysis, the reaction selectively produces 5-alkylated chromones. In contrast, Ru(II) catalysis leads to the formation of 5-alkenylated chromones. (Scheme 10).[15]



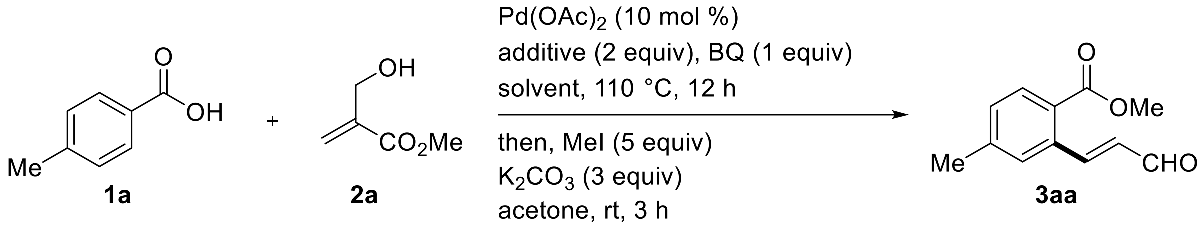
Scheme 10. C5 Alkylation and Alkenylation Reactions of Chromones with Allyl Alcohols

3.2 Present Study

Herein, we report the Pd-catalyzed *ortho*-selective carboxylate directed C–H functionalization of arenes with MBH alcohols as the coupling partner. The reaction using unsubstituted MBH alcohol gives aryl acrylaldehydes, whereas aryl substituted MBH alcohol leads to the formation α-benzyl β-ketoesters. The substrate scope, functional group diversity, substrate switchable selectivity and synthetic utilities are the important practical features. Initially, we probed the reaction conditions to envision the C–H functionalization of benzoic acid **1a** and MBH alcohol **2a** as the model substrates with Pd(OAc)$_2$ as the catalyst (Table 1). To our delight, the C–H alkenylation proceeded with decarboxylation to afford aryl acrylaldehyde **3aa** in 72% yield, when the substrates **1a** (1 equiv) and **2a** (1.1 equiv) were reacted utilizing Pd(OAc)$_2$ (10 mol %), Ag$_2$CO$_3$ (2 equiv) and BQ (1 equiv) in HFIP at 110 °C for 12 h followed by esterification of the carboxylic acid at room temperature for 3 h. Additives such as Na$_2$CO$_3$, K$_2$CO$_3$ and Cs$_2$CO$_3$ in place of Ag$_2$CO$_3$ produced the product in lower yields. Further, additives like Ag$_2$O, AgOAc, NaOAc, and KOAc failed to provide the target product, whereas solvents such as TFE, TCE and MeOH resulted in diminished yields. Control experiments confirmed that both BQ and Ag$_2$CO$_3$ were crucial for the reaction.

Having optimized the reaction conditions, the scope of C–H alkenylation was investigated employing benzoic acids **1b-r** with MBH alcohol **2a** (Table 2). Benzoic acids featuring electron-donating groups in the *para*-position, methoxy **1b** and phenoxy **1c**, afforded **3ba** and **3ca** in yields of 73% and 65%, respectively. *para*-Halogen substituted benzoic acids, fluoro **1d** and bromo **1e** groups, resulted in the formation of **3da** and **3ea** in yields of 74% and 51%, respectively. However, electron-withdrawing

Table 1. Optimization of Reaction Conditions[a]

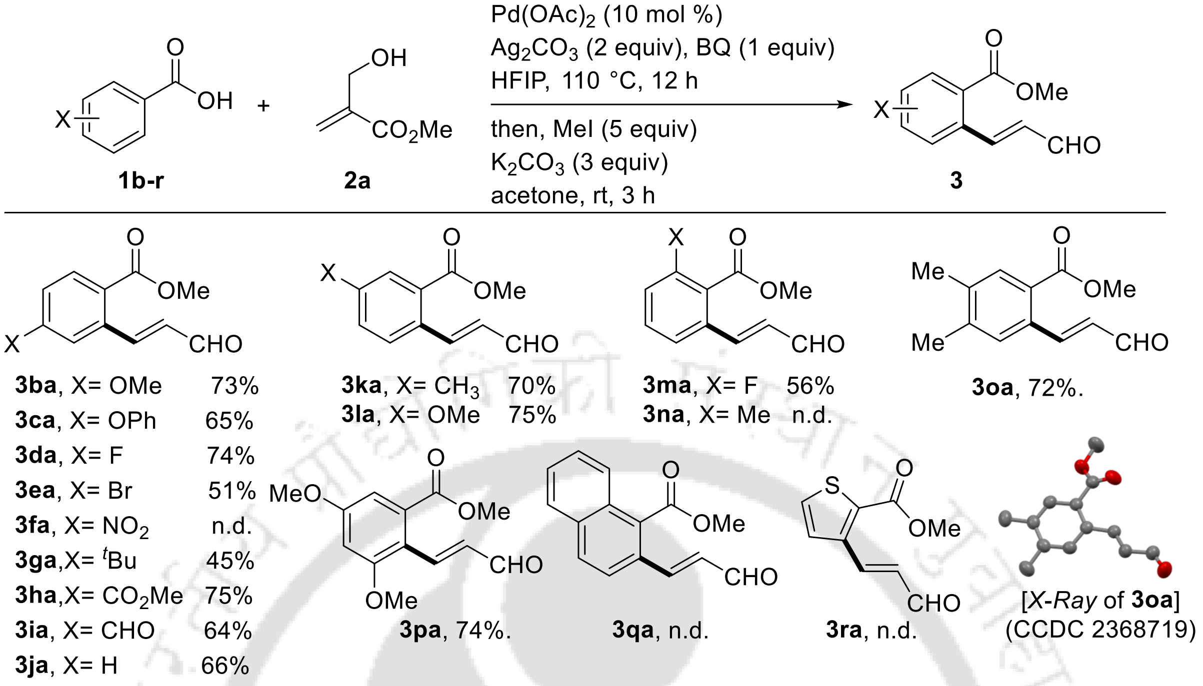


1a **2a** **3aa**

Entry	Additive	Solvent	**3aa** (Yield, %)[b]
1	**Ag_2CO_3**	**HFIP**	**72**
2	Na_2CO_3	HFIP	trace
3	K_2CO_3	HFIP	24
4	Cs_2CO_3	HFIP	30
5	Ag_2O	HFIP	n.d.
6	AgOAc	HFIP	n.d.
7	NaOAc	HFIP	n.d.
8	KOAc	HFIP	n.d.
9	Ag_2CO_3	TFE	58
10	Ag_2CO_3	TCE	56
11	Ag_2CO_3	MeOH	35
12	Ag_2CO_3	EtOH	20
13	Ag_2CO_3	Propan-2-ol	n.d.
14	Ag_2CO_3	$PhCF_3$	n.d.
15	Ag_2CO_3	$(CH_2Cl)_2$	n.d.
16	-	HFIP	n.d.
17[c]	Ag_2CO_3	HFIP	n.d.
18[d]	Ag_2CO_3	HFIP	n.d.
19[e]	Ag_2CO_3	HFIP	55
20[f]	Ag_2CO_3	HFIP	45

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.11 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2 equiv), BQ (1 equiv), Solvent (1 mL), 110 °C, 12 h, then MeI (5 equiv), K_2CO_3 (3 equiv), acetone (1.5 mL) rt, 3h. [b] Isolated yield. [c] In absence of BQ. [d] In absence of $Pd(OAc)_2$. [e] Ag_2CO_3 (1 equiv). [f] At 80 °C. n.d. = not detected. TFE = 2,2,2-trifluoroethanol. TCE = 2,2,2-trichloroethanol. HFIP = 1,1,1,3,3,3-hexafluoroisopropanol. BQ = 1,4-benzoquinone.

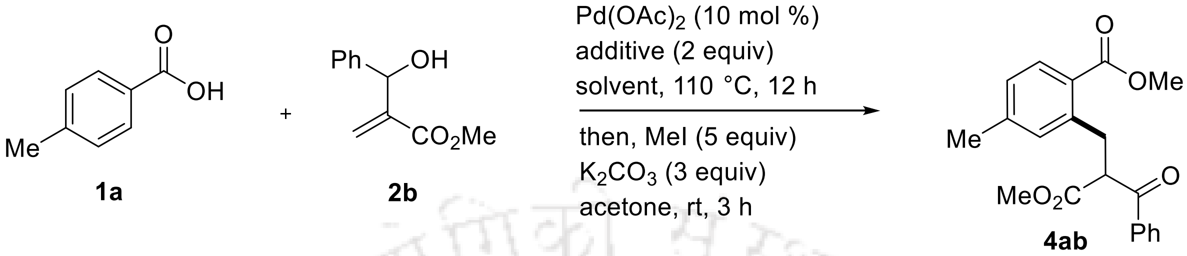
Table 2. Substrate Scope of C–H Alkenylation[a,b]



[a]Reaction conditions: **1b-r** (0.1 mmol), **2a** (0.11 mmol), Pd(OAc)$_2$ (10 mol %), Ag$_2$CO$_3$ (2 equiv), BQ (1 equiv), HFIP (1 mL), 110 °C, 12 h, then MeI (5 equiv), K$_2$CO$_3$ (3 equiv), acetone (1.5 mL) rt, 3h. [b]Isolated yield. n.d. = not detected.

para-nitro group bearing benzoic acid **1f** was an unsuccessful substrate. Notably, *tert*-butyl **1g** group at the *para*-position of benzoic acid produced **3ga** in a yield of 45%. Remarkably, benzoic acids bearing an ester **1h** as well as a formyl **1i** at the *para*-position resulted in the formation of **3ha** and **3ia** in yields of 75% and 64%, respectively. Moreover, free benzoic acid **1j** afforded the desired product **3ja** in 66% yield, whereas *meta* substituted methyl **1k** and methoxy **1l** substituents were found to be conducive to the formation of **3ka** and **3la**, in yields of 70% and 75%, respectively. This regioselectivity might be due to the steric hindrance at the alternate site. Further, *ortho*-fluoro **1m** resulted in the generation of **3ma** in 56% yield, whereas *ortho*-methyl **1n** failed to undergo reaction, which might be due to the steric hindrance near the coupling site. In addition, the 3,4-dimethyl **1o** and 3,5-dimethoxy **1p** benzoic acids yielded **3oa** and **3pa** in 72% and 74% yields, respectively. The structure of **3oa** was determined through single-crystal *X*-ray analysis (CCDC 2368719). However, naphthyl **1q** and thiophene **1r** carboxylic acids failed to yield the desired products. This may be attributed to steric hindrance near the coupling site in the case of **1q** and potential chelation of the heteroatom with the catalyst in the case of **1r**.

Table 3. Optimization of Reaction Conditions[a]

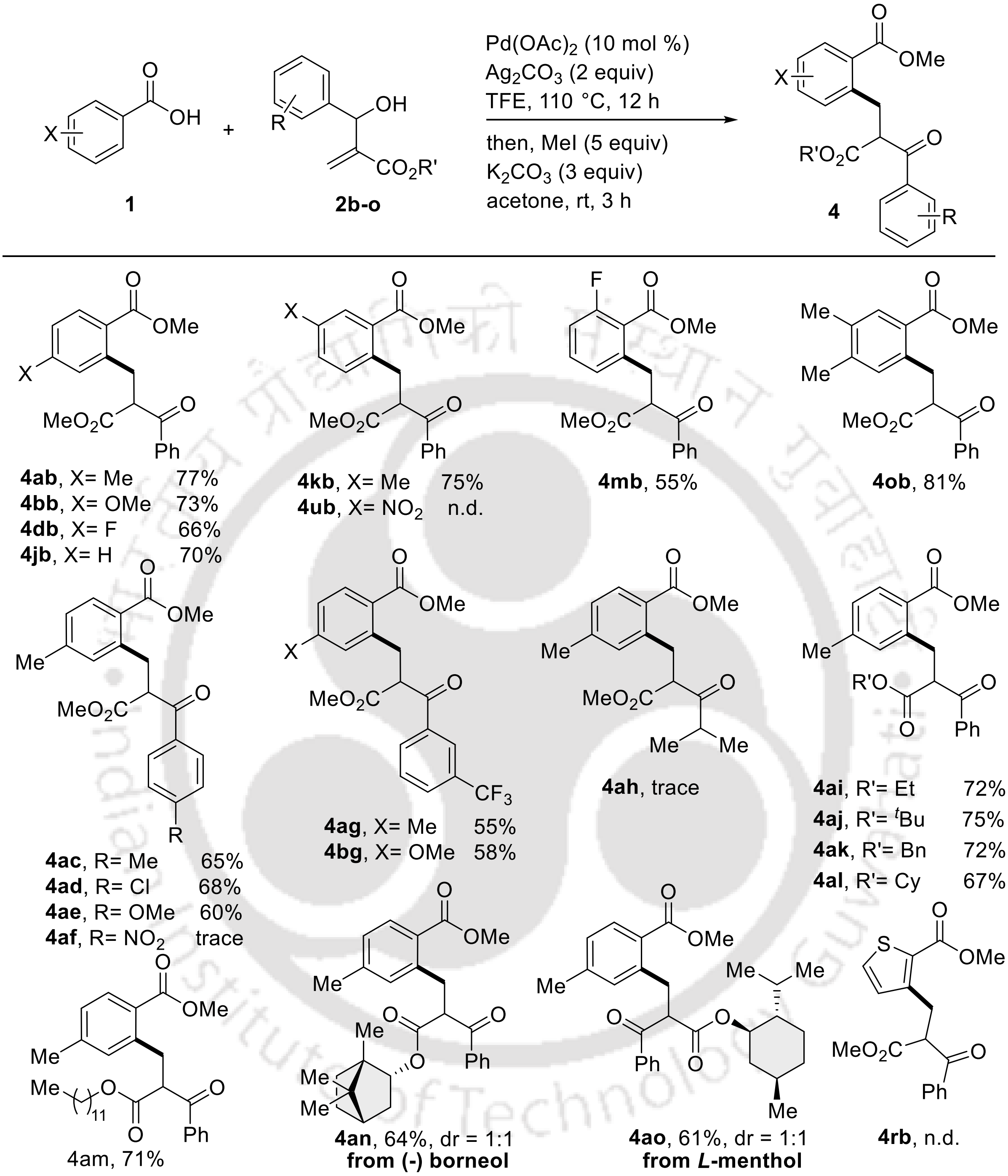


Entry	Additive	Solvent	**4ab** (Yield, %)[b]
1[c]	Ag_2CO_3	HFIP	51
2	Ag_2CO_3	HFIP	67
3	**Ag_2CO_3**	**TFE**	**77**
4	Ag_2CO_3	TCE	44
5	Ag_2CO_3	MeOH	27
6	Ag_2CO_3	EtOH	25
7	Ag_2CO_3	Propan-2-ol	n.d.
8	Ag_2CO_3	$PhCF_3$	n.d.
9	Ag_2CO_3	$(CH_2Cl)_2$	30
10	-	TFE	n.d.
11[d]	Ag_2CO_3	TFE	n.d.
12[e]	Ag_2CO_3	TFE	50
13[f]	Ag_2CO_3	TFE	41

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.11 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2 equiv), Solvent (1 mL), 110 °C, 12 h, then MeI (5 equiv), K_2CO_3 (3 equiv), acetone (1.5 mL) rt, 3h. [b]Isolated yield. [c]In presence of BQ (1 equiv). [d]In absence of $Pd(OAc)_2$. [e]Ag_2CO_3 (1 equiv). [f]At 80 °C. n.d. = not detected. TFE = 2,2,2-trifluoroethanol. TCE = 2,2,2-trichloroethanol. HFIP = 1,1,1,3,3,3-hexafluoroisopropanol. BQ = 1,4-benzoquinone.

Interestingly, when the reaction was carried out with phenyl-substituted MBH alcohol **2b** and benzoic acid **1a**, we observed C–H alkylation instead of alkenylation, producing *β*-ketoester **4ab** in a 54% yield (Table 3, entry 1). Intrigued by this outcome, we proceeded to optimize the C–H alkylation reaction using benzoic acid **1a** and MBH alcohol **2b** as the model

Table 4. Substrate Scope of C–H Alkylation[a,b]



4ab, X= Me 77%
4bb, X= OMe 73%
4db, X= F 66%
4jb, X= H 70%

4kb, X= Me 75%
4ub, X= NO$_2$ n.d.

4mb, 55%

4ob, 81%

4ac, R= Me 65%
4ad, R= Cl 68%
4ae, R= OMe 60%
4af, R= NO$_2$ trace

4ag, X= Me 55%
4bg, X= OMe 58%

4ah, trace

4ai, R'= Et 72%
4aj, R'= ^{t}Bu 75%
4ak, R'= Bn 72%
4al, R'= Cy 67%

4am, 71%

4an, 64%, dr = 1:1
from (-) borneol

4ao, 61%, dr = 1:1
from *L*-menthol

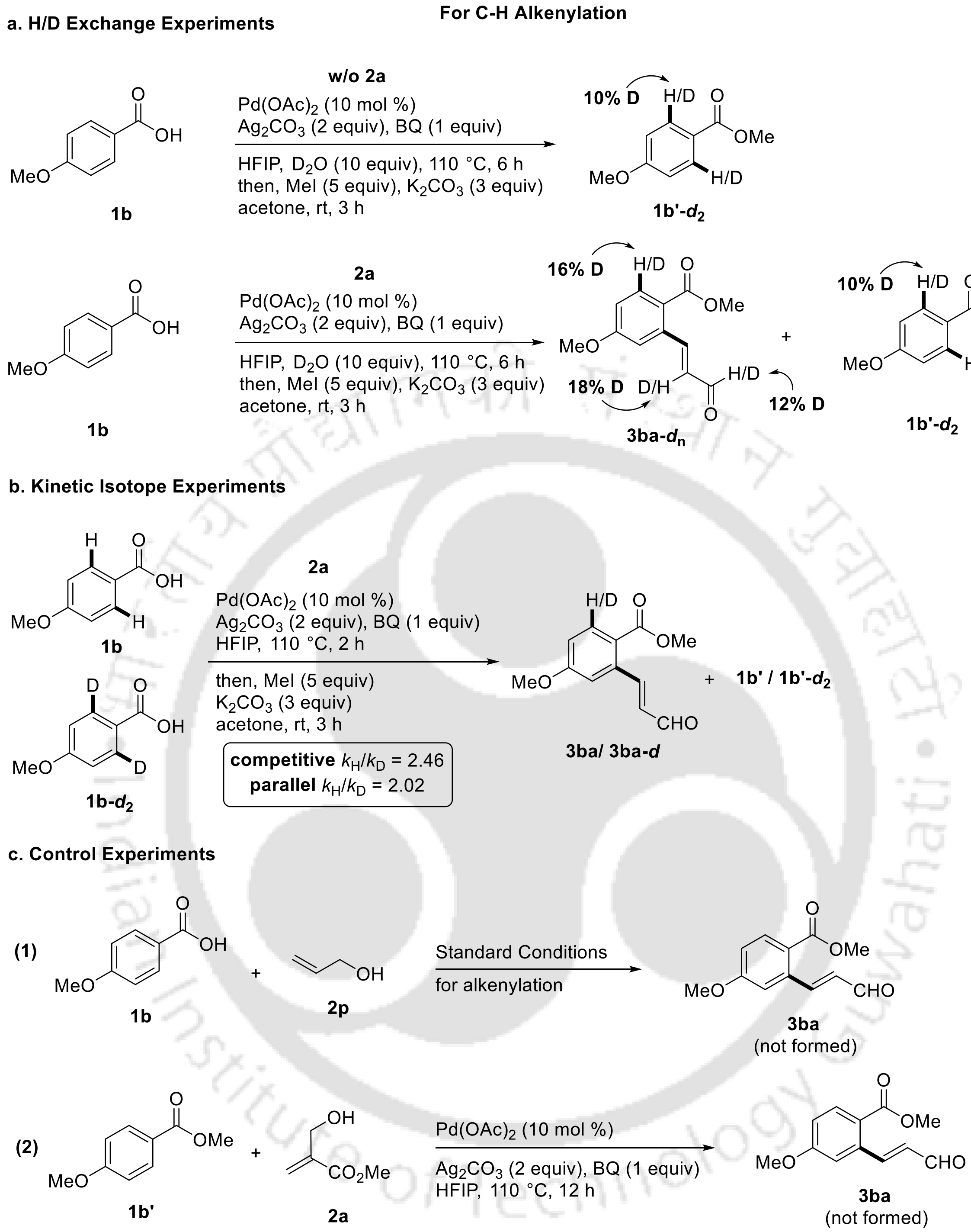
4rb, n.d.

[a]Reaction conditions: benzoic acids **1** (0.1 mmol), **2b-o** (0.11 mmol), Pd(OAc)$_2$ (10 mol %), Ag$_2$CO$_3$ (2 equiv), TFE (1 mL), 110 °C, 12 h, then MeI (5 equiv), K$_2$CO$_3$ (3 equiv), acetone (1.5 mL), rt, 3h. [b]Isolated yield. n.d. = not detected.

substrates. We found that the optimal conditions involved using $Pd(OAc)_2$ (10 mol %) and Ag_2CO_3 (2 equiv) in TFE at 110 °C for 12 h, followed by esterification of the carboxylic acid, which afforded **4ab** in 77% yield (Table 3, entry 3). Solvents such as HFIP, TCE and MeOH resulted in less yields. Control experiment confirmed that the reaction was unsuccessful in the absence of Ag_2CO_3, and the starting materials was recovered intact.

With the optimized conditions established, the scope of C–H alkylation was investigated using a series of benzoic acids in conjunction with MBH alcohols **2b-o** (Table 4). Benzoic acids featuring *para*-substituents such as methoxy **1b** and fluoro **1d** when reacted with **2b** to afford **4bb** and **4db** in yields of 73% to 66%, respectively. Moreover, unsubstituted benzoic acid **1j** afforded the target **4jb** in 70% yield. *meta*-Methyl **1k** and *ortho*-fluoro **1m** benzoic acids facilitated the formation of **4kb** and **4mb** in yields of 75% and 55%, respectively, whereas *meta*-nitro **1u** benzoic acid failed to undergo reaction and the starting materials were recovered. However, 3,4-dimethyl substituted benzoic acid **1o** underwent reaction to afford **4ob** in 81% yield. Subsequent investigations involved varying the aryl and ester groups of aryl-substituted MBH alcohols **2c-o** with benzoic acids **1a-b**. Variants such as *para*-methyl **2c**, *para*-chloro **2d** and *para*-methoxy **2e** at the aryl ring of MBH alcohol yielded *β*-ketoester **4ac-ae** in 60-68% yields. In contrast, *para*-nitrophenyl bearing MBH alcohol **2f** produced a trace amount of the product **4af**. Moreover, *meta*-trifluoromethylphenyl-substituted alcohol **2g**, in combination with benzoic acids **1a** and **1b**, yielded **4ag** and **4bg** in yields of 55% and 58%, respectively, whereas the aliphatic aldehyde derived MBH alcohol **2h** afforded **4ah** in a trace amount. Variation in the ester group of the MBH alcohol, such as ethyl **2i**, *tert*-butyl **2j**, benzyl **2k** and cyclohexyl **2l**, in combination with benzoic acid **1a**, resulted in the successful formation of **4ai-al** in yields ranging from 67% to 75%. Additionally, using long-chain dodecyl **2m**, natural products such as (-)-borneol **2n**, and *L*-menthol **2o** tethered phenyl-substituted MBH alcohols, led to the formation of *β*-ketoesters **4am-ao** in yields ranging from 61% to 71%. However, thiophene carboxylic acid **1r** failed to afford the desired product, which might be due to complex formation with the Pd-catalyst.

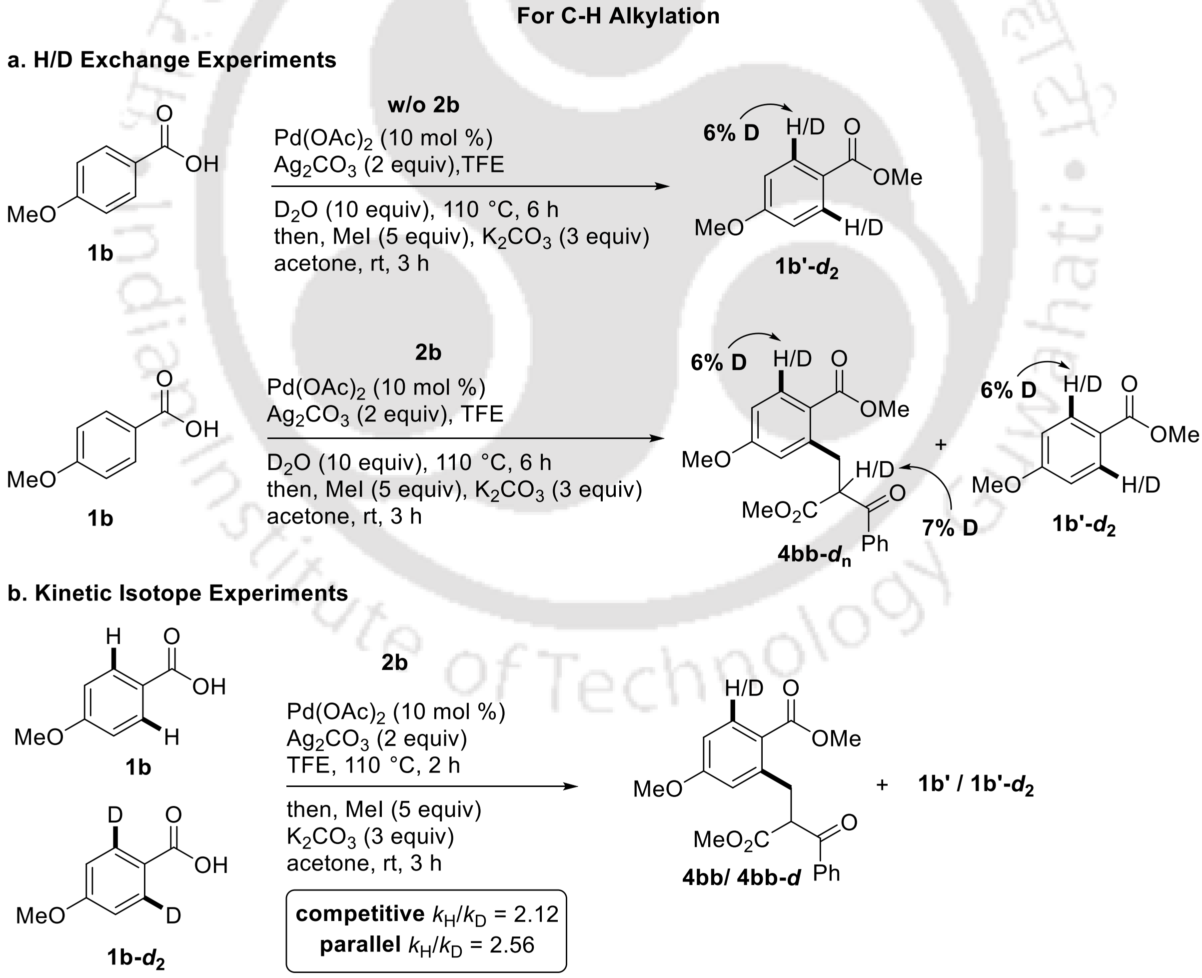
To get insights into the catalytic pathways, H/D scrambling experiments using D_2O as a co-solvent in the absence of **2a** or **2b** showed deuterium incorporation of 10% at the *ortho* positions of **1b** under the C–H alkenylation condition (Scheme 11a) and 6% at the *ortho* positions of **1b** under the C–H alkylation condition (Scheme 12a). These results indicate that the C–H activation step involved in both C–H alkenylation and alkylation is likely reversible. Further, in the presence of coupling partner **2a** or **2b**, deuterium incorporations were observed



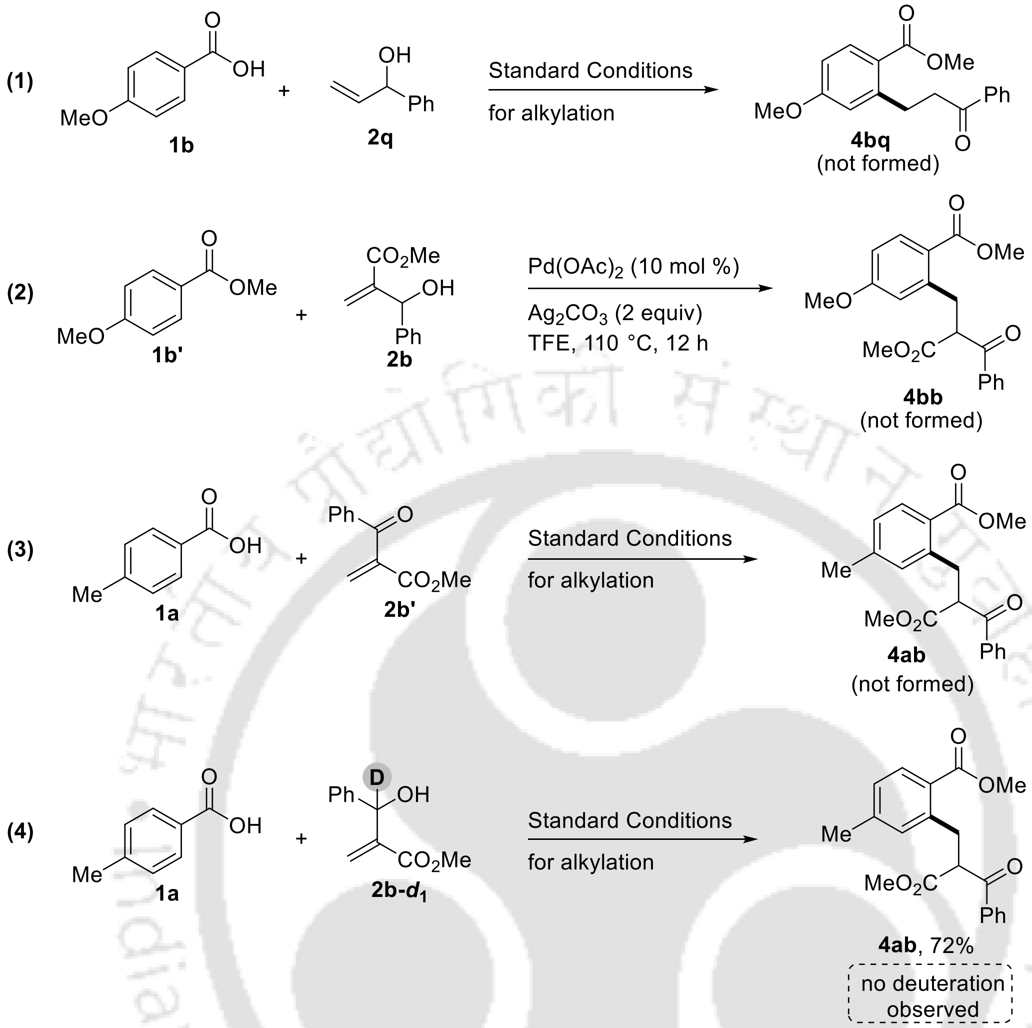
Scheme 11. Preliminary Mechanistic Investigation: For C–H Alkenylation

at the *ortho* positions as well as the alkenylated residue of **3ba-d_n** (Scheme 11a) and alkylated residue of **4bb-d_n** (Scheme 12a). In addition, the intermolecular kinetic isotope experiments of **1b** and **1b-d_2** with **2a** under C–H alkenylation exhibited k_H/k_D= 2.46 (competitive) and 2.02 (parallel) (Scheme 11b), whereas the intermolecular kinetic isotope experiments of **1b** and **1b-d_2** with **2b** under C–H alkylation produced k_H/k_D = 2.12 (competitive) and 2.56 (parallel)

(Scheme 12b). These results might imply that the C–H bond cleavage might be involved in the rate-determining step. Additionally, control experiments were carried out in which 4-methoxybenzoic acid **1b** was reacted with allylic alcohol **2p** under C–H alkenylation (Scheme 11c(1)) and with allylic alcohol **2q** under C–H alkylation (Scheme 12c(1)). In both cases, the target products **3ba** and **4bq** were not obtained, suggesting that the ester group of the MBH alcohol is essential for these transformations. Moreover, the methyl ester derivative of 4-methoxybenzoic acid **1b′** also failed to generate the target products **3ba** (Scheme 11c(2)) and **4bb** (Scheme 12c(2)). In addition, the reaction of 4-methylbenzoic acid **1a** with enone **2b′** was unsuccessful to furnish **4ab** (Scheme 12c(3)), which reveals that an enone intermediate might not be involved. Additionally, the reaction of 4-methylbenzoic acid **1a** with deuterated MBH alcohol **2b-*d₁*** afforded **4ab** without deuterium incorporation at the alkyl residue (Scheme 12c(4)), consistent with the involvement of a selective *β*-hydride elimination pathway.

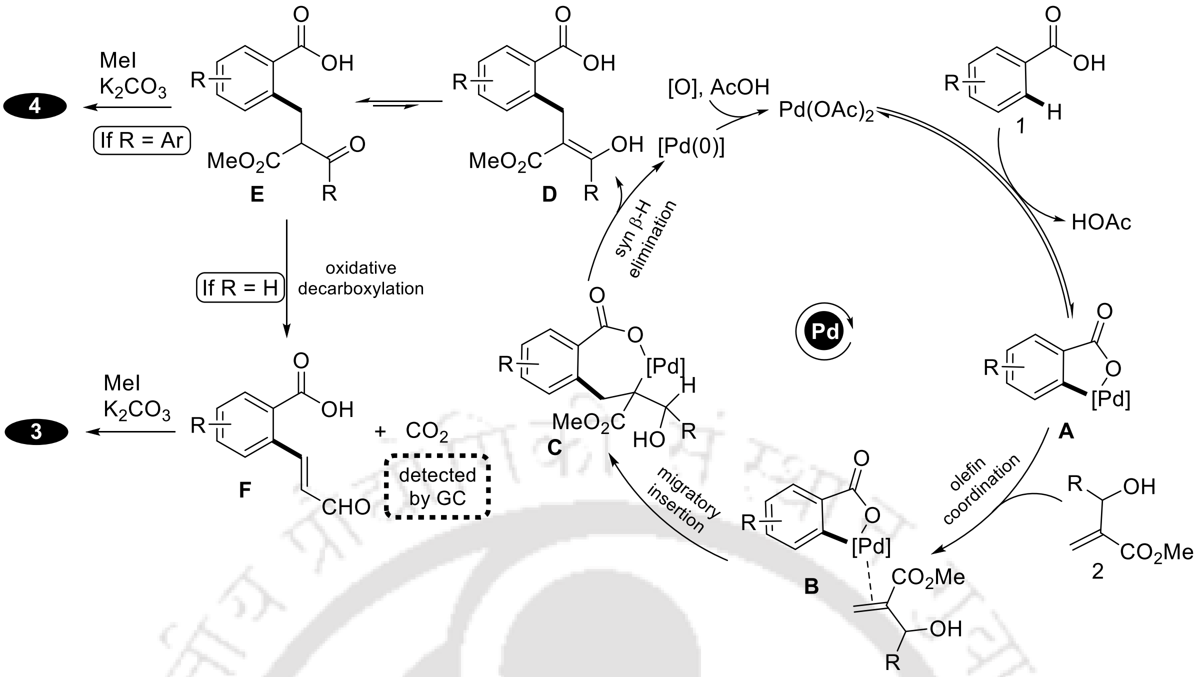


c. Control Experiments

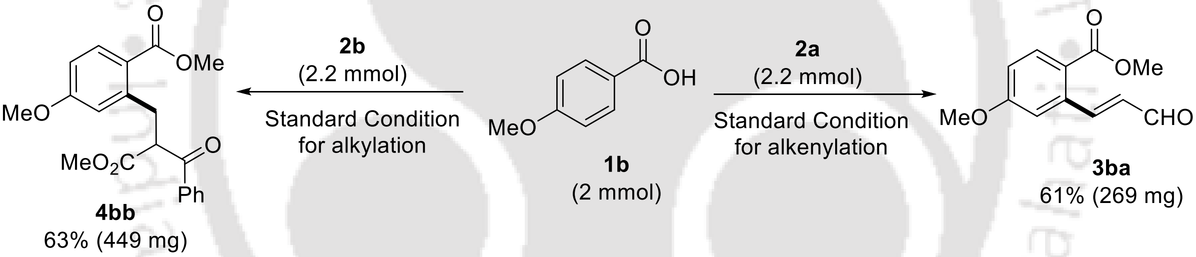


Scheme 12. Preliminary Mechanistic Investigation: For C–H Alkylation

Based on these experimental results and literature precedents,[2,14-17] a plausible reaction pathway is presented in Scheme 13. Initially, chelation of the carboxylate of benzoic acid **1** with Pd(OAc)₂ can form the palladacycle **A**, which can make chelation with double bond of MBH alcohol **2** to give **B**. The later may undergo migratory insertion into the Pd-carbon bond to produce the seven membered palladacycle **C**. The syn *β*-hydride elimination can lead to the formation of **D** that can tautomerize to yield **E**. When R = aryl, esterification of intermediate **E** furnishes the alkylated **4**. In contrast, when R = H, **E** undergoes oxidative decarboxylation[17] with CO₂ liberation (detected by GC) to afford **F**, which subsequently undergoes esterification to deliver the alkenylated product **3**. The Pd(0) species undergoes reoxidation to regenerate the active Pd(II) catalyst, thereby completing the catalytic cycle.

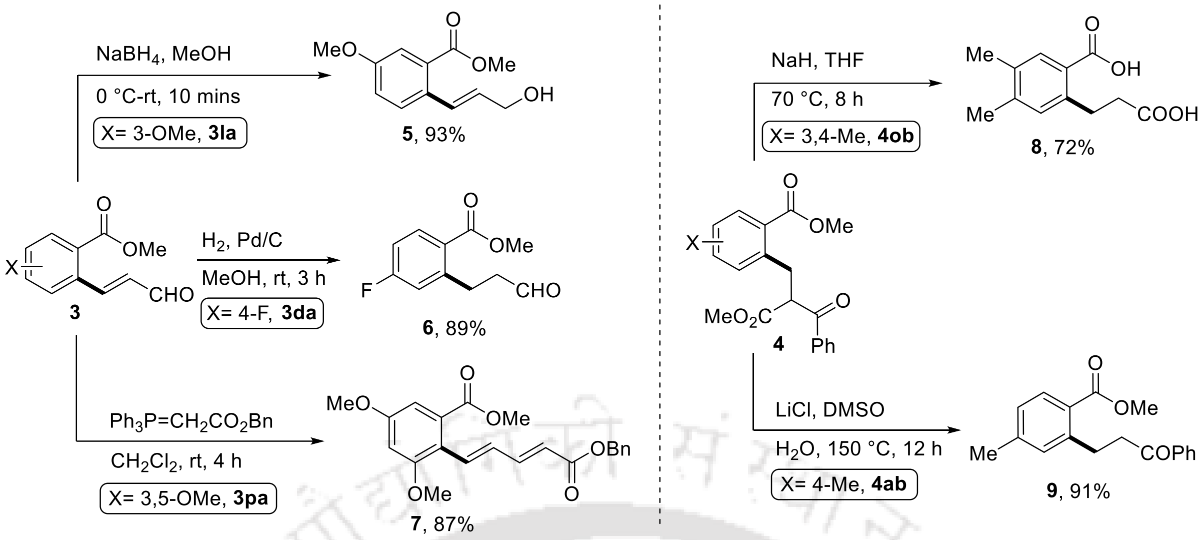


Scheme 13. Plausible Reaction Pathway



Scheme 14. Scale-up Syntheses

To assess the scalability of the C–H alkenylation reaction, the reaction of **1b** and **2a** was examined as the representative examples (Scheme 14). This reaction yielded **3ba** in 61% yield (269 mg). Similarly, the scale-up of the C–H alkylation reaction was conducted by employing **1b** and **2b** as the representative examples (Scheme 14), resulting in the formation of **4bb** in 63% yield (449 mg). In addition, a series of post-synthetic transformations were performed to demonstrate the synthetic utility of the methodology (Scheme 15). The Reduction of **3la** with $NaBH_4$ selectively reduced the aldehyde group while leaving the double bond intact, affording allylic alcohol **5** in 93% yield. Catalytic hydrogenation of **3da** resulted in the formation of **6** in 89% yield. A Wittig reaction of **3pa** with $Ph_3P{=}CH_2CO_2Bn$ provided the di-alkenylated **7** in 87% yield. The reaction of the alkylated **4ob** with NaH in THF at 70 °C gave **8** in 72% yield, while Krapcho decarboxylation of **4ab** delivered **9** in 91% yield.



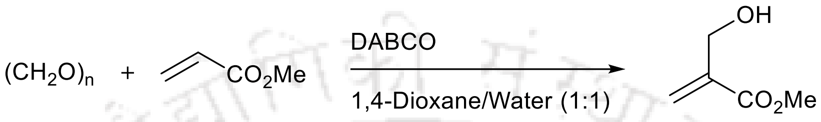
Scheme 15. Post-Synthetic Transformations

In conclusion, a Pd-catalyzed, substrate switchable carboxylate-directed C–H alkenylation and alkylation of benzoic acids has been developed using MBH alcohols as coupling partners. The alkenylation delivers aryl acrylaldehydes, while the alkylation furnishes α-benzyl β-ketoesters. Notable features of this protocol include substrate switchable reactivity, scalability, functional group tolerance, and broad substrate scope.

3.3 Experimental Section

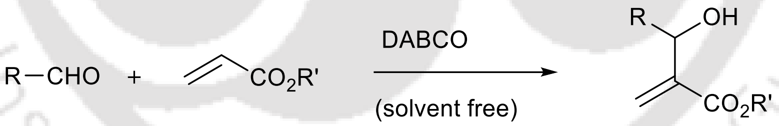
General Information. $Pd(OAc)_2$ (97%), Ag_2CO_3, Ag_2O, AgOAc (≥99.99%), NaOAc (98%), KOAc (98%), Na_2CO_3, K_2CO_3, Cs_2CO_3, 2,2,2-trifluoroethanol (TFE), 2,2,2-trichloroethanol (TCE), 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) and benzoic acids of Sigma-Aldrich, BLD Pharm and TCI chemicals were used as received. MeOH, CH_2Cl_2 and $(CH_2Cl)_2$ 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 EtOAc 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, dd = doublet of doublets 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-18 (Göttingen, Germany).

General Procedure for the Preparation of MBH Alcohol 2a.



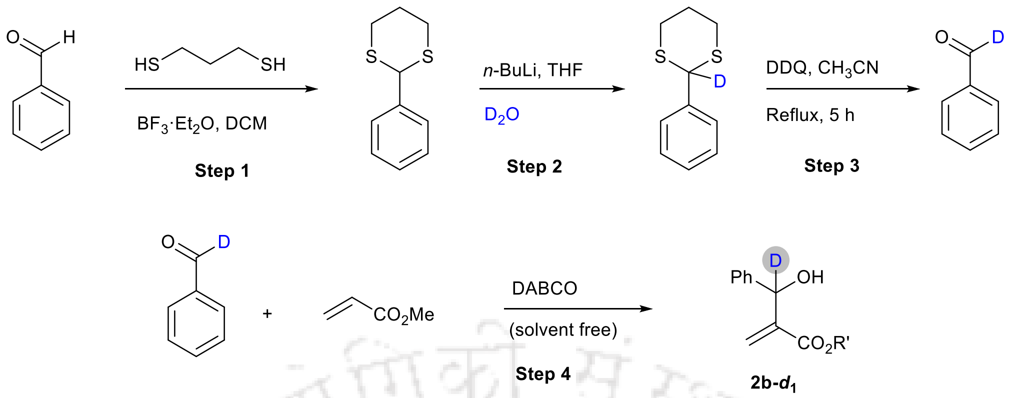
To a solution of paraformaldehyde (20 mmol, 600 mg, 1.0 equiv) in dioxane/water (1:1) (30 mL, 0.6 M), methyl acrylate (60 mmol, 1.72 g, 3.0 equiv) and DABCO (20 mmol, 2.240 g, 1.0 equiv) were added and stirred at room temperature for 12 h. After completion (monitored by TLC), the reaction mixture was diluted with EtOAc (20 mL) and washed successively with saturated solution of $NaHCO_3$ (2 x 20 mL) and brine (1 x 10 mL). Drying of the organic layer over Na_2SO_4 and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford the MBH alcohol **2a**.

General Procedure for the Preparation of MBH Alcohols 2b-o.



Aldehyde (20 mmol, 1.0 equiv), acrylate (60 mmol, 3.0 equiv) and DABCO (20 mmol, 2.24 g, 1.0 equiv) were stirred at room temperature under solvent free condition for 3 h to 7 days. After completion (monitored by TLC), the reaction mixture was diluted with EtOAc (20 mL) and washed successively with saturated solution of $NaHCO_3$ (2 x 20 mL) and brine (1 x 10 mL). Drying of the organic layer over Na_2SO_4 and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford the MBH alcohol **2b-o**.

Procedure for the Preparation of Deuterated MBH Alcohol 2b-*d*₁.



Step 1: To a stirred solution of benzaldehyde (6.0 mmol, 636 mg, 1.0 equiv) and propane-1,3-dithiol (6.0 mmol, 649 mg, 1.0 equiv) in CH_2Cl_2 (20 mL, 0.3 M) were slowly added $BF_3{\cdot}Et_2O$ (3 mmol, 0.37 mL, 0.3 equiv) at 0 °C. The resulting mixture was allowed to warm to room temperature and continued to the stirring for 30 min until the disappearance of benzaldehyde was determined by TLC analysis. The reaction was quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford the corresponding 2-phenyl-1,3-dithiane in 91% (1.1 g) yield.

Step 2: To a stirred solution of 2-phenyl-1,3-dithiane (3 mmol, 589 mg, 1 equiv) in THF (15 mL, 0.2 M) was added *n*-BuLi (1.6 M in hexane solution, 6 mmol, 5.5 mL, 2 equiv) at -35 °C under N_2 atmosphere. After stirring for 3 h, D_2O (34.4 mmol, 0.6 mL, 4 equiv) was added into the reaction mixture. After completion (monitored by TLC), the mixture was diluted with H_2O (5 mL) and extracted with EtOAc (3 x 15 mL). Drying (Na_2SO_4) and evaporation of the solvent gave deuterated 2-phenyl-1,3-dithiane residue, which was used for the next step without further purification.

Step 3: To a stirred solution of deuterated 2-phenyl-1,3-dithiane (3 mmol, 592 mg, 1.0 equiv) in CH_3CN (15 mL, 0.2 M) was added DDQ (3.3 mmol, 749 mg, 1.0 equiv) and the resulting mixture was refluxed at 90 °C for 5 h. After completion, the solvent was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 (10 mL) and passed through a short pad of celite. Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford the deuterated benzaldehyde in 85% (273 mg) yield.

Step 4: The deuterated benzaldehyde (step 3) was reacted with methyl acrylate as described in the general procedure for the preparation of MBH alcohol to produce the deuterated MBH alcohol **2b-*d*$_1$**.

General Procedure for the Pd-Catalyzed C–H Alkenylation of Benzoic acids with MBH Alcohols. Benzoic acid **1** (0.1 mmol, 1.0 equiv), MBH alcohol **2a** (0.11 mmol, 1.1 equiv), $Pd(OAc)_2$ (0.01 mmol, 2.3 mg, 0.1 equiv), Ag_2CO_3 (0.2 mmol, 55 mg, 2.0 equiv) and 1,4-benzoquinone (0.1 mmol, 11 mg, 1.0 equiv) were stirred in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) (1 mL, 0.1 M) at 110 ° C (in a pre-heated oil bath) in a sealed tube for 12 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (5 mL) and passed through a short celite pad. Evaporation of the solvent gave a residue, which was stirred with K_2CO_3 (0.3 mmol, 41.5 mg, 3.0 equiv) and MeI (0.5 mmol, 31 μL, 5 equiv) in acetone (2 mL, 0.05 M) at room temperature for 3 h. After completion (monitored by TLC), the solvent was evaporated under reduced pressure and resulting residue was mixed with water (10 mL) and extracted with EtOAc (2 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford **3**.

Scale-up Synthesis of 3ba. 4-Methoxybenzoic acid **1b** (2 mmol, 304 mg, 1.0 equiv), MBH alcohol **2a** (2.2 mmol, 255 mg, 1.1 equiv), $Pd(OAc)_2$ (0.2 mmol, 45 mg, 0.1 equiv), Ag_2CO_3 (4 mmol, 1.1 g, 2.0 equiv) and 1,4-benzoquinone (2 mmol, 216 mg, 1.0 equiv) were stirred in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) (10 mL, 0.2 M) at 110 ° C (in a pre-heated oil bath) in a sealed tube for 12 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (20 mL) and passed through a short celite pad. Evaporation of the solvent gave a residue that was stirred with K_2CO_3 (6 mmol, 828 mg, 3.0 equiv) and MeI (10 mmol, 0.6 mL, 5.0 equiv) in acetone (20 mL, 0.1 M) at room temperature for 3 h. After completion (monitored by TLC), the solvent was evaporated under reduced pressure and resulting residue was mixed with water (30 mL) and extracted with EtOAc (2 x 30 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford **3ba** in 61% (269 mg) yield.

General Procedure for the Pd-Catalyzed C–H Alkylation of Benzoic acids with MBH Alcohols. Benzoic acid **1** (0.1 mmol, 1.0 equiv), MBH alcohol **2b-o** (0.11 mmol, 1.1 equiv), $Pd(OAc)_2$ (0.01 mmol, 2.3 mg, 0.1 equiv) and Ag_2CO_3 (0.2 mmol, 55 mg, 2.0 equiv) were stirred in 2,2,2-trifluoroethanol (TFE) (1 mL, 0.1 M) at 110 °C (in a pre-heated oil bath) in a sealed tube for 12 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (5 mL) and passed through a short pad of celite. Evaporation of the solvent gave a residue that was stirred with K_2CO_3 (0.3 mmol, 41.5 mg, 3.0 equiv) and MeI (0.5 mmol, 31 µL, 5.0 equiv) in acetone (2 mL, 0.05 M) at room temperature for 3 h. After completion (monitored by TLC), the solvent was evaporated under reduced pressure and resulting residue was mixed with water (10 mL) and extracted with EtOAc (2 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford **4**.

Scale-up Synthesis of 4bb. 4-Methoxybenzoic acid **1b** (2 mmol, 304 mg, 1.0 equiv), MBH alcohol **2b** (2.2 mmol, 384 mg, 1.1 equiv), $Pd(OAc)_2$ (0.2 mmol, 45 mg, 0.1 equiv), Ag_2CO_3 (4 mmol, 1.1 g, 2.0 equiv) were stirred in 2,2,2- trifluoroethanol (TFE) (10 mL, 0.2 M) at 110 °C (in a pre-heated oil bath) in a sealed tube for 12 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (20 mL) and passed through a small celite pad. Evaporation of the solvent gave a residue that was stirred with K_2CO_3 (6 mmol, 828 mg, 3.0 equiv) and MeI (10 mmol, 0.6 mL, 5.0 equiv) in acetone (20 mL, 0.1 M) at room temperature for 3 h. After completion (monitored by TLC), the solvent was evaporated under reduced pressure and resulting residue was mixed with water (30 mL) and extracted with EtOAc (2 x 30 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford **4bb** in 63% (449 mg) yield.

Post-Synthetic Transformations

Synthesis of 5. To a stirred solution of **3la** (0.1 mmol, 20.4 mg, 1.0 equiv) in MeOH (2 mL, 0.05 M) was added $NaBH_4$ (0.2 mmol, 7.6 mg, 2.0 equiv) at 0 °C under N_2 atmosphere. The reaction was allowed to stir for 10 minutes at room temperature. After completion (monitored by TLC), the solvent was evaporated and the residue was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford **5** in 93% (20.7 mg) yield.

Synthesis of 6. To a stirred solution of **3da** (0.1 mmol, 18.5 mg, 1.0 equiv) in MeOH (2 mL, 0.05 M), Pd/C (10 mol %, 1 mg) was added under hydrogen balloon and allowed to stir for 3 h at room temperature. After completion (monitored by TLC), the reaction mixture was passed through a short celite pad using EtOAc (10 mL). Evaporation of the solvent gave a residue that was purified on silica gel column chromatography to afford **6** in 89% (18.7 mg) yield.

Synthesis of 7. To a stirred solution of **3pa** (0.1 mmol, 25 mg, 1.0 equiv) in CH_2Cl_2 (1 mL, 0.1 M), $Ph_3P{=}CH_2CO_2Bn$ (0.11 mmol, 45 mg, 1.1 equiv) was added and the reaction was allowed to stir for 4 h at room temperature. After completion (monitored by TLC), the solvent was evaporated under reduced pressure and the residue was purified on silica gel chromatography using n-hexane and EtOAc as an eluent to afford **7** in 87% (33 mg) yield.

Synthesis of 8. A solution of **4ob** (0.1 mmol, 35.5 mg, 1.0 equiv) and a suspension of NaH (0.11 mmol, 4.5 mg, 60 % dispersion in mineral oil, 1.1 equiv) in THF (2 mL, 0.05 M) was stirred at 70 °C for 12 h. After completion (monitored by TLC), the reaction mixture was quenched with saturated aq. NH_4Cl (5 mL) and the aqueous layer was extracted using EtOAc (2 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford **8** in 72% (16 mg) yield.

Synthesis of 9. To a stirred solution of **4ab** (0.1 mmol, 34 mg, 1.0 equiv) in DMSO (1 mL, 0.1 M) and H_2O (0.5 mmol, 10 µL, 5.0 equiv), LiCl (0.5 mmol, 21 mg, 5.0 equiv) was added. The resultant solution was stirred at 150 °C for 12 h under argon atmosphere. After completion (monitored by TLC), the reaction mixture was cooled to room temperature and extracted with EtOAc (2 x 10 mL). The organic layer was washed with brine (1 x 10 mL) and water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford **9** in 91% (25.7 mg) yield.

Mechanistic Investigations

C–H Alkenylation

H/D Exchange Experiment of 1b with D_2O in Absence of 2a. 4-Methoxybenzoic acid **1b** (0.1 mmol, 15.2 mg), $Pd(OAc)_2$ (0.01 mmol, 2.3 mg), Ag_2CO_3 (0.2 mmol, 55 mg), 1,4-benzoquinone (0.1 mmol, 11 mg) and D_2O (1 mmol, 18 µL) were stirred in HFIP (1 mL) at 110 ° C (in a pre-heated oil bath) in a sealed tube for 6 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (5 mL) and passed through a short pad of celite. Evaporation of the solvent gave a residue that was stirred with K_2CO_3 (0.3 mmol, 41.5 mg) and MeI (0.5 mmol, 31 µL) in acetone (2 mL) at room temperature for 3 h. After completion (monitored by TLC), the solvent was evaporated under reduced pressure and residue was mixed with water (10 mL) and extracted with EtOAc (2 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford **1b-*d*n**. The deuterium incorporation of **1b-*dn*** was calculated based on its 400 MHz ^{1}H NMR spectrum.

C–H Alkenylation

H/D Exchange Experiment of 1b with D_2O in Presence of 2a. 4-Methoxybenzoic acid **1b** (0.1 mmol, 15.2 mg), MBH alcohol **2a** (0.11 mmol, 12.8 mg), $Pd(OAc)_2$ (0.01 mmol, 2.3 mg), Ag_2CO_3 (0.2 mmol, 55 mg), 1,4-benzoquinone (0.1 mmol, 11 mg) and D_2O (1 mmol, 18 µL) were stirred in HFIP (1 mL) at 110 ° C (in a pre-heated oil bath) in a sealed tube for 6 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (5 mL) and passed through a short pad of celite. Evaporation of the solvent gave a residue that was stirred with K_2CO_3 (0.3 mmol, 41.5 mg) and MeI (0.5 mmol, 31 µL) in acetone (2 mL) at room temperature for 3 h. After completion (monitored by TLC), the solvent was evaporated under reduced pressure and the residue was mixed with water (10 mL) and extracted with EtOAc (2 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford **3ba-*dn*** and **1b-*d*n**. The deuterium incorporation of **1b-*dn*** and **3ba-*dn*** were calculated based on their respective 400 MHz ^{1}H NMR spectrum.

C–H Alkylation

H/D Exchange Experiment of 1b with D_2O in Absence of 2b. 4-Methoxybenzoic acid **1b** (0.1 mmol, 15.2 mg), $Pd(OAc)_2$ (0.01 mmol, 2.3 mg), Ag_2CO_3 (0.2 mmol, 55 mg) and D_2O (1 mmol, 18 µL) were stirred in TFE (1 mL) at 110 °C (in a pre-heated oil bath) in a sealed tube for 6 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (5 mL) and passed through a short pad of celite. Evaporation of the solvent gave a residue that was stirred with K_2CO_3 (0.3 mmol, 41.5 mg) and MeI (0.5 mmol, 31 µL) in acetone (2 mL) at room temperature for 3 h. After completion (monitored by TLC), the solvent was evaporated under reduced pressure and the residue was mixed with water (10 mL) and extracted with EtOAc (2 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford **1b-*d*n**. The deuterium incorporation of **1b-*dn*** was calculated based on its 400 MHz ^{1}H NMR spectrum.

C–H Alkylation

H/D Exchange Experiment of 1b with D_2O in Presence of 2b. 4-Methoxybenzoic acid **1b** (0.1 mmol, 15.2 mg), MBH alcohol **2b** (0.11 mmol, 21 mg), $Pd(OAc)_2$ (10 mol %, 0.01 mmol, 2.3 mg), Ag_2CO_3 (0.2 mmol, 55 mg) and D_2O (1 mmol, 18 µL) were stirred in TFE (1 mL) at

110 °C (in a pre-heated oil bath) in a sealed tube for 6 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (5 mL) and passed through a short celite pad. Evaporation of the solvent gave a residue that was stirred with K_2CO_3 (0.3 mmol, 41.5 mg) and MeI (0.5 mmol, 31 μL) in acetone (2 mL) at room temperature for 3 h. After completion (monitored by TLC), the solvent was evaporated under reduced pressure and the residue was mixed with water (10 mL) and extracted using EtOAc (2 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford **4bb-*d*$_n$** and **1b-*d*$_n$**. The deuterium incorporation of **1b-*d*$_n$** and **4bb-*d*$_n$** were calculated based on their respective 400 MHz ^{1}H NMR spectrum (See the following ^{1}H NMR spectrums).

Preparation of 4-Methoxylbenzoic-2,6-*d*$_2$ acid 1b-*d*$_2$. 4-Methoxylbenzoic acid **1b** (0.50 mmol, 68 mg), [Ru(O_2CAd)$_2$(*p*-cymene)] (5 mol %, 14.9 mg) and D_2O (5 mmol, 90 μL) were stirred in 1,4-dioxane (1 mL) 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 passed through a short pad of celite and all the volatiles were removed under reduced pressure and the residue was purified using silica gel column chromatography with n-hexane and EtOAc as an eluent to afford **1b-*d*$_2$** [91% D].

Kinetic Isotope Effect Experiments

C–H Alkenylation

Parallel: 4-Methoxylbenzoic acid **1b** (15.2 mg) or **1b-*d*$_2$** [91% D] (15.4 mg), 0.1 mmol), MBH alcohol **2a** (0.11 mmol, 12.8 mg), Pd(OAc)$_2$ (10 mol %, 0.01 mmol, 2.3 mg), Ag_2CO_3 (0.2 mmol, 55 mg) and 1,4-benzoquinone (0.1 mmol, 11 mg) were stirred in HFIP (1 mL) at 110 ° C (in a pre-heated oil bath) in a sealed tube for 2 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (10 mL) and passed through a short celite pad. Evaporation of the solvent gave a residue that was stirred with K_2CO_3 (0.3 mmol, 41.5 mg) and MeI (0.5 mmol, 31 μL) in acetone (2 mL) at room temperature for 1 h. The solvent was removed under vacuum and purification was performed as described in the general procedure to afford **3ba** and **3ba-*d***. The KIE value was determined to be $k_H/k_D = 2.02$ on the basis of ^{1}H NMR analysis.

C–H Alkenylation

Competitive: 4-Methoxylbenzoic acid **1b** (0.05 mmol, 7.6 mg), 4-methoxylbenzoic acid-*d*$_2$ **1b-*d*$_2$** [91% D] (0.05 mmol, 7.7 mg), MBH alcohol **2a** (0.11 mmol, 12.8 mg), Pd(OAc)$_2$ (10 mol %, 0.01 mmol, 2.3 mg), Ag_2CO_3 (0.2 mmol, 55 mg) and 1,4-benzoquinone (0.1 mmol, 11 mg) were stirred in HFIP (1 mL) at 110 °C (in a pre-heated oil bath) in a sealed tube for 2 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (10 mL) and passed through a short celite pad. Evaporation of the solvent gave a residue that was stirred with K_2CO_3 (0.3 mmol, 41.5 mg) and MeI (0.5 mmol, 31 μL) in acetone (2 mL) at room temperature for 1 h. The solvent was removed under vacuum and purification was performed as described in the general procedure to afford a mixture of **3ba**/**3ba-*d***. The KIE value was determined to be $k_H/k_D = 2.46$ on the basis of ^{1}H NMR analysis.

C–H Alkylation

Parallel: 4-Methoxylbenzoic acid (**1b** (15.2 mg) or **1b-*d*₂** [91% D] (15.4 mg), 0.1 mmol), MBH alcohol **2b** (0.11 mmol, 21 mg), $Pd(OAc)_2$ (10 mol %, 0.01 mmol, 2.3 mg) and Ag_2CO_3 (0.2 mmol, 55 mg) were stirred in TFE (1 mL) at 110 °C (in a pre-heated oil bath) in a sealed tube for 2 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (10 mL) and passed through a short celite pad. Evaporation of the solvent gave a residue that was stirred with K_2CO_3 (0.3 mmol, 41.5 mg) and MeI (0.5 mmol, 31 μL) in acetone (2 mL) at room temperature for 1 h. The solvent was removed under vacuum and purification was performed as described in the general procedure to afford **4bb** and **4bb-*d***. The KIE value was determined to be $k_H/k_D = 2.56$ on the basis of ^{1}H NMR analysis.

C–H Alkylation

Competitive: 4-Methoxylbenzoic acid **1b** (0.05 mmol, 7.6 mg), 4-methoxylbenzoic acid-d_2 **1b-*d*₂** [91% D] (0.05 mmol, 7.7 mg), MBH alcohol **2a** (0.11 mmol, 21 mg), $Pd(OAc)_2$ (10 mol %, 0.01 mmol, 2.3 mg) and Ag_2CO_3 (0.2 mmol, 55 mg) were stirred in TFE (1 mL) at 110 °C (in a pre-heated oil bath) in a sealed tube for 2 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (20 mL) and passed through a short celite pad. Evaporation of the solvent gave a residue that was stirred with K_2CO_3 (0.3 mmol, 41.5 mg) and MeI (0.5 mmol, 31 μL) in acetone (2 mL) at room temperature for 1 h. The solvent was removed under vacuum and purification was performed as described in the general procedure to afford a mixture of **4bb**/**4bb-*d***. The KIE value was determined to be $k_H/k_D = 2.12$ on the basis of ^{1}H NMR analysis.

Control Experiment (1)

C–H Alkenylation: 4-Methoxylbenzoic acid **1b** (0.1 mmol, 15.2 mg, 1.0 equiv), prop-2-en-1-ol **2p** (0.11 mmol, 6.4 mg, 1.1 equiv), $Pd(OAc)_2$ (0.01 mmol, 2.3 mg, 0.1 equiv), Ag_2CO_3 (0.2 mmol, 55 mg, 2.0 equiv) and 1,4-benzoquinone (0.1 mmol, 11 mg, 1.0 equiv) were stirred in

HFIP (1 mL) at 110 ° C (in a pre-heated oil bath) in a sealed tube for 12 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (20 mL) and passed through a short celite pad. Evaporation of the solvent gave a residue that was stirred with K_2CO_3 (0.3 mmol, 41.5 mg, 3.0 equiv) and MeI (0.5 mmol, 31 µL, 5.0 equiv) in acetone (2 mL) at room temperature for 3 h. The formation of **3ba** was not observed.

C–H Alkylation: 4-Methoxylbenzoic acid **1b** (0.1 mmol, 15.2 mg, 1.0 equiv), 1-phenylprop-2-en-1-ol **2q** (0.11 mmol, 14.8 mg, 1.1 equiv)**,** $Pd(OAc)_2$ (0.01 mmol, 2.3 mg, 0.1 equiv) and Ag_2CO_3 (0.2 mmol, 55 mg, 2.0 equiv) were stirred in TFE (1 mL) at 110 °C (in a pre-heated oil bath) in a sealed tube for 12 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (20 mL) and passed through a short celite pad. Evaporation of the solvent gave a residue that was stirred with K_2CO_3 (0.3 mmol, 41.5 mg, 3.0 equiv) and MeI (0.5 mmol, 31 µL, 5.0 equiv) in acetone (2 mL) at room temperature for 3 h. The formation of **4bq** was not observed.

Control Experiment (2)

C–H Alkenylation: Methyl 4-methoxybenzoate **1b′** (0.1 mmol, 16.6 mg, 1.0 equiv), methyl 2-(hydroxymethyl)acrylate **2a** (0.11 mmol, 12.8 mg, 1.1 equiv), $Pd(OAc)_2$ (0.01 mmol, 2.3 mg, 0.1 equiv), Ag_2CO_3 (0.2 mmol, 55 mg, 2.0 equiv) and 1,4-benzoquinone (0.1 mmol, 11 mg, 1.0 equiv) were stirred in HFIP (1 mL) at 110 ° C (in a pre-heated oil bath) in a sealed tube for 12 h. The formation of **3ba** was not observed.

C–H Alkylation: Methyl 4-methoxybenzoate **1b′** (0.1 mmol, 16.6 mg, 1.0 equiv), methyl 2-(hydroxy(phenyl)methyl)acrylate **2b** (0.11 mmol, 21 mg, 1.1 equiv)**,** $Pd(OAc)_2$ (0.01 mmol, 2.3 mg, 0.1 equiv) and Ag_2CO_3 (0.2 mmol, 55 mg, 2.0 equiv) were stirred in TFE (1 mL) at 110 °C (in a pre-heated oil bath) in a sealed tube for 12 h. The formation of **4bb** was not observed.

Control Experiment (3): 4-Methylbenzoic acid **1a** (0.1 mmol, 13.6 mg, 1.0 equiv), methyl 2-benzoylacrylate **2b′** (0.11 mmol, 21mg, 1.1 equiv), $Pd(OAc)_2$ (0.01 mmol, 2.3 mg, 0.1 equiv) and Ag_2CO_3 (0.2 mmol, 55 mg, 2.0 equiv) were stirred in TFE (1 mL) at 110 °C (in a pre-heated oil bath) in a sealed tube for 12 h. The formation of alkylated **4ab** was not formed.

Control Experiment (4): 4-Methylbenzoic acid **1a** (0.1 mmol, 13.6 mg, 1.0 equiv), methyl 2-(hydroxy(phenyl)methyl-*d*) acrylate **2b-*d*$_1$** (0.11 mmol, 21.2 mg, 1.1 equiv), $Pd(OAc)_2$ (0.01

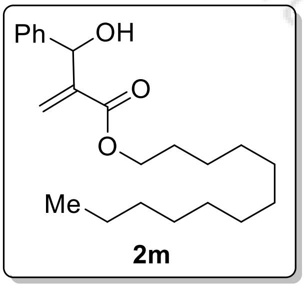
mmol, 2.3 mg, 0.1 equiv) and Ag_2CO_3 (0.2 mmol, 55 mg, 2.0 equiv) were stirred in TFE (1 mL) at 110 °C (in a pre-heated oil bath) in a sealed tube for 12 h. In the isolated alkylated product **4ab**, no deuteration incorporation was observed.

Determination of CO_2 Evolution using GC Analysis. 4-Methylbenzoic acid **1a** (2.0 mmol, 272 mg, 1.0 equiv), methyl 2-(hydroxymethyl)acrylate **2a** (2.2 mmol, 255 mg, 1.1 equiv), $Pd(OAc)_2$ (0.2 mmol, 45 mg, 0.1 equiv), Ag_2CO_3 (4 mmol, 1.1 g, 2.0 equiv) and 1,4-benzoquinone (2 mmol, 216 mg, 1.0 equiv) were stirred in HFIP (5 mL) at 110 °C (in a pre-heated oil bath) in a sealed tube for 12 h. The pressure tube was cooled to 0 °C, the evolved gas was syringed out and detected by PerkinElmer clarus590 GC instrument using Elite Plot-Q column (30 m length x 530 μm x 20 μm ID) with the following conditions:

TCD starting temperature: 40 °C
Oven temperature: 60 °C
Time at starting temperature: 0 min
Hold time: 5 min
Ramp: 28 °C/ min up to 200 °C
Flow rate: 5 ml/ min (N_2)
Split ration: 20
Inlet temperature: 40 °C
Detector temperature TCD: 200 °C

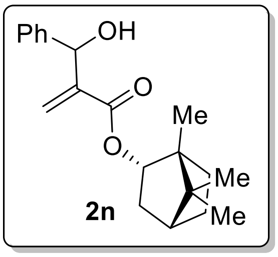
3.4 Characterization Data

Characterization Data of Newly Synthesized MBH Alcohols



2m

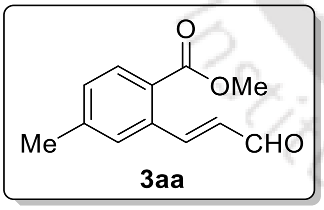
Dodecyl 2-(hydroxy(phenyl)methyl)acrylate 2m. Analytical TLC on silica gel, 1:10 EtOAc/hexane $R_f = 0.47$; colorless liquid; yield 81% (281 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (d, $J = 7.2$ Hz, 2H), 7.34 (t, $J = 7.2$ Hz, 2H), 7.29-7.26 (m, 1H), 6.34 (s, 1H), 5.82 (s, 1H), 5.55 (s, 1H), 4.13-4.06 (m, 2H), 3.11 (bs, 1H), 1.60-1.58 (m, 2H), 1.31-1.26 (m, 18H), 0.88 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.5, 142.3, 141.5, 128.5, 127.9, 126.7, 126.0, 73.5, 65.2, 32.0, 29.8, 29.7, 29.68, 29.60, 29.5, 29.3, 28.6, 26.0, 22.8, 14.2; FT-IR (neat) 3447, 2923, 2854, 1711, 1630, 1456, 1269, 1149, 1040, 955 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{22}H_{34}O_3Na$ 369.2400; Found 369.2399.



2n

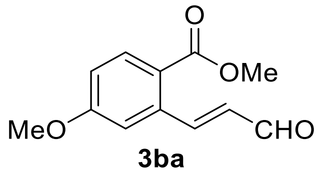
(1R,2S,4R)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 2-(hydroxy-(phenyl)methyl)acrylate 2n. Analytical TLC on silica gel, 1:10 EtOAc/hexane R_f = 0.41; colorless liquid; yield 79% (248 mg); 1:1 mixture of diastereomers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.31 (m, 8H), 7.29-7.25 (m, 2H), 6.38 (s, 2H), 5.85 (t, *J* = 1.6 Hz, 1H), 5.84 (t, *J* = 1.2 Hz, 1H), 5.56-5.54 (m, 2H), 4.91-4.86 (m, 2H), 3.11 (d, *J* = 5.6 Hz, 1H), 3.05 (d, *J* = 5.6 Hz, 1H), 2.36-2.24 (m, 2H), 1.84-1.61 (m, 7H), 1.32-1.23 (m, 2H), 1.18-1.05 (m, 2H), 0.93-0.88 (m, 1H), 0.87-0.84 (m, 12H), 0.77 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 166.6, 142.5, 142.4, 141.5, 128.6, 128.5, 128.0, 127.9, 126.8, 126.7, 126.0, 125.7, 80.9, 80.8, 73.5, 73.4, 48.9, 47.9, 44.9, 36.7, 36.6, 28.0, 27.9, 27.4, 27.3, 19.7, 18.9, 13.5, 13.4; FT-IR (neat) 3450, 2953, 2879, 1705, 1630, 1453, 1267, 1152, 1022, 955 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{20}H_{26}O_3Na$ 337.1774; Found 337.1772.

Characterization Data of the Products



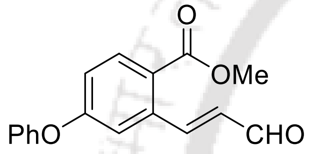
3aa

Methyl (*E*)-4-methyl-2-(3-oxoprop-1-en-1-yl)benzoate 3aa. Analytical TLC on silica gel, 1:9 EtOAc/hexane R_f = 0.50; colorless solid; mp 77-78 ºC; yield 72% (15 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (d, *J* = 8.0 Hz, 1H), 8.44 (d, *J* = 16.0 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.44 (s, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 6.60 (dd, *J* = 16.0, 8.0 Hz, 1H), 3.93 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 167.2, 152.0, 143.5, 136.2, 131.4, 131.2, 131.1, 128.8, 126.8, 52.4, 21.7; FT-IR (neat) 2924, 1712, 1678, 1604, 1438, 1267, 1207, 1121, 1081 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{12}H_{13}O_3$ 205.0859; Found 205.0859.



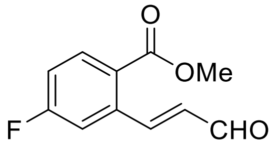
3ba

Methyl (*E*)-4-methoxy-2-(3-oxoprop-1-en-1-yl)benzoate 3ba. Analytical TLC on silica gel, 1:9 EtOAc/hexane $R_f = 0.34$; colorless solid; mp 82-83 °C; yield 73% (16 mg); ^{1}H NMR (600 MHz, CDCl$_3$) δ 9.77 (d, *J* = 7.8 Hz, 1H), 8.50 (d, *J* = 16.2 Hz, 1H), 8.02 (d, *J* = 9.0 Hz, 1H), 7.08 (d, *J* = 2.4 Hz, 1H), 6.98 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.58 (dd, *J* = 16.2, 7.8 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 194.3, 166.8, 162.8, 152.1, 138.5, 133.5, 131.3, 121.7, 115.6, 113.2, 55.8, 52.3; FT-IR (neat) 2925, 1704, 1678, 1594, 1440, 1332, 1238, 1123, 1031 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{12}H_{13}O_4$ 221.0808; Found 221.0808.



3ca

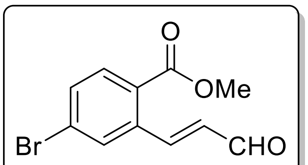
Methyl (*E*)-2-(3-oxoprop-1-en-1-yl)-4-phenoxybenzoate 3ca. Analytical TLC on silica gel, 1:9 EtOAc/hexane $R_f = 0.41$; brown sticky liquid; yield 65% (18 mg); ^{1}H NMR (600 MHz, CDCl$_3$) δ 9.74 (d, *J* = 7.8 Hz, 1H), 8.46 (d, *J* = 16.2 Hz, 1H), 8.02 (d, *J* = 9.0 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.24 (t, *J* = 7.2 Hz, 1H), 7.16-7.15 (m, 1H), 7.07 (d, *J* = 7.8 Hz, 2H), 7.04-7.03 (m, 1H), 6.47 (dd, *J* = 15.6, 7.8 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 194.1, 166.6, 161.5, 155.1, 151.3, 138.6, 133.6, 131.6, 130.4, 125.2, 123.4, 120.4, 118.9, 116.4, 52.5; FT-IR (neat) 2925, 2878, 1709, 1678, 1594, 1445, 1332, 1238, 1123, 1033 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{17}H_{15}O_4$ 283.0965; Found 283.0964.



3da

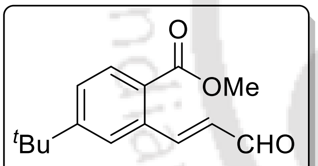
Methyl (*E*)-4-fluoro-2-(3-oxoprop-1-en-1-yl)benzoate 3da. Analytical TLC on silica gel, 1:9 EtOAc/hexane $R_f = 0.53$; colorless solid; mp 94-95 °C; yield 74% (15 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.77 (d, *J* = 7.6 Hz, 1H), 8.47-8.42 (m, 1H), 8.08 (dd, *J* = 8.8, 5.6 Hz, 1H), 7.32 (dd, *J* = 9.6, 2.8 Hz, 1H), 7.20-7.15 (m, 1H), 6.58 (dd, *J* = 15.6, 7.6 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 193.8, 166.3, 166.2 ($J_{C\text{-}F}$ = 249.0

Hz), 150.2, 139.2 ($J_{C\text{-}F}$ = 8.5 Hz), 134.0 ($J_{C\text{-}F}$ = 9.2 Hz), 132.0, 125.7 ($J_{C\text{-}F}$ = 3.2 Hz), 117.4 ($J_{C\text{-}F}$ = 21.4 Hz), 115.1 ($J_{C\text{-}F}$ = 22.9 Hz), 52.7; ^{19}F NMR (565 MHz, CDCl$_3$) δ -105.18; FT-IR (neat) 2920, 1716, 1686, 1559, 1439, 1274, 1238, 1124, 1033 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{11}H_{10}O_3F$ 209.0608; Found 209.0595.



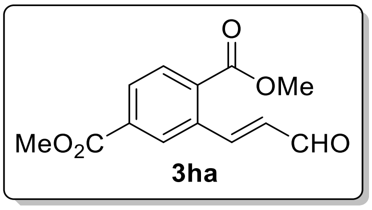
3ea

Methyl (*E*)-4-bromo-2-(3-oxoprop-1-en-1-yl)benzoate 3ea. Analytical TLC on silica gel, 1:9 EtOAc/hexane R_f = 0.48; yellow solid; mp 127-128 °C; yield 51% (14 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.76 (d, *J* = 7.6 Hz, 1H), 8.36 (d, *J* = 16.0 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 2.0 Hz, 1H), 7.63 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.59 (dd, *J* = 16.0, 7.6 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 193.7, 166.5, 149.9, 138.1, 133.3, 132.7, 132.1, 131.1, 128.2, 127.7, 52.8; FT-IR (neat) 2922, 1714, 1686, 1557, 1438, 1274, 1238, 1123, 1030 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{11}H_{10}O_3Br$ 268.9808; Found 268.9804.



3ga

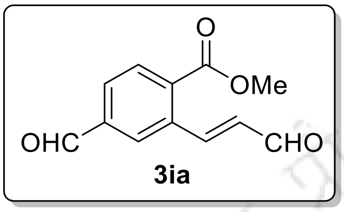
Methyl (*E*)-4-(*tert*-butyl)-2-(3-oxoprop-1-en-1-yl)benzoate 3ga. Analytical TLC on silica gel, 1:9 EtOAc/hexane R_f = 0.55; yellow sticky liquid; yield 45% (11 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.77 (d, *J* = 7.6 Hz, 1H), 8.47 (d, *J* = 16.0 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.64-7.63 (m, 1H), 7.52 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.63 (dd, *J* = 15.6, 7.6 Hz, 1H), 3.93 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 194.4, 167.2, 156.5, 152.5, 136.0, 131.2, 131.1, 127.6, 126.8, 125.1, 52.5, 35.3, 31.1; FT-IR (neat) 2934, 1716, 1677, 1605, 1438, 1265, 1207, 1121, 1079 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{15}H_{19}O_3$ 247.1329; Found 247.1329.



3ha

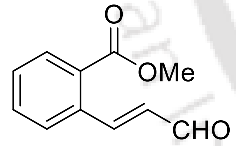
Dimethyl (*E*)-2-(3-oxoprop-1-en-1-yl)terephthalate 3ha. Analytical TLC on silica gel, 1:9 EtOAc/hexane R_f = 0.44; yellow solid; mp 114-115 °C; yield

75% (18.6 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.78 (d, *J* = 7.6 Hz, 1H), 8.36 (d, *J* = 16.0 Hz, 1H), 8.31-8.30 (m, 1H), 8.14-8.11 (m, 1H), 8.08-8.06 (m, 1H), 6.70 (dd, *J* = 15.6, 7.6 Hz, 1H), 3.97 (s, 3H), 3.96 (s, 3H) ; ^{13}C NMR (100 MHz, CDCl$_3$) δ 193.8, 166.5, 165.6, 150.1, 136.2, 133.9, 133.1, 132.1, 131.3, 130.9, 129.2, 52.9, 52.8; FT-IR (neat) 2922, 1715, 1711, 1675, 1594, 1439, 1333, 1238, 1123, 1029 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{13}H_{13}O_5$ 249.0757; Found 249.0767.



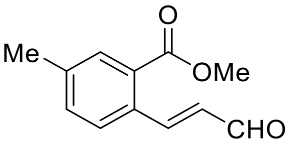
3ia

Methyl (*E*)-4-formyl-2-(3-oxoprop-1-en-1-yl)benzoate 3ia. Analytical TLC on silica gel, 1:9 EtOAc/hexane R_f = 0.43; yellow solid; mp 79-80 °C; yield 64% (14 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 10.12 (s, 1H), 9.80 (d, *J* = 7.6 Hz, 1H), 8.37 (d, *J* = 16.0 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 8.13-8.12 (m, 1H), 7.99 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.71 (dd, *J* = 16.0, 7.6 Hz, 1H), 3.99 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 193.6, 190.9, 166.3, 149.7, 138.9, 137.0, 134.2, 132.4, 132.0, 130.5, 129.2, 53.1; FT-IR (neat) 2953, 1725, 1670, 1600, 1460, 1332, 1210, 1159, 1056 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{12}H_{11}O_4$ 219.0652; Found 219.0639.



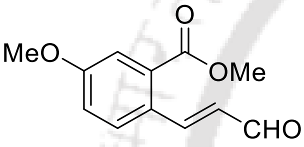
3ja

Methyl (*E*)-2-(3-oxoprop-1-en-1-yl)benzoate 3ja. Analytical TLC on silica gel, 1:9 EtOAc/hexane R_f = 0.43; yellow liquid; yield 66% (25 mg); ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.76 (d, *J* = 7.8 Hz, 1H), 8.43 (d, *J* = 15.9 Hz, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 6.62 (dd, *J* = 15.9, 7.8 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 194.2, 167.2, 151.6, 136.1, 132.8, 131.3, 131.2, 130.4, 129.7, 128.1, 52.6; FT-IR (neat) 2955, 1723, 1674, 1460, 1332, 1210, 1159 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{11}H_{11}O_3$ 191.0703; Found 191.0703.



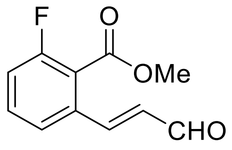
3ka

Methyl (*E*)-5-methyl-2-(3-oxoprop-1-en-1-yl)benzoate 3ka. Analytical TLC on silica gel, 1:9 EtOAc/hexane $R_f = 0.50$; colorless solid; mp 69-70 °C; yield 70% (14 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (d, *J* = 8.0 Hz, 1H), 8.38 (d, *J* = 16.0 Hz, 1H), 7.83 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 9.6 Hz, 1H), 6.61 (dd, *J* = 16.0, 7.6 Hz, 1H), 3.94 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 167.4, 151.6, 141.1, 133.5, 133.1, 131.8, 130.6, 129.7, 128.0, 52.6, 21.4; FT-IR (neat) 2925, 1712, 1678, 1606, 1438, 1267, 1208, 1121, 1079 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{13}O_3$ 205.0859; Found 205.0866.



3la

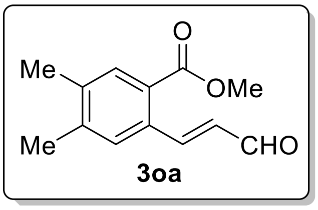
Methyl (*E*)-5-methoxy-2-(3-oxoprop-1-en-1-yl)benzoate 3la. Analytical TLC on silica gel, 1:9 EtOAc/hexane $R_f = 0.44$; colorless solid; mp 74-76 °C; yield 75% (16.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, *J* = 8.0 Hz, 1H), 8.34 (d, *J* = 15.6 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.49 (d, *J* = 2.8 Hz, 1H), 7.10 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.57 (dd, *J* = 15.6, 7.6 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.3, 167.0, 161.2, 151.0, 131.4, 129.5, 128.0, 118.7, 116.0, 55.8, 52.7; FT-IR (neat) 2955, 1720, 1677, 1599, 1496, 1273, 1231, 1122, 1071 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{13}O_4$ 221.0808; Found 221.0808.



3ma

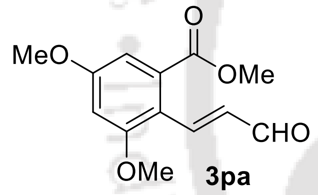
Methyl (*E*)-2-fluoro-6-(3-oxoprop-1-en-1-yl)benzoate 3ma. Analytical TLC on silica gel, 1:9 EtOAc/hexane $R_f = 0.54$; colorless solid; mp 87-88 °C; yield 56% (11.6 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 16.0 Hz, 1H), 7.52-7.47 (m, 2H), 7.21 (t, *J* = 9.0 Hz, 1H), 6.67 (dd, *J* = 16.0, 8.0 Hz, 1H), 4.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.4, 165.2, 161.6 ($J_{C\text{-}F} = 250.0$ Hz), 148.2 ($J_{C\text{-}F} = 3.0$ Hz), 135.3 ($J_{C\text{-}F} = 2.9$ Hz), 132.4 ($J_{C\text{-}F} = 8.8$ Hz), 132.0, 123.0 ($J_{C\text{-}F} = 3.4$ Hz), 121.6 ($J_{C\text{-}F} = 16.1$ Hz), 118.4 ($J_{C\text{-}}$

$_F$ = 22.2 Hz), 53.2; ^{19}F NMR (470 MHz, CDCl$_3$) δ -111.71; FT-IR (neat) 2922, 1715, 1685, 1557, 1438, 1274, 1238, 1123, 1031 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{11}H_{10}O_3F$ 209.0608; Found 209.0606.



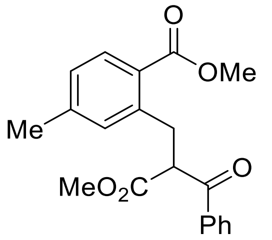
3oa

Methyl (*E*)-4,5-dimethyl-2-(3-oxoprop-1-en-1-yl)benzoate 3oa. Analytical TLC on silica gel, 1:9 EtOAc/hexane R$_f$ = 0.45; yellow solid; mp 94-95 °C; yield 72% (16 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.73 (d, *J* = 8.0 Hz, 1H), 8.41 (d, *J* = 16.0 Hz, 1H), 7.80 (s, 1H), 7.43 (s, 1H), 6.60 (dd, *J* = 15.6, 7.6 Hz, 1H), 3.92 (s, 3H), 2.34-2.33 (m, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 194.4, 167.4, 151.9, 142.1, 139.8, 133.5, 132.4, 130.4, 129.2, 127.2, 52.4, 20.1, 19.8; FT-IR (neat) 2926, 1715, 1676, 1604, 1438, 1267, 1207, 1120, 1080 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{13}H_{15}O_3$ 219.1016; Found 219.1014.



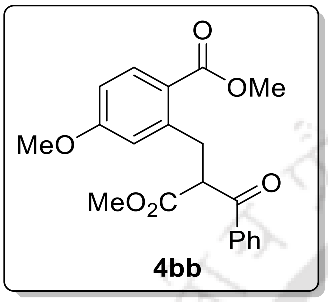
3pa

Methyl (*E*)-3,5-dimethoxy-2-(3-oxoprop-1-en-1-yl)benzoate 3pa. Analytical TLC on silica gel, 1:9 EtOAc/hexane R$_f$ = 0.31; yellow solid; mp 104-105 °C; yield 74% (18.5 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.62 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 16.0 Hz, 1H), 6.96-6.87 (m, 2H), 6.63 (d, *J* = 2.4 Hz, 1H), 3.93 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.1, 168.0, 161.9, 160.8, 147.2, 134.7, 132.4, 116.1, 106.8, 101.7, 56.0, 55.8, 52.9; FT-IR (KBr) 2953, 1722, 1672, 1597, 1460, 1330, 1209, 1159, 1057 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{13}H_{15}O_5$ 251.0914; Found 251.0913.



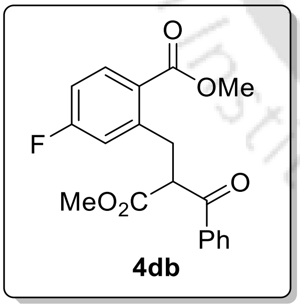
4ab

Methyl 2-(2-benzoyl-3-methoxy-3-oxopropyl)-4-methylbenzoate 4ab. Analytical TLC on silica gel, 1:9 EtOAc/hexane R$_f$ = 0.37; colorless liquid; yield 77% (26 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.92 (d, *J* = 7.9 Hz, 2H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.04 (d, *J* = 7.9 Hz, 2H), 4.95 (t, *J* = 7.2 Hz, 1H), 3.85 (s, 3H), 3.60 (d, *J* = 8.8 Hz, 5H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 195.3, 170.1, 167.8, 143.0, 140.4, 136.6, 133.5, 133.3, 131.4, 128.9, 128.7, 127.8, 126.6, 55.1, 52.5, 52.1, 34.3, 21.5; FT-IR (neat) 2954, 1720, 1686, 1585, 1437, 1266, 1242, 1122, 1082 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{20}H_{20}O_5Na$ 363.1203; Found 363.1203.



4bb

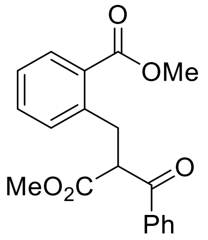
Methyl 2-(2-benzoyl-3-methoxy-3-oxopropyl)-4-methoxybenzoate 4bb. Analytical TLC on silica gel, 1:9 EtOAc/hexane R$_f$ = 0.30; colorless liquid; yield 73% (26 mg); ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.94-7.92 (m, 3H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 2.4 Hz, 1H), 6.74 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.97 (t, *J* = 7.8 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.65-3.61 (m, 5H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 195.3, 170.1, 167.2, 162.4, 143.0, 136.6, 133.6, 133.5, 128.9, 128.7, 121.4, 117.6, 112.6, 55.5, 54.9, 52.6, 52.0, 34.7; FT-IR (neat) 3003, 2291, 2253, 1712, 1633, 1441, 1375, 1039 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{20}H_{20}O_6Na$ 379.1152; Found 379.1152.



4db

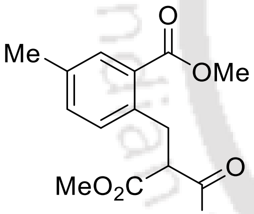
Methyl 2-(2-benzoyl-3-methoxy-3-oxopropyl)-4-fluorobenzoate 4db. Analytical TLC on silica gel, 1:9 EtOAc/hexane R$_f$ = 0.42; colorless liquid; yield 66% (23 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.98-7.94 (m, 3H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 2H), 7.02 (dd, *J* = 9.6, 2.4 Hz, 1H), 6.96-6.92 (m, 1H), 4.94 (t, *J* = 7.32 Hz, 1H), 3.86 (s, 3H), 3.68-3.57 (m, 5H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 194.8, 169.8, 166.8, 165.7 ($J_{C\text{-}F}$ = 252.0 Hz), 144.0 ($J_{C\text{-}F}$ = 8.6 Hz), 136.4, 133.9 ($J_{C\text{-}F}$ = 9.3 Hz), 133.7, 128.9, 128.8, 125.6 ($J_{C\text{-}F}$ = 2.8 Hz), 119.6 ($J_{C\text{-}F}$ = 21.7 Hz), 114.3 ($J_{C\text{-}F}$ = 15.0 Hz), 54.9, 52.7, 52.3, 34.1; ^{19}F NMR (376

MHz, $CDCl_3$) δ -106.41; FT-IR (neat) 2954, 1721, 1687, 1587, 1437, 1269, 1242, 1122, 1081 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{18}O_5F$ 345.1133; Found 345.1134.



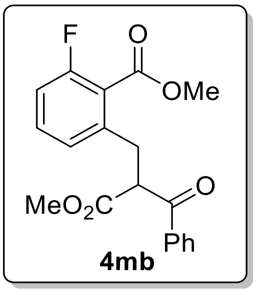
4jb

Methyl 2-(2-benzoyl-3-methoxy-3-oxopropyl)benzoate 4jb. Analytical TLC on silica gel, 1:9 EtOAc/hexane $R_f = 0.51$; colorless liquid; yield 70% (23 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (t, *J* = 7.8 Hz, 3H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.29-7.24 (m, 2H), 4.97 (t, *J* = 7.3 Hz, 1H), 3.88 (s, 3H), 3.62 (d, *J* = 11.4 Hz, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.2, 170.1, 167.8, 140.2, 136.6, 133.6, 132.6, 132.3, 131.2, 129.6, 128.9, 128.7, 127.1, 55.1, 52.6, 52.3, 34.2; FT-IR (neat) 2954, 1721, 1687, 1587, 1437, 1265, 1242, 1145, 1077 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{19}H_{18}O_5Na$ 349.1046; Found 349.1051.



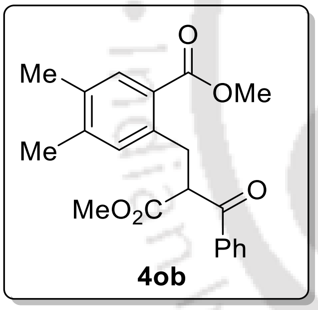
4kb

Methyl 2-(2-benzoyl-3-methoxy-3-oxopropyl)-5-methylbenzoate 4kb. Analytical TLC on silica gel, 1:9 EtOAc/hexane $R_f = 0.39$; colorless liquid; yield 75% (25.5 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.2 Hz, 2H), 7.73 (s, 1H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 2H), 7.16 (s, 2H), 4.94 (t, *J* = 7.2 Hz, 1H), 3.86 (s, 3H), 3.61-3.53 (m, 5H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 170.1, 168.0, 137.1, 136.8, 136.6, 133.5, 133.1, 132.5, 131.7, 129.4, 128.9, 128.7, 55.3, 52.5, 52.2, 33.8, 21.0; FT-IR (neat) 2955, 1719, 1686, 1587, 1438, 1269, 1240, 1123, 1080 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{20}H_{20}O_5Na$ 363.1203; Found 363.1203.



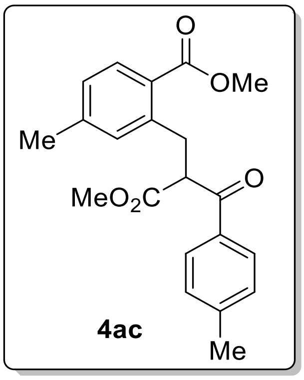
4mb

Methyl 2-(2-benzoyl-3-methoxy-3-oxopropyl)-6-fluorobenzoate 4mb. Analytical TLC on silica gel, 1:9 EtOAc/hexane $R_f = 0.45$; colorless liquid; yield 55% (19 mg); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.92 (d, *J* = 8.5 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 2H), 7.24-7.23 (m, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.95 (t, *J* = 8.5 Hz, 1H), 4.88 (t, *J* = 7.5 Hz, 1H), 3.92 (s, 3H), 3.63 (s, 3H), 3.38 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 194.7, 169.6, 166.2, 161.3 ($J_{C\text{-}F}$ = 250.7 Hz), 139.3 ($J_{C\text{-}F}$ = 2.0 Hz), 136.3, 133.8, 131.8 ($J_{C\text{-}F}$ = 9.1 Hz), 128.9, 128.8, 126.7 ($J_{C\text{-}F}$ = 3.2 Hz), 121.7 ($J_{C\text{-}F}$ = 15.5 Hz), 114.8 ($J_{C\text{-}F}$ = 21.8 Hz), 55.0, 52.8, 52.7, 33.0; ^{19}F NMR (470 MHz, CDCl$_3$) δ -113.06; FT-IR (neat) 2954, 1718, 1687, 1587, 1439, 1264, 1244, 1123, 1081 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{19}H_{18}O_5F$ 345.1133; Found 345.1133.



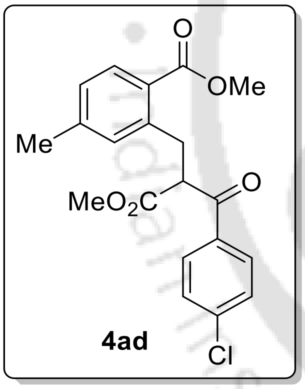
4ob

Methyl 2-(2-benzoyl-3-methoxy-3-oxopropyl)-4,5-dimethylbenzoate 4ob. Analytical TLC on silica gel, 1:9 EtOAc/hexane $R_f = 0.44$; colorless liquid; yield 81% (29 mg); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.92 (d, *J* = 7.5 Hz, 2H), 7.70 (s, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.01 (s, 1H), 4.92 (t, *J* = 7.5 Hz, 1H), 3.84 (s, 3H), 3.61 (s, 3H), 3.59-3.54 (m, 2H), 2.21 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 195.4, 170.2, 167.9, 141.6, 137.7, 136.7, 135.4, 133.9, 133.5, 132.4, 128.9, 128.7, 126.7, 55.3, 52.5, 52.0, 33.8, 19.8, 19.3; FT-IR (neat) 2958, 1721, 1687, 1587, 1437, 1269, 1242, 1123, 1081, cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{21}H_{23}O_5$ 355.1540; Found 355.1542.



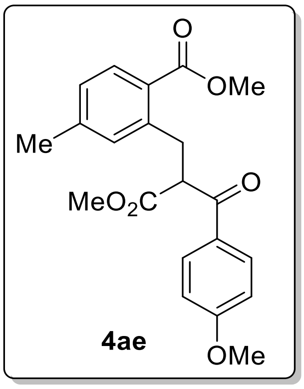
4ac

Methyl 2-(3-methoxy-2-(4-methylbenzoyl)-3-oxopropyl)-4-methylbenzoate 4ac. Analytical TLC on silica gel, 1:9 EtOAc/hexane R_f = 0.44; colorless liquid; yield 65% (23 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84-7.82 (m, 3H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.05-7.04 (m, 2H), 4.91 (t, *J* = 7.5 Hz, 1H), 3.85 (s, 3H), 3.60-3.58 (m, 5H), 2.38 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.8, 170.3, 167.8, 144.5, 142.9, 140.5, 134.1, 133.3, 131.4, 129.4, 129.0, 127.8, 126.6, 55.0, 52.5, 52.1, 34.2, 21.8, 21.5; FT-IR (neat) 2954, 1722, 1687, 1587, 1437, 1269, 1242, 1122, 1081, cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{23}O_5$ 355.1540; Found 355.1538.



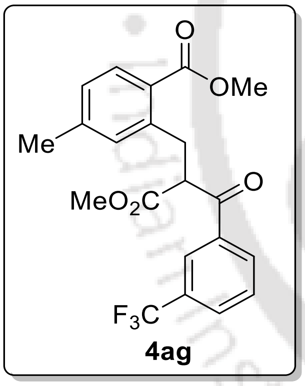
4ad

Methyl 2-(2-(4-chlorobenzoyl)-3-methoxy-3-oxopropyl)-4-methylbenzoate 4ad. Analytical TLC on silica gel, 1:9 EtOAc/hexane R_f = 0.42; colorless liquid; yield 68% (25.5 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.8 Hz, 2H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.06-7.04 (m, 2H), 4.92 (t, *J* = 7.2 Hz, 1H), 3.86 (s, 3H), 3.61 (s, 3H), 3.58-3.54 (m, 2H), 2.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.3, 169.9, 167.7, 143.1, 140.2, 140.1, 135.0, 133.4, 131.4, 130.3, 129.1, 127.9, 126.5, 55.1, 52.6, 52.1, 34.2, 21.5; FT-IR (neat) 2953, 1721, 1685, 1587, 1437, 1269, 1242, 1123, 1081, cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{20}O_5Cl$ 375.0994; Found 375.0994.



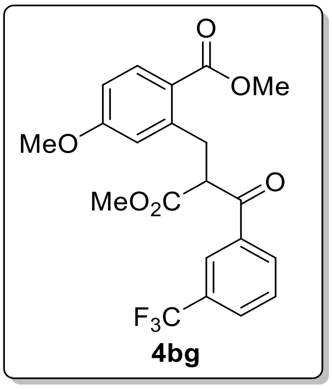
4ae

Methyl 2-(3-methoxy-2-(4-methoxybenzoyl)-3-oxopropyl)-4-methylbenzoate 4ae. Analytical TLC on silica gel, 1:9 EtOAc/hexane $R_f = 0.37$; colorless liquid; yield 60% (22 mg); ^{1}H NMR ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, $J = 9.0$ Hz, 2H), 7.82 (d, $J = 7.9$ Hz, 1H), 7.09-7.01 (m, 2H), 6.87 (d, $J = 9.0$ Hz, 2H), 4.89 (t, $J = 7.2$ Hz, 1H), 3.85 (d, $J = 3.3$ Hz, 6H), 3.63-3.56 (m, 5H), 2.28 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.6, 170.3, 167.8, 163.9, 142.9, 140.5, 133.3, 131.4, 131.3, 129.8, 127.7, 126.7, 113.9, 55.6, 54.9, 52.4, 52.1, 34.3, 21.5; FT-IR (neat) 2957, 1721, 1689, 1587, 1440, 1269, 1244, 1123, 1081, cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{23}O_6$ 371.1489; Found 371.1490.

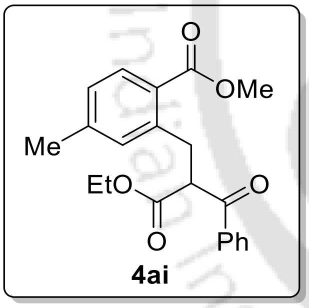


4ag

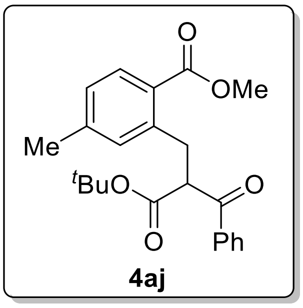
Methyl 2-(3-methoxy-3-oxo-2-(3-(trifluoromethyl)benzoyl)-propyl)-4-methylbenzoate 4ag. Analytical TLC on silica gel, 1:9 EtOAc/hexane $R_f = 0.34$; colorless liquid; yield 55% (22.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.08 (d, $J = 8.0$ Hz, 1H), 7.82 (d, $J = 8.8$ Hz, 1H), 7.76 (d, $J = 8.0$ Hz, 1H), 7.54 (t, $J = 8.0$ Hz, 1H), 7.05-7.04 (m, 2H), 5.00 (t, $J = 7.6$ Hz, 1H), 3.86 (s, 3H), 3.63 (s, 3H), 3.58 (d, $J = 7.6$ Hz, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 169.8, 167.7, 143.2, 140.0, 137.2, 133.5, 131.9, 131.5, 131.4, 131.2, 129.9 ($J_{C\text{-}F} = 3.5$ Hz), 129.4, 128.0, 126.4, 125.8 ($J_{C\text{-}F} = 5.2$ Hz), 55.0, 52.6, 52.1, 34.4, 21.5; ^{19}F NMR (565 MHz, $CDCl_3$) δ -62.86; FT-IR (neat) 2954, 1721, 1686, 1587, 1437, 1270, 1242, 1122, 1080, cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{20}O_5F_3$ 409.1257; Found 409.1266.


4bg

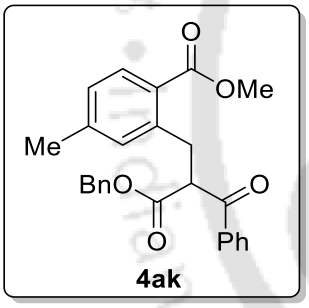
Methyl 4-methoxy-2-(3-methoxy-3-oxo-2-(3-(trifluoromethyl)-benzoyl)propyl)benzoate 4bg. Analytical TLC on silica gel, 1:9 EtOAc/hexane R_f = 0.34; colorless liquid; yield 58% (24.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.8 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 6.77-6.73 (m, 2H), 5.02 (t, *J* = 7.2 Hz, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.64-3.61 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 169.7, 167.2, 162.5, 142.7, 137.1, 133.6, 132.0, 131.9 129.9 ($J_{C\text{-}F}$ = 3.1 Hz), 129.4, 129.3, 125.9 ($J_{C\text{-}F}$ = 4.1 Hz), 121.3, 118.0, 112.6, 55.5, 54.8, 52.7, 52.0, 34.8; ^{19}F NMR (565 MHz, $CDCl_3$) δ -62.87; FT-IR (neat) 3001, 2294, 2256, 1712, 1633, 1441, 1375, 1081 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{20}O_6F_3$ 425.1206; Found 425.1205.


4ai

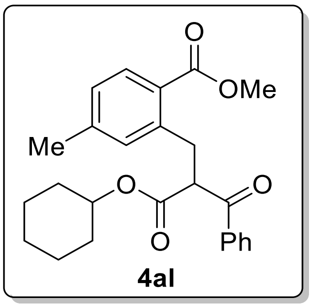
Methyl 2-(2-benzoyl-3-ethoxy-3-oxopropyl)-4-methylbenzoate 4ai. Analytical TLC on silica gel, 1:9 EtOAc/hexane R_f = 0.48; colorless liquid; yield 72% (25.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.2 Hz, 2H), 7.84 (d, *J* = 7.9 Hz, 1H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.10-7.01 (m, 2H), 4.94-4.85 (m, 1H), 4.10-4.03 (m, 2H), 3.84 (s, 3H), 3.66-3.61 (m, 1H), 3.55 (dd, *J* = 13.2, 7.8 Hz, 1H), 2.29 (s, 3H), 1.08 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.3, 169.7, 167.8, 142.9, 140.5, 136.7, 133.4, 133.3, 131.4, 128.8, 128.7, 127.8, 126.6, 61.4, 55.4, 52.0, 34.2, 21.5, 14.1; FT-IR (neat) 2952, 1715, 1687, 1610, 1444, 1266, 1231, 1186, 1083 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{23}O_5$ 355.1540; Found 355.1540.


4aj

Methyl 2-(2-benzoyl-3-(*tert*-butoxy)-3-oxopropyl)-4-methylbenzoate 4aj. Analytical TLC on silica gel, 1:9 EtOAc/hexane $R_f = 0.51$; colorless liquid; yield 75% (29 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, $J = 7.8$ Hz, 2H), 7.84 (d, $J = 8.0$ Hz, 1H), 7.52 (t, $J = 7.4$ Hz, 1H), 7.41 (t, $J = 7.7$ Hz, 2H), 7.09 (s, 1H), 7.06 (d, $J = 8.1$ Hz, 1H), 4.75 (dd, $J = 8.1, 6.4$ Hz, 1H), 3.84 (s, 3H), 3.65 (dd, $J = 13.3, 6.3$ Hz, 1H), 3.47 (dd, $J = 13.3, 8.3$ Hz, 1H), 2.30 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.5, 168.8, 167.8, 142.7, 140.7, 136.9, 133.5, 133.2, 131.4, 128.8, 128.6, 127.6, 126.6, 81.9, 56.7, 52.0, 33.9, 27.8, 21.5; FT-IR (neat) 2977, 2924, 1719, 1692, 1594, 1447, 1267, 1147, 1083 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{23}H_{26}O_5Na$ 405.1672; Found 405.1672.

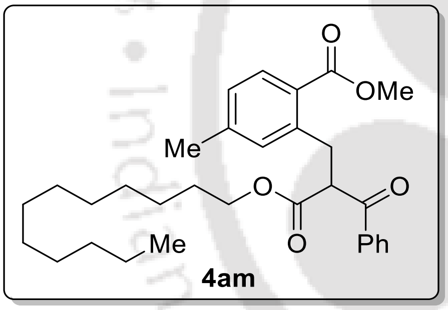

4ak

Methyl 2-(2-benzoyl-3-(benzyloxy)-3-oxopropyl)-4-methylbenzoate 4ak. Analytical TLC on silica gel, 1:9 EtOAc/hexane $R_f = 0.44$; colorless liquid; yield 72% (30 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, $J = 7.2$ Hz, 2H), 7.82 (d, $J = 8.0$ Hz, 1H), 7.52 (t, $J = 7.2$ Hz, 1H), 7.38 (t, $J = 8.0$ Hz, 2H), 7.26-7.23 (m, 3H), 7.10-7.08 (m, 2H), 7.05-7.02 (m, 2H), 5.07-5.00 (m, 2H), 4.98-4.94 (m, 1H), 3.82 (s, 3H), 3.70-3.64 (m, 1H), 3.59-3.54 (m, 1H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 169.5, 167.7, 143.0, 140.4, 136.6, 135.5, 133.5, 133.4, 131.4, 128.9, 128.7, 128.5, 128.3, 128.0, 127.8, 126.6, 67.0, 55.5, 52.1, 34.2, 21.5; FT-IR (neat) 2951, 1715, 1687, 1610, 1448, 1267, 1218, 1161, 1083 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{26}H_{25}O_5$ 417.1697; Found 417.1697.



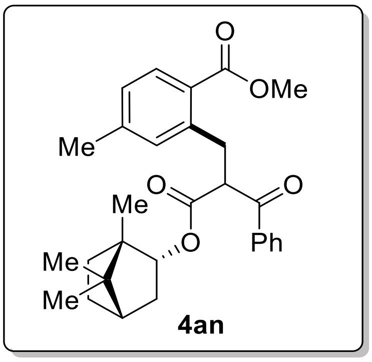
4al

Methyl 2-(2-benzoyl-3-(cyclohexyloxy)-3-oxopropyl)-4-methylbenzoate 4al. Analytical TLC on silica gel, 1:9 EtOAc/hexane $R_f = 0.49$; colorless liquid; yield 67% (27.4 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, $J = 7.2$ Hz, 2H), 7.83 (d, $J = 8.0$ Hz, 1H), 7.52 (t, $J = 7.2$ Hz, 1H), 7.41 (t, $J = 8.0$ Hz, 2H), 7.08-7.05 (m, 2H), 4.86-4.83 (m, 1H), 4.72-4.66 (m, 1H), 3.84 (s, 3H), 3.71-3.66 (m, 1H), 3.52-3.47 (m, 1H), 2.29 (s, 3H), 1.53-1.14 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 169.2, 167.7, 142.8, 140.6, 136.7, 133.4, 131.4, 128.8, 128.6, 127.7, 126.6, 73.6, 55.9, 52.0, 34.0, 31.24, 31.22, 25.4, 23.45, 23.38, 21.5; FT-IR (neat) 2979, 2926, 1718, 1692, 1594, 1448, 1268, 1147, 1081 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{25}H_{29}O_5$ 409.2010; Found 409.2008.

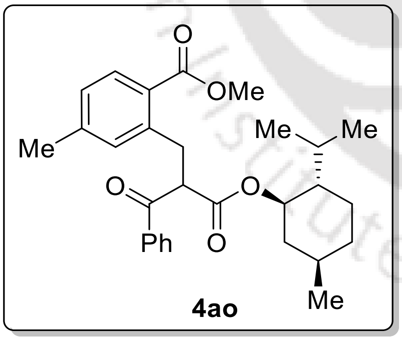


4am

Methyl 2-(2-benzoyl-3-(dodecyloxy)-3-oxopropyl)-4-methylbenzoate 4am. Analytical TLC on silica gel, 1:9 EtOAc/hexane $R_f = 0.52$; colorless liquid; yield 71% (35 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, $J = 7.9$ Hz, 2H), 7.84 (d, $J = 7.9$ Hz, 1H), 7.52 (t, $J = 7.0$ Hz, 1H), 7.41 (t, $J = 7.7$ Hz, 2H), 7.09-7.03 (m, 2H), 4.90 (t, $J = 7.2$ Hz, 1H), 3.98 (td, $J = 6.5, 2.7$ Hz, 2H), 3.84 (s, 3H), 3.64 (dd, $J = 13.2, 6.6$ Hz, 1H), 3.55 (dd, $J = 13.3, 7.8$ Hz, 1H), 2.29 (s, 3H), 1.45-1.41 (m, 2H), 1.25-1.09 (m, 18H), 0.88 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.2, 169.7, 167.8, 142.9, 140.6, 136.7, 133.4, 133.4, 131.4, 128.9, 128.7, 127.8, 126.6, 65.6, 55.5, 52.1, 34.1, 32.1, 29.8, 29.8, 29.7, 29.6, 29.5, 29.3, 28.5, 25.8, 22.8, 21.5, 14.3; FT-IR (neat) 2933, 2917, 1719, 1692, 1594, 1447, 1268, 1147, 1083 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{31}H_{43}O_5$ 495.3105; Found 495.3110.

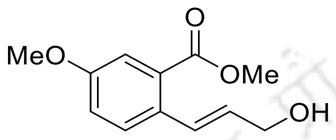


Methyl 2-(2-benzoyl-3-oxo-3-(((1S,4S)-1,7,7-trimethyl-bicyclo-[2.2.1]heptan-2-yl)oxy)propyl)-4-methylbenzoate 4an. Analytical TLC on silica gel, 1:9 EtOAc/hexane R_f = 0.44; colorless liquid; yield 64% (29.6 mg); 1:1 mixture of diastereomers; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.97 (t, *J* = 7.0 Hz, 4H), 7.87-7.84 (m, 2H), 7.53 (t, *J* = 7.0 Hz, 2H), 7.44-7.40 (m, 4H), 7.10-7.05 (m, 4H), 4.89 (t, *J* = 7.0 Hz, 2H), 4.73 (t, *J* = 9.5 Hz, 2H), 3.85-3.83 (m, 6H), 3.74-3.68 (m, 2H), 3.53-3.47 (m, 2H), 2.30 (s, 6H), 2.24-2.12 (m, 2H), 1.66-1.63 (m, 2H), 1.56-1.51 (m, 4H), 1.15-1.02 (m, 4H), 0.90-0.84 (m, 2H), 0.80-0.78 (m, 12H), 0.72 (s, 3H), 0.50 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 194.97, 194.95, 170.0, 169.9, 167.7, 142.9, 140.7, 140.6, 136.8, 133.43, 133.38, 133.3, 131.5, 128.9, 128.8, 128.7, 127.8, 126.63, 126.60, 81.3, 81.2, 56.0, 55.8, 52.0, 48.8, 47.9, 47.8, 44.9, 44.8, 36.4, 36.3, 34.0, 33.8, 28.0, 27.8, 27.0, 21.5, 19.7, 18.9, 13.5, 13.1; FT-IR (neat) 2953, 1719, 1690, 1610, 1449, 1267, 1233, 1187, 1083 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{29}H_{35}O_5$ 463.2479; Found 463.2477.



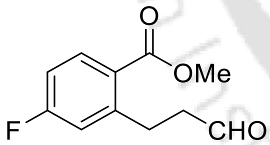
Methyl 2-(2-benzoyl-3-(((1S,2R,5R)-5-isopropyl-2-methylcyclohexyl)oxy)-3-oxopropyl)-4-methylbenzoate 4ao. Analytical TLC on silica gel, 1:9 EtOAc/hexane R_f = 0.44; colorless liquid; yield 61% (28.3 mg); 1:1 mixture of diastereomers; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.98 (d, *J* = 7.5 Hz, 2H), 7.92 (d, *J* = 7.5 Hz, 2H), 7.86 (t, *J* = 8.5 Hz, 2H), 7.55-7.51 (m, 2H), 7.43-7.38 (m, 4H), 7.10-7.06 (m, 4H), 4.88-4.85 (m, 2H), 4.56-4.49 (m, 2H), 3.84 (s, 6H), 3.76-3.68 (m, 2H), 3.51-3.41 (m, 2H), 2.31-2.30 (m, 6H), 1.80-1.78 (m, 1H), 1.67-1.65 (m, 1H), 1.56-1.52 (m, 6H), 1.40-1.32 (m, 2H), 1.23-1.16 (m, 4H), 0.93-0.86 (m, 4H), 0.84 (d, *J* = 6.5 Hz, 3H), 0.80 (d, *J* = 6.5 Hz, 3H), 0.72 (d, *J*

= 7.5 Hz, 3H), 0.62 (d, *J* = 7.0 Hz, 3H), 0.53 (d, *J* = 7.0 Hz, 3H), 0.33 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.2, 194.7, 169.4, 169.1, 167.8, 167.7, 142.9, 140.6, 136.8, 136.6, 133.5, 133.43, 133.41, 133.3, 131.54, 131.46, 128.9, 128.8, 128.64, 128.58, 127.8, 127.7, 126.6, 126.5, 75.6, 75.5, 56.4, 55.8, 52.05, 52.02, 46.8, 40.7, 40.5, 34.22, 34.19, 34.16, 34.0, 31.4, 31.3, 25.73, 25.67, 23.1, 22.9, 22.11, 22.07, 21.5, 20.9, 20.8, 15.7; FT-IR (neat) 2953, 2869, 1718, 1688, 1611, 1449, 1266, 1231, 1185, 1083 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{29}H_{37}O_5$ 465.2636; Found 465.2636.



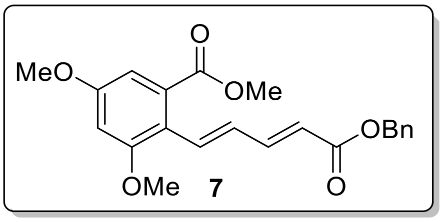
5

Methyl (*E*)-2-(3-hydroxyprop-1-en-1-yl)-5-methoxybenzoate 5. Analytical TLC on silica gel, 1:9 EtOAc/hexane R_f = 0.36; colorless liquid; yield 93% (20.7 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.5 Hz, 1H), 7.38-7.37 (m, 1H), 7.30 (d, *J* = 15.5 Hz, 1H), 7.04-7.02 (m, 1H), 6.20-6.15 (m, 1H), 4.32 (d, *J* = 6.0 Hz, 2H), 3.90 (s, 3H), 3.86-3.84 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 158.8, 131.3, 129.8, 129.7, 129.6, 128.9, 118.8, 114.8, 64.1, 55.6, 52.3; FT-IR (neat) 3440, 2954, 1720, 1594, 1438, 1256, 1207, 1137, 1072 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{12}H_{14}O_4Na$ 245.0784; Found 245.0787.

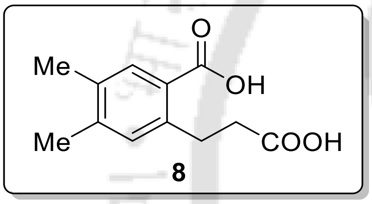


6

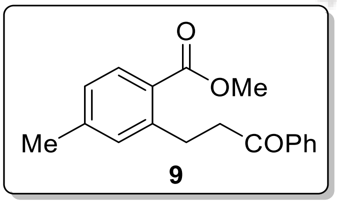
Methyl 4-fluoro-2-(3-oxopropyl)benzoate 6. Analytical TLC on silica gel, 1:9 EtOAc/hexane R_f = 0.42; colorless liquid; yield 89% (18.7 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (t, *J* = 1.2 Hz, 1H), 8.00-7.96 (m, 1H), 7.01-6.94 (m, 2H), 3.88 (s, 3H), 3.28 (t, *J* = 9.0 Hz, 2H), 2.84-2.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 166.8, 166.2 ($J_{C\text{-}F}$ = 252.0 Hz), 146.5 ($J_{C\text{-}F}$ = 8.4 Hz), 134.0 ($J_{C\text{-}F}$ = 9.3 Hz), 125.3 ($J_{C\text{-}F}$ = 3.0 Hz), 118.3 ($J_{C\text{-}F}$ = 21.4 Hz), 113.8 ($J_{C\text{-}F}$ = 21.2 Hz), 52.2, 45.3, 27.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ -106.59; FT-IR (neat) 2956, 1717, 1630, 1594, 1442, 1256, 1208, 1137, 1072 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{12}O_3F$ 211.0765; Found 211.0761.



Methyl 2-((1*E*,3*E*)-5-(benzyloxy)-5-oxopenta-1,3-dien-1-yl)-3,5-dimethoxybenzoate 7. Analytical TLC on silica gel, 1:9 EtOAc/hexane $R_f = 0.44$; yellow solid; mp 75-76 °C; yield 87% (33 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 15.5, 11.5 Hz, 1H), 7.40-7.31 (m, 5H), 7.19 (d, *J* = 15.5 Hz, 1H), 6.95 (dd, *J* = 15.5, 11.0 Hz, 1H), 6.82-6.81 (m, 1H), 6.59-6.58 (m, 1H), 5.95 (d, *J* = 15.5 Hz, 1H), 5.21 (s, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 167.2, 160.3, 159.8, 147.1, 136.4, 134.9, 133.8, 130.5, 128.7, 128.3, 128.2, 120.1, 118.2, 105.8, 101.8, 66.2, 56.0, 55.7, 52.7; FT-IR (neat) 2949, 1712, 1596, 1457, 1327, 1241, 1210, 1125, 1058 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{23}O_6$ 383.1489; Found 383.1489.



2-(2-Carboxyethyl)-4,5-dimethylbenzoic acid 8. Analytical TLC on silica gel, 6:4 EtOAc/hexane $R_f = 0.30$; colorless solid; mp >200 °C; yield 72% (16 mg); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.36 (bs, 2H), 7.60 (s, 1H), 7.09 (s, 1H), 3.06 (t, *J* = 7.6 Hz, 2H), 2.46 (t, *J* = 8.0 Hz, 2H), 2.22 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.9, 168.5, 140.7, 139.6, 134.2, 132.1, 131.6, 127.3, 35.5, 28.8, 19.3, 18.8; FT-IR (neat) 3440, 2954, 1710, 1594, 1438, 1256, 1207, 1137 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{15}O_4$ 223.0965; Found 223.0960.



Methyl 4-methyl-2-(3-oxo-3-phenylpropyl)benzoate 9. Analytical TLC on silica gel, 1:9 EtOAc/hexane $R_f = 0.32$; colorless liquid; yield 91% (25.7 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.5 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.54 (t, *J* = 7.0 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 2H), 7.15 (s, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 3.87 (s, 3H), 3.35-3.34 (m, 4H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.7, 167.9, 143.7, 143.0, 137.1, 133.1, 132.4, 131.3, 128.7, 128.3, 127.2, 126.6, 52.0, 40.8, 29.6, 21.6; FT-IR (neat)

2926, 1717, 1685, 1448, 1268, 1204, 1082, 973 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{19}O_3$ 283.1329; Found 283.1328.

Crystal Data and Structure Refinement for 3oa.

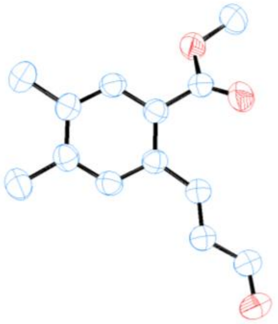


Figure 1. ORTEP diagram of **methyl (*E*)-4,5-dimethyl-2-(3-oxoprop-1-en-1-yl)benzoate 3oa** (CCDC No 2368719) with 50% ellipsoid. H-Atoms are omitted for clarity.

CCDC	**2368719**
Identification code	**3oa**
Empirical formula	$C_{13}H_{14}O_3$
Formula weight	218.24
Crystal habit, colour	Block, Colorless
Temperature, *T*/K	298 K
Wavelength, λ/Å	0.71073 Å
Crystal system	Triclinic
Space group	P -1
Unit cell dimensions	a = 8.402(3) Å b = 8.472(3) Å c = 9.245(4) Å α= 109.344(11) β= 101.143(11) γ = 100.258(11)

Volume, V/Å^3	588.0
Z	2
Calculated density, Mg·m^{-3}	1.233
Absorption coefficient, μ/mm^{-1}	0.087
F(000)	232
θ range for data collection	2.426 to 26.001
Limiting indices	$-10 \leq h \leq 10$, $-10 \leq k \leq 10$, $-11 \leq l \leq 11$
Reflection collected / unique	2304/ 1770
Completeness to θ	99.3%
Absorption correction	Multi-scan
Refinement method	SHELXL 2018/3 (Sheldrick, 2015)
Data / restraints / parameters	2304/ 0/ 148
Goodness–of–fit on F^2	1.087
Final R indices [I >2sigma(I)]	R1 = 0.0548, wR2 = 0.1271
R indices (all data)	R1 = 0.0734, wR2 = 0.1416

3.5 References

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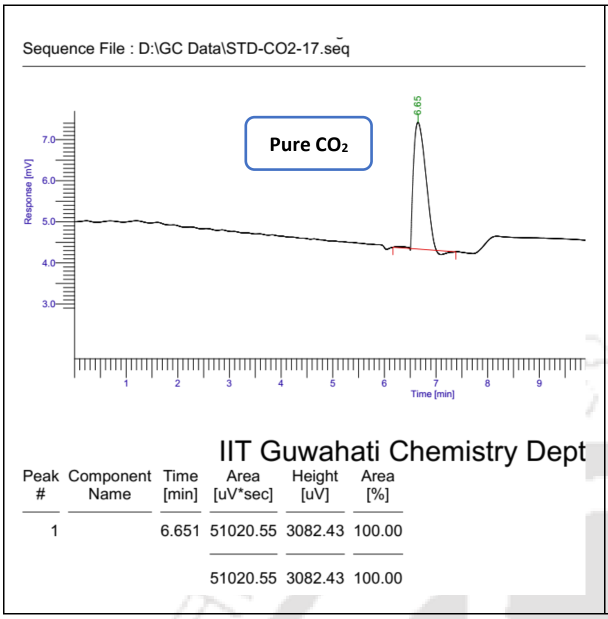
3.6 Gas Chromatograms



Sequence File : D:\GC Data\STD-CO2-17.seq

IIT Guwahati Chemistry Dept

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]
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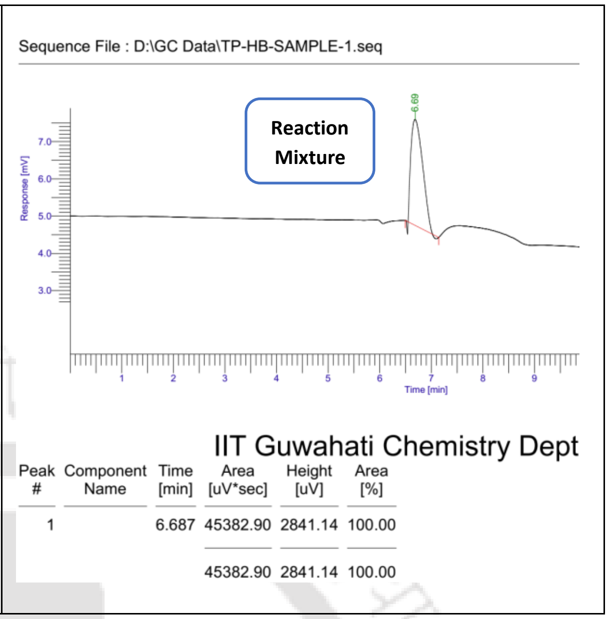
			51020.55	3082.43	100.00



Sequence File : D:\GC Data\TP-HB-SAMPLE-1.seq

IIT Guwahati Chemistry Dept

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]
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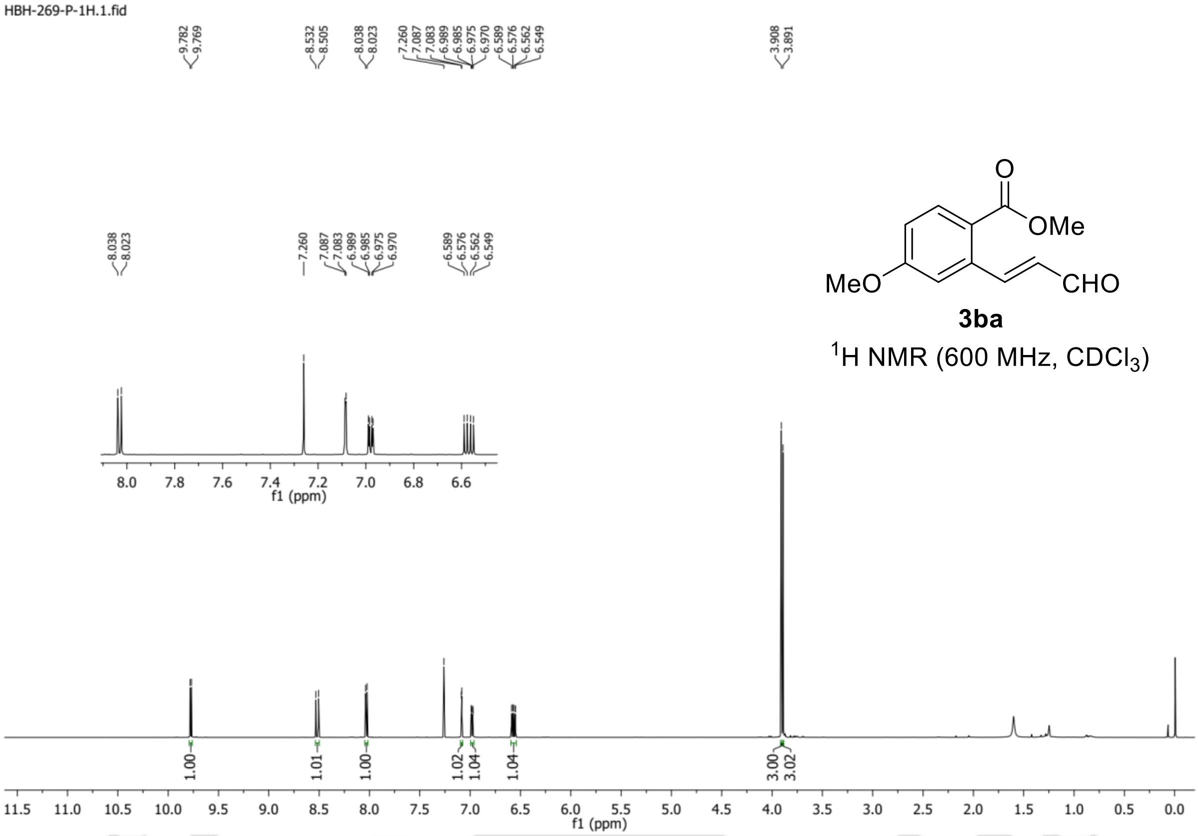
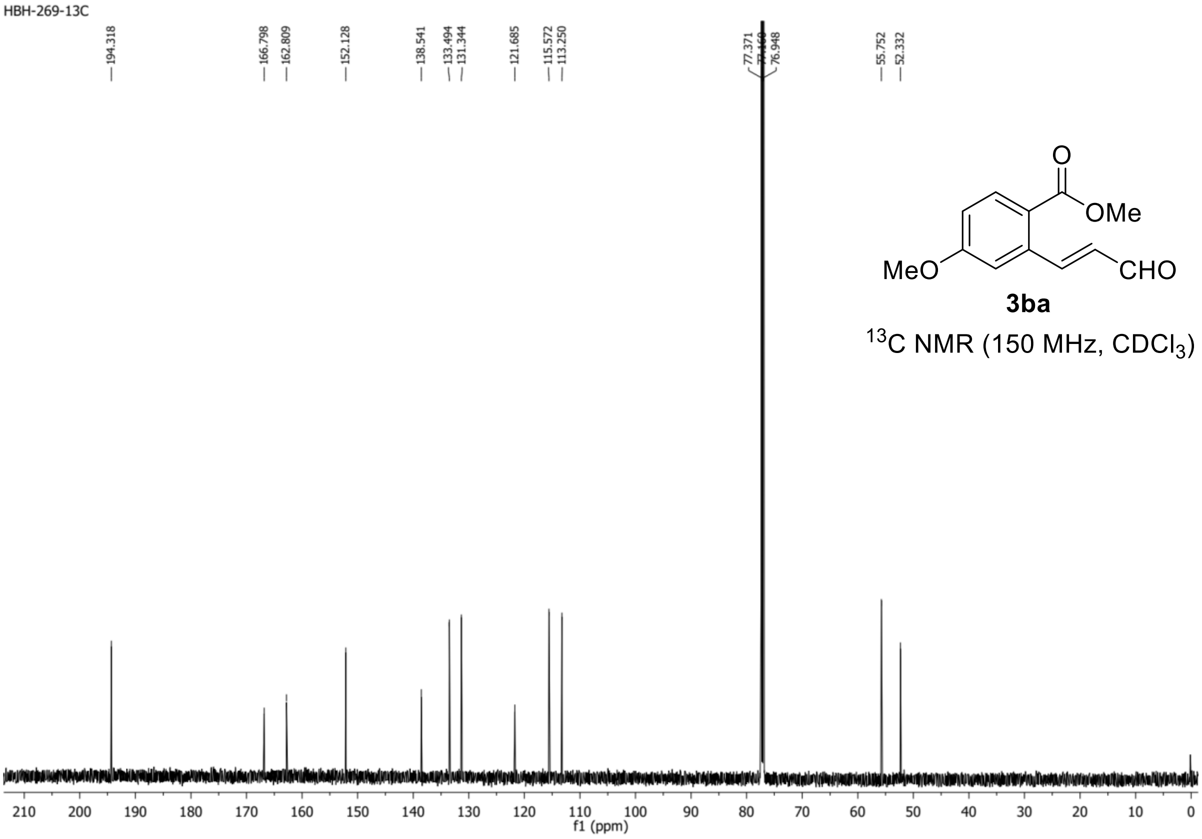
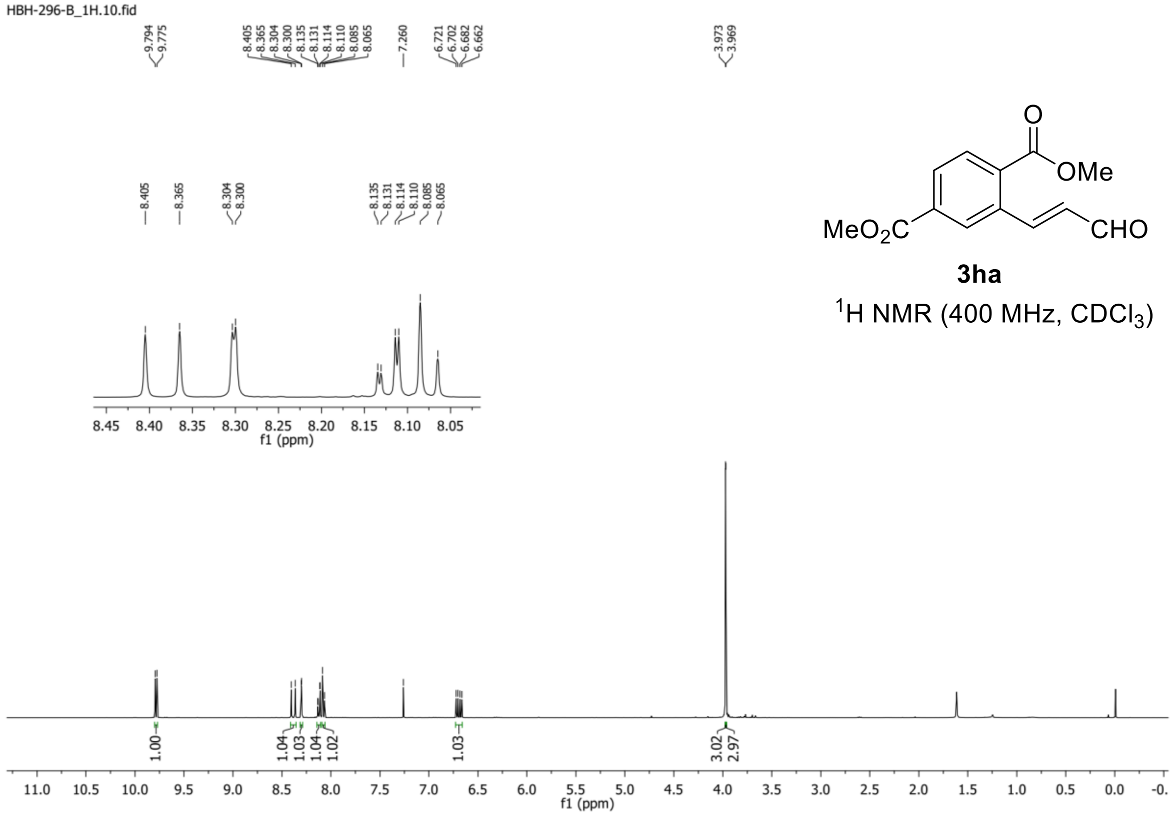
			45382.90	2841.14	100.00

3.7 Selected NMR Spectra

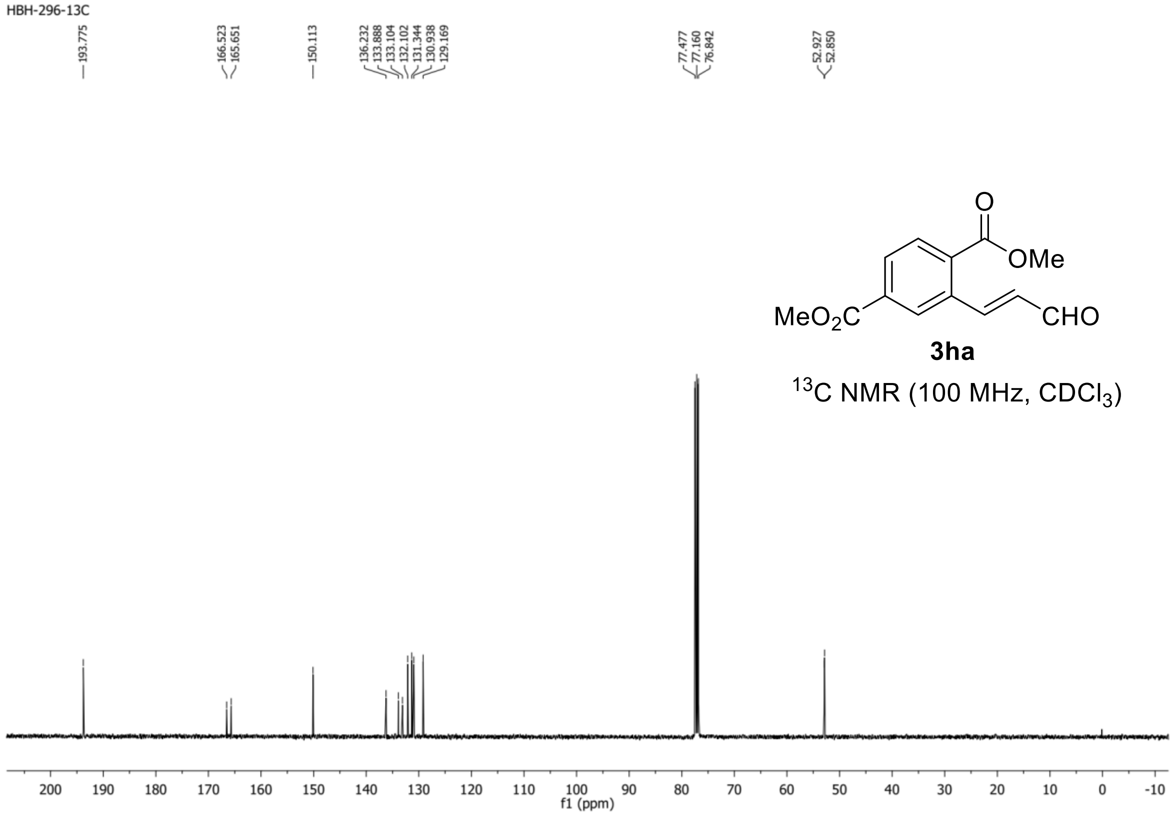






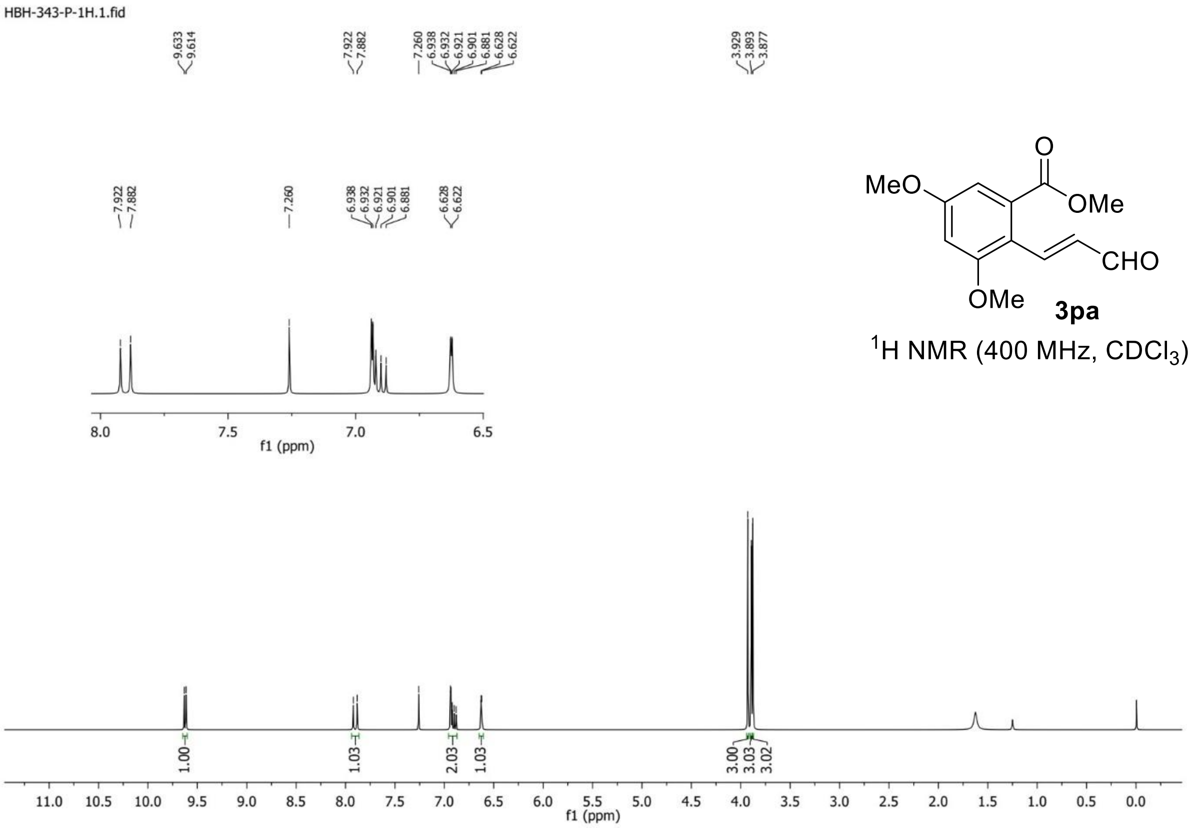
3ha

^{1}H NMR (400 MHz, $CDCl_3$)



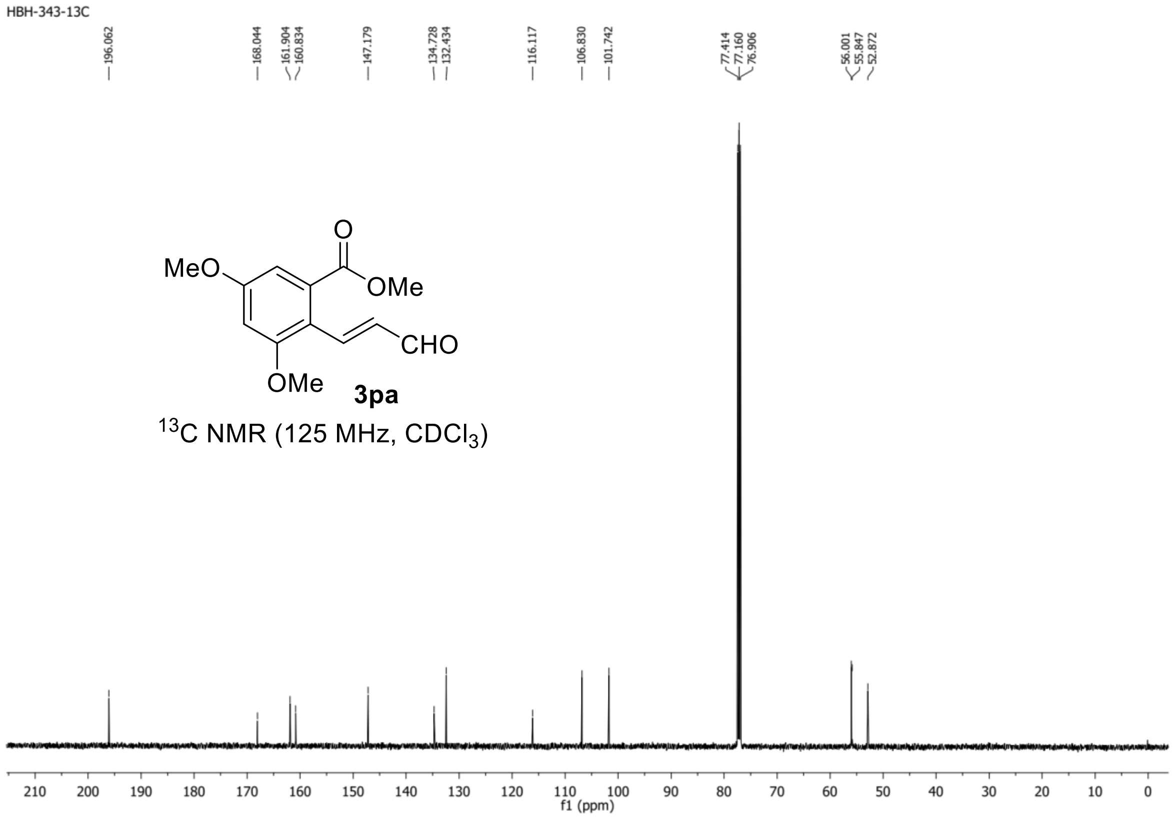
3ha

^{13}C NMR (100 MHz, $CDCl_3$)



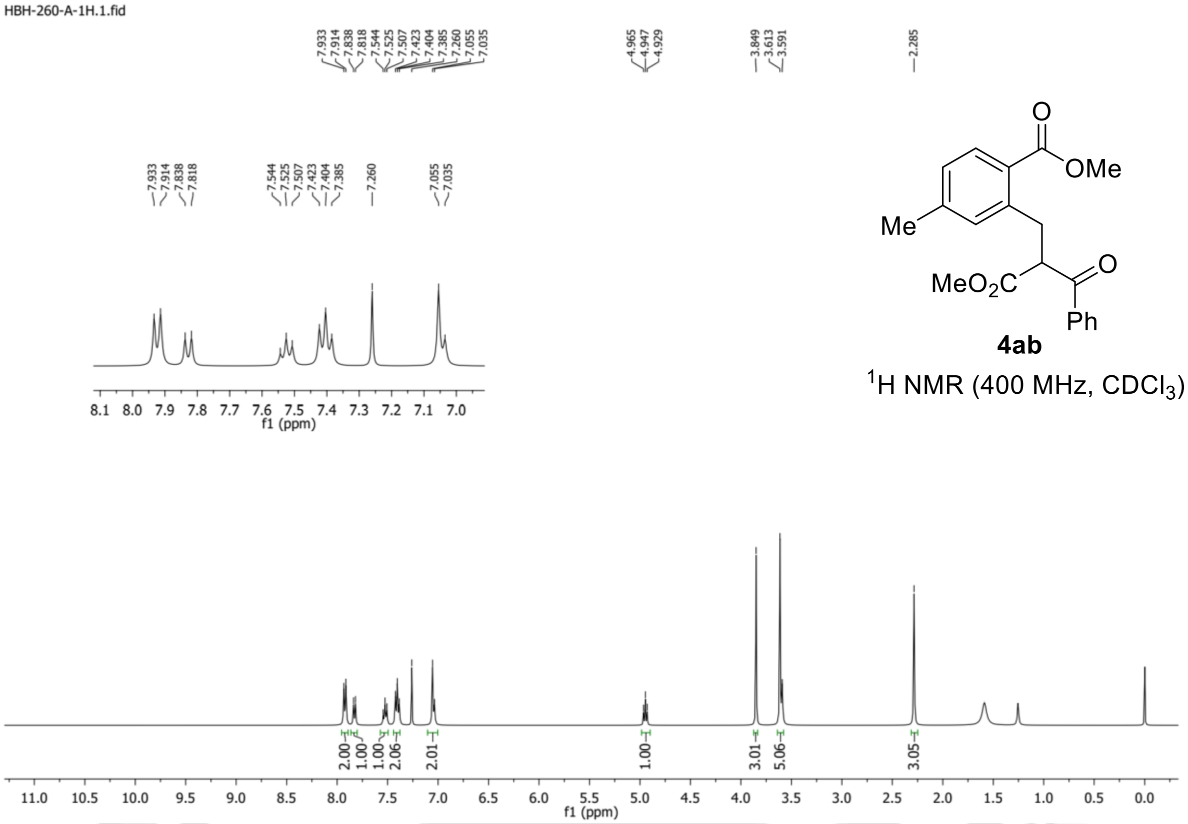
3pa

^{1}H NMR (400 MHz, CDCl$_3$)



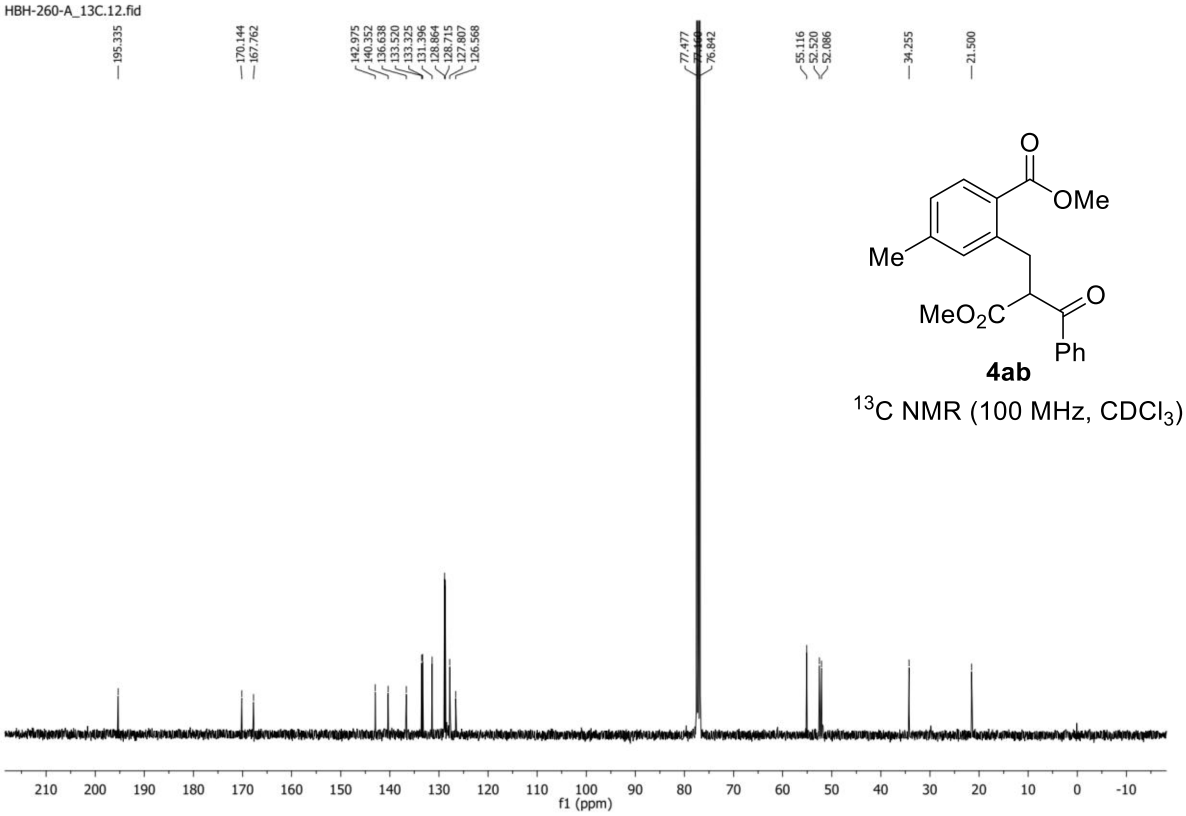
3pa

^{13}C NMR (125 MHz, CDCl$_3$)



4ab

^{1}H NMR (400 MHz, $CDCl_3$)



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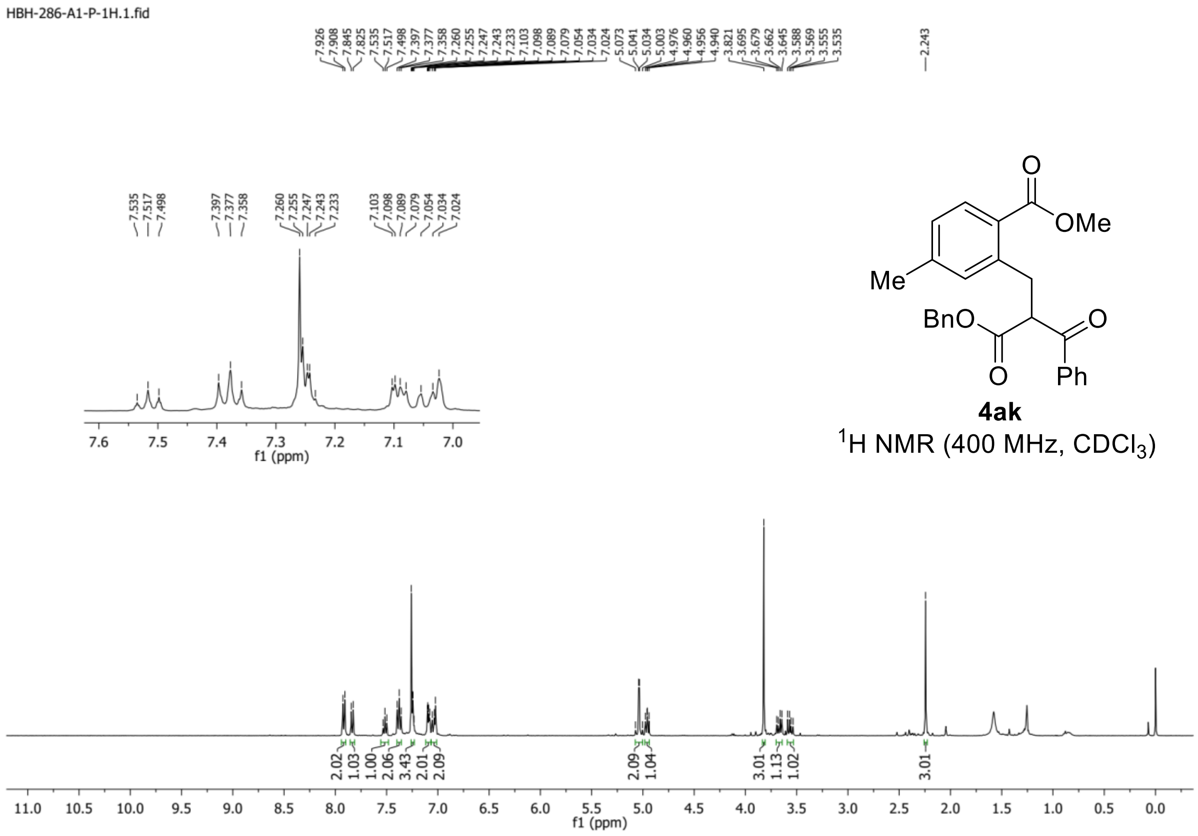
^{13}C NMR (100 MHz, $CDCl_3$)



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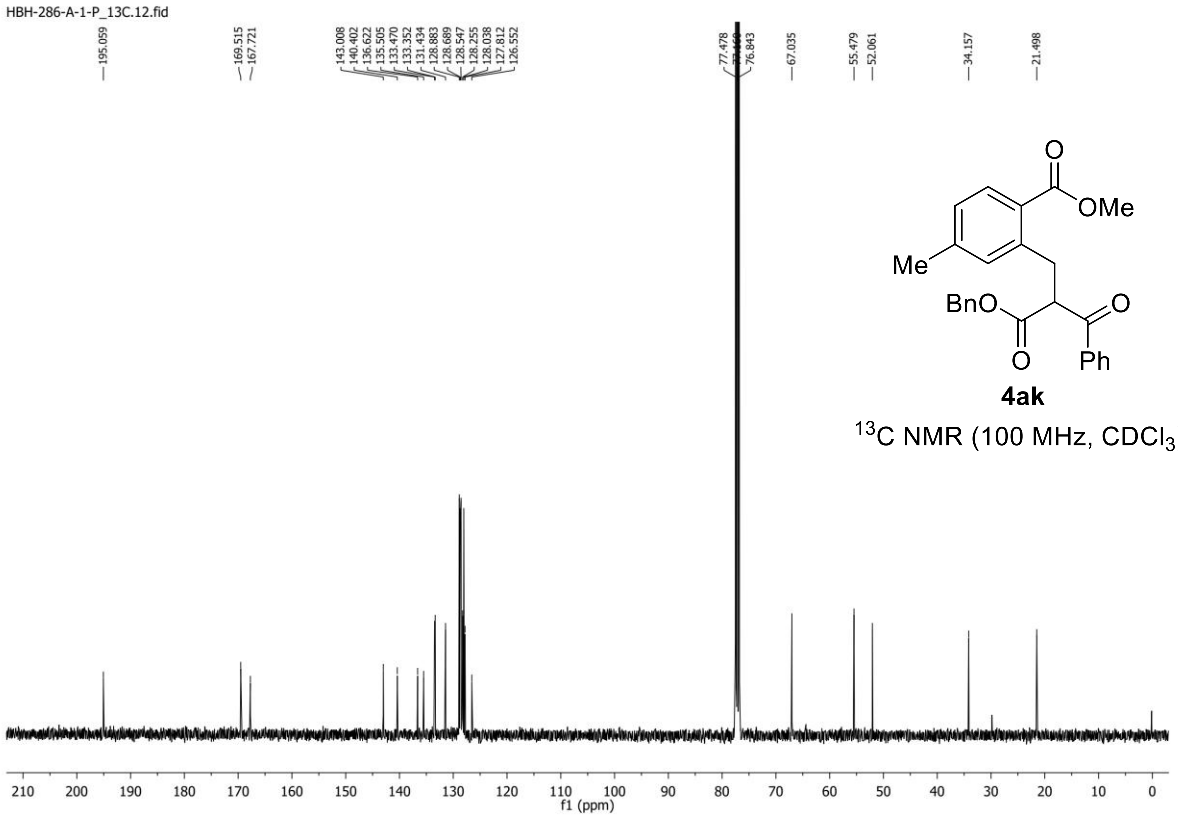
^{1}H NMR (400 MHz, $CDCl_3$)

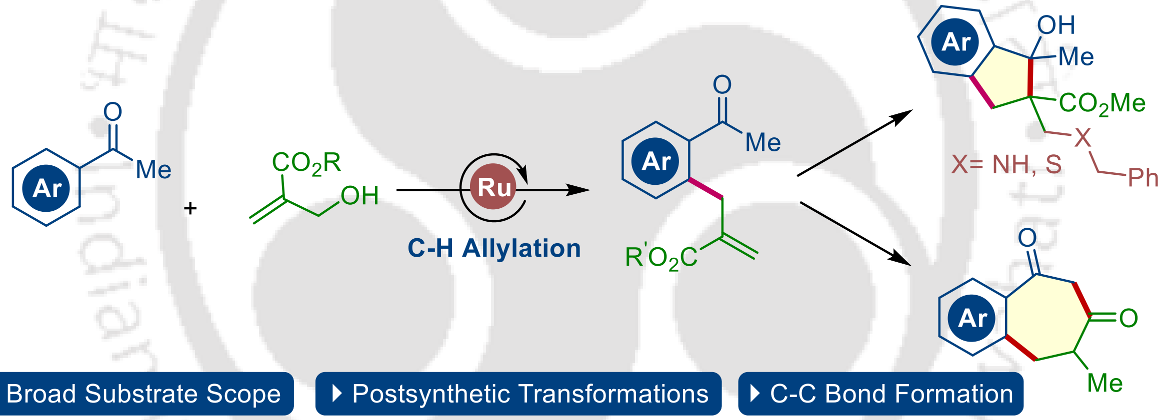


4ak

^{13}C NMR (100 MHz, $CDCl_3$)

Chapter 4

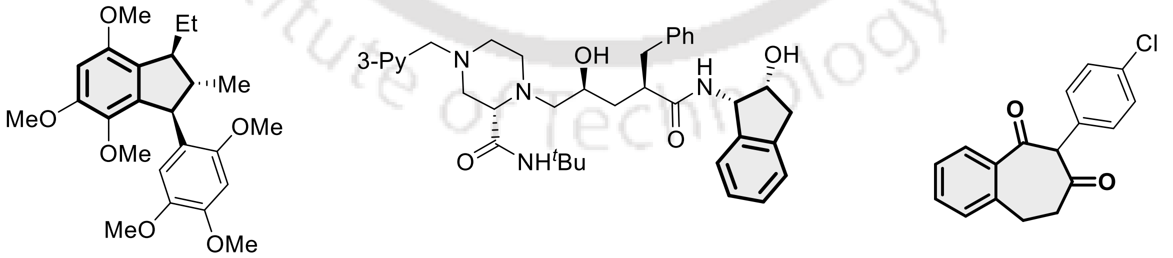
Weak-Chelation-Assisted C–H Allylation of Aryl Ketones Using Morita-Baylis-Hillman Alcohols



Chem. Commun. **2026**. DOI:10.1039/D5CC07391J.

Weak-Chelation-Assisted C–H Allylation of Aryl Ketones Using Morita-Baylis-Hillman Alcohols

Ketones are among the widely studied DGs in C–H functionalization, owing to their abundance in organic molecules.[1] The carbonyl oxygen can chelate to a transition-metal-catalyst, enabling proximal C–H activation and subsequent formation of C–C or C–Heteroatom bonds with high regioselectivity. Such ketone-directed transformations have been extensively applied in the synthesis of complex molecules, offering a powerful strategy for building structural diversity from simple ketone.[2, 6-8] Further, the regioselective C–H allylation of arenes has conventionally relied on pre-activated allyl electrophiles,[3] such as allyl acetates, carbonates, phosphates, halides or allenes. In contrast, the direct utilization of non-activated allyl alcohols, wherein the hydroxyl group serves as the leaving group, presents a more atom- and step-economical alternative.[4, 10, 11] However, a key challenge in employing allylic alcohols for C–H allylation lies in the poor leaving group ability of the hydroxyl moiety which often promotes *β*-hydride elimination, leading to carbonyl compounds. This *β*-hydride elimination tendency, involving weakly coordinating ketone-DG, remains well-explored.[5] However, ketone-directed C–H allylation using allyl alcohols remains scarce. Morita-Baylis-Hillman (MBH) alcohols, a class of allylic alcohol, are valuable substrates in organic synthesis. While the pre-activated MBH acetates and carbonates have been employed in C–H functionalization with various DGs to access allylated products,[12-14] the direct utilization of MBH alcohols for C–H allylation has not been reported.



Asarone dimer
Insect Growth Regulator

Indinavir
HIV Protease Inhibitor

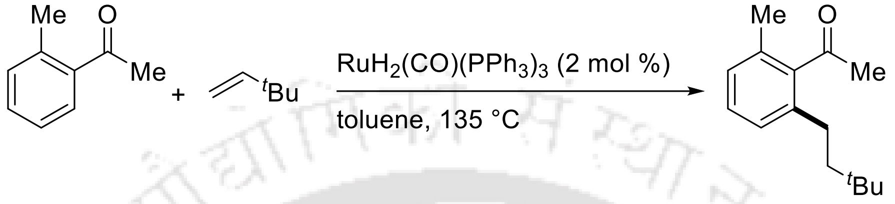
Cyclic β-diketone
Anticoagulant Properties

Figure 1. Examples of Biologically Important Indanes and Benzo-Fused Seven Membered Cyclic *β*-Diketones

4.1 Literature

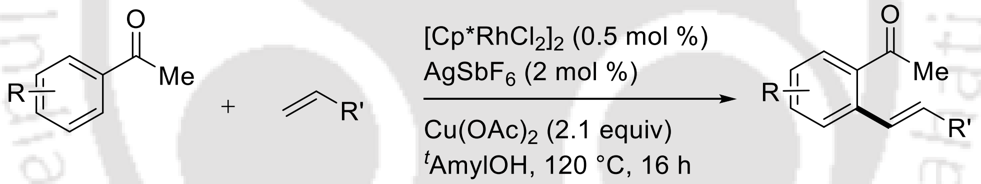
4.1.1 C–H Functionalization of Aryl Ketones

In one of the earliest reports Murai and co-workers demonstrated the Ru(II) catalyzed *ortho* alkylation of aryl ketones where a pendant heteroatom could function as a chelating group to achieve site selectivity (Scheme 1).[6]



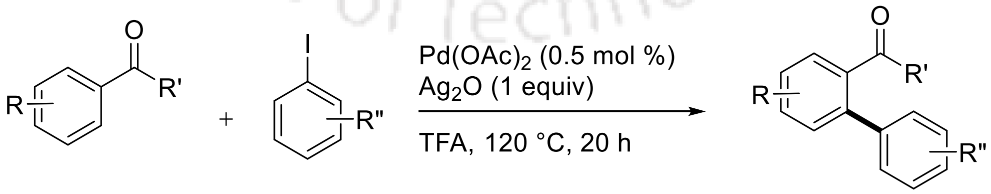
Scheme 1. Ru(II) Catalyzed *ortho* C–H Alkylation of Aryl Ketones

Glorius group demonstrated a Rh(III)-catalyzed *ortho*-olefination of acetophenones using a broad range of olefins, including styrene and acrylates (Scheme 1).[7] This protocol efficiently employs ketone DG, operates with low catalyst loading and delivers moderate to high yields of alkenylated products.



Scheme 2. Rh(III)-Catalyzed Oxidative *ortho* C–H Alkenylation of Acetophenones

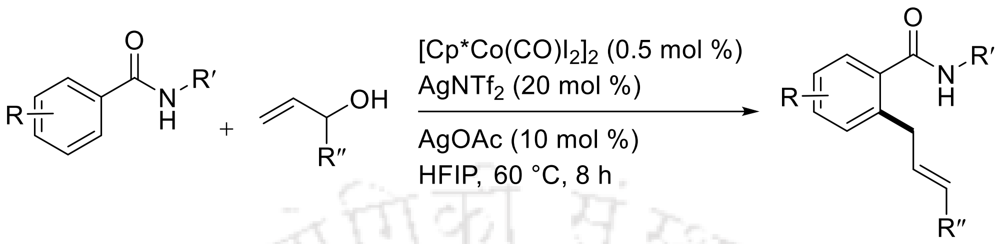
Cheng group reported a selective Pd(II)-catalyzed C–H arylation of aryl ketones using aryl iodides as coupling partners. (Scheme 3).[8] The protocol operates with a low catalyst loading and affords moderate to good yields of the arylated products.



Scheme 3. Pd(II)-Catalyzed C–H Arylation of Aryl Ketones

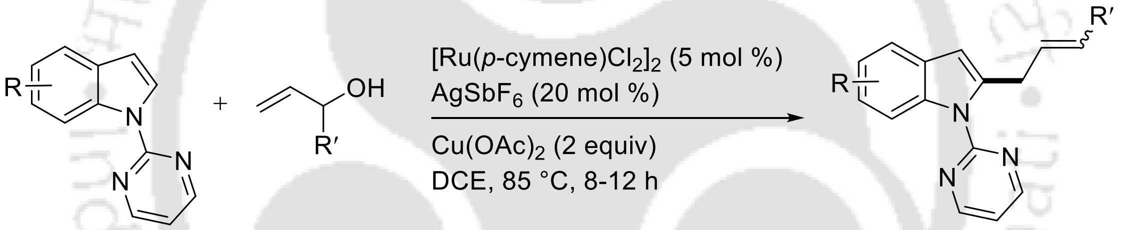
4.1.2 C–H Allylation Using Allylic Alcohols

Yoshino and co-workers developed a Co(III)-catalyzed dehydrative C–H allylation of benzamides using allyl alcohols as allylating agent (Scheme 4).[9] This protocol offers a practical and scalable approach to synthesize allylated amides with good functional group tolerance.



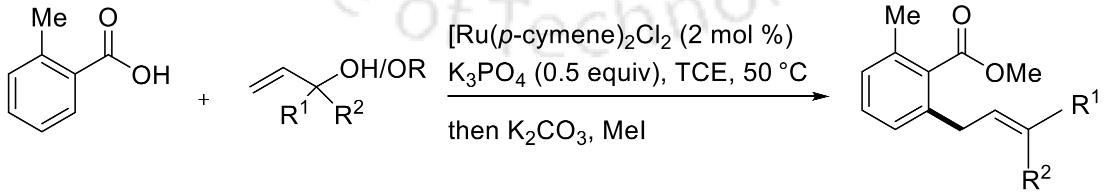
Scheme 4. C–H Allylation of Benzamides with Allyl Alcohols

Kapur group developed a Ru(II)-catalyzed, site-selective C–H allylation of indoles using unactivated allyl alcohols with a removable *N*-pyridyl DG (Scheme 5).[10] The reaction proceeds with C2-selectivity and yields allylated products with high functional group tolerance.



Scheme 5. C–H Allylation of Indoles with Allyl Alcohols

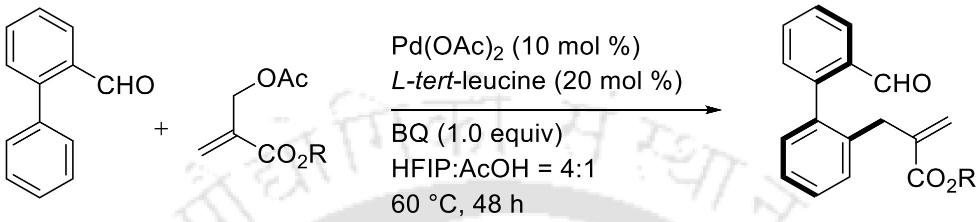
Gooßen, group developed a Ru(II)-catalyzed, carboxylate-directed *ortho* C–H allylation of aromatic carboxylates using non-activated allyl alcohols or allyl ethers (Scheme 6).[11] The protocol tolerates a wide range of substituents on both the carboxylate and allyl partners, including sterically demanding and natural-product-derived substrates.



Scheme 6. C–H Allylation of Aromatic Carboxylates with Allyl Alcohols

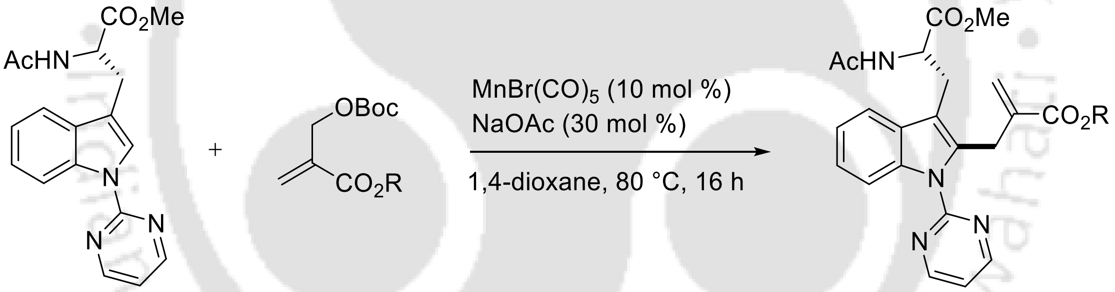
4.1.3 C–H Allylation Using MBH Adducts

Shi group developed a Pd(II)-catalyzed atroposelective C–H allylation enabling access to axially chiral biaryl aldehydes using MBH acetates as coupling partners (Scheme 7).[12] Using *L-tert*-leucine as a catalytic chiral transient auxiliary and *β*-O elimination, the method achieves high enantioselectivity.



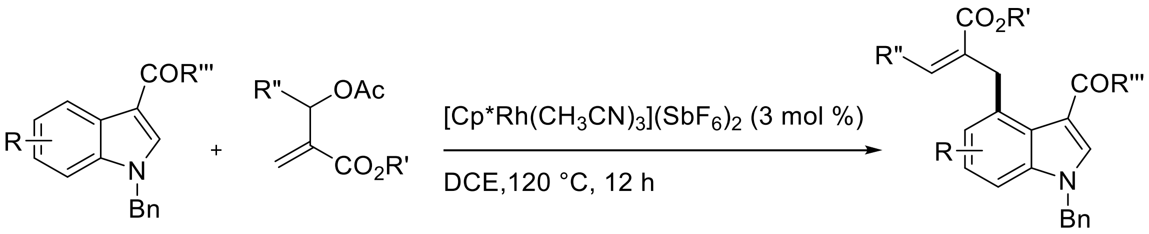
Scheme 7. Pd(II)-Catalyzed Atroposelective C–H Allylation of Biaryl Aldehydes

Ackermann group reported a Mn(I)-catalyzed bioorthogonal C–H allylation at the C2-position of structurally complex peptide tethered indoles using MBH carbonates as coupling partner and using pyrimidine as DG (Scheme 8).[13]



Scheme 8. Mn(I)-Catalyzed Bioorthogonal C2 Allylation of Indoles

Our group reported a C4-allylation of indoles with MBH adducts using Rh(III)-catalysis *via* a redox-neutral pathway with a weakly coordinating acetyl DG. The method proceeds shows excellent site- and functional-group selectivity, and tolerates a broad range of indole substrates and MBH adducts, including those derived from natural products (Scheme 9).[14]



Scheme 9. Rh(III)-Catalyzed C4 Allylation of Indoles with MBH Adducts

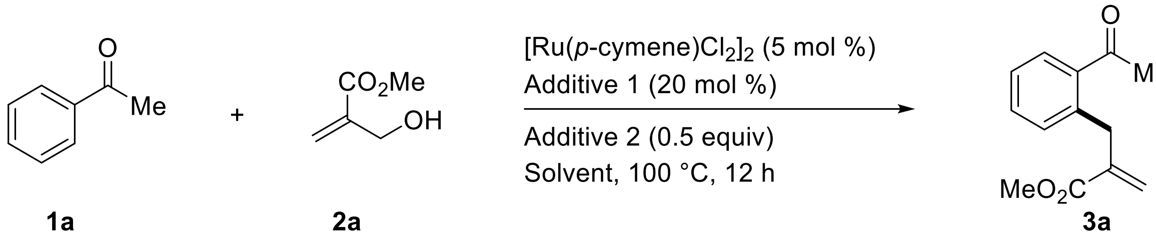
4.2 Present Study

Herein, we report a Ru-catalyzed, keto-directed *ortho*-selective C–H allylation of aryl ketones using MBH alcohols as coupling partner to furnish functionalized α-benzyl acrylates. Additionally, the resulting allylated products, containing both a keto group and a terminal activated alkene, are demonstrated to undergo post-synthetic transformations to produce multi substituted indanes and benzo-fused seven membered cyclic β-diketones, structural motifs commonly found in biologically active scaffolds (Figure 1).[15]

Initially, the reaction conditions were examined for the C–H functionalization of acetophenone **1a** with MBH alcohol **2a** as the model substrates, using $[Ru(p\text{-cymene})Cl_2]_2$ as the catalyst (Table 1). Gratifyingly, the C–H allylation proceeded efficiently to afford methyl 2-(2-acetylbenzyl)acrylate **3a** in 73% yield when **1a** (1 equiv) and **2a** (1.5 equiv) were stirred with $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%) and $Cu(OAc)_2$ (1 equiv) in $(CH_2Cl)_2$ at 100 °C for 12 h. Notably, replacing $Cu(OAc)_2$ with its hydrated form, $Cu(OAc)_2{\cdot}H_2O$, further improved the yield to 85%. In contrast, $Zn(OAc)_2$ did not enhance the reaction outcome. Screening alternative silver salts as additives, such as AgOTf and $AgNTf_2$, resulted in diminished yields compared to $AgSbF_6$. Evaluation of various solvents-including $(CH_2Cl)_2$, CH_2Cl_2, 1,4-dioxane, TFE, HFIP and CH_3CN-identified $(CH_2Cl)_2$ as optimal solvent. Control experiments confirmed that $AgSbF_6$, $Cu(OAc)_2{\cdot}H_2O$ and $[Ru(p\text{-cymene})Cl_2]_2$ are essential for product formation.

With the optimized reaction conditions, the scope of the C–H allylation was explored using a variety of aryl ketones **1** and MBH alcohols **2** (Table 2). Using **2a** as the coupling partner, aryl ketones bearing diverse *para*-substituents, including bromo **1b**, methyl **1c**, ethyl **1d**, phenyl **1e**, nitro **1f**, trifluoromethyl **1g**, ethoxy **1h**, *tert*-butyl **1i** and ester **1j**, produced the allylated products **3b-j** in yields ranging from 66 to 86%. Substituents at the *ortho* position, such as methyl **1k** and fluoro **1l**, afforded **3k** and **3l** with yields of 77% and 80%, respectively. Similarly, *meta*-substituted aryl ketones with fluoro **1m** delivered **3m** in 81% yield. However, in case of *meta*-methoxy acetophenone **1n**, the reaction gave an inseparable mixture of regioisomers **3n** and **3n′** in a 1.16:1 ratio, with 79% yield. Moreover, 3',4'-dichloroacetophenone **1o**, 3',4'-(methylenedioxy)acetophenone **1p**, 2-acetylthiophene **1q** and 1-acetylnaphthalene **1r** successfully underwent allylation to furnish **3o-r** in yields ranging from 74 to 81%. Similarly, tetralone **1s**, benzophenone **1t** and 4-acetylacetophenone **1u** produced monoallylated **3s-u** in yields of 67-82%. Further, varying the ester group in the MBH alcohol

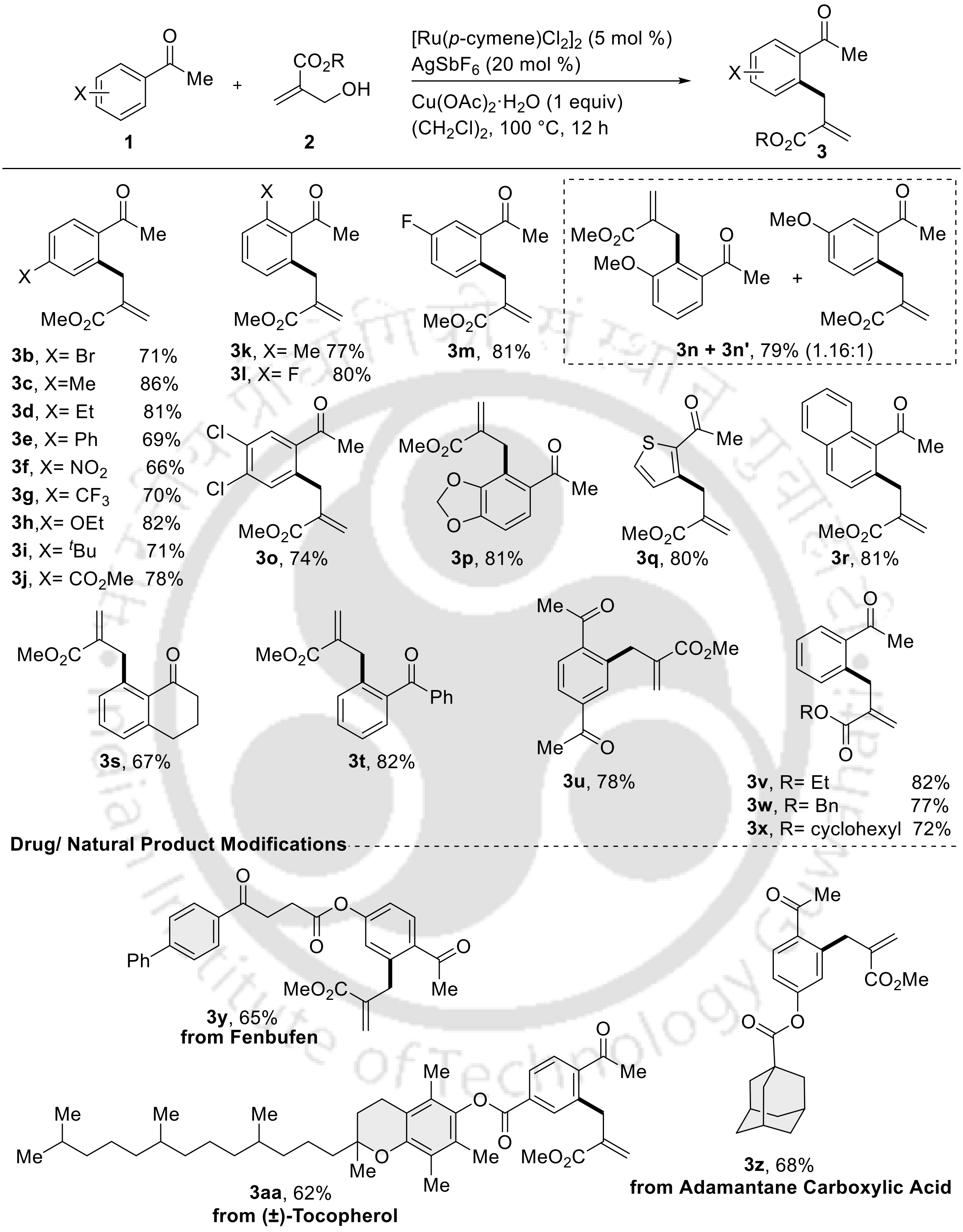
Table 1. Optimization of the Reaction Conditions[a]



Entry	Additive 1	Additive 2	Solvent	**3a** (Yield, %)[b]
1	$AgSbF_6$	$Cu(OAc)_2$	$(CH_2Cl)_2$	73
2	**$AgSbF_6$**	**$Cu(OAc)_2\cdot H_2O$**	**$(CH_2Cl)_2$**	**85**
3	$AgSbF_6$	$Zn(OAc)_2$	$(CH_2Cl)_2$	57
4	AgOTf	$Cu(OAc)_2\cdot H_2O$	$(CH_2Cl)_2$	66
5	$AgNTf_2$	$Cu(OAc)_2\cdot H_2O$	$(CH_2Cl)_2$	73
6	$AgSbF_6$	$Cu(OAc)_2\cdot H_2O$	CH_2Cl_2	67
7	$AgSbF_6$	$Cu(OAc)_2\cdot H_2O$	1,4-Dioxane	75
8	$AgSbF_6$	$Cu(OAc)_2\cdot H_2O$	TFE	62
9	$AgSbF_6$	$Cu(OAc)_2\cdot H_2O$	HFIP	70
10	$AgSbF_6$	$Cu(OAc)_2\cdot H_2O$	CH_3CN	n.d.
11	-	$Cu(OAc)_2\cdot H_2O$	$(CH_2Cl)_2$	n.d.
12	$AgSbF_6$	-	$(CH_2Cl)_2$	n.d.
13[c]	$AgSbF_6$	$Cu(OAc)_2\cdot H_2O$	$(CH_2Cl)_2$	n.d.
14[d]	$AgSbF_6$	$Cu(OAc)_2\cdot H_2O$	$(CH_2Cl)_2$	n.d.
15[e]	$AgSbF_6$	$Cu(OAc)_2\cdot H_2O$	$(CH_2Cl)_2$	71
16[f]	$AgSbF_6$	$Cu(OAc)_2\cdot H_2O$	$(CH_2Cl)_2$	55
17[g]	$AgSbF_6$	$Cu(OAc)_2\cdot H_2O$	$(CH_2Cl)_2$	67
18[h]	$AgSbF_6$	$Cu(OAc)_2\cdot H_2O$	$(CH_2Cl)_2$	40

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %), additive 1 (20 mol %), additive 2 (1 equiv), solvent (1 mL), 100 °C, 12 h. [b] Isolated yield. [c] In absence of $[Ru(p\text{-cymene})Cl_2]_2$. [d] Using $[CoCp^*(CO)I_2]$ (5 mol %) instead of $[Ru(p\text{-cymene})Cl_2]_2$. [e] $Cu(OAc)_2\cdot H_2O$ (2 equiv) used. [f] $Cu(OAc)_2\cdot H_2O$ (0.5 equiv) used. [g] At 120 °C. [h] At 60 °C. n.d = not detected. TFE = 2,2,2-trifluoroethanol. HFIP = 1,1,1,3,3,3-hexafluoro-isopropanol.

Table 2. Substrate Scope of Aryl Ketones and MBH Alcohols[a,b]

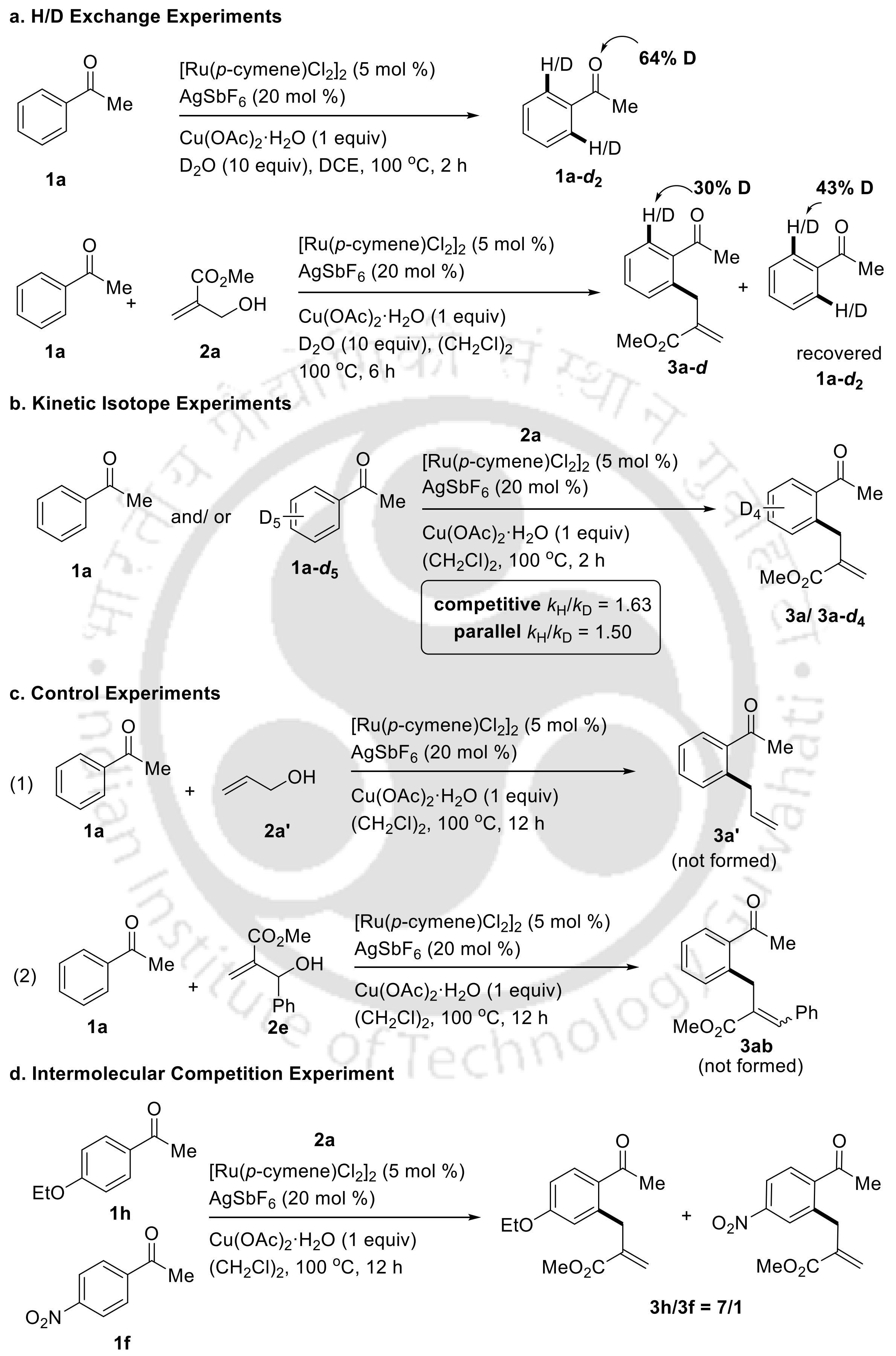


[a]Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %), $AgSbF_6$ (20 mol %), $Cu(OAc)_2·H_2O$ (1 equiv), $(CH_2Cl)_2$, (1 mL), 100 °C, 12 h. [b]Isolated yield.

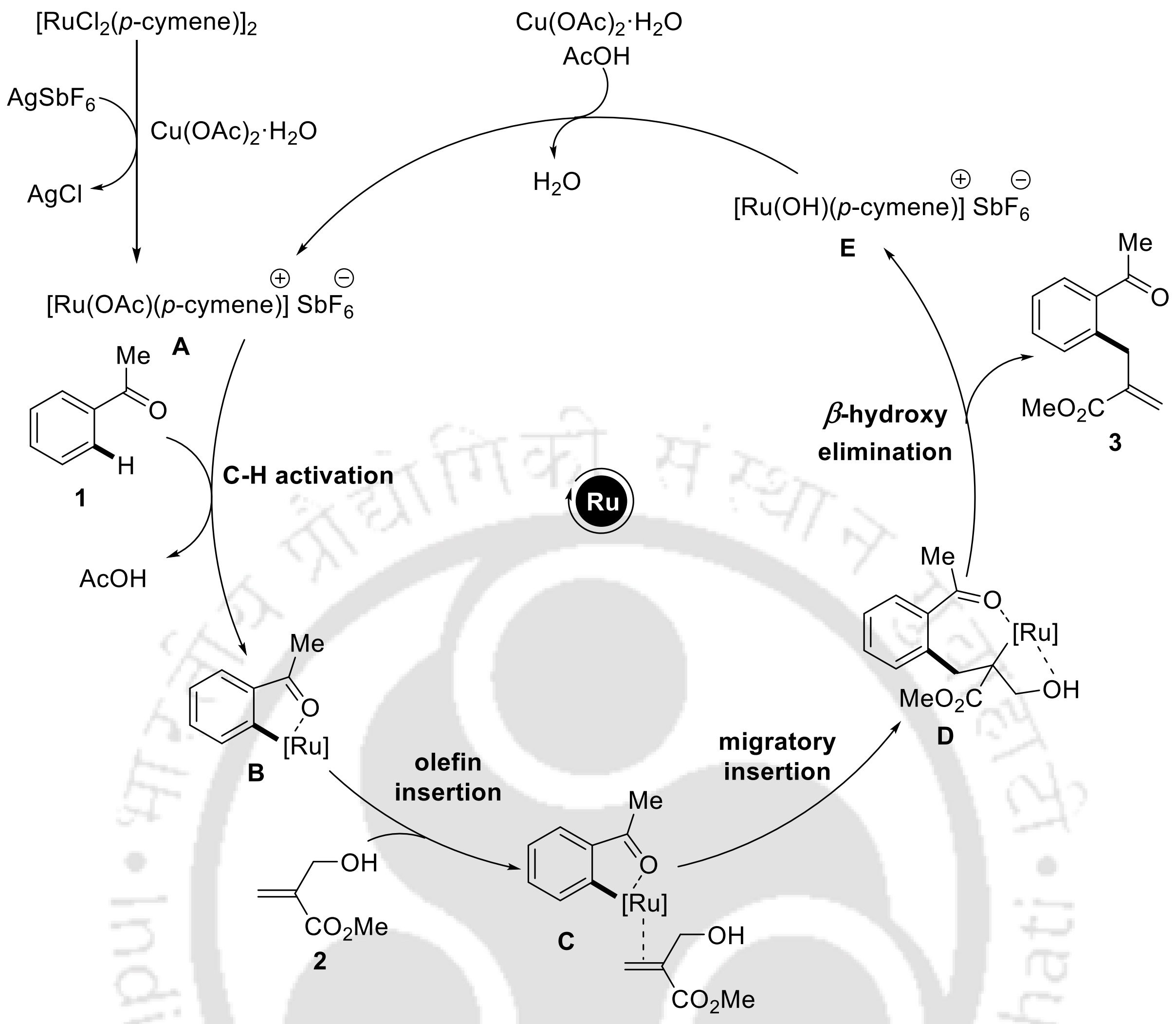
coupling partner, using ethyl **2b**, benzyl **2c** and cyclohexyl **2d** in combination with acetophenone **1a**, produced the allylated **3v-x** in yields ranging from 72 to 82%. Notably, aryl ketones derived from drug molecules and natural products like, fenbufen **1v**, adamantane carboxylic acid **1w**, and (±)-tocopherol **1x** afforded the allylated **3y-z** and **3aa** in 62-68% yields.

To gain insights into the reaction pathway, preliminary mechanistic studies were conducted. H/D exchange experiments using D_2O as a co-solvent were performed in the absence and presence of coupling partner **2a**. The results showed deuterium incorporation of 64% at the *ortho* positions of **1a** in absence of **2a** and showed deuterium incorporation of 43% at the *ortho* positions of recovered **1a-*d*₂** in presence of **2a** (Scheme 10a). These findings suggest that the C–H activation step involved in C–H allylation is likely reversible. Moreover, a deuterium incorporation of 30% was observed at the other *ortho*-position of **3a-*d*** but no deuteration incorporation was observed at the allyl handle of **3a-*d***. This might suggest that a η^3-π allyl complex might not be involved during the transformation.[14] In addition, the intermolecular kinetic isotope experiments of **1a** and **1a-*d*₅** with **2a** produced k_H/k_D =1.63 (competitive) and k_H/k_D =1.50 (parallel), which suggests that the initial C–H bond cleavage might be involved in the rate-determining step (Scheme 10b). Further, when acetophenone **1a** was reacted with allylic alcohol **2a′**, no allylated product was obtained (Scheme 10c(1)), underscoring the essential role of the ester functionality in facilitating the transformation. Additionally, the reaction of acetophenone **1a** with phenyl-substituted MBH alcohol **2e** failed to yield the allylated **3ab** (Scheme 10c(2)). This lack of reactivity may be attributed to the increased steric hindrance imparted by the phenyl substituent. In addition, an intermolecular competitive experiment between aryl ketones bearing an electron-donating 4-ethoxy group **1h** and an electron-withdrawing 4-nitro group **1f** afforded **3h** and **3f** in a 7:1 ratio, as determined by ^{1}H NMR (Scheme 10d). This outcome highlights the significant influence of electronic effects on the reactivity of aryl ketones in this transformation.

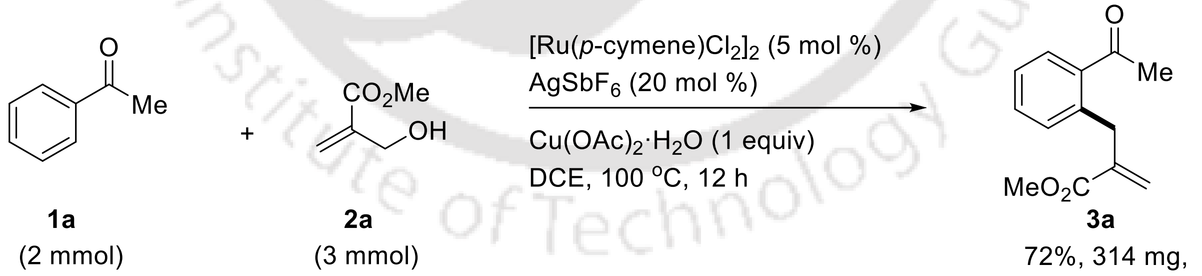
Based on the experimental findings and established literature precedents,[4, 10-14] a plausible reaction mechanism is proposed in scheme 11. The transformation is initiated by the formation of the cationic Ru(II) catalyst **A**, which subsequently coordinates to the carbonyl oxygen of aryl ketone. This is followed by proximal *ortho* C–H bond activation, leading to the formation of the ruthenacycle **B**. Coordination of the MBH alcohol's double bond generates **C**, which undergoes migratory insertion to furnish **D**. Subsequent *β*-hydroxy elimination from **D** affords the allylated product **3**. The catalytic cycle is completed by regeneration of the active catalyst **A** through the action of $Cu(OAc)_2·H_2O$ and AcOH.



Scheme 10. Preliminary Mechanistic Investigations

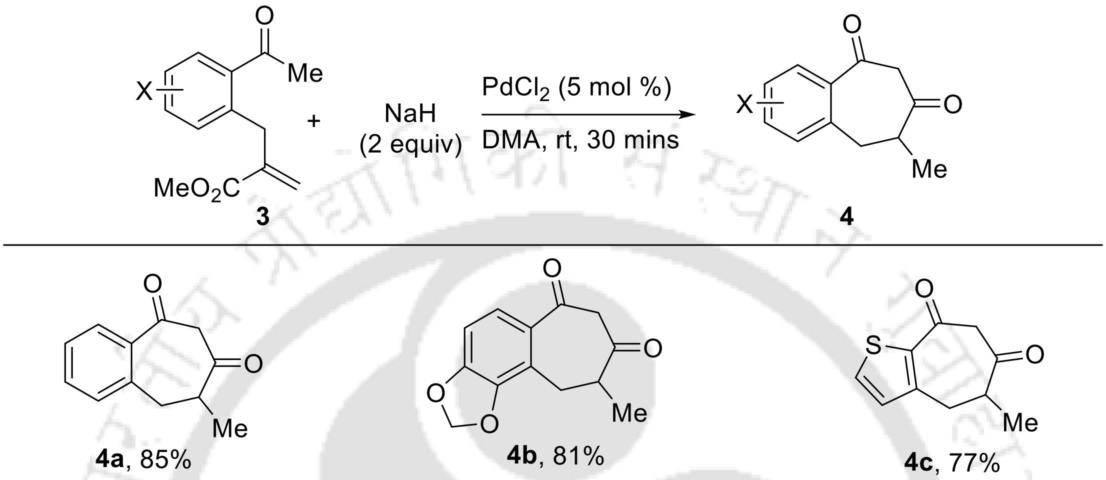


Scheme 11. Plausible Reaction Pathway



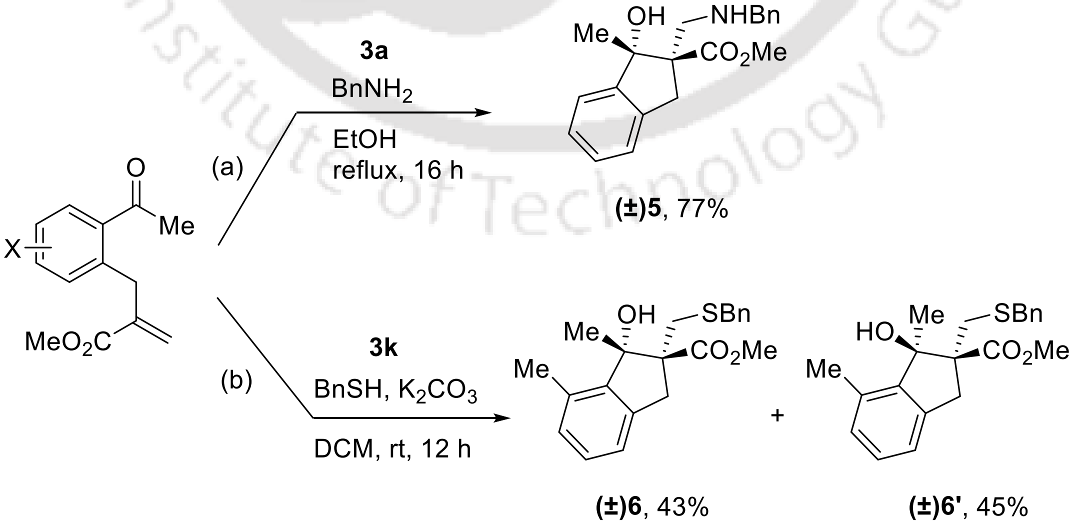
Scheme 12. Scale-up Synthesis

Lastly, to assess the scalability of the procedure, the reaction between **1a** and **2a** was examined as a representative example (Scheme 12). This reaction yielded **3a** in 72% yield (314 mg). Interestingly, when the allylated product **3** was reacted in presence of NaH (2 equiv) and $PdCl_2$ (5 mol %) in dimethyl acetamide (DMA) for 0.5 h, gave benzofused seven membered cyclic *β*-diketones **4a-c** in 77-85% yields (Scheme 13) *via* a Michael addition-Claisen condensation cascade. Moreover, a tandem Michael addition with benzyl amine followed by aldol condensation of **3a** resulted in the formation of multi substituted indane **(±)-5** in 77% yield. (Scheme 14a) Similarly, a tandem Michael addition with benzyl mercaptan followed by aldol condensation of **3k** resulted in the formation of both the diastereomers of multi-substituted indane **(±)-6** and **(±)-6′** in 43% and 45% yields, respectively (Scheme 14b).

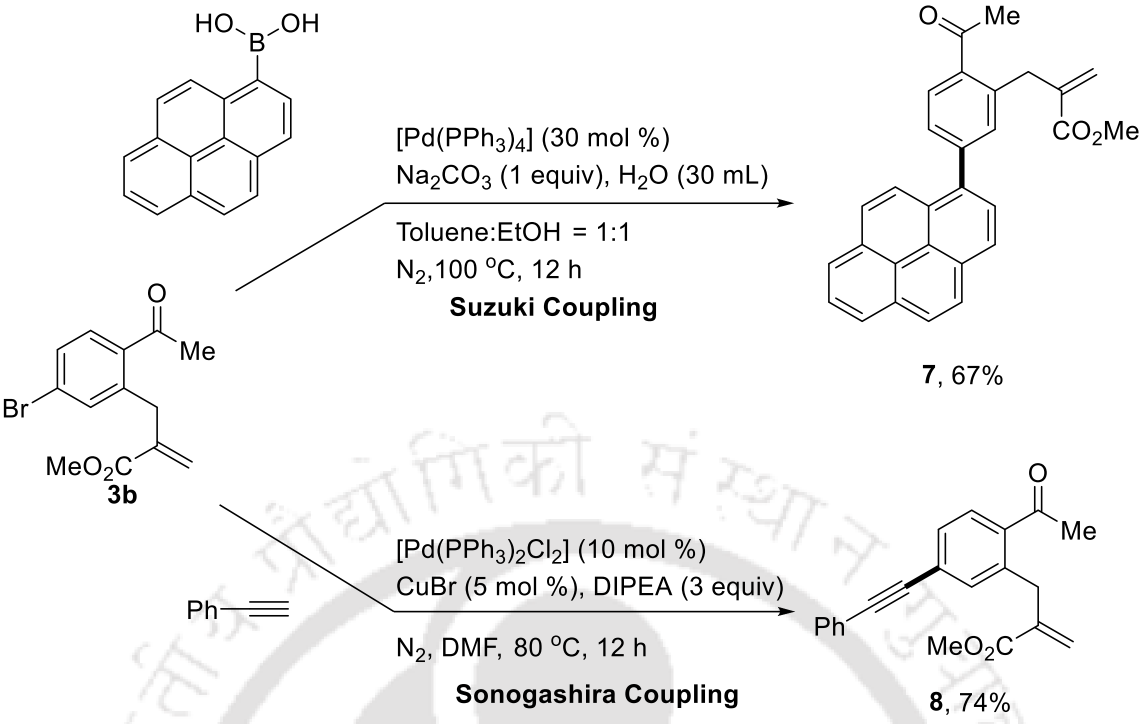


Scheme 13. Synthesis of Benzo-Fused Seven Membered Cyclic *β*-Diketones

In addition, some other post-synthetic transformations were conducted to showcase the applicability (Scheme 15). Suzuki coupling of **3b** with pyrene boronic acid and Sonogashira coupling with phenylacetylene furnished C–C cross-coupled **7** and **8** in 67% and 74% yields, respectively. These synthetic transformations underscore the versatility of the allylated products for constructing diverse cyclic and acyclic architectures.



Scheme 14. Synthesis of Multi-Substituted Indanes



Scheme 15. Post-Synthetic Transformations

In conclusion, we have developed a Ru-catalyzed, ketone-directed C–H allylation of aryl ketones using MBH alcohols as coupling partners to furnish *β*-benzyl acrylates. The resulting allylated products proved to be versatile intermediates, undergoing diverse post-synthetic transformations to afford multi-substituted indanes and benzo-fused seven-membered cyclic *β*-diketones. The substrate scope, functional group tolerance and late-stage diversifications are the important practical features of this methodology.

4.3 Experimental Section

General Information. $[Ru(p\text{-cymene})Cl_2]_2$ (97%), $AgSbF_6$ (98%), Ag_2O (99%), AgOTf (>99.99%), $AgNTf_2$ (99.9%), $Cu(OAc)_2$ (98%), $Cu(OAc)_2{\cdot}H_2O$ (98%), $Zn(OAc)_2$ (>98%), $PdCl_2$ (99.99%), K_2CO_3 (>99.5%), NaH (60% dispersion in mineral oil), *N*,*N*-dimethylacetamide (DMA) (>99.5%), 2,2,2-trifluoroethanol (TFE) (>99%), 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) (>99%), benzyl amine, benzyl mercaptan and aryl ketones of Sigma-Aldrich, BLD Pharm and TCI chemicals were used as received. Ethanol, 1,4-dioxane, dichloromethane (DCM) and 1,2-dichloroethane (DCE) were dried prior to use as per the standard procedure. Silica gel-G/GF254 plates (Merck) were used for TLC analysis with a mixture of hexane and EtOAc as the eluent. Column chromatography was carried out using Rankem silica gel (60-120 mesh). Bruker Avance III 400 and 500 MHz NMR spectrometers were used to record (^{1}H, ^{13}C, ^{19}F, COSY, NOESY, HSQC and HMBC) 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, dd = doublet of doublets and m = multiplet. Structural assignments of **4a-c**, **(±)5**, **(±)6** and **(±)6′** were made with additional information from COSY, NOESY HSQC and HMBC experiments. 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.

General Procedure for the Ru-Catalyzed C–H Allylation of Aryl Ketones using Morita-Baylis-Hillman Alcohols. Aryl ketone **1** (0.1 mmol, 1.0 equiv), MBH alcohol **2a** (0.15 mmol, 1.5 equiv), [Ru(*p*-cymene)Cl_2]$_2$ (0.005 mmol, 3.06 mg, 0.05 equiv), $AgSbF_6$ (0.02 mmol, 6.87 mg, 0.2 equiv) and $Cu(OAc)_2{\cdot}H_2O$ (0.1 mmol, 20 mg, 1.0 equiv) were stirred in $(CH_2Cl)_2$ (1 mL, 0.1 M) at 100 °C (in a pre-heated oil bath) in a sealed tube for 12 h. After completion (monitored by TLC), the reaction mixture was diluted with EtOAc (5 mL) and passed through a short celite pad. Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford **3**.

Scale-up Synthesis of 3a. Acetophenone 1a (2 mmol, 240 mg, 1.0 equiv), MBH alcohol 2a (3 mmol, 348 mg, 1.5 equiv), [Ru(*p*-cymene)Cl_2]$_2$ (0.1 mmol, 61.2 mg, 0.05 equiv), $AgSbF_6$ (0.4 mmol, 137 mg, 0.2 equiv) and $Cu(OAc)_2{\cdot}H_2O$ (2 mmol, 400 mg, 1.0 equiv) were stirred in $(CH_2Cl)_2$ (4 mL, 0.5 M) at 100 °C (in a pre-heated oil bath) in a sealed tube for 12 h. The work up and purification have been performed as described in the general procedure to furnish 3a in 72% (314 mg) yield.

Post-synthetic Transformations

Synthesis of 4.[16] $PdCl_2$ (0.01 mmol, 1.8 mg, 5 mol %) and sodium hydride (0.4 mmol, 16 mg, 2.0 equiv, 60% dispersion in oil) were stirred in *N*,*N*-dimethylacetamide (DMA) (1.0 mL, 0.2 M) at room temperature under N_2 for 5 min. Compound **3** (0.2 mmol, 1.0 equiv) in DMA (0.5 mL) was then added and the reaction mixture was stirred at room temperature for 30 mins. After completion (monitored by TLC), saturated aqueous NH_4Cl (5 mL) was added. The resulting mixture was extracted with EtOAc (2 x 10 mL), and the combined organic extracts were washed with water (10 mL) and brine (10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford **4**.

Synthesis of 5. Compound **3a** (0.2 mmol, 43.6 mg, 1.0 equiv) and benzyl amine (0.4 mmol, 43 mg, 2.0 equiv) were dissolved in EtOH (5 mL, 0.04 M) and refluxed in a pre-heated oil-bath for 16 h. After completion (monitored by TLC), the solvent was evaporated and the residue was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford (±)-**5** in 77% yield.

Synthesis of 6 and 6′. Compound **3k** (0.2 mmol, 46.5 mg, 1.0 equiv), benzyl mercaptan (0.4 mmol, 50 mg, 2.0 equiv) and K_2CO_3 (0.2 mmol, 27.6 mg, 1.0 equiv) were stirred in dichloromethane (DCM) (5 mL, 0.04 M) at room temperature for 12 h. After completion (monitored by TLC), the reaction was quenched with water (5 mL) and extracted with EtOAc (2 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford a separable mixture of diastereomers (±)-**6** and (±)-**6′** in 43% and 45% yields, respectively.

Synthesis of 7. Compound **3b** (0.2 mmol, 40 mg, 1.0 equiv), pyren-1-ylboronic acid (0.2 mmol, 49 mg, 1.0 equiv), $Pd(PPh_3)_4$ (0.006 mmol, 7 mg, 30 mol %), Na_2CO_3 (0.2 mmol, 22 mg, 1.0 equiv) and H_2O (50 μL) were stirred in toluene/EtOH (1:1, 2 mL) at 100 °C in an oil bath for 12 h under N_2 atmosphere. After completion (monitored by TLC), the reaction mixture was cooled to room temperature and passed through a short pad of celite using dichloromethane (10 mL). Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford **7** in 67% yield.

Synthesis of 8. Compound **3b** (0.2 mmol, 40 mg, 1.0 equiv), phenylacetylene (0.6 mmol, 61.3 mg, 3.0 equiv), $Pd(PPh_3)_2Cl_2$ (0.02 mmol, 14 mg, 10 mol %,), CuBr (0.01 mmol, 1.4 mg, 5 mol %) and DIPEA (0.6 mmol, 77.6 mg, 3.0 equiv) were stirred in DMF (1 mL, 0.2 M) at 80 °C for 4 h under N_2 atmosphere. After completion (monitored by TLC), the reaction mixture was cooled to room temperature and diluted with EtOAc (10 mL). The organic phase was washed with brine (1 x 10 mL) and ice-cold water (2 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford **8** in 74% yield.

Mechanistic Investigation

H/D Exchange Experiment of 1a with D_2O in Absence of 2a. Acetophenone **1a** (0.1 mmol, 12 mg, 1.0 equiv), [Ru(*p*-cymene)Cl_2]$_2$ (0.005 mmol, 3 mg, 0.05 equiv), $AgSbF_6$ (0.02 mmol, 6.87 mg, 0.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (0.1mmol, 20 mg, 1.0 equiv) and D_2O (1 mmol, 18 µL, 10.0 equiv) were stirred in $(CH_2Cl)_2$ (1 mL, 0.1 M) at 100 °C (in a pre-heated oil bath) in a sealed tube for 2 h. The reaction mixture was diluted with EtOAc (5 mL) and passed through a short celite pad. Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford **1a-*d*₂**.

H/D Exchange Experiment of 1a with D_2O in Presence of 2a. Acetophenone **1a** (0.1 mmol, 12 mg, 1.0 equiv), MBH alcohol **2a** (0.15 mmol, 17.4 mg, 1.5 equiv), [Ru(*p*-cymene)Cl_2]$_2$ (0.005 mmol, 3 mg, 0.05 equiv), $AgSbF_6$ (0.02 mmol, 6.87 mg, 0.2 equiv), $Cu(OAc)_2 \cdot H_2O$ (0.1mmol, 20 mg, 1.0 equiv) and D_2O (1 mmol, 18 µL, 10.0 equiv) were stirred in $(CH_2Cl)_2$ (1 mL, 0.1 M) at 100 °C (in a pre-heated oil bath) in a sealed tube for 6 h. The reaction mixture was diluted with EtOAc (5 mL) and passed through a short celite pad. Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and EtOAc as an eluent to afford **3a-*d*** and **1a-*d*₂**. The deuterium incorporation of **3a-*d*** and **1a-*d*₂** was calculated based on their respective 400 MHz ^{1}H NMR spectrum

Preparation of 1-(phenyl-*d*₅)ethan-1-one 1a-*d*₅.[17] To a stirred solution benzene-d_6 (11.8 mmol, 1 mL) and $AlCl_3$ (14.7 mmol, 1.9 g) in CS_2 (4 mL) at 0 °C under N_2 atmosphere, acetyl chloride (14.7 mmol, 1 mL) in CS_2 (4 mL) was added. The resulting mixture allowed to stir at room temperature for 5 h and then at 50 °C for 3 h. The reaction mixture was then cooled to room temperature and poured into ice-cold water and extracted using CH_2Cl_2 (3 x 15 mL). The organic layer was washed with aqueous Na_2CO_3 (20 mL) and water (10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and ethyl acetate as eluent to provide [D_5]-acetophenone **1a-*d*₅** in 78% (1.1 g) yield.

Parallel Experiment: Acetophenone **1a** (0.1 mmol, 12 mg, 1.0 equiv) or **1a-*d*₅** (0.1 mmol, 12.5 mg, 1.0 equiv), MBH alcohol **2a** (0.15 mmol, 17.4 mg, 1.5 equiv), [Ru(*p*-cymene)Cl_2]$_2$ (0.005 mmol, 3 mg, 0.05 equiv), $AgSbF_6$ (0.02 mmol, 6.87 mg, 0.2 equiv) and $Cu(OAc)_2 \cdot H_2O$ (0.1mmol, 20 mg, 1.0 equiv) were stirred in $(CH_2Cl)_2$ (1 mL, 0.1 M) at 100 °C (in a pre-heated oil bath) in a sealed tube for 2 h. Both the reaction mixtures were combined and passed through a short celite pad using EtOAc (5 mL). The solvent was removed under reduced pressure and the purification was performed as described in the general procedure to afford a mixture **3a** and **3a-*d*$_4$**. The KIE value was determined to be k_H/k_D = 1.50 on the basis of ^{1}H NMR analysis.

Competitive Experiment: Acetophenone **1a** (0.1 mmol, 12 mg, 1.0 equiv), 1-(phenyl-*d*$_5$)ethan-1-one **1a-*d*$_5$** (0.1 mmol, 12.5 mg, 1.0 equiv), MBH alcohol **2a** (0.15 mmol, 17.4 mg, 1.5 equiv), [Ru(*p*-cymene)Cl$_2$]$_2$ (0.005 mmol, 3 mg, 0.05 equiv), AgSbF$_6$ (0.02 mmol, 6.87 mg, 0.2 equiv) and Cu(OAc)$_2$·H$_2$O (0.1mmol, 20 mg, 1.0 equiv) were stirred in (CH$_2$Cl)$_2$ (1 mL, 0.1 M) at 100 ° C (in a pre-heated oil bath) in a sealed tube for 2 h. The reaction mixture was diluted with EtOAc (5 mL) and passed through a short celite pad. The solvent was removed under reduced pressure and the purification was carried out as described in the general procedure to afford a mixture of **3a** and **3a-*d*$_4$**. The KIE value was determined to be k_H/k_D = 1.63 on the basis of ^{1}H NMR analysis.

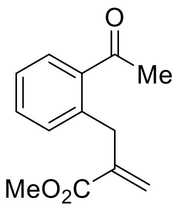
Control Experiment (1). Acetophenone **1a** (0.1 mmol, 12 mg, 1.0 equiv), prop-2-en-1-ol **2a′** (0.15 mmol, 8.7 mg, 1.5 equiv), [Ru(*p*-cymene)Cl$_2$]$_2$ (0.005 mmol, 3 mg, 0.05 equiv), AgSbF$_6$ (0.02 mmol, 6.87 mg, 0.2 equiv) and Cu(OAc)$_2$·H$_2$O (0.1mmol, 20 mg, 1.0 equiv) were stirred in (CH$_2$Cl)$_2$ (1 mL, 0.1 M) at 100 °C (in a pre-heated oil bath) in a sealed tube for 12 h. The corresponding allylated product **3a′** was not formed.

Control Experiment (2) Acetophenone **1a** (0.1 mmol, 12 mg, 1.0 equiv), methyl 2-(hydroxy(phenyl)methyl)acrylate **2e** (0.15 mmol, 28.8 mg, 1.5 equiv), [Ru(*p*-cymene)Cl$_2$]$_2$ (0.005 mmol, 3 mg, 0.05 equiv), AgSbF$_6$ (0.02 mmol, 6.87 mg, 0.2 equiv) and Cu(OAc)$_2$·H$_2$O (0.1mmol, 20 mg, 1.0 equiv) were stirred in (CH$_2$Cl)$_2$ (1 mL, 0.1 M) at 100 °C (in a pre-heated oil bath) in a sealed tube for 12 h. The corresponding allylated product **3ab** was not formed.

Intermolecular Competition Experiment. Aryl ketones **1h** (0.1 mmol, 16.4 mg, 1.0 equiv) and **1f** (0.1 mmol, 16.5 mg, 1.0 equiv), MBH alcohol **2e** (0.15 mmol, 17.4 mg, 1.5 equiv), [Ru(*p*-cymene)Cl$_2$]$_2$ (0.01 mmol, 3 mg, 0.05 equiv), AgSbF$_6$ (0.04 mmol, 6.87 mg, 0.2 equiv) and Cu(OAc)$_2$·H$_2$O (0.2 mmol, 20 mg, 1.0 equiv) were stirred in (CH$_2$Cl)$_2$ (1 mL, 0.1 M) at 100 °C (in a pre-heated oil bath) in a sealed tube for 12 h. The reaction mixture was diluted with EtOAc (5 mL) and passed through a short celite pad. Evaporation of the solvent gave a mixture of **3h** and **3f** in 7:1 ratio, calculated from 400 MHz ^{1}H NMR spectroscopy.

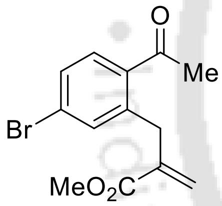
4.4 Characterization Data

Characterization Data of the Products



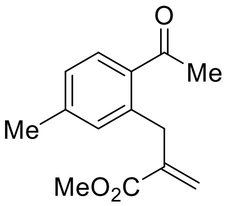
3a

Methyl 2-(2-acetylbenzyl)acrylate 3a. Analytical TLC on silica gel, 1:10 EtOAc/hexane $R_f = 0.55$; colorless liquid; yield 85% (18.6 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, $J = 7.5$ Hz, 1H), 7.42 (t, $J = 7.5$ Hz, 1H), 7.32 (t, $J = 7.5$ Hz, 1H), 7.25 (d, $J = 7.4$ Hz, 1H), 6.19 (s, 1H), 5.26 (s, 1H), 3.92 (s, 2H), 3.74 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 167.5, 140.2, 138.4, 138.3, 131.9, 131.6, 129.4, 126.7, 126.0, 52.0, 35.7, 29.7; FT-IR (neat) 2953 , 1723, 1676, 1609, 1436, 1264, 1259, 1144, 1065 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{13}H_{14}NaO_3$ 241.0835; Found 241.0837.



3b

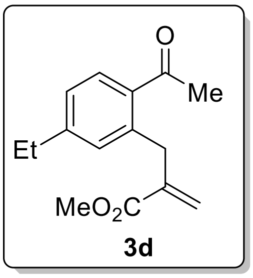
Methyl 2-(2-acetyl-5-bromobenzyl)acrylate 3b. Analytical TLC on silica gel, 1:10 EtOAc/hexane $R_f = 0.48$; light yellow liquid; yield 71% (21 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, $J = 8.5$ Hz, 1H), 7.44 (d, $J = 8.5$ Hz, 1H), 7.41 (s, 1H), 6.22 (s, 1H), 5.33 (s, 1H), 3.88 (s, 2H), 3.74 (s, 3H), 2.54 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.8, 167.2, 140.9, 139.5, 137.0, 134.7, 130.8, 129.8, 126.6, 126.2, 52.1, 35.4, 29.7; FT-IR (neat) 2945, 1718, 1679, 1604, 1433, 1267, 1257, 1145, 1057 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{14}O_3Br$ 297.0121; Found 297.0110.



3c

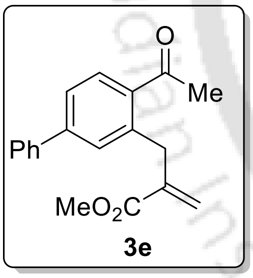
Methyl 2-(2-acetyl-5-methylbenzyl)acrylate 3c. Analytical TLC on silica gel, 1:10 EtOAc/hexane $R_f = 0.52$; colorless liquid; yield 86% (20 mg); ^1H NMR (500

MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 7.04 (s, 1H), 6.16 (s, 1H), 5.22 (s, 1H), 3.90 (s, 2H), 3.74 (s, 3H), 2.53 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.1, 167.6, 142.3, 140.4, 138.9, 135.2, 132.8, 130.0, 127.3, 125.7, 52.0, 35.8, 29.5, 21.5; FT-IR (neat) 2952 ,2924, 1719, 1682, 1609, 1436, 1267, 1257, 1144, 1057 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{16}NaO_3$ 255.0992; Found 255.0993.



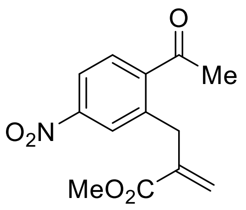
3d

Methyl 2-(2-acetyl-5-ethylbenzyl)acrylate 3d. Analytical TLC on silica gel, 1:10 EtOAc/hexane R_f = 0.42; colorless liquid; yield 81% (20 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.07 (s, 1H), 6.16 (s, 1H), 5.21 (s, 1H), 3.92 (s, 2H), 3.75 (s, 3H), 2.66 (q, *J* = 7.5 Hz, 2H), 2.54 (s, 3H), 1.23 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.1, 167.7, 148.5, 140.4, 138.9, 135.4, 131.7, 130.2, 126.0, 125.7, 52.0, 35.9, 29.5, 28.8, 15.3; FT-IR (neat) 2966, 1721, 1683, 1608, 1436, 1256, 1200, 1146 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{19}O_3$ 247.1329; Found 247.1330.



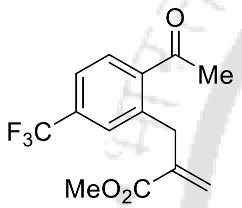
3e

Methyl 2-((4-acetyl-[1,1'-biphenyl]-3-yl)methyl)acrylate 3e. Analytical TLC on silica gel, 1:10 EtOAc/hexane R_f = 0.50; colorless liquid; yield 69% (20 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 7.5 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.49-7.44 (m, 3H), 7.39 (t, *J* = 7.5 Hz, 1H), 6.20 (s, 1H), 5.31 (s, 1H), 4.01 (s, 2H), 3.76 (s, 3H), 2.60 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.2, 167.6, 144.4, 140.2, 139.9, 139.3, 136.7, 130.7, 130.4, 129.1, 128.3, 127.3, 126.0, 125.2, 52.1, 35.9, 29.7; FT-IR (neat) 2967, 1724, 1683, 1605, 1436, 1256, 1203, 1147 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{19}O_3$ 295.1329; Found 295.1322.



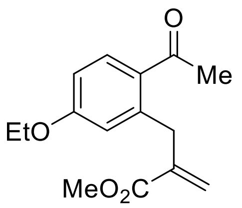
3f

Methyl 2-(2-acetyl-5-nitrobenzyl)acrylate 3f. Analytical TLC on silica gel, 1:10 EtOAc/hexane $R_f = 0.34$; yellow liquid; yield 66% (17.4 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15-8.13 (m, 2H), 7.71 (d, $J = 8.0$ Hz, 1H), 6.30 (s, 1H), 5.51 (s, 1H), 3.92 (s, 2H), 3.72 (s, 3H), 2.62 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.4, 166.8, 148.9, 144.4, 140.1, 138.6, 129.1, 127.7, 126.1, 121.7, 52.2, 35.4, 30.3; FT-IR (neat) 2976, 1718, 1679, 1604, 1433, 1256, 1204, 1156 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{14}NO_5$ 264.0866; Found 264.0858.



3g

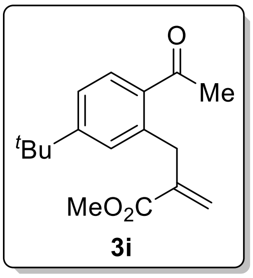
Methyl 2-(2-acetyl-5-(trifluoromethyl)benzyl)acrylate 3g. Analytical TLC on silica gel, 1:10 EtOAc/hexane $R_f = 0.44$; colorless liquid; yield 70% (20 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, $J = 8.0$ Hz, 1H), 7.56 (d, $J = 8.0$ Hz, 1H), 7.52 (s, 1H), 6.24 (s, 1H), 5.37 (s, 1H), 3.92 (s, 2H), 3.74 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.6, 167.1, 141.9, 139.3, 139.0, 133.1 ($J_{C\text{-}F} = 32.2$ Hz), 128.9, 128.4 ($J_{C\text{-}F} = 3.5$ Hz), 127.0, 123.6 ($J_{C\text{-}F} = 3.6$ Hz), 122.6 ($J_{C\text{-}F} = 270.8$ Hz), 52.2, 35.4, 30.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ -63.08; FT-IR (neat) 2918, 1721, 1697, 1438, 1331, 1254, 1130, 1092 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{14}O_3F_3$ 287.0890; Found 287.0890.



3h

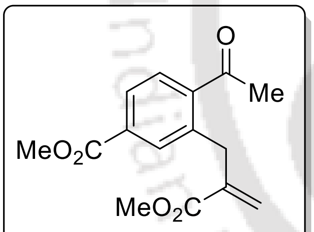
Methyl 2-(2-acetyl-5-ethoxybenzyl)acrylate 3h. Analytical TLC on silica gel, 1:10 EtOAc/hexane $R_f = 0.35$; colorless liquid; yield 82% (21.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, $J = 8.8$ Hz, 1H), 6.79-6.76 (m, 1H), 6.74-6.73 (m, 1H), 6.16 (s, 1H), 5.23 (s, 1H), 4.06 (q, $J = 7.2$ Hz, 2H), 3.95 (s, 2H), 3.74 (s, 3H), 2.51 (s, 3H), 1.41 (t, $J = 6.8$

Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.3, 167.6, 161.6, 142.1, 140.1, 132.8, 129.9, 125.6, 118.1, 111.7, 63.7, 52.0, 36.3, 29.1, 14.7; FT-IR (neat) 2926, 1720, 1676, 1602, 1566, 1436, 1249, 1140, 1065 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{19}O_4$ 263.1278; Found 263.1278.



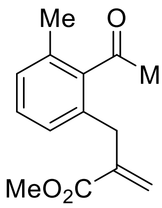
3i

Methyl 2-(2-acetyl-5-(*tert*-butyl)benzyl)acrylate 3i. Analytical TLC on silica gel, 1:10 EtOAc/hexane $R_f = 0.50$; colorless liquid; yield 71% (19.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, $J = 8.5$ Hz, 1H), 7.32 (d, $J = 8.0$ Hz, 1H), 7.26 (s, 1H), 6.16 (s, 1H), 5.20 (s, 1H), 3.95 (s, 2H), 3.75 (s, 3H), 2.54 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.1, 167.7, 155.3, 140.6, 138.6, 135.1, 129.9, 129.4, 125.5, 123.5, 52.0, 36.1, 35.0, 31.2, 29.5; FT-IR (neat) 2955, 1721, 1681, 1604, 1433, 1277, 1257, 1143, 1054 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{23}O_3$ 275.1642; Found 275.1644.



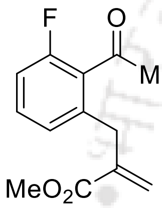
3j

Methyl 4-acetyl-3-(2-(methoxycarbonyl)allyl)benzoate 3j. Analytical TLC on silica gel, 1:10 EtOAc/hexane $R_f = 0.43$; colorless liquid; yield 78% (21.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, $J = 8.0$ Hz, 1H), 7.92 (s, 1H), 7.66 (d, $J = 7.5$ Hz, 1H), 6.22 (s, 1H), 5.31 (s, 1H), 3.93 (s, 3H), 3.90 (s, 2H), 3.73 (s, 3H), 2.58 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.0, 167.2, 166.3, 142.5, 139.6, 138.3, 132.7, 132.4, 128.6, 127.8, 126.6, 52.6, 52.1, 35.4, 30.1; FT-IR (neat) 2936, 1734, 1690, 1460, 1253, 1238, 1145, 1096 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{17}O_5$ 277.1071; Found 277.1081.



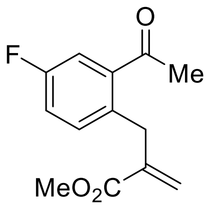
3k

Methyl 2-(2-acetyl-3-methylbenzyl)acrylate 3k. Analytical TLC on silica gel, 1:10 EtOAc/hexane $R_f = 0.46$; colorless liquid; yield 77% (18 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 7.20 (t, $J = 8.0$ Hz, 1H), 7.06 (d, $J = 7.5$ Hz, 1H), 7.00 (d, $J = 8.0$ Hz, 1H), 6.28 (s, 1H), 5.38 (s, 1H), 3.74 (s, 3H), 3.54 (s, 2H), 2.48 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.2, 167.3, 142.9, 139.4, 133.3, 132.7, 128.9, 128.8, 127.5, 127.4, 52.1, 35.1, 32.6, 19.4; FT-IR (neat) 2952, 1720, 1681, 1604, 1436, 1265, 1257, 1146, 1057 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{17}O_3$ 233.1172; Found 233.1172.



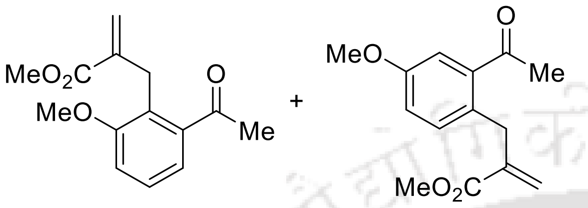
3l

Methyl 2-(2-acetyl-3-fluorobenzyl)acrylate 3l. Analytical TLC on silica gel, 1:10 EtOAc/hexane $R_f = 0.47$; colorless liquid; yield 80% (19 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.27 (m, 1H), 7.02 (d, $J = 7.6$ Hz, 1H), 6.98 (t, $J = 9.6$ Hz, 1H), 6.24-6.23 (m, 1H), 5.41-5.40 (m, 1H), 3.72 (s, 3H), 3.69 (s, 2H), 2.54 (d, $J = 3.2$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.5, 167.1, 159.2 ($J_{C-F} = 245.7$ Hz), 139.4, 138.7 ($J_{C-F} = 33.7$ Hz), 131.2 ($J_{C-F} = 91.2$ Hz), 129.2 ($J_{C-F} = 165.0$ Hz), 127.1, 126.5 ($J_{C-F} = 27.5$ Hz), 114.1 ($J_{C-F} = 22.5$ Hz), 52.1, 34.8, 32.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ -114.53; FT-IR (neat) 2927, 1721, 1696, 1438, 1322, 1254, 1130, 1094 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{13}H_{13}NaO_3F$ 259.0741; Found 259.0736.



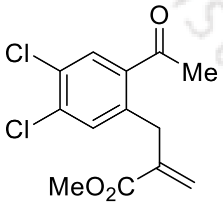
3m

Methyl 2-(2-acetyl-4-fluorobenzyl)acrylate 3m. Analytical TLC on silica gel, 1:10 EtOAc/hexane $R_f = 0.53$; colorless liquid; yield 81% (19 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, $J = 8.0$ Hz, 1H), 7.35-7.30 (m, 1H), 7.19 (t, $J = 8.4$ Hz, 1H), 6.16 (s, 1H), 5.14 (s, 1H), 3.90 (s, 2H), 3.77 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 201.0, 167.3, 160.7 ($J_{C\text{-}F}$ = 246.1 Hz), 140.9 ($J_{C\text{-}F}$ = 34.0 Hz), 138.7, 128.1 ($J_{C\text{-}F}$ = 87.0 Hz), 125.2 ($J_{C\text{-}F}$ = 162.0 Hz), 125.1, 124.6 ($J_{C\text{-}F}$ = 34.0 Hz), 118.5 ($J_{C\text{-}F}$ = 236.0 Hz), 52.1, 29.9, 27.5; ^{19}F NMR (376 MHz, CDCl$_3$) δ -115.18; FT-IR (neat) 2918, 1720, 1695, 1436, 1331, 1254, 1130, 1092 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for C$_{13}$H$_{14}$O$_3$F 237.0921; Found 237.0912.



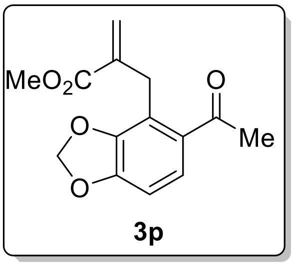
3n + 3n'

Methyl 2-(2-acetyl-4-methoxybenzyl)-acrylate 3n+3n′. Analytical TLC on silica gel, 1:10 EtOAc/hexane R$_f$ = 0.45; colorless liquid; yield 79% (19.6 mg); mixture of regioisomers 1.16:1; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.29 (t, *J* = 8.0 Hz, 1H, major), 7.19 (d, *J* = 8.0 Hz, 1H, major), 7.17-7.15 (m, 1.79H, major + minor), 6.99 (d, *J* = 8.5 Hz, 1H, major), 6.96-6.94 (m, 0.86 H, minor), 6.15 (s, 0.86 H, minor), 6.08 (s, 1H, major), 5.24 (s, 0.86 H, minor), 5.02 (s, 1H, major), 3.82-3.81 (m, 6.31 H, major + minor), 3.79 (s, 3H, major), 3.77 (s, 3H, major), 3.73 (s, 2.58 H, minor), 2.53-2.52 (m, 5.59 H, major + minor); ^{13}C NMR (125 MHz, CDCl$_3$) δ 202.5, 201.7, 167.8, 167.6, 158.4, 158.0, 141.0, 140.5, 139.5, 139.4, 133.0, 130.0, 127.6, 126.1, 125.7, 124.2, 120.5, 116.5, 115.2, 113.4, 56.0, 55.6, 52.0, 34.8, 30.2, 29.7, 28.1; FT-IR (neat) 2951, 1716, 1687, 1631, 1436, 1267, 1219, 1135, 1048 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for C$_{14}$H$_{16}$NaO$_4$ 271.0941; Found 271.0942.

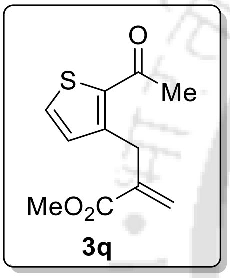


3o

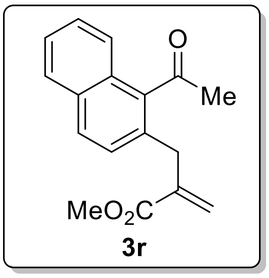
Methyl 2-(2-acetyl-4,5-dichlorobenzyl)acrylate 3o. Analytical TLC on silica gel, 1:10 EtOAc/hexane R$_f$ = 0.39; colorless liquid; yield 74% (21 mg); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.73 (s, 1H), 7.35 (s, 1H), 6.24 (s, 1H), 5.38 (s, 1H), 3.86 (s, 2H), 3.74 (s, 3H), 2.55 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 199.6, 167.0, 139.1, 138.8, 137.7, 135.8, 133.4, 131.1, 130.7, 126.9, 52.2, 35.0, 29.7; FT-IR (neat) 2954, 1721, 1666, 1593, 1448, 1268, 1207, 1139, 1056 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for C$_{13}$H$_{13}$O$_3$Cl$_2$ 287.0236; Found 287.0236.


3p

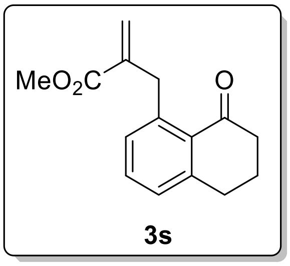
Methyl 2-((5-acetylbenzo[*d*][1,3]dioxol-4-yl)methyl)acrylate 3p. Analytical TLC on silica gel, 1:10 EtOAc/hexane $R_f = 0.45$; colorless liquid; yield 81% (21 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.0 Hz, 1H), 6.75 (d, *J* = 8.5 Hz, 1H), 6.11 (s, 1H), 6.00 (s, 2H), 5.12 (s, 1H), 3.92 (s, 2H), 3.78 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.0, 167.6, 150.0, 147.9, 138.7, 132.1, 126.1, 124.3, 120.8, 106.1, 101.8, 52.1, 29.1, 28.7; FT-IR (neat) 2952, 1717, 1675, 1598, 1450, 1261, 1207, 1139, 1056 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{15}O_5$ 263.0914; Found 263.0912.


3q

Methyl 2-((2-acetylthiophen-3-yl)methyl)acrylate 3q. Analytical TLC on silica gel, 1:10 EtOAc/hexane $R_f = 0.44$; colorless liquid; yield 80% (18 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 5.0 Hz, 1H), 6.98 (d, *J* = 5.0 Hz, 1H), 6.22 (s, 1H), 5.48 (s, 1H), 4.04 (s, 2H), 3.75 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.0, 167.5, 145.7, 138.7, 136.6, 132.2, 129.9, 126.6, 52.1, 32.2, 29.8; FT-IR (neat) 2924, 1719, 1679, 1604, 1438, 1267, 1207, 1125, 1071 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{13}O_3S$ 225.0580; Found 225.0582.

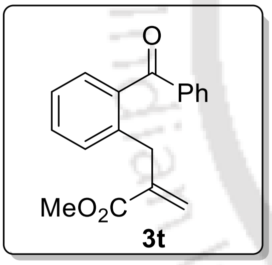

3r

Methyl 2-((1-acetylnaphthalen-2-yl)methyl)acrylate 3r. Analytical TLC on silica gel, 1:10 EtOAc/hexane $R_f = 0.52$; colorless liquid; yield 81% (22 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.83 (m, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.64-7.62 (m, 1H), 7.53-7.46 (m, 2H), 7.28 (d, *J* = 8.4 Hz, 1H), 6.32-6.31(m, 1H), 5.41-5.40 (m, 1H), 3.75 (s, 3H), 3.72 (s, 2H), 2.66 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.0, 167.2, 139.6, 139.2, 132.3, 130.8, 129.2, 129.1, 128.5, 127.7, 127.6, 127.1, 126.1, 124.4, 52.2, 35.3, 33.4; FT-IR (neat) 2968, 1723, 1685, 1605, 1437, 1253, 1203, 1148 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{17}H_{16}NaO_3$ 271.0992; Found 271.0990.



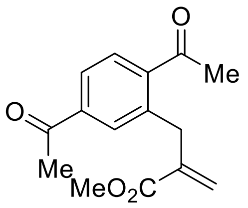
3s

Methyl 2-((8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)methyl)acrylate 3s. Analytical TLC on silica gel, 1:10 EtOAc/hexane R_f = 0.42; colorless liquid; yield 67% (16.4 mg); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.36 (t, *J* = 7.5 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.13 (s, 1H), 5.14 (s, 1H), 4.06 (s, 2H), 3.77 (s, 3H), 2.97 (t, *J* = 6.0 Hz, 2H), 2.62 (t, *J* = 6.2 Hz, 2H), 2.08 (p, *J* = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 199.7, 168.0, 146.3, 141.3, 140.6, 132.5, 131.2, 130.5, 127.9, 125.0, 52.1, 41.0, 36.9, 31.2, 23.0; FT-IR (neat) 2956, 1717, 1688, 1631, 1436, 1269, 1220, 1135, 1049 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{15}H_{17}O_3$ 245.1172; Found 245.1170.



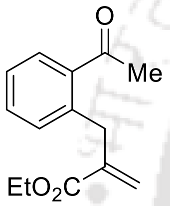
3t

Methyl 2-(2-benzoylbenzyl)acrylate 3t. Analytical TLC on silica gel, 1:10 EtOAc/hexane R_f = 0.40; colorless liquid; yield 82% (23 mg); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.78 (d, *J* = 7.5 Hz, 2H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.46-7.42 (m, 3H), 7.34-7.27 (m, 3H), 6.17 (s, 1H), 5.37 (s, 1H), 3.75 (s, 2H), 3.64 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 198.3, 167.3, 139.6, 138.9, 138.0, 137.8, 133.3, 131.0, 130.6, 130.4, 129.1, 128.5, 127.2, 126.0, 52.0, 35.2; FT-IR (neat) 2951, 1722, 1664, 1597, 1448, 1266, 1203, 1139, 940 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{18}H_{17}O_3$ 281.1172; Found 281.1173.



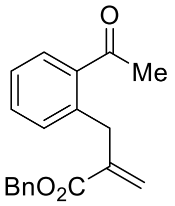
3u

Methyl 2-(2,5-diacetylbenzyl)acrylate 3u. Analytical TLC on silica gel, 1:10 EtOAc/hexane $R_f = 0.53$; colorless liquid; yield 78% (20.3 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.83 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 6.22 (s, 1H), 5.33 (s, 1H), 3.91 (s, 2H), 3.73 (s, 3H), 2.60 (s, 3H), 2.58 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 197.5, 167.2, 142.6, 139.6, 138.8, 138.5, 131.4, 128.9, 126.7, 126.5, 52.1, 35.5, 30.1, 26.9; FT-IR (neat) 2953, 1719, 1688, 1632, 1437, 1356, 1257, 1201, 1145 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{17}O_4$ 261.1121; Found 261.1120.



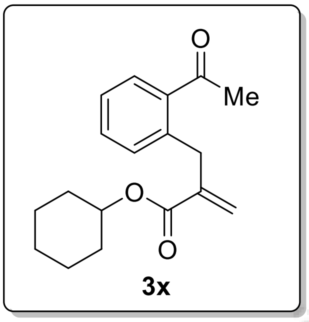
3v

Ethyl 2-(2-acetylbenzyl)acrylate 3v. Analytical TLC on silica gel, 1:10 EtOAc/hexane $R_f = 0.44$; colorless liquid; yield 82% (19 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 7.5 Hz, 1H), 6.19 (s, 1H), 5.25 (s, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 3.92 (s, 2H), 2.56 (s, 3H), 1.26 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 167.1, 140.5, 138.5, 138.4, 131.9, 131.6, 129.3, 126.6, 125.8, 60.9, 35.7, 29.7, 14.3; FT-IR (neat) 2954, 1722, 1681, 1604, 1436, 1267, 1204, 1146, 1047 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{17}O_3$ 233.1172; Found 233.1172.



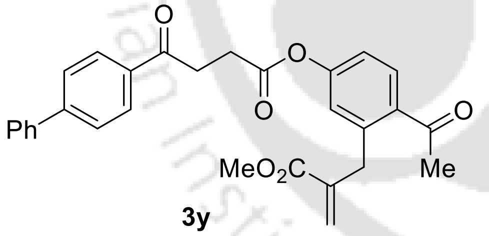
3w

Benzyl 2-(2-acetylbenzyl)acrylate 3w. Analytical TLC on silica gel, 1:10 EtOAc/hexane $R_f = 0.46$; colorless liquid; yield 77% (18 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.66 (m, 1H), 7.42-7.24 (m, 8H), 6.26-6.25 (m, 1H), 5.32-5.31 (m, 1H), 5.17 (s, 2H), 3.94 (s, 2H), 2.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 166.9, 140.1, 138.5, 138.3, 136.1, 131.8, 131.6, 129.3, 128.6, 128.2, 128.1, 126.6, 126.5, 66.6, 35.7, 29.7; FT-IR (neat) 2951, 1724, 1684, 1603, 1448, 1266, 1203, 1141, 1040 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{19}O_3$ 295.1329; Found 295.1314.



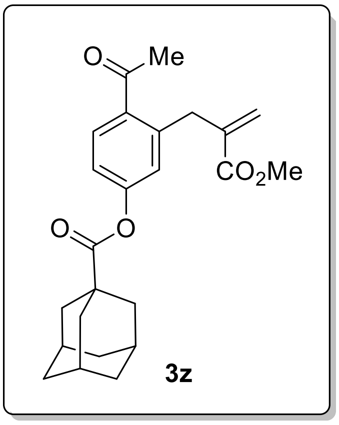
3x

Cyclohexyl 2-(2-acetylbenzyl)acrylate 3x. Analytical TLC on silica gel, 1:10 EtOAc/hexane R_f = 0.51; colorless liquid; yield 72% (20.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.27-7.26 (m, 1H), 6.20-6.19 (m, 1H), 5.27-5.26 (m, 1H), 4.84-4.78 (m, 1H), 3.92 (s, 2H), 2.56 (s, 3H), 1.83-1.78 (m, 2H), 1.70-1.64 (m, 2H), 1.54-1.47 (m, 1H), 1.45-1.34 (m, 4H), 1.32-1.25 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.0, 166.5, 140.8, 138.7, 138.4, 131.7, 131.5, 129.2, 126.5, 125.8, 73.0, 35.8, 31.6, 29.8, 25.6, 23.7; FT-IR (neat) 2946, 1719, 1685, 1630, 1436, 1269, 1220, 1135, 1044 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{23}O_3$ 287.1642; Found 287.1644.



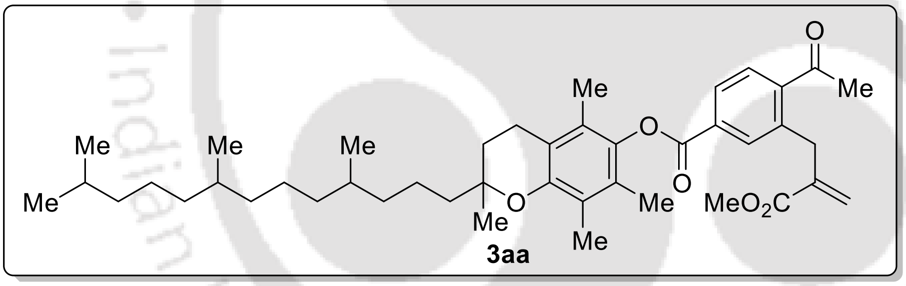
3y

4-Acetyl-3-(2-(methoxycarbonyl)allyl)phenyl 4-([1,1'-biphenyl]-4-yl)-4-oxobutanoate 3y. Analytical TLC on silica gel, 1:5 EtOAc/hexane R_f = 0.34; sticky brown solid; yield 65% (30.6 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 7.5 Hz, 2H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.0 Hz, 1H), 7.12 (d, *J* = 9.5 Hz, 1H), 7.03 (s, 1H), 6.21 (s, 1H), 5.32 (s, 1H), 3.93 (s, 2H), 3.74 (s, 3H), 3.46 (t, *J* = 6.5 Hz, 2H), 3.04 (t, *J* = 6.5 Hz, 2H), 2.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.6, 197.5, 171.2, 167.4, 153.0, 146.3, 141.1, 139.9, 139.6, 135.5, 135.2, 131.1, 129.1, 128.8, 128.5, 127.5, 127.4, 126.4, 124.8, 119.8, 52.1, 35.7, 33.5, 29.7, 28.7; FT-IR (neat) 2925, 1761, 1716, 1683, 1603, 1438, 1356, 1254, 1132, 1056 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{29}H_{26}NaO_6$ 493.1622; Found 493.1610.



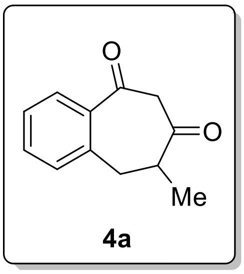
3z

4-Acetyl-3-(2-(methoxycarbonyl)allyl)phenyl adamantane-1-carboxylate 3z. Analytical TLC on silica gel, 1:10 EtOAc/hexane $R_f = 0.35$; colorless liquid; yield 68% (27 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, $J = 8.5$ Hz, 1H), 7.04-7.02 (m, 1H), 6.94 (s, 1H), 6.20 (s, 1H), 5.28 (s, 1H), 3.92 (s, 2H), 3.74 (s, 3H), 2.55 (s, 3H), 2.09 (s, 3H), 2.05 (s, 6H), 1.80-1.74 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 175.8, 167.4, 153.4, 141.0, 139.7, 135.3, 131.1, 126.3, 125.0, 119.8, 52.1, 41.3, 38.8, 36.5, 35.7, 29.7, 28.0; FT-IR (neat) 2908, 1751, 1721, 1687, 1604, 1577, 1259, 1205, 1042 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{29}O_5$ 397.2010; Found 397.2009.



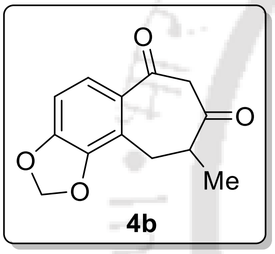
3aa

2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-yl 4-acetyl-3-(2-(methoxycarbonyl)allyl)benzoate 3aa. Analytical TLC on silica gel, 1:10 EtOAc/hexane $R_f = 0.41$; colorless liquid; yield 62% (42 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, $J = 8.0$ Hz, 1H), 8.12 (s, 1H), 7.73 (d, $J = 8.0$ Hz, 1H), 6.25 (s, 1H), 5.38 (s, 1H), 3.95 (s, 2H), 3.74 (s, 3H), 2.62 (s, 3H), 2.12 (s, 3H), 2.04 (s, 3H), 2.00 (s, 3H), 1.87-1.78 (m, 2H), 1.55-1.50 (m, 2H), 1.42-1.37 (m, 4H), 1.30-1.21 (dm, 12H), 1.16-1.05 (m, 8H), 0.87-0.84 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.0, 167.2, 164.4, 149.7, 143.0, 140.6, 139.5, 138.5, 134.8, 133.2, 131.9, 128.8, 128.4, 126.9, 126.8, 125.1, 123.4, 117.7, 75.3, 52.1, 39.5, 37.5, 35.4, 32.9, 30.1, 28.1, 24.96, 24.95, 24.6, 22.9, 22.8, 21.2, 20.8, 19.9, 19.8, 13.2, 12.4, 12.0; FT-IR (neat) 2926, 2867, 1733, 1696, 1460, 1238, 1148, 1099 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{43}H_{63}O_6$ 675.4619; Found 675.4619.



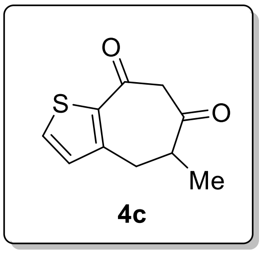
4a

8-Methyl-8,9-dihydro-5*H*-benzo[7]annulene-5,7(6*H*)-dione 4a. Analytical TLC on silica gel, 1:5 EtOAc/hexane R_f = 0.60; yellow liquid; yield 85% (32 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.36 (t, *J* = 6.8 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 4.09 (d, *J* = 14.4 Hz, 1H), 4.00 (d, *J* = 14.4 Hz, 1H), 3.40 (dd, *J* = 15.2, 4.0 Hz, 1H), 3.18 (dd, *J* = 15.6, 8.4 Hz, 1H), 2.82-2.73 (m, 1H), 1.19 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 192.5, 140.3, 136.2, 133.8, 131.4, 130.2, 127.8, 58.6, 46.2, 38.5, 16.2; FT-IR (neat) 2922, 1715, 1676, 1604, 1438, 1241, 1207, 1121, 1081 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{12}H_{13}O_2$ 189.0910; Found 189.0904.



4b

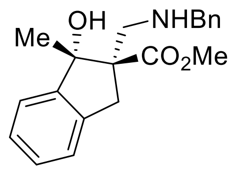
9-Methyl-9,10-dihydro-6*H*-cyclohepta[3,4]benzo[1,2-*d*][1,3]dioxole-6,8(7*H*)-dione 4b. Analytical TLC on silica gel, 1:5 EtOAc/hexane R_f = 0.51; yellow liquid; yield 81% (37.6 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 6.07 (s, 2H), 4.08 (d, *J* = 14.0 Hz, 1H), 3.97 (d, *J* = 13.5 Hz, 1H), 3.34 (d, *J* = 16 Hz, 1H), 3.10 (dd, *J* = 15.5, 8.5 Hz, 1H), 2.76-2.72 (m, 1H), 1.22 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.9, 190.1, 151.4, 146.6, 130.7, 126.5, 121.8, 107.7, 102.0, 58.6, 45.5, 29.4, 16.4; FT-IR (neat) 2922, 1715, 1672, 1622, 1455, 1349, 1279, 1053 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{13}H_{13}O_4$ 233.0808; Found 233.0809.



4c

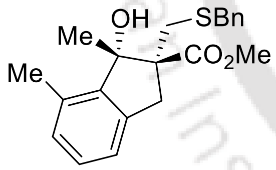
5-Methyl-4,5-dihydro-6*H*-cyclohepta[*b*]thiophene-6,8(7*H*)-dione 4c. Analytical TLC on silica gel, 1:5 EtOAc/hexane R_f = 0.47; yellow liquid; yield 77% (30 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 5.0 Hz, 1H), 6.99 (d, *J* = 5.0 Hz, 1H), 4.13 (d, *J* = 13.0 Hz, 1H), 3.99 (d, *J* = 13.0 Hz, 1H), 3.37 (dd, *J* = 15.5, 3.0 Hz, 1H), 3.15 (dd, *J* = 15.5, 8.5

Hz, 1H), 2.77-2.70 (m, 1H), 1.22 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.4, 183.2, 147.8, 139.5, 134.5, 131.6, 58.4, 44.9, 33.4, 17.4; FT-IR (neat) 2925, 1709, 1651, 1457, 1417, 1289, 1242, 1172 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{10}H_{11}O_2S$ 195.0474; Found 195.0475.



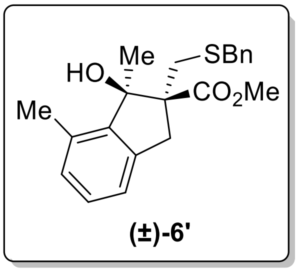
(±)-5

Methyl-2-((benzylamino)methyl)-1-hydroxy-1-methyl-2,3-dihydro-1*H*-indene-2-carboxylate (±)-**5.** Analytical TLC on silica gel, 1:20 EtOAc/hexane R_f = 0.50; colorless liquid; yield 77% (50 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.6 Hz, 1H), 7.29-7.17 (m, 7H), 7.11 (d, *J* = 7.6 Hz, 1H), 3.77 (s, 3H), 3.69-3.58 (m, 3H), 3.11 (d, *J* = 12.4 Hz, 1H), 2.81 (d, *J* = 12.0 Hz, 1H), 2.63 (d, *J* = 16.4 Hz, 1H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 148.3, 138.9, 137.2, 128.6, 128.0, 127.9, 127.5, 127.3, 124.5, 123.2, 84.9, 59.9, 54.1, 53.7, 52.2, 38.2, 27.6; FT-IR (neat) 3330, 2949, 2840, 1719, 1454, 1231, 1203, 1123, 1094 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{24}O_3N$ 326.1751; Found 326.1751.



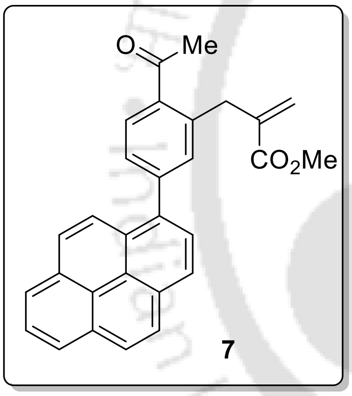
(±)-6

Methyl-2-((benzylthio)methyl)-1-hydroxy-1,7-dimethyl-2,3-dihydro-1*H*-indene-2-carboxylate (±)-**6.** Analytical TLC on silica gel, 1:50 EtOAc/hexane R_f = 0.52; colorless liquid; yield 43% (30.6 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.19 (m, 5H), 7.11 (t, *J* = 7.5 Hz, 1H), 6.97 (t, *J* = 7.5 Hz, 2H), 3.76 (s, 3H), 3.67-3.60 (m, 2H), 3.36 (d, *J* = 16.5 Hz, 1H), 3.14 (d, *J* = 12.5 Hz, 1H), 3.05 (d, *J* = 16.5 Hz, 1H), 2.60 (d, *J* = 13.0 Hz, 1H), 2.43 (s, 3H), 2.28 (s, 1H), 1.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 141.6, 138.3, 137.9, 134.8, 129.9, 129.0, 128.6, 128.2, 127.1, 122.9, 85.3, 64.2, 52.2, 37.8, 35.8, 35.5, 24.9, 17.8; FT-IR (neat) 3503, 2927, 1725, 1453, 1272, 1223, 1175, 1029 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{21}H_{24}NaO_3S$ 379.1338; Found 379.1334.



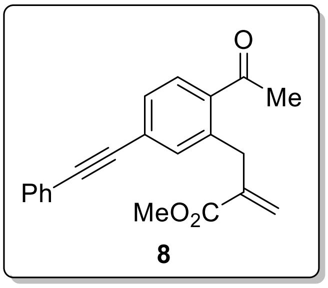
(±)-6'

Methyl-2-((benzylthio)methyl)-1-hydroxy-1,7-dimethyl-2,3-dihydro-1*H*-indene-2-carboxylate (±)-**6′.** Analytical TLC on silica gel, 1:50 EtOAc/hexane $R_f = 0.58$; colorless liquid; yield 45% (32 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.30 (m, 4H), 7.25-7.22 (m, 1H), 7.09 (t, $J = 7.6$ Hz, 1H), 6.96 (t, $J = 6.8$ Hz, 2H), 3.72 (s, 2H), 3.66-3.65 (m, 4H), 3.44 (d, $J = 16.0$ Hz, 1H), 3.05 (d, $J = 12.4$ Hz, 1H), 2.83 (d, $J = 16.0$ Hz, 1H), 2.70 (d, $J = 12.4$ Hz, 1H), 2.46 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 143.8, 138.6, 138.3, 134.7, 130.3, 129.1, 128.6, 128.3, 127.2, 122.4, 85.3, 63.1, 52.4, 38.9, 38.1, 35.3, 22.3, 18.5; FT-IR (neat) 3457, 2951, 1599, 1454, 1305, 1199, 1071 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{21}H_{24}O_3SNa$ 379.1338; Found 379.1335.



7

Methyl 2-(2-acetyl-5-(pyren-1-yl)benzyl)acrylate 7. Analytical TLC on silica gel, 1:50 EtOAc/hexane $R_f = 0.60$; brown liquid; yield 67% (56 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24-8.21 (m, 2H), 8.18 (d, $J = 7.5$ Hz, 1H), 8.11-8.10 (m, 3H), 8.06-8.02 (m, 2H), 7.95 (d, $J = 7.5$ Hz, 1H), 7.90 (d, $J = 8.0$ Hz, 1H), 7.60 (d, $J = 7.5$ Hz, 1H), 7.55 (s, 1H), 6.25 (s, 1H), 5.43 (s, 1H), 4.08 (s, 2H), 3.78 (s, 3H), 2.69 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.6, 167.5, 144.7, 140.1, 138.9, 136.8, 136.3, 134.1, 131.6, 131.2, 131.0, 129.8, 128.8, 128.5, 128.0, 127.9, 127.5, 127.4, 126.3, 126.2, 125.5, 125.2, 125.1, 125.0, 124.9, 124.8, 52.1, 35.9, 29.8; FT-IR (neat) 2924, 1718, 1683, 1602, 1435, 1251, 1198, 1147, 959 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{29}H_{23}O_3$ 419.1642; Found 419.1642.



8

Methyl 2-(2-acetyl-5-(phenylethynyl)benzyl)acrylate 8. Analytical TLC on silica gel, 1:50 EtOAc/hexane $R_f = 0.52$; brown liquid; yield 74% (47 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.0 Hz, 1H), 7.55-7.53 (m, 2H), 7.48-7.46 (m, 1H), 7.42-7.41 (m, 1H), 7.37-7.35 (m, 3H), 6.23-6.22 (m, 1H), 5.31-5.30 (m, 1H), 3.92 (s, 2H), 3.76 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.0, 167.4, 139.8, 138.9, 137.5, 134.8, 131.9, 129.7, 129.5, 128.9, 128.6, 126.8, 126.3, 122.8, 92.0, 88.6, 52.1, 35.5, 29.7; FT-IR (neat) 2951, 2210, 1719, 1685, 1603, 1437, 1251, 1121, 1038 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{19}O_3$ 319.1329; Found 319.1331.

4.5 References

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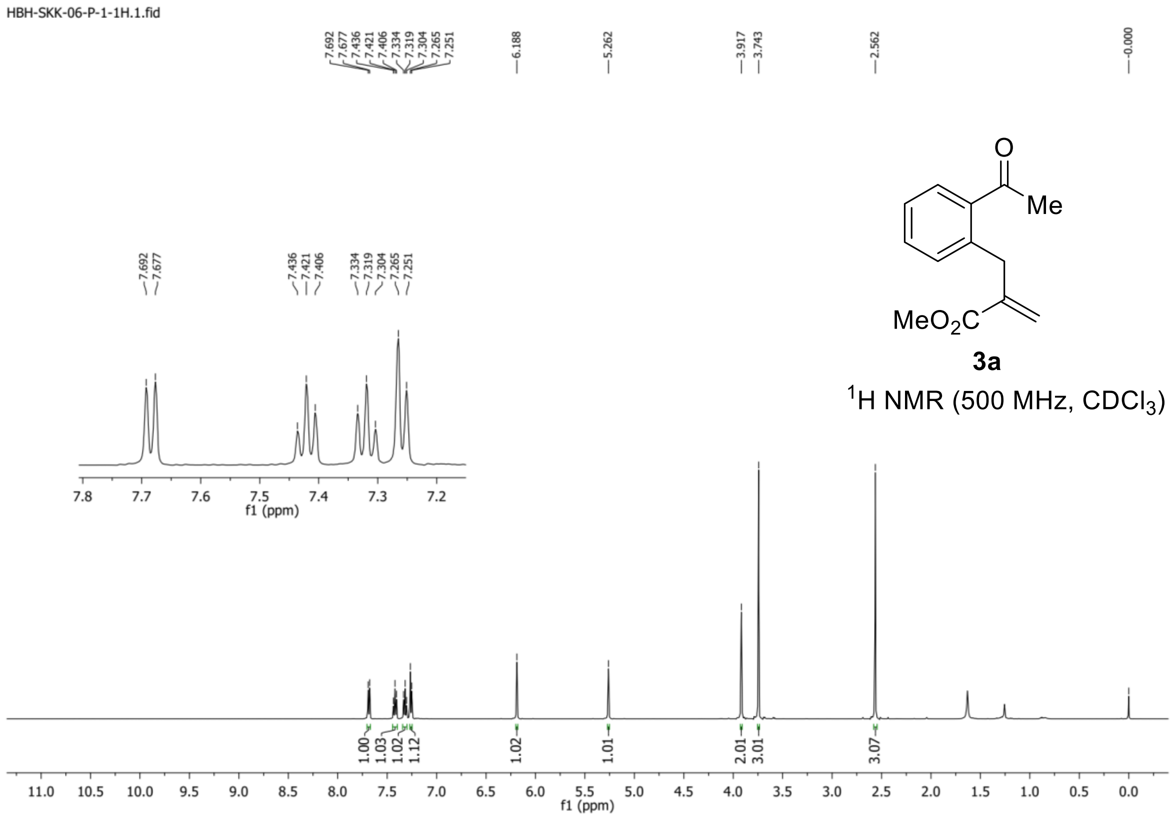
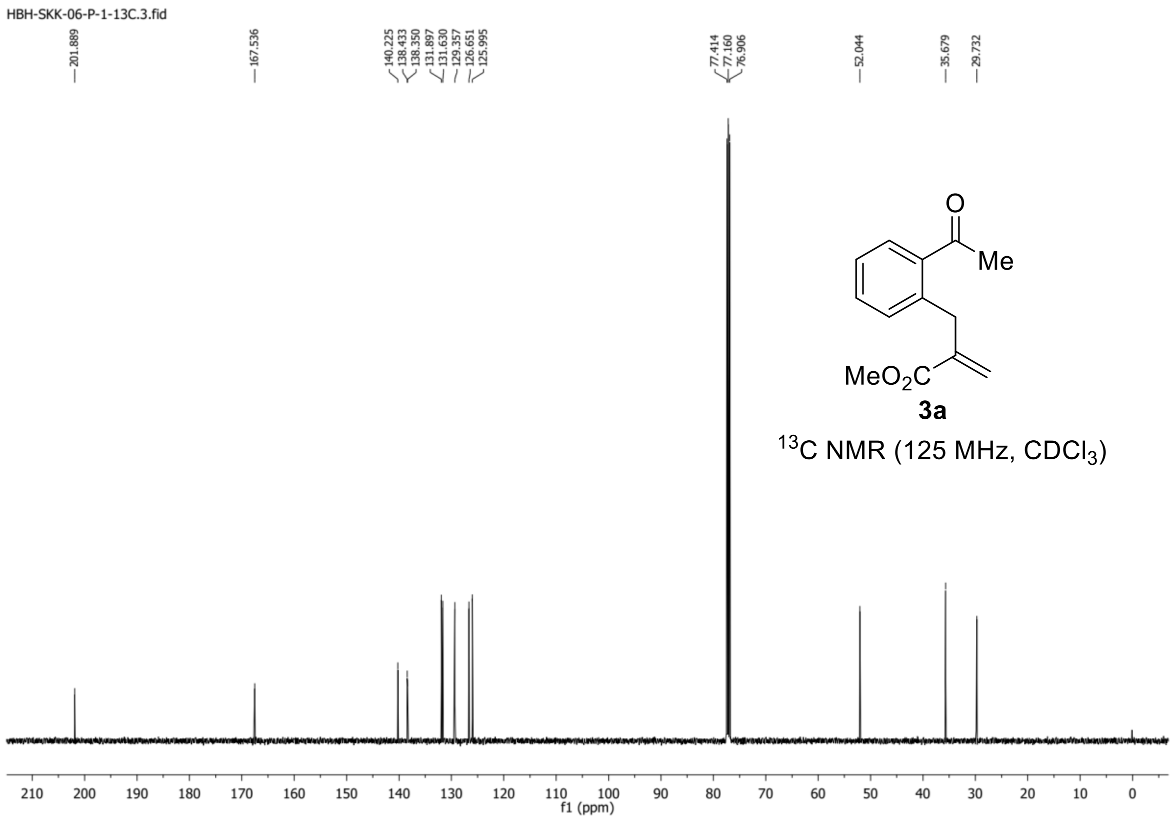
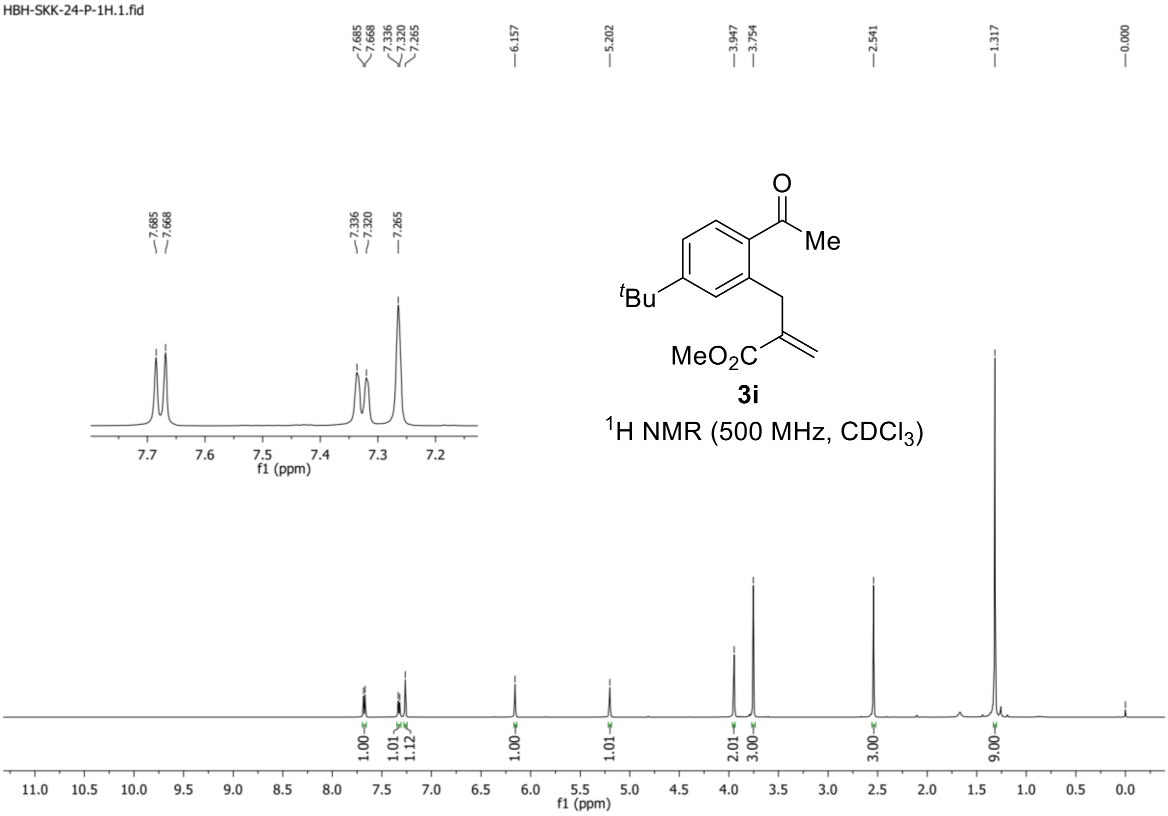
4.6 Selected NMR Spectra

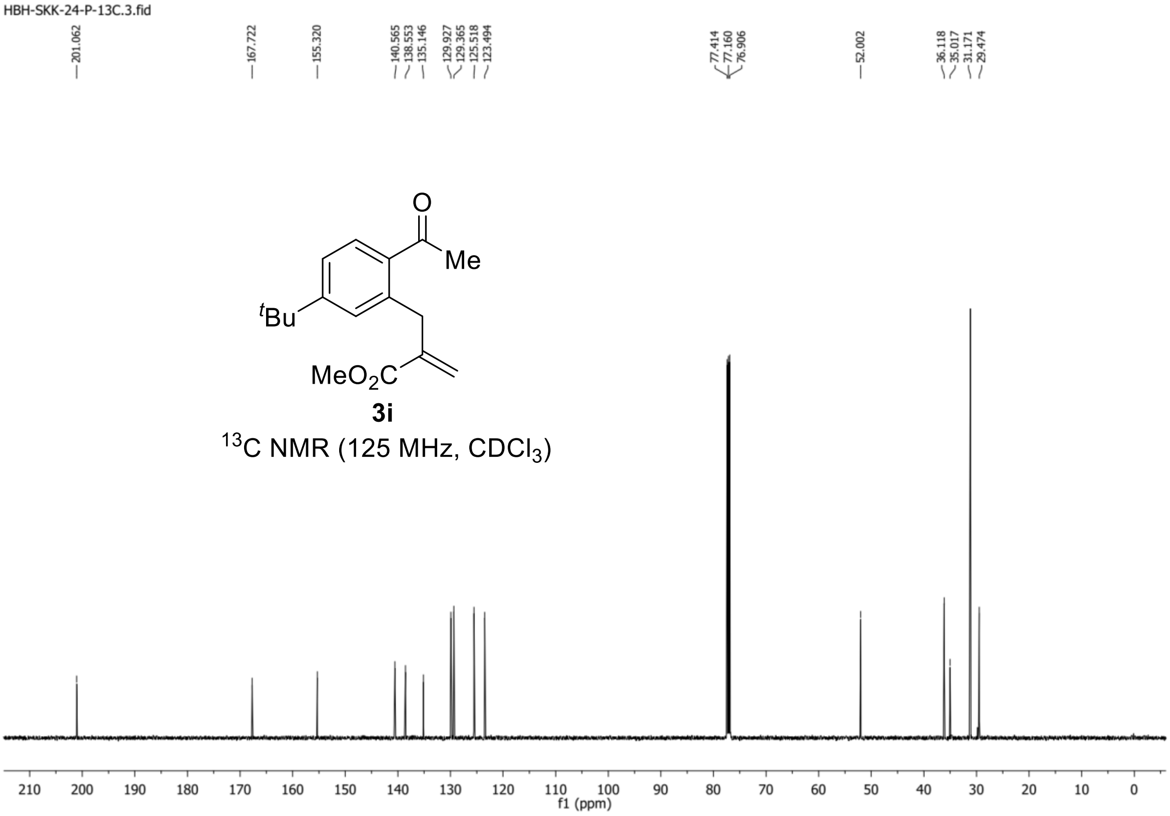






3i

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



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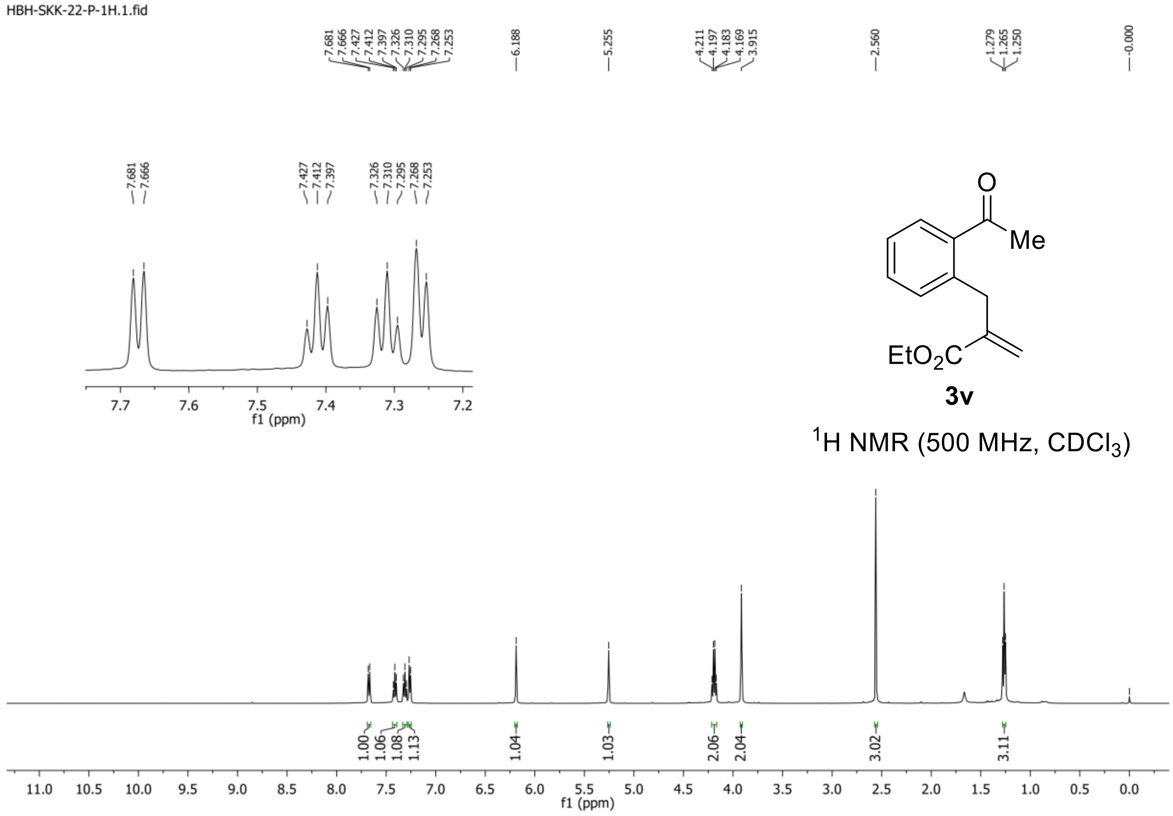
^{13}C NMR (125 MHz, $CDCl_3$)



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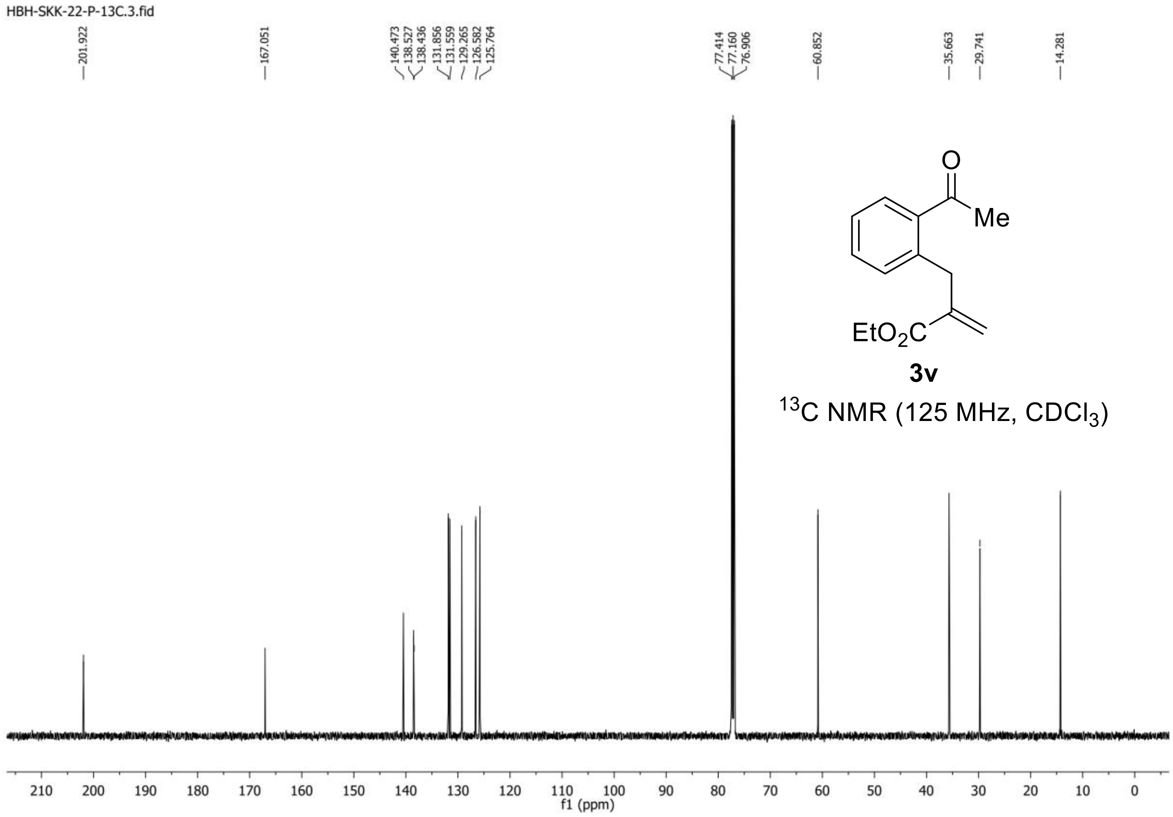

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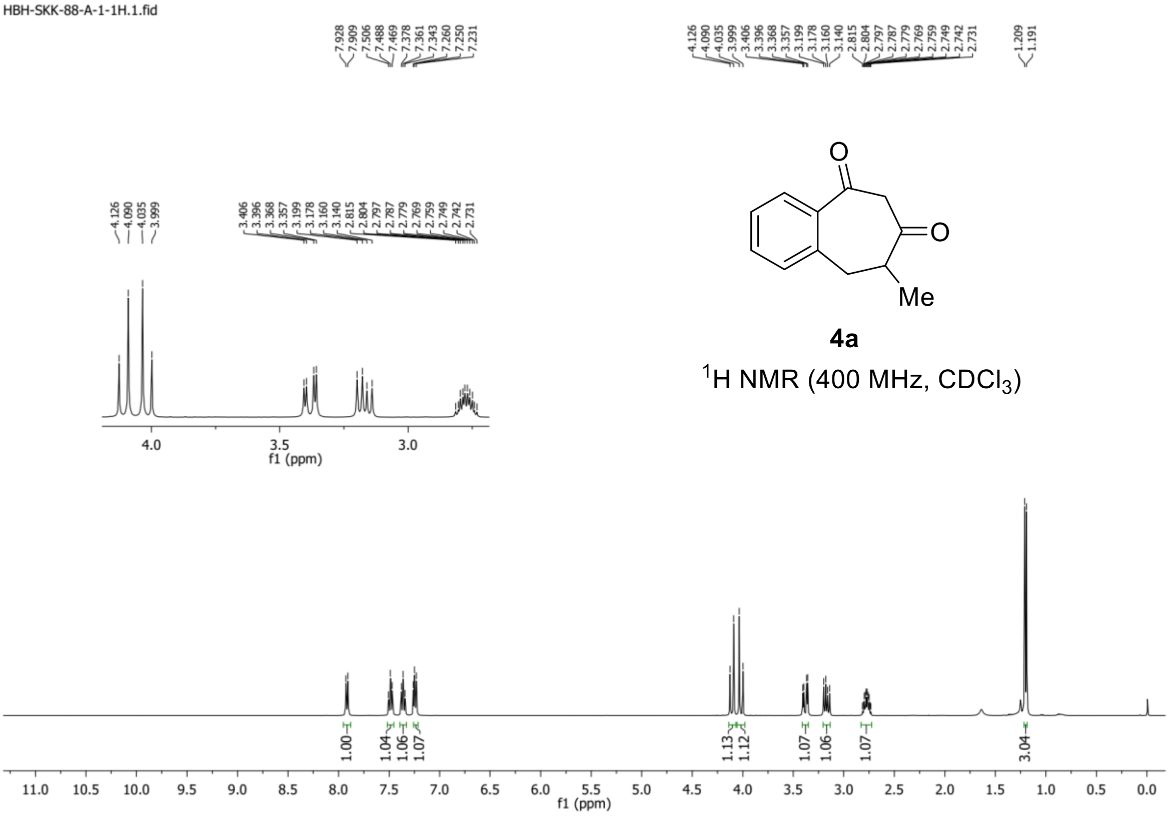

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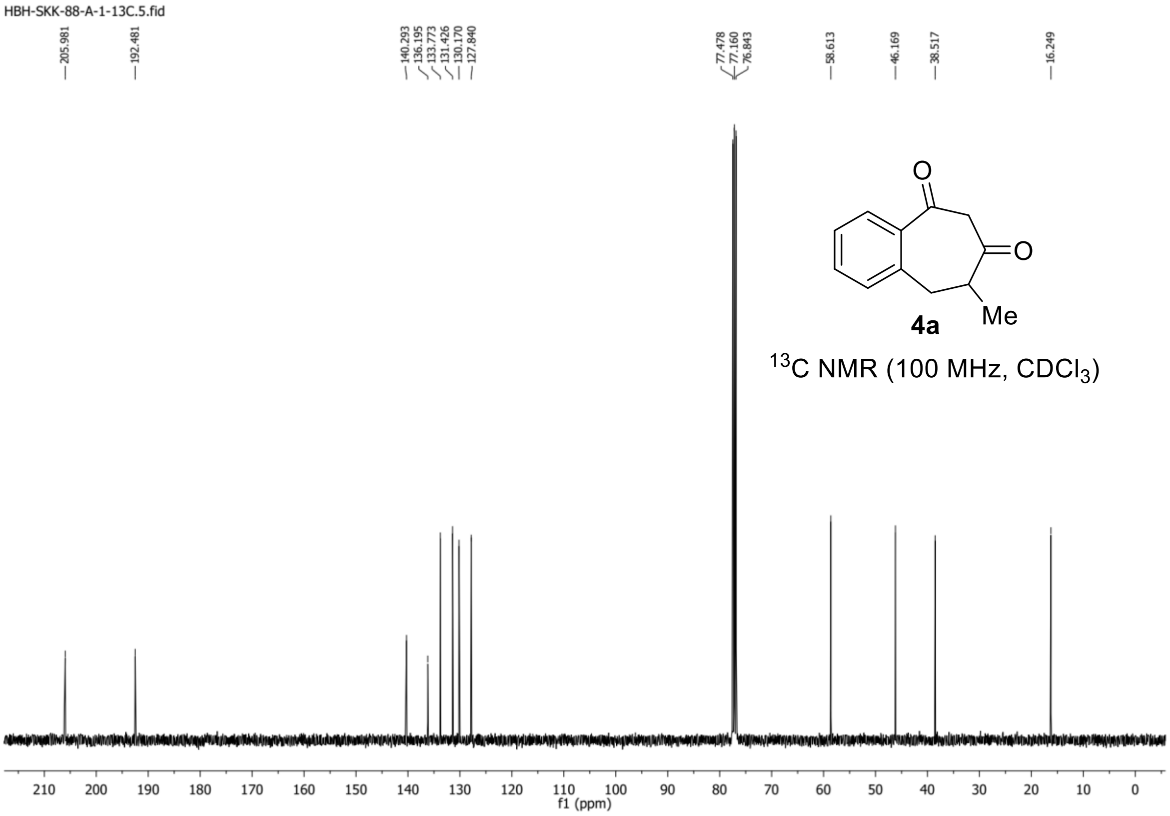

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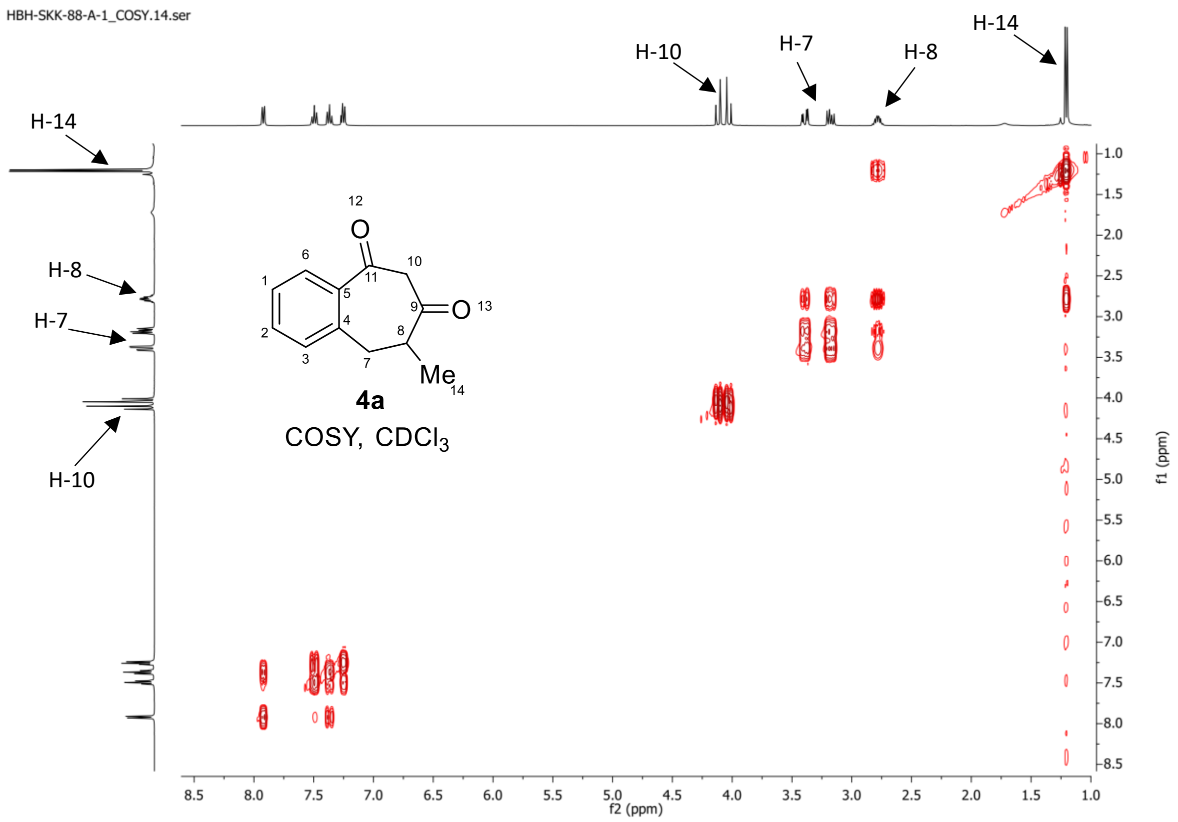
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12
O
6
10
1
11
5
9
O 13
2
4
8
3
7
Me
14
4a
COSY, CDCl3
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f2 (ppm)
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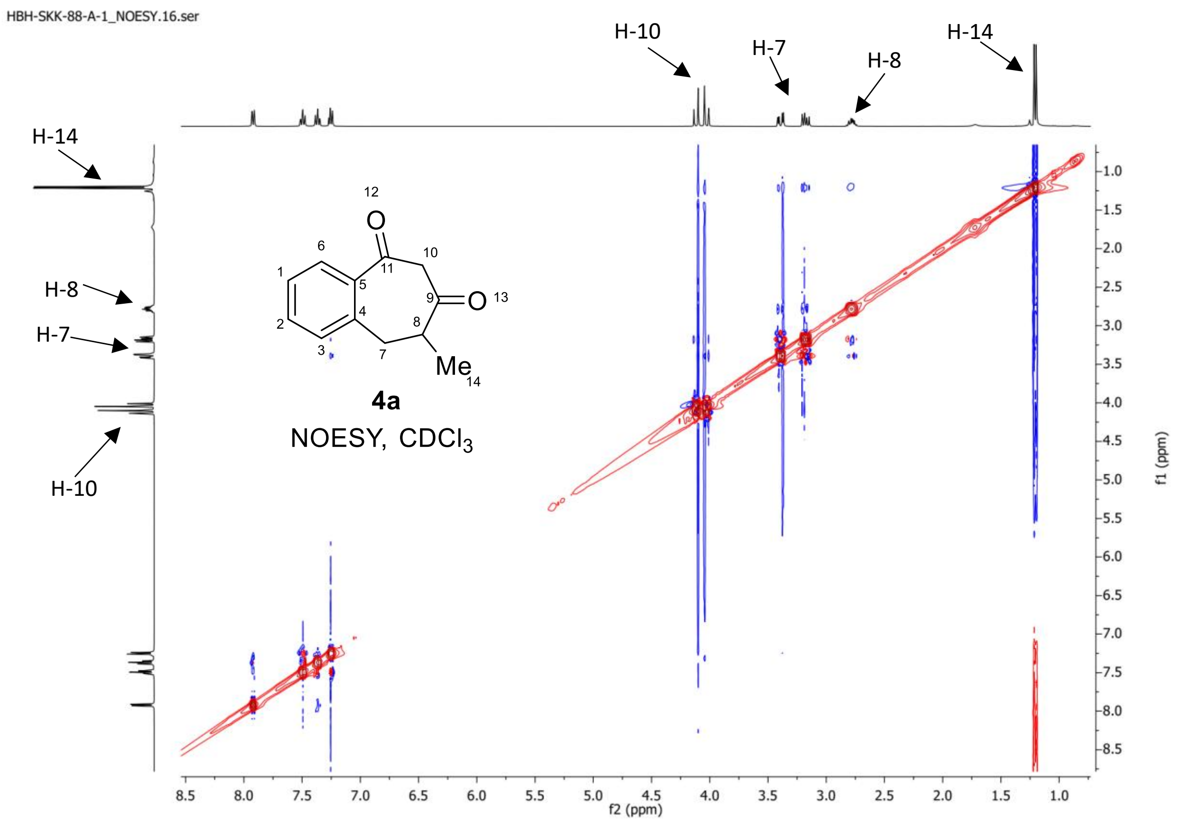
f1 (ppm)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O 13
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8
3
7
Me
14
4a
NOESY, CDCl3
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f2 (ppm)
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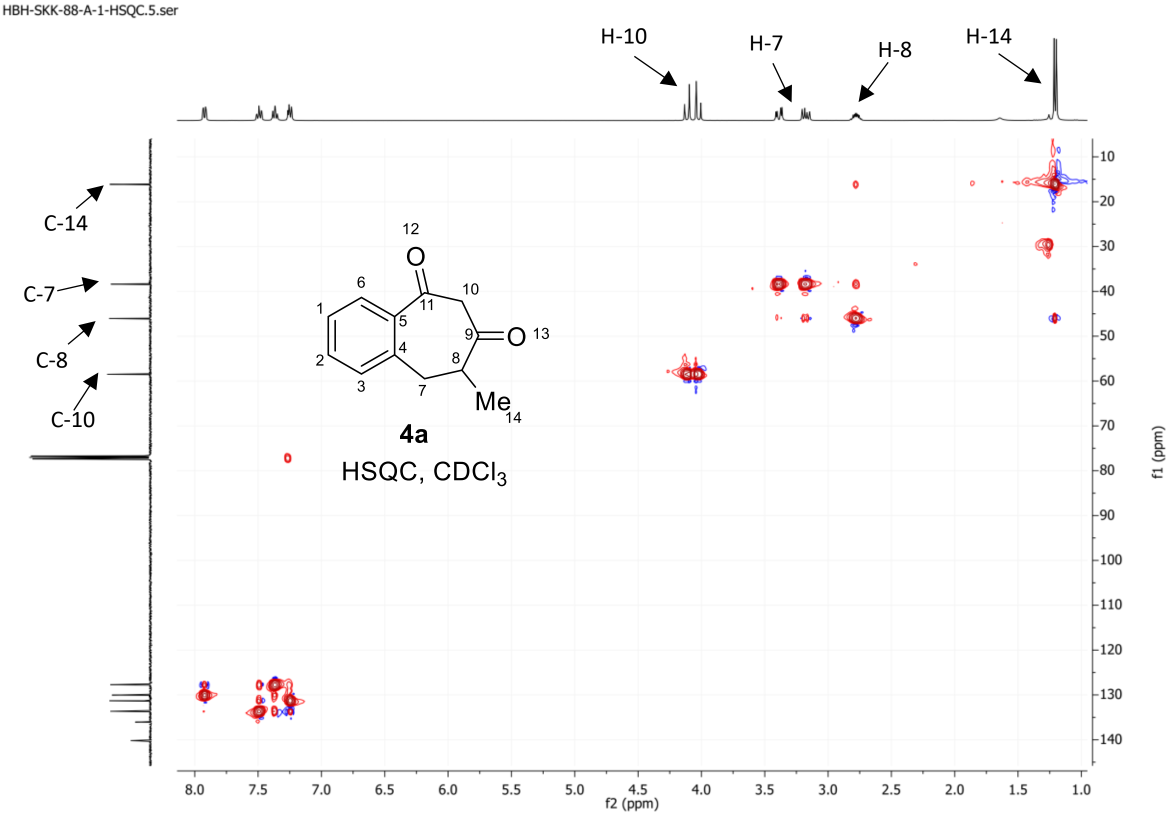
f1 (ppm)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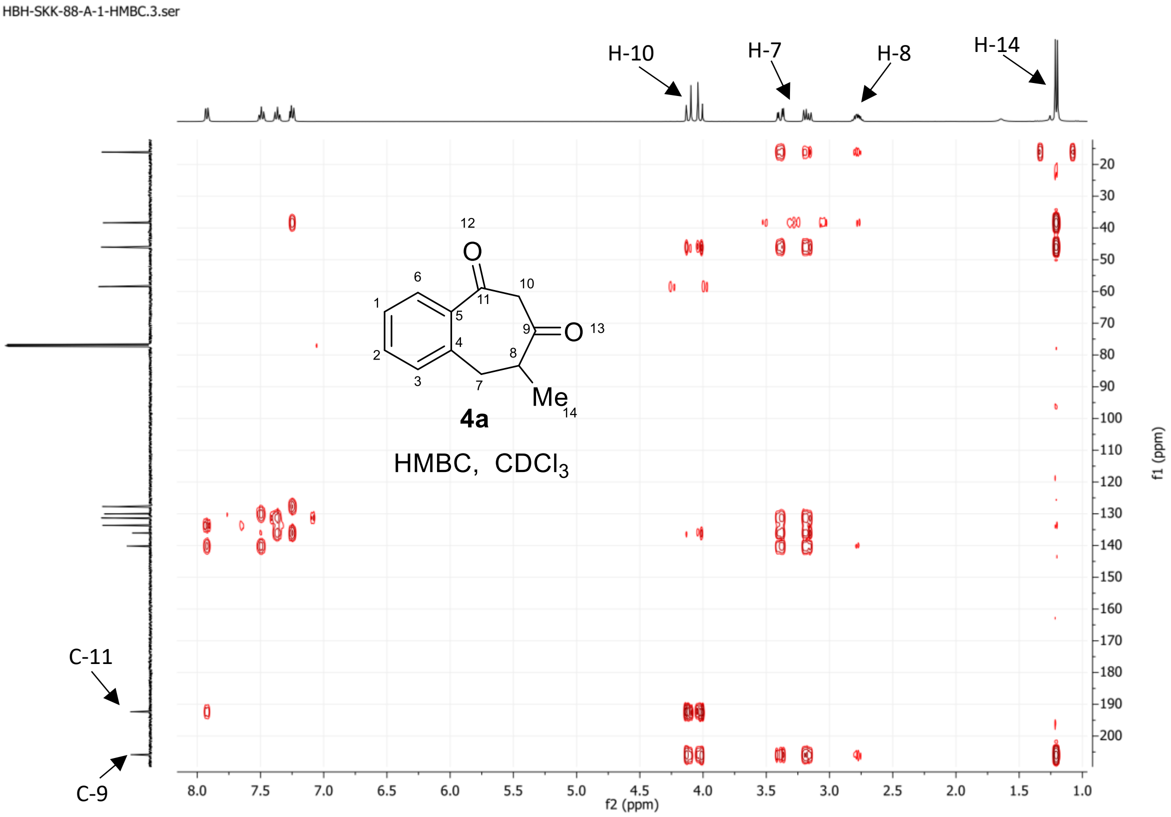
14
4a
HSQC, CDCl3
f2 (ppm)
f1 (ppm)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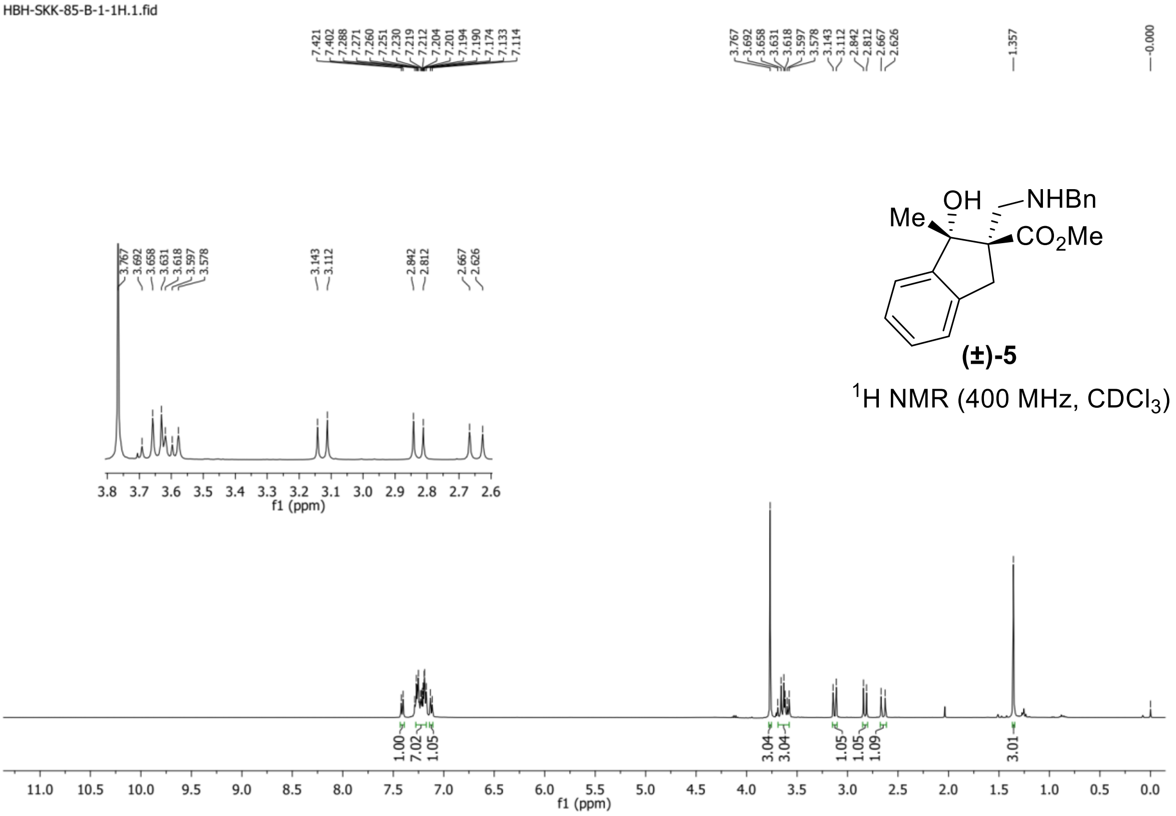
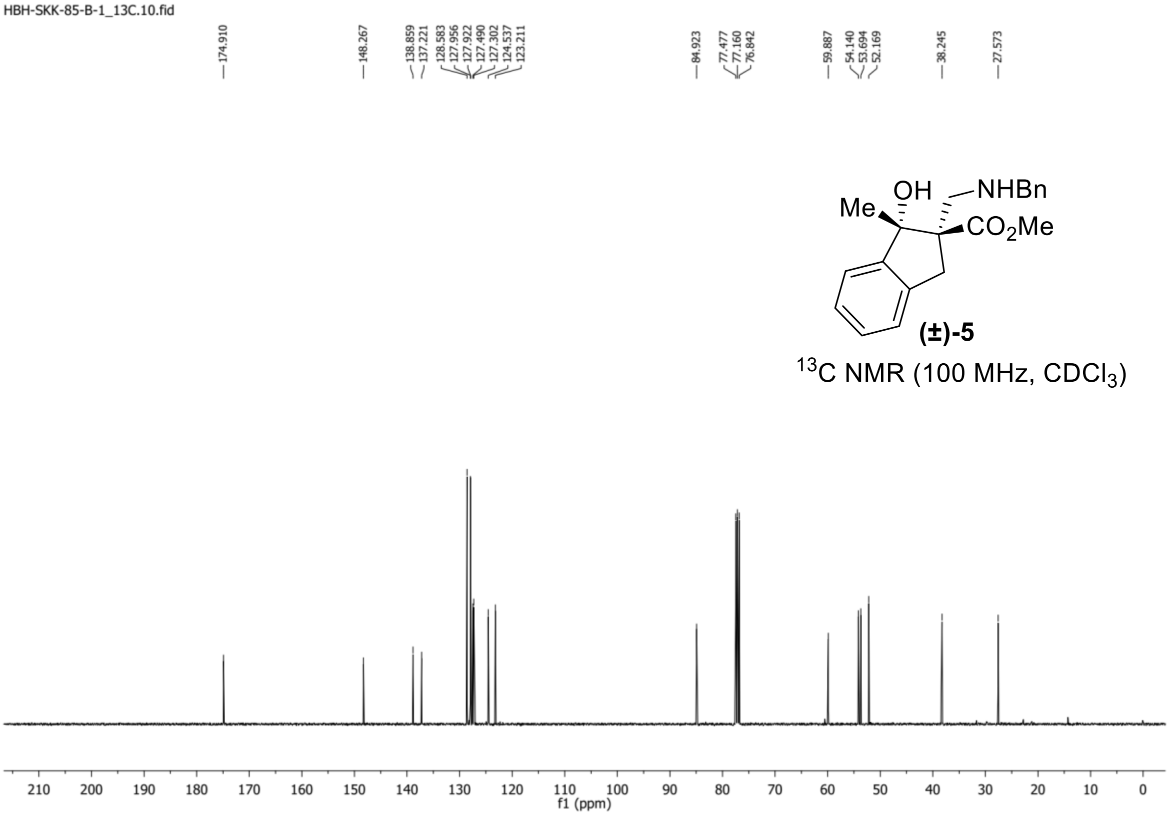
C-11
C-9
f2 (ppm)
f1 (ppm)



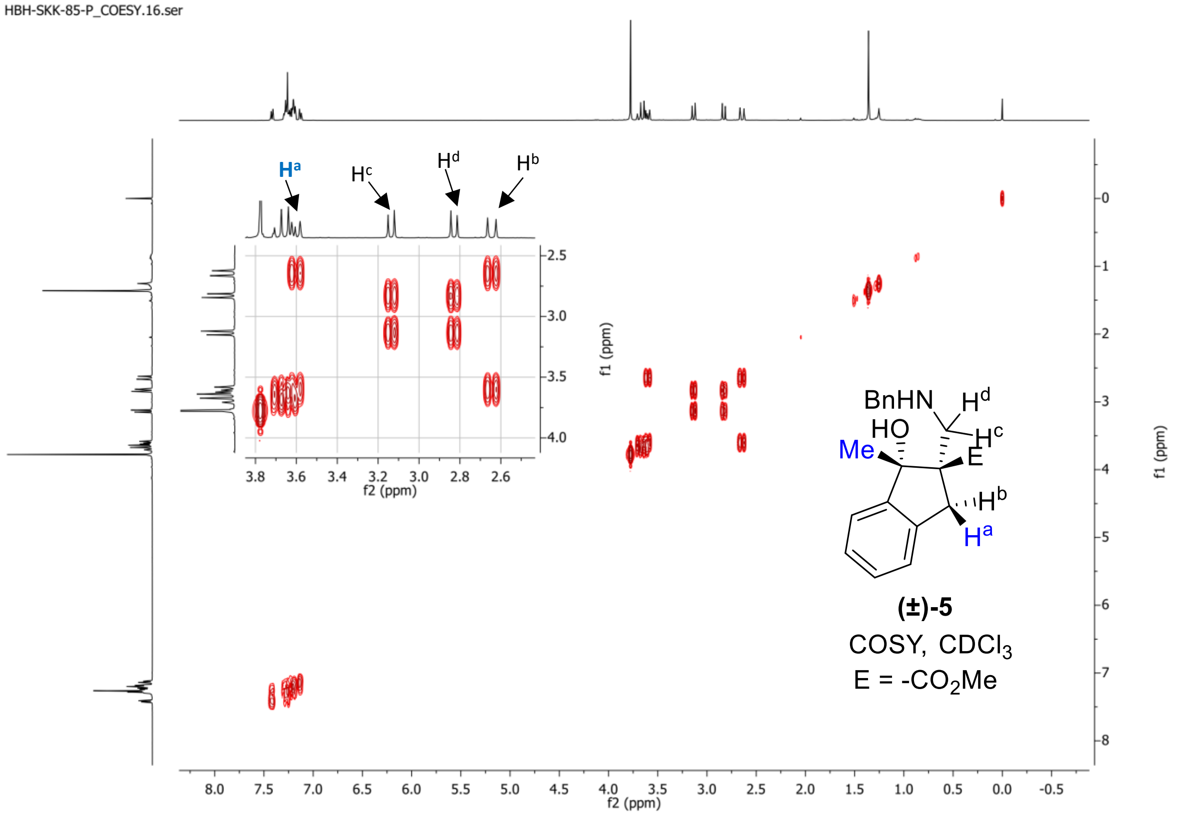
(±)-5

^{1}H NMR (400 MHz, CDCl$_3$)



(±)-5

^{13}C NMR (100 MHz, CDCl$_3$)



(±)-5
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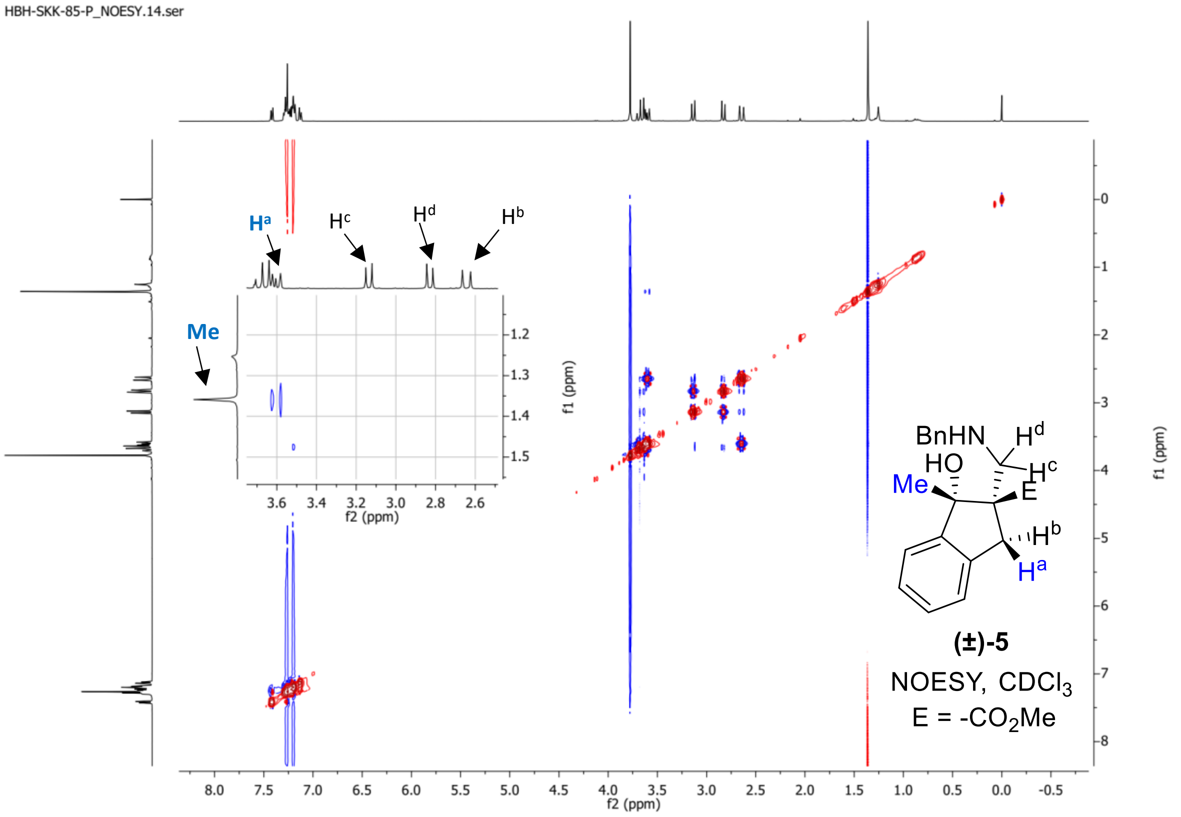

(±)-5
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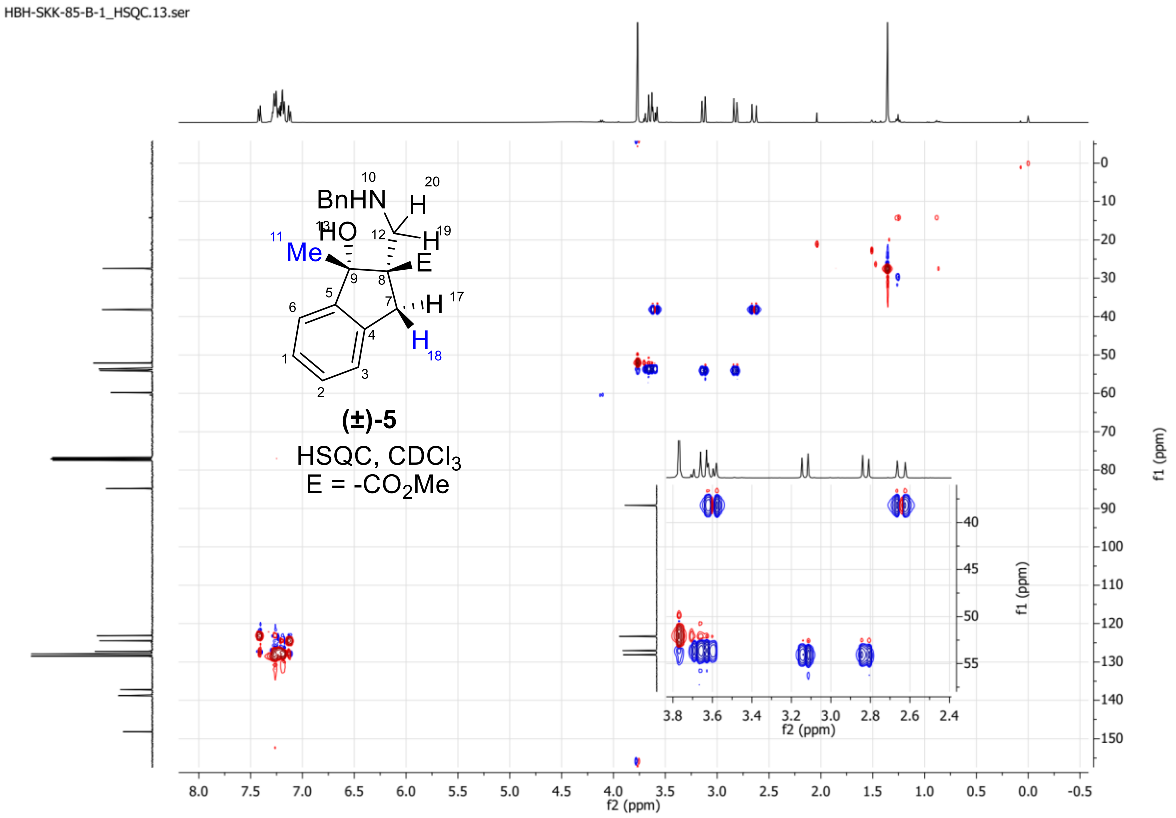
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3
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(±)-5
HSQC, CDCl$_3$
E = -CO$_2$Me
f2 (ppm)
f1 (ppm)
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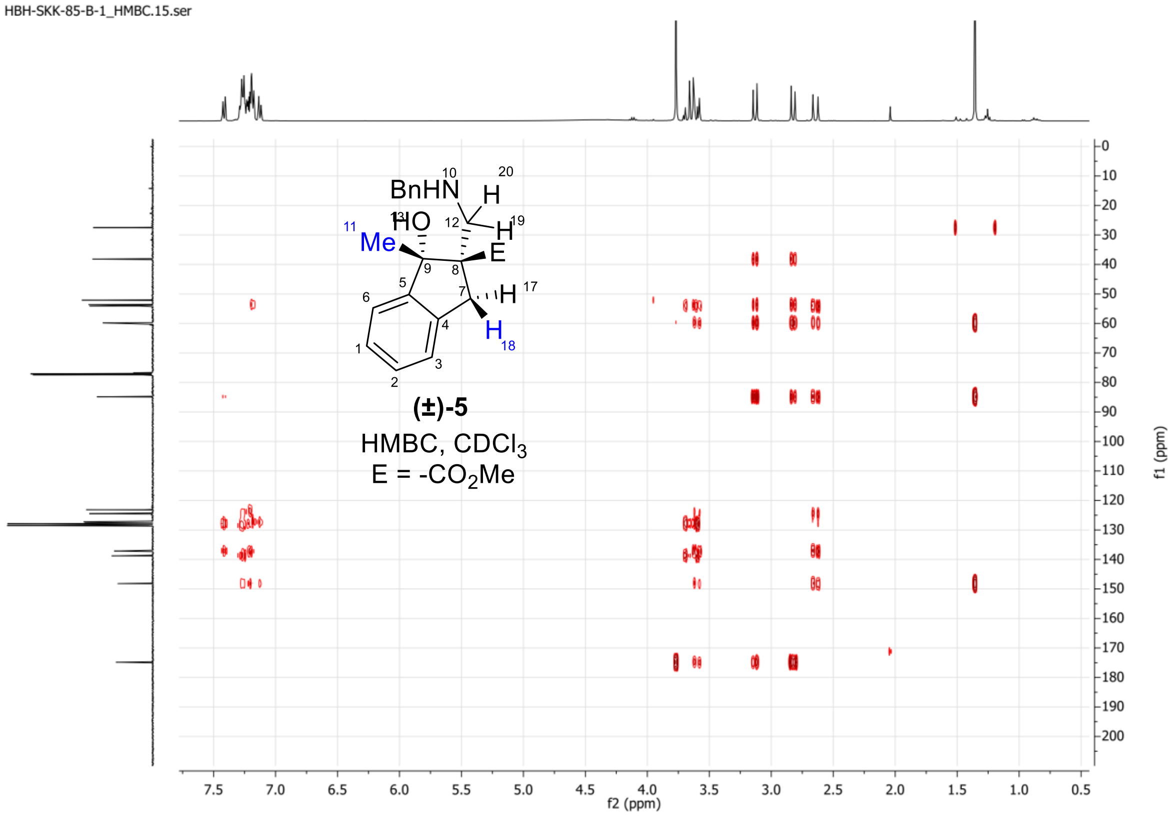
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7
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4
18
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3
2
(±)-5
HMBC, CDCl$_3$
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f2 (ppm)
f1 (ppm)
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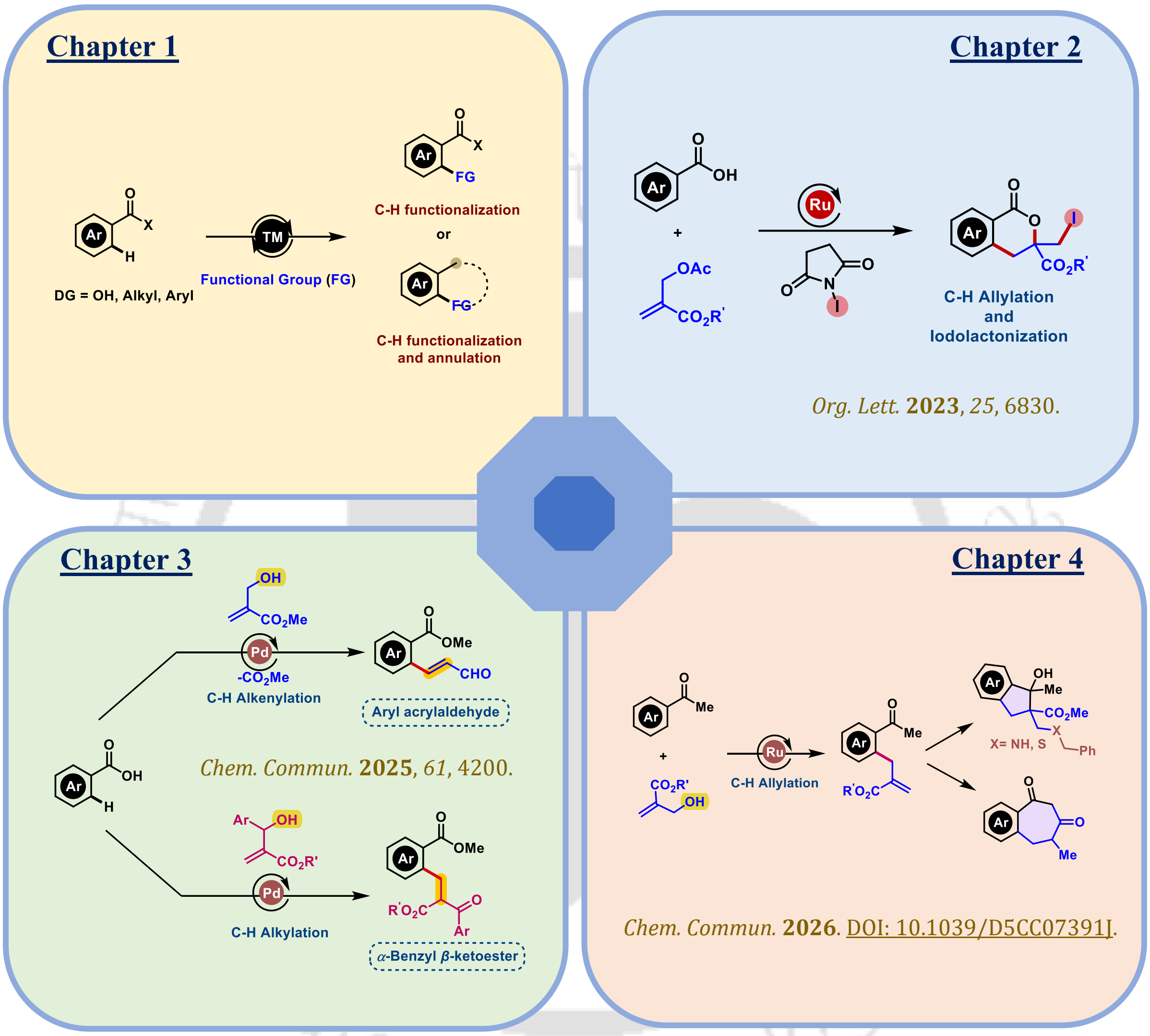
Thesis Overview



Org. Lett. **2023**, *25*, 6830.

Chem. Commun. **2025**, *61*, 4200.

Chem. Commun. **2026**. DOI: 10.1039/D5CC07391J.

Summary

This thesis reports the development of sustainable native functional group directed C–H functionalization strategies that enable site-selective transformations without the use of exogenous directing groups. By leveraging transition-metal catalysis, along with the use of carboxylic acids and ketones as weakly coordinating yet effective directing groups, and by employing Morita–Baylis–Hillman (MBH) adducts as versatile coupling partners, the work advances step and atom economical strategies for constructing molecular complexity. The developed methodologies exhibit broad substrate scope and excellent functional group tolerance, while showcasing MBH adducts as underexplored yet highly effective coupling partners.

In chapter 1, we have discussed recent advances in C–H functionalization, highlighting the use of native functional groups, such as carboxylic acids and ketones, for site-selective transformations. Their natural abundance, biological relevance, and weak coordinating ability enable efficient C–H activation without exogenous DGs. When combined with annulation strategies, this approach enhances step and atom economy, providing streamlined access to diverse and medicinally important molecular architectures. This chapter provides an overview of reported methodologies on native carboxylate- and ketone-directed C–H functionalization and annulation of arenes.

In chapter 2, we have described a redox-neutral Ru(II)-catalyzed sequential C–H allylation and iodolactonization of benzoic acids with MBH adducts in water, affording isochroman-1-ones, core motifs of benzolactone scaffolds. The method uses water as solvent, avoids external oxidants, and demonstrates substrate scope, scalability and functional group tolerance. Its applicability to late-stage modification of natural products and drug molecules underscores its synthetic utility.

In chapter 3, we have demonstrated a Pd(II)-catalyzed, carboxylate-directed *ortho* C–H functionalization of arenes with MBH alcohols. The reaction outcome is dependent on the substitution pattern of the MBH alcohol: unsubstituted MBH alcohols afford aryl acrylaldehydes, whereas aryl-substituted MBH alcohols yield α-benzyl β-ketoesters. The method offers broad scope, functional group tolerance, scalability and switchable reactivity, underscoring its synthetic utility.

In chapter 4, we have developed a Ru(II)-catalyzed, ketone-directed *ortho* C–H allylation of aryl ketones with MBH alcohols, affording *α*-benzyl acrylates. The allylated products undergo post-synthetic transformations to yield bioactive scaffolds such as multi-substituted indanes and benzo-fused cyclic *β*-diketones. The method offers broad scope, functional group tolerance, and highlights MBH alcohols as underexplored yet powerful coupling partners.

List of Publications

From Thesis Work

1. **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.

2. **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.

3. **Bhattacharyya**, **H.**; Saha, S.; Khamrai, S.; Verma, K.; Roy, S.; Punniyamurthy, T. Ruthenium-Catalyzed Weak-Chelation-Assisted C–H Allylation of Aryl Ketones Using Morita-Baylis-Hillman Alcohols: Access to α-Benzyl Acrylates. *Chem. Commun.* **2026**. https://doi.org/10.1039/D5CC07391J.

From Others

4. 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.

5. 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.

6. 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.

7. 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.

8. 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.

9. 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.

Conferences Attended

1. **Poster Presentation** on "Redox-Neutral Site-Selective C–H Allylation and Iodolactonization of Benzoic Acids Using Morita-Baylis-Hillman Adducts in Water" at **32nd CRSI National Symposium in Chemistry**, February 2024, Department of Chemistry, BITS Pilani, Rajasthan.

2. **Poster Presentation** on "Redox-Neutral Site-Selective C–H Allylation and Iodolactonization of Benzoic Acids Using Morita-Baylis-Hillman Adducts in Water" at **RIC-2024**, SAB, Indian Institute of Technology Guwahati, Assam.

3. **Poster Presentation** on "Palladium-Catalyzed Substrate-Switchable C–H Alkenylation and Alkylation of Benzoic Acids Using MBH Alcohols" at **FICS-2024**, Indian Institute of Technology Guwahati, Assam.