Transition-Metal-Catalyzed Weak Chelating *N*-Oxide Directed C-H Functionalization of Quinolines

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
March 2025

Santu Mandal

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CERTIFICATE

This is to certify that Mr. Santu Mandal has been working under my supervision since September 2020. I am forwarding his thesis entitled "*Transition-Metal-Catalyzed Weak Chelating N-Oxide Directed C-H Functionalization of Quinolines*" 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
March 2025

Prof. Tharmalingam Punniyamurthy
Supervisor

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Santu Mandal

List of Abbreviations

Ar	aryl
Ac	acetyl
acac	acetylacetone
AcOH	acetic acid
Ad	adamantane
Å	angstrom (10^{-8} cm)
BHT	butylated hydroxytoluene
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BQ	benzoquinone
CCDC	Cambridge crystallographic data center
CMD	concerted metalation deprotonation
Cp*	1,2,3,4,5-pentamethylcyclopentadiene
Cy	cyclohexyl
Cyp	cyclopropanol
p-cymene	4-isopropyltoluene
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DFT	density functional theory
DG	directing group
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
equiv	equivalent
ee	enantiomeric excess
Et	ethyl
EtOAc	ethyl acetate
ESI	electrospray ionization
EWG	electron wthdrawing group
Fig	figure
FT-IR	Fourier transform infrared spectroscopy

FG	functional group
Fmoc	9-fluorenylmethoxycarbonyl
gm	gram
HFIP	hexafluoroisopropanol
het	heterocyclic
HRMS	high-resolution mass spectrometry
Hz	hertz
^{i}Pr	isopropyl
LA	Lewis acid
LG	leaving group
Me	methyl
MHz	megahertz
mp	melting point
mg	milligram
mL	milliliter
MPAA	monoprotected amino acids
MS	molecular sieves
MsCl	methanesulfonyl chloride
MW	microwave
m/z	mass to charge ratio
N-Ac-L-Phe	*N*-acetyl-L-phenylalanine
Naph	naphthyl
NBE	norbornene
NHC	*N*-heterocyclic carbene
nm	nanometer
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
ORTEP	oak ridge thermal ellipsoid plot
Piv	pivaloyl
PivOH	pivalic acid
py	pyridyl
PG	protecting group
Ph	phenyl

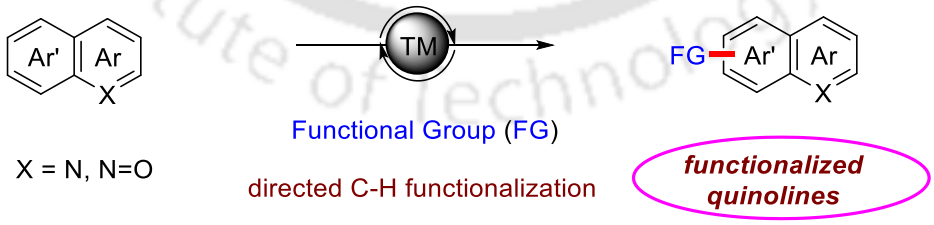
QN	quinoline
QNO	quinoline *N*-oxide
R_f	retardation factor
rt	room temperature
S_EAr	electrophilic aromatic substitution
t-AmOH	*tert*-amyl alcohol
t-BuOH	*tert*-butyl alcohol
TCE	trichloroethylene
TEMPO	2,2,6,6-tetramethylpiperidin-1-oxyl
THF	tetrahydrofuran
Tf	trifluoromethanesulfonyl
TFE	2,2,2-trifluoroethanol
TLC	thin layer chromatography
TM	transition metal
TMS	trimethylsilyl
TMSCN	trimethylsilyl cyanide
Ts	toluenesulfonyl
VCP	vinylcyclopropane
X-Phos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
μL	microliter
μW	microwatt

Abstract

The thesis is organized into four chapters. The initial chapter delineates a detailed analysis on C-H functionalization for the modification of quinoline under transition-metal-catalysis. The second chapter deals with C8-allylation of quinoline *N*-oxides (QNOs) using vinylcyclopropanes (VCPs) as allyl source under Rh-catalysis. The third chapter demonstrates a Co(III)-catalyzed site-selective C8-alkylation of quinolines *N*-oxides using cyclopropanols (Cyp) as the alkylating agent *via* C-H/C-C bond activation. The fourth chapter focuses on Pd(II)-catalyzed relay C-H activation of 8-methylquinoline *N*-oxides with maleimides resulted dual C(sp^3)–H/C7(sp^2)–H activation and annulation.

Chapter 1. Site-selective C-H Functionalization of Quinolines

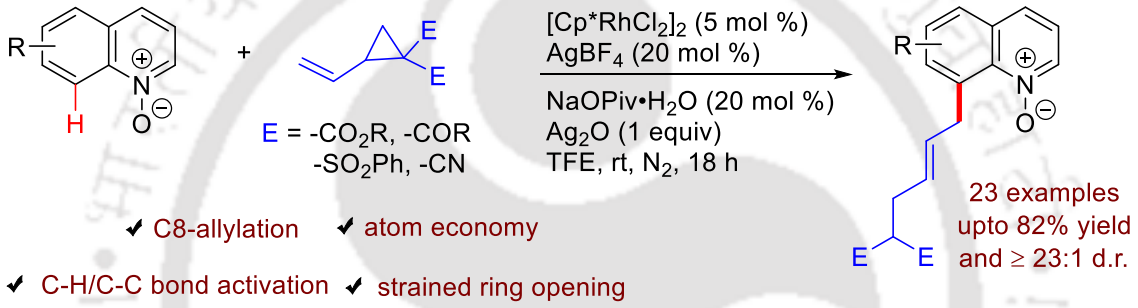
In recent decades, quinolines having a widespread occurrence in numerous bioactive molecules, has experienced the advancement on the functionalization through C-H bond functionalization. *N*-Heterocyclic quinoline scaffold encompasses seven distinctive C-H bonds for the functionalization among which the more acidic C2-H bond of the pyridine core has been explored considerably. While C3- and C4-selectivity and the functionalization of remote C-H bonds of the benzenoid nucleus (C5-C8) continues to be a synthetically challenging. Moreover, the methyl C(sp^3)-H bond of 8-methylquinoline provides C8-substituted quinoline derivative of remarkable pharmacological properties. This chapter covers the synthetic modification of quinolines through directing group (DG) assisted C-H functionalization. The potential future scopes are discussed as objectives which ultimately aids in identifying the thesis's goals (Scheme 1).



Scheme 1. Transition-Metal-Catalyzed C-H Functionalization of Quinolines

Chapter 2. C8-H Allylation of Quinoline *N*-Oxides with Vinylcyclopropanes

The C-H allylation offers a key C-C bonds forming reaction with diverse synthetic functional handle. These allylations sometimes face atom economy issues due to the loss of leaving group (LG). In this context, synthesis of 8-allylquinolines are very challenging, owing to its anti-hepatitis properties. Vinylcyclopropane (VCP) has just appeared as a promising allylating agent providing the atom- and step-saving route. Here, integration of C-H functionalization with challenging C-C cleavage has enabled the direct synthesis of 8-allylquinolines under Rh(III)-catalysis. The C8-allylation of quinoline proceeds at room temperature and uses *N*-oxides as DG (Scheme 2). The reaction encompasses of notable features including excellent *E/Z*-selectivities and cinchonidine alkaloid modification.



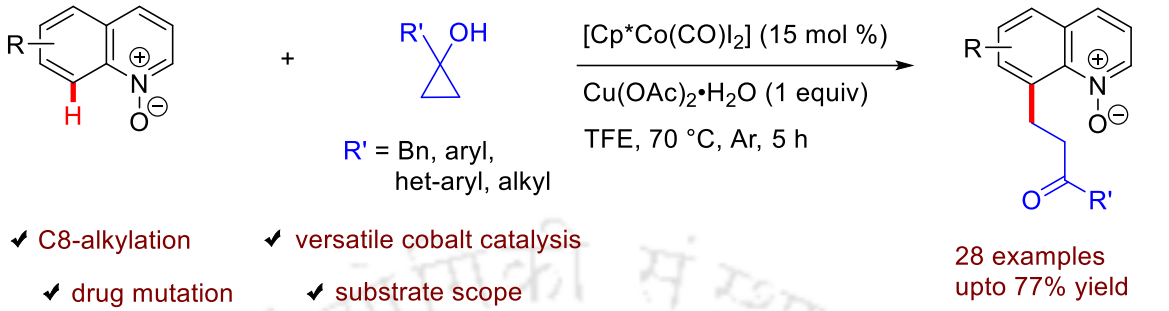
Chem. Commun. **2023**, *59*, 2823.

Scheme 2. Rh(III)-Catalyzed C8-Allylation of Quinolines

Chapter 3. C8-Alkylation of Quinolines with Cyclopropanols

Among the functionalization of less reactive C8-H bond of quinoline *N*-oxide, C8-alkylation has become the area of interest due to their potential applications. Over the period, alkylating coupling partners such as activated and un-activated alkenes, alkynes, carbenes etc. were realized in these alkylation studies. However, majority of these reactions have been performed employing rare 4d- and 5d-transition-metal-catalysts, whereas, the studies utilizing 3d-transition metals are still scarce. Owing to their high abundance, cost-effective and less hazardous nature, 3d-transition metals have been the first preference in C-H functionalization. Moreover, these metals provide the goal of achieving sustainability and promote novel reactivity in organic synthesis. In this context, the 3d-transition-metal-catalysts, particularly, high-valent Co-complex has been chosen as robust catalyst for the synthesis of C8-alkylated quinolines. In continuing our interest in C-H functionalization, cyclopropanol came out to be a unique alkyl source, *β*-aryl ketones as additional functional handle. Thus an efficient C8-alkylation of

quinoline *N*-oxides using cyclopropanols under Cp*Co(III)-catalysis has been reported (Scheme 3). The key advantages include mutation of natural products and drug molecules, site-selectivity and functional group tolerance.

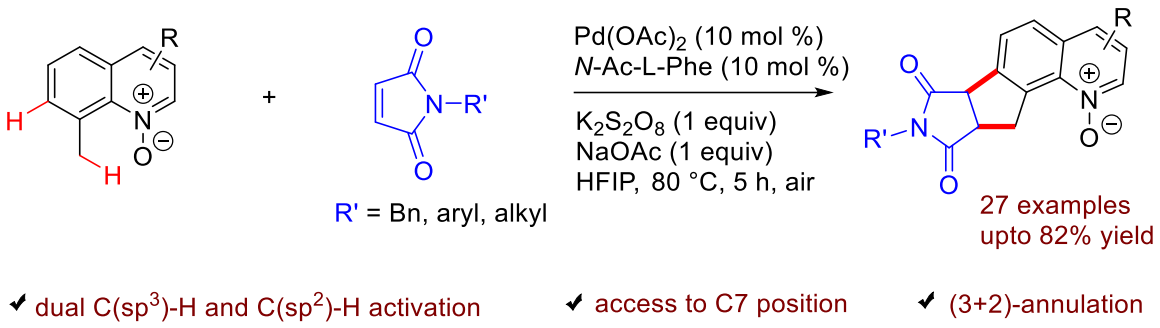


Org. Lett. **2023**, *25*, 7805.

Scheme 3. Co(III)-Catalyzed C8-Alkylation of Quinolines

Chapter 4. Dual C(sp^3)-H/C(sp^2)-H Functionalization of 8-Methylquinoline *N*-Oxides

Although significant progress on the functionalization of the C2-H and C8-H bonds of quinoline has been made, the studies toward the activation of C5-7-H bonds are still scarce. On the other hand, quinoline functionalization with a less reactive C(sp^3)-H bond, attracted significant attention. In this chapter, our goal is to access the C7-H bond *via* of quinoline relay C-H activation. It has been observed that C7-functionalization is hardly studied and to the best of our knowledge, no specific study was performed towards its selective functionalization with the aim of broad substrate scope. Herein, we have developed a dual C(sp^3)-H and C7-H bonds functionalization of 8-methylquinoline *N*-oxides using relaying coupling reactivity of maleimide (Scheme 4). Maleimides proved to be a versatile coupling partners in C-H functionalization/annulation with extensive applications in therapeutic sciences. The reaction sequence employs *N*-oxide as a weak chelating DG, in comparison with a strong chelating DG which facilitates the formation of the alkylation or Heck type product. The 2-fold C(sp^3)-H and C7(sp^2)-H functionalization and [3 + 2]-annulation are the notable features.



✔ dual C(sp^3)-H and C(sp^2)-H activation ✔ access to C7 position ✔ (3+2)-annulation

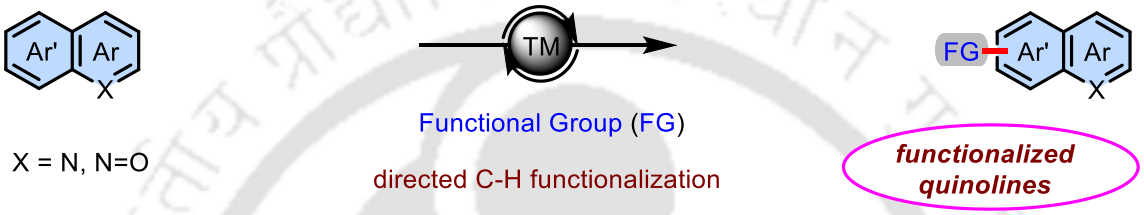
Org. Lett. **2024**, *26*, 7560.

Scheme 4. Pd(II)-Catalyzed Dual C-H Functionalization and Annulation of 8-Methylquinolines

Contents

Chapter 1

Site-selective C-H Functionalization of Quinolines



Site-selective C-H Functionalization of Quinolines

The versatile aza-heterocyclic scaffolds quinolines are most prevalent with their applications in natural products, functional materials and pharmaceuticals (Fig. 1).[1,2] Thus, the synthesis of quinolines and its derivatization is important in organic synthesis.[3] The traditional synthetic processes like Skraup, Friedländer, and Doebner-Miller use condensation strategies using amines and carbonyl compounds.[4]

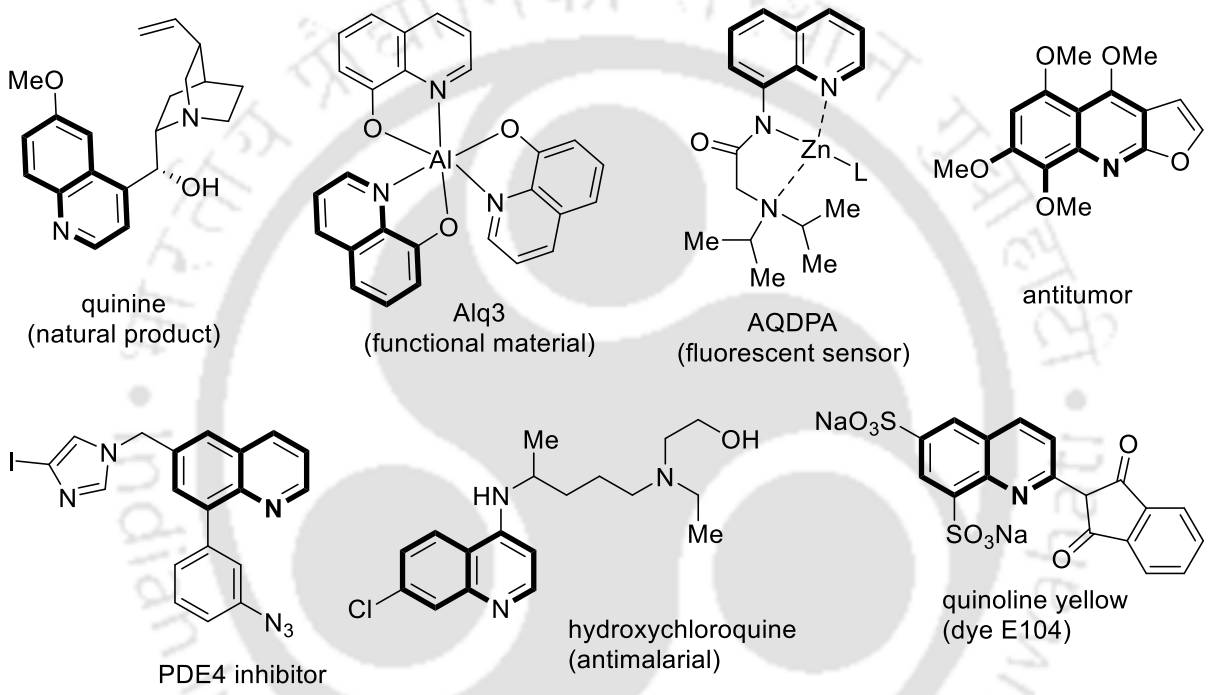


Figure 1. Representative Examples of Quinolines with their Diverse Applications

The major issues with these methods are generally substitution at unwanted position and harsh acidic reaction conditions. Electron-deficient nature of quinoline ring and the interaction of sp^2-hybridized nitrogen atom with electrophiles or Lewis acids often reduces reactivity towards the electrophilic aromatic substitution reactions (S_EAr). In addition, nucleophilic aromatic substitution reactions are unfavorable in presence of organo-lithium or -magnesium reagents, metal-halogen etc. which limit the functional group diversities.[5] Motivated by these challenges, organic community has made intensive efforts for the processes with high functional group compatibility. Therefore, the C-H functionalization concept is just appeared which does not require any pre-functionalized precursors, allowing both atom and step economy. Thus, the process has revolutionized the art of organic synthesis by performing straightforward complex

molecule synthesis from easily accessible feedstocks.[6] The quinoline scaffold contains seven distinctive C-H bonds (C2-C8) for functionalization. The inherent reactivity and more acidic nature of pyridinoid C2-H bond makes significant functionalization exploration.[7] However, the other pyridinoid (C3, C4) and benzenoid (C5-C7) C-H bonds are hardly studied.[8a] While, functionalization of the remote and less reactive C8-H bond of the benzenoid nucleus continues to be a challenging synthetic endeavor. In this regard, quinoline *N*-oxide came out as viable substrates for regio-selective introduction of various functional group at C8-position through its weak chelating *N*-oxide DG.[8b] Moreover, simple preparation and removal techniques with different reactivities of *N*-oxide, making this substrate exceptionally versatile. The quest for quinoline functionalization is not confined solely to sp^2 C-H bonds rather it has been extended to include methyl C(sp^3)-H bond of 8-methylquinolines for the derivatization,[9] providing array of C8-substituted quinoline derivatives. C8-Functionalized quinolines exhibit remarkable pharmacological activities, such as antimalarial, anti-hepatitis, and antibacterial properties.[2] Following wide therapeutic potential and distinct physicochemical properties of functionalized quinolines, this chapter discusses their preparation via DG assisted C-H bond functionalization.

1.1 Literature Study

As previously mentioned, functionalization of the quinoline scaffolds are crucial considering their broad applications. Therefore, it is essential to know about the previous advancements. As per the literature,[8] site-selective C-H functionalization strategies for C2-C7 positions of quinoline have been represented in Figure 2. We will discuss the achievements using these strategies in the rest of this chapter.

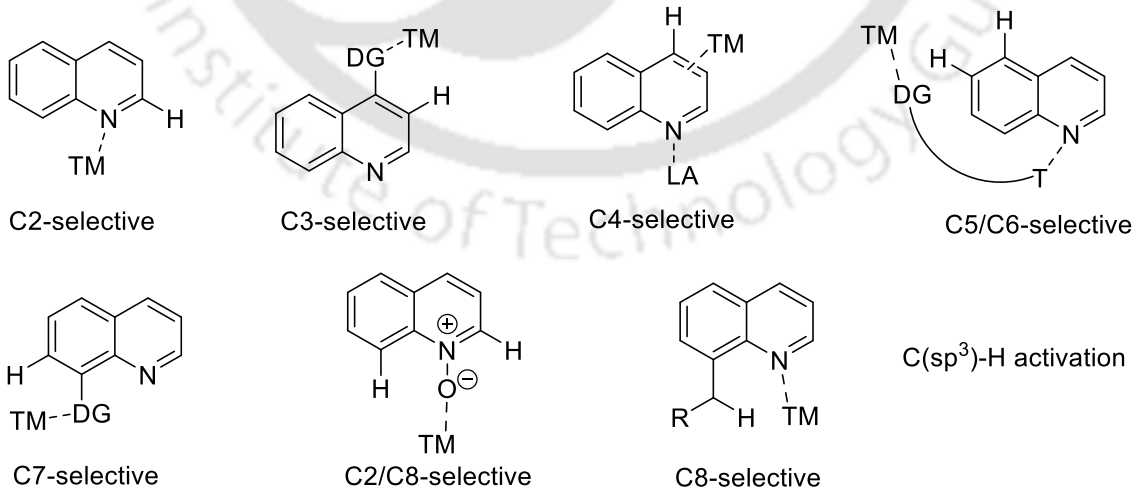
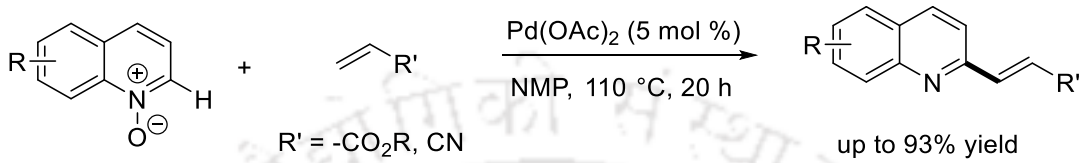


Figure 2. Key Intermediates in Quinolines C-H Functionalization

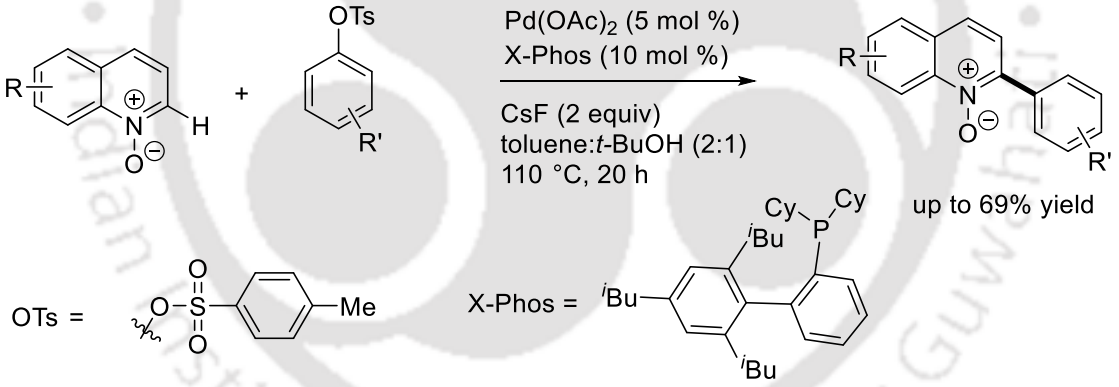
1.1.1 C(sp^2)-H Functionalization of Quinolines

In 2009, Cui and Wu proposed a Pd(II)-catalyzed alkenylation of quinoline *N*-oxides with acrylates under redox neutral conditions (Scheme 1).[10] According to the authors hypothesis, *N*-oxide moiety may act as both a DG and an oxidant. The substrate scope variations revealed electron rich quinoline *N*-oxides were well tolerated while the presence of strong electron withdrawing nitro group in the quinoline gave no reactions.



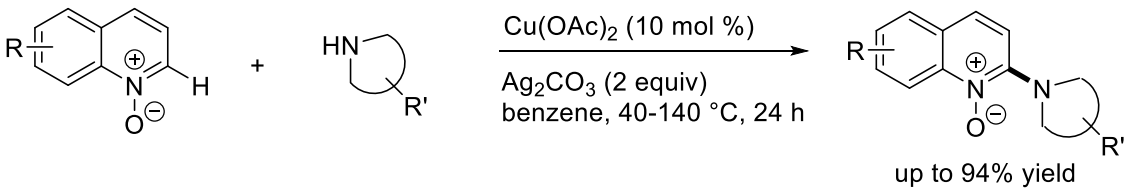
Scheme 1. Pd(II)-Catalyzed C2-Alkenylation of Quinoline *N*-Oxides

Ackermann group reported the Pd-catalyzed direct C2-arylation of quinolines using aryl tosylates as aryl source (Scheme 2).[11] The screening of ligands, bases, solvent systems and additives emphasized the crucial role of X-Phos and CsF in a *t*-BuOH/toluene (2:1) mixture. The selective C2-arylation was achieved in good to moderate yields.



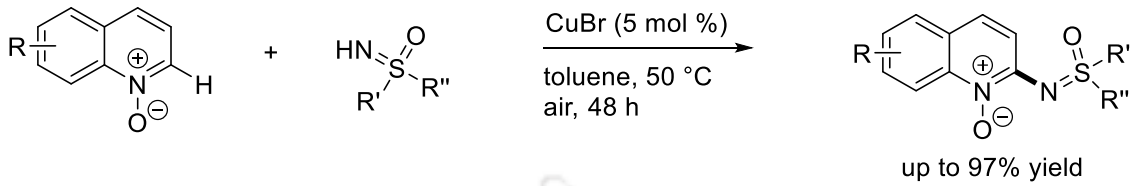
Scheme 2. Pd (II)-Catalyzed C2-Arylation

Li and co-workers described a copper-catalyzed C2-amination/amidation of QNOs with lactams/cyclic amines (Scheme 3).[12] Besides the quinoline scope, the reaction was investigated with various size of lactams for amidation. Moreover, cyclic amines such as piperidine, pyrrolidine, morpholine and piperazine were exhibited excellent reactivities.



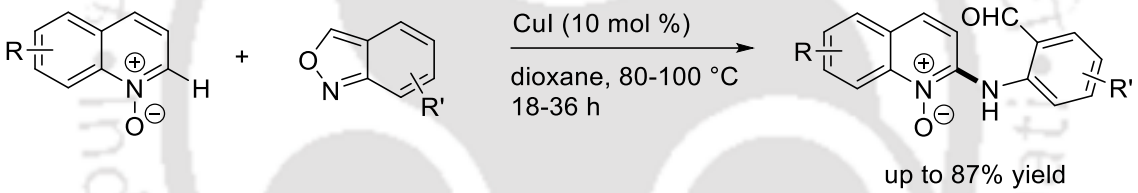
Scheme 3. Copper Catalyzed C2-Amination/Amidation of QNOs

Bolm and co-workers described the copper-catalyzed direct sulfoximination of quinoline *N*-oxides through C-H/N-H dehydrogenative coupling with sulfoximines (Scheme 4).[13] The QNOs, irrespective of substituents at neighboring carbons, produced excellent yields, showing that the substitution pattern, electronic effects or bulky substituents had no significant effect.



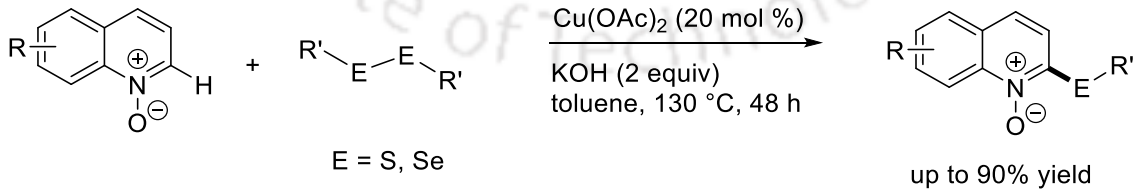
Scheme 4. C2-Sulfoximination of Quinoline *N*-oxides under Cu-Catalysis

Samanta group reported a redox neutral copper-catalyzed C2-arylamination utilizing anthranils as a coupling partner (Scheme 5).[14] The sensitive acetal group was cleaved to produce the targeted product, generating an additional aldehyde functional group for further functionalization. In the post-synthetic-modifications authors achieved several important *N*-heterocyclic scaffolds.



Scheme 5. C2-Arylamination of Quinoline *N*-oxides with Anthranils

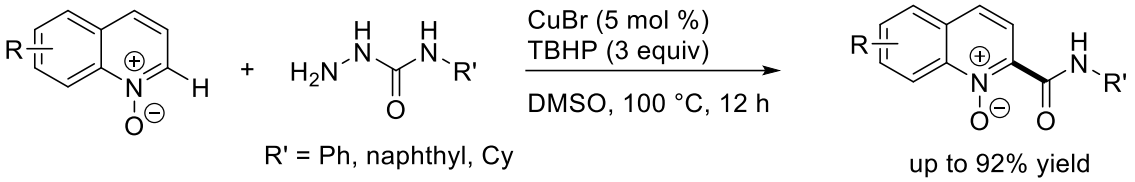
A C2-selective thiolation of QNOs was observed under the Cu-catalysis using bisulfides (Scheme 6).[15] Scope of the reaction was studied with various QNOs and disulfides, furnishing moderate to good yields. Moreover, the reaction scope was extended to selenylation using diphenyl and dimethyl diselenide, producing the products in 90% and 60% yields, respectively.



Scheme 6. C2-Thiolation and Selenylation of QNOs under Cu(II)-Catalysis

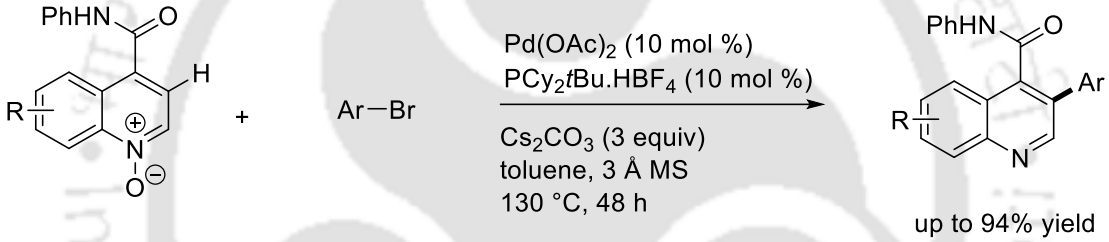
Wang group reported the copper-catalyzed C2-carbamoylation of QNOs employing hydrazinecarboxamides as a coupling partner (Scheme 7).[16] The protocol was suitable over a series of *N*-phenyl hydrazinecarboxamides along with *N*-cyclohexyl and *N*-naphthyl

substituents. The mechanistic investigation infers that a radical intermediate might be formed with the assistance of TBHP.



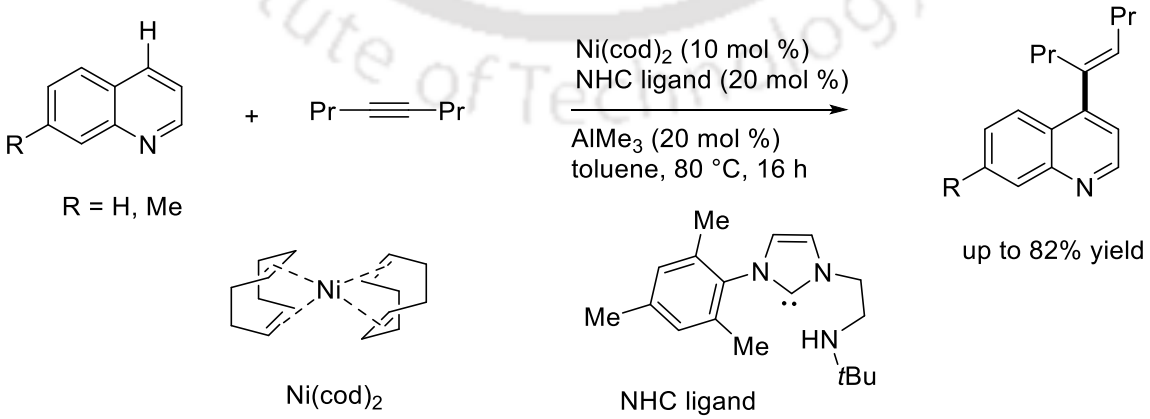
Scheme 7. Cu(II)-Catalyzed C2-Carbamoylation of QNOs with Hydrazinecarboxamides

An amide DG assisted C3-H arylation of quinolines under Pd(II)-catalysis have been reported (Scheme 8).[17] Following its optimization for the pyridine substrate, the process was extended to the quinoline substrates where it produced exclusive C3-arylation. Control studies revealed that an aryl bromide with ortho substitution and absence of DG at the C4 position produced no result.



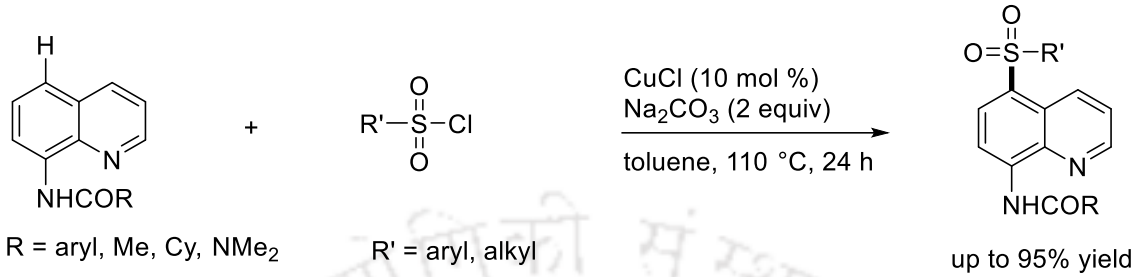
Scheme 8. Pd-Catalyzed DG Assisted C3-Arylation with Aryl Bromides

Ong's group reported a bimetallic Ni-$AlMe_3$ system for the C4-alkenylation of pyridines and quinolines (Scheme 9).[18] This method offers remote *para* C-H functionalization using cooperative interaction between Ni and Al, showcasing reactivity and selectivity of bimetallic catalysis.



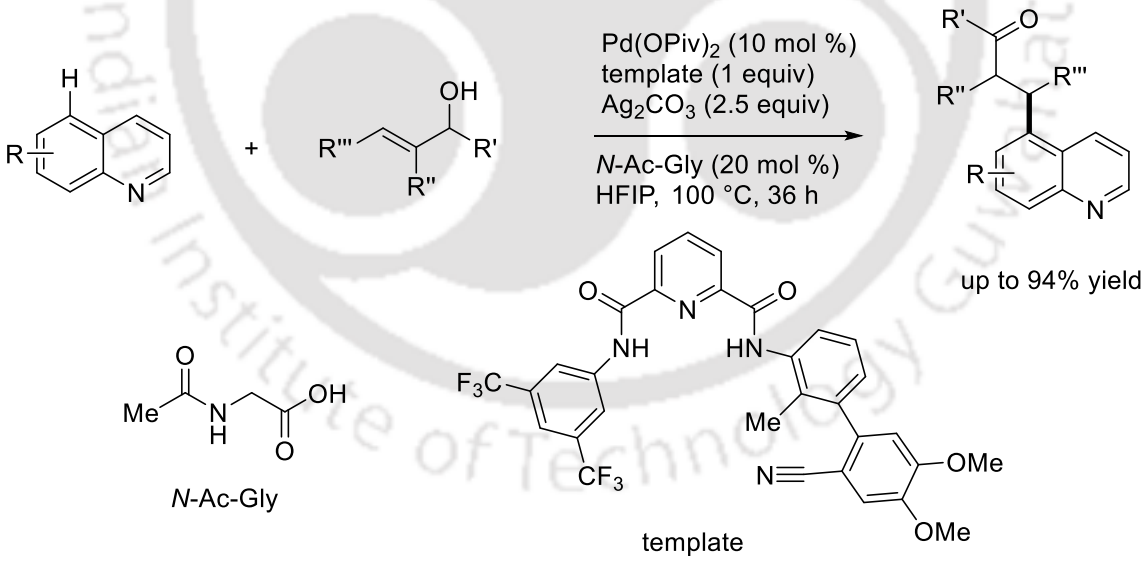
Scheme 9. Bimetallic Ni/Al-Catalyzed LA-Assisted C4-Alkenylation

A Cu(I)-catalyzed C5-sulfonylation of quinoline was achieved by Wei and co-workers (Scheme 10).[19] The authors employ 8-aminoquinolines and aryl sulfonyl chloride as the substrates for the desired C5-H functionalization. The substrate scope was tolerated with excellent regio-selectivity.



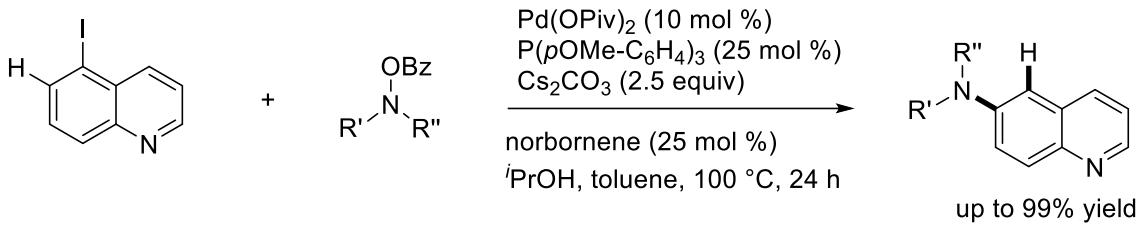
Scheme 10. Cu-Catalyzed C5-Sulfonylation of Quinolines with Arylsulfonyl Chlorides

Maiti and co-workers developed template assisted C5-alkylation of quinolines using allylic alcohols as the coupling partner under Pd(II)-catalysis (Scheme 11).[20] A careful optimization of ligands and templates was required to improve the selectivity and efficiency towards the C5-alkylation. The scope of the reaction was extended to various quinolines and allyl alcohols, led to desired products in moderate to good yields.



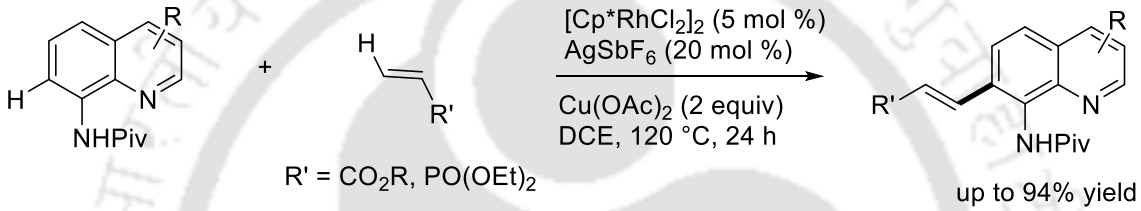
Scheme 11. TDG-Assisted C5-Alkylation of Quinolines with Allyl Alcohols

Dong and co-workers used 5-iodoquinoline as a substrate to demonstrate C6-amination under Pd/norbornene co-operative catalysis (Scheme 12).[21] The reaction conditions rely on robust engineering catalytic systems to ensure precise and superior reactivity.



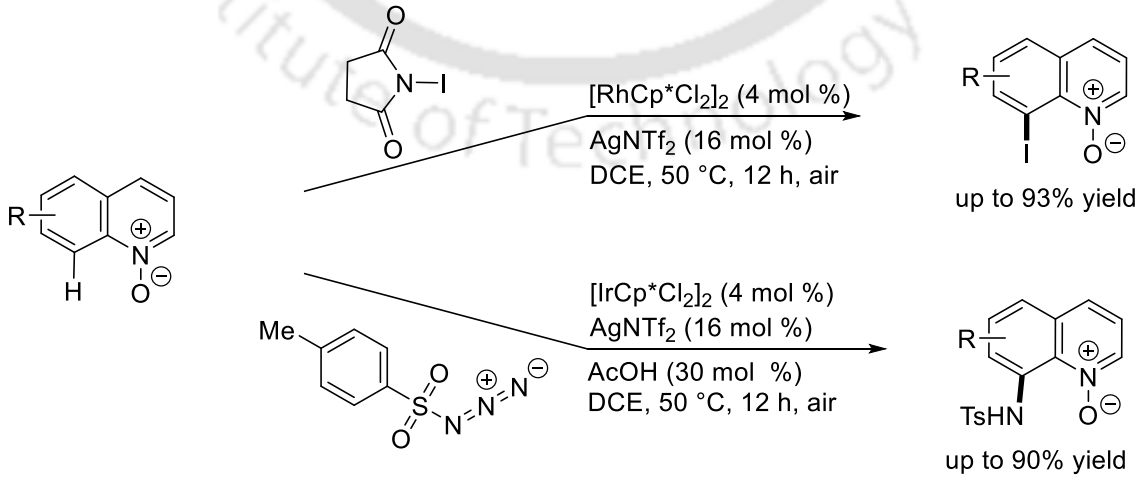
Scheme 12. Pd(II)-Catalyzed C6-amination of 5-Iodoquinoline with *N*-Benzoyloxyamines

Shi and co-workers developed a Rh(III)-catalyzed NHPiv-assisted C7-olefination of quinolines (Scheme 13).[22] This study is not specifically implemented the C7-functionalization. However, the authors accomplished an alternative route to achieve this selectivity by installing a DG at C8 position.



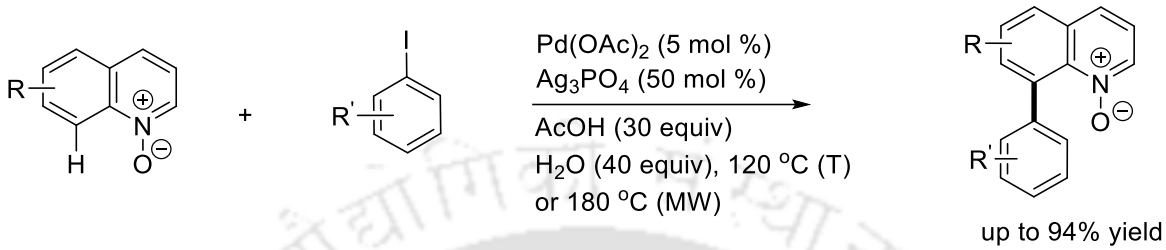
Scheme 13. DG-Assisted C7-Alkenylation of Quinolines under Rh-Catalysis

A very early research on quinoline functionalization by Chang group, where the team introduced iodine and sulfonamide group at C8-position using *N*-iodosuccinimide and aryl sulfonyl azides as the coupling sources, respectively (Scheme 14).[23] Interestingly, iodination occurred under Rh-catalysis whereas, sulfonamidation is under Ir-catalysis. Use of *N*-oxide as DG resulted excellent C8 regio-selectivity.



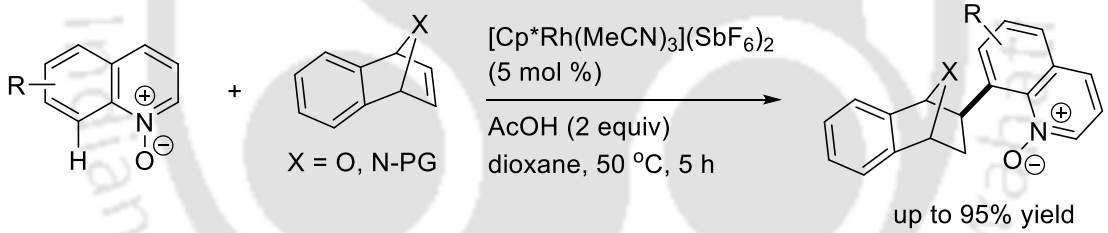
Scheme 14. Regio-selective Iodination and Sulfonamidation of Quinoline *N*-Oxides

Later, Larionov and co-workers reported the Pd(II)-catalyzed C8-arylation of quinoline *N*-oxides with iodoarenes (Scheme 15).[24] The reaction exhibited a broad synthetic scope and led to the formation of diversely substituted 8-arylquinolines. The author displayed this reaction under microwave irradiation (μW) at 180 °C, where it improves the reaction completion time which is just less than an hour.



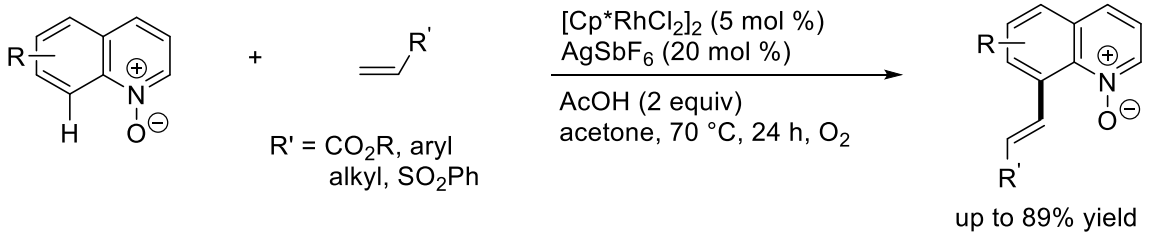
Scheme 15. C8-Arylation of QNOs with Aryl Iodides under Pd(II)-Catalysis

Recently, Liu and co-workers developed a Rh(III)-catalyzed C8-hydroarylation of quinoline *N*-oxide using oxa-/aza-benzo-norbornadienes as coupling partner (Scheme 16).[25] The protocol suited for broad range of QNOs to produce heterobicyclic core retained hydroarylated scaffolds. The authors introduced the method for one-step synthesis of epibatidine analogues.



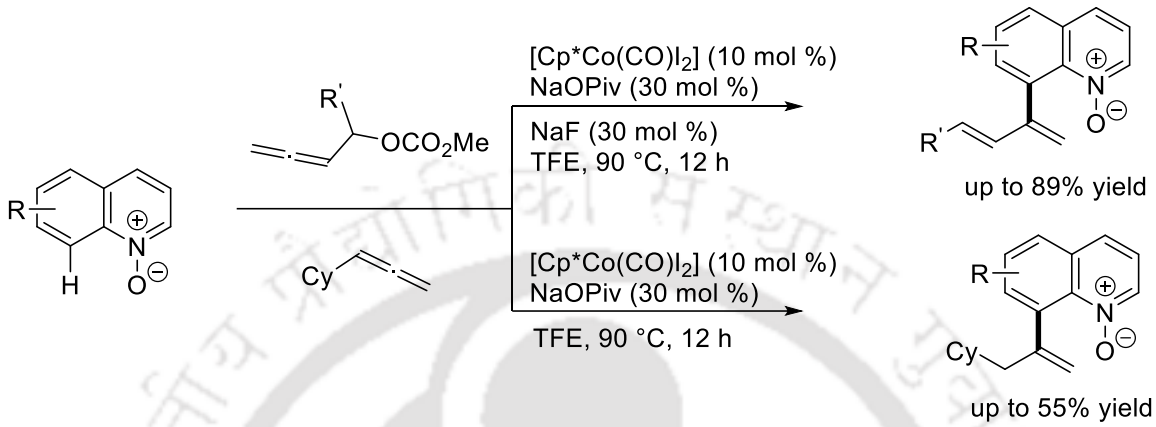
Scheme 16. Rh-Catalyzed C8-Hydroarylation of QNOs

Sharma and co-workers reported C8-alkenylation of QNO with both the activated and un-activated olefins under Rh(III) catalysis (Scheme 17).[26] The reaction uses molecular oxygen as sole oxidant, eliminating the need of external oxidant.



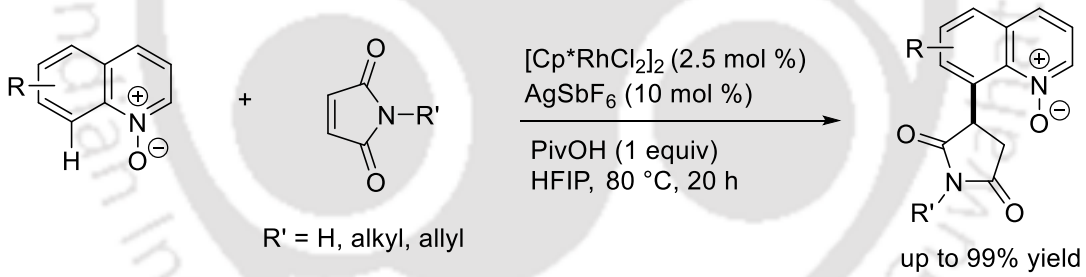
Scheme 17. Rh/O_2-Catalyzed C8-Olefination of Quinoline *N*-Oxides

Volla and co-workers introduced allenes as the coupling partner for dienylation with QNOs under Co(III)-catalysis (Scheme 18).[27] The allene moiety was equipped with a carbonate leaving group which plays a crucial role in determining this as dienylating agent. For example, the alkenylated product was formed with cyclohexyl-substituted allene substrates as shown in the scheme.



Scheme 18. C8-Dienylation and -Alkenylation of QNOs with Allenes

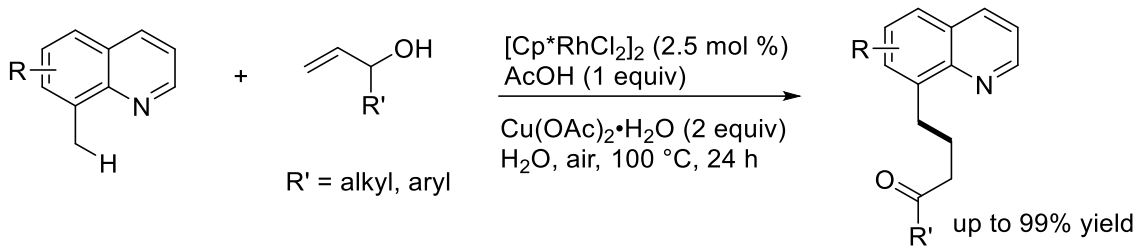
Kim and co-workers reported C8-alkylation of QNOs with maleimides under Rh-catalysis (Scheme 19).[28] The reaction was compatible with broad range QNO and maleimide derivatives.



Scheme 19. C8-Alkylation of QNOs with Maleimides under Rh(III)-Catalysis

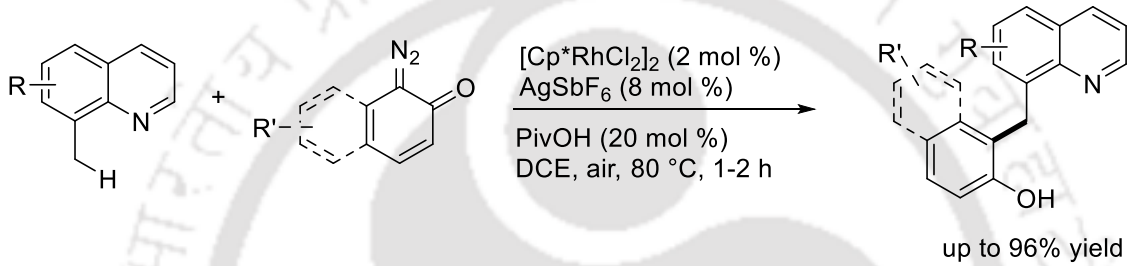
1.1.2 C(sp^3)-H Functionalization of 8-Methylquinolines

Kim and co-workers achieved C(sp^3)-H alkylation of 8-methylquinolines with allylic alcohols as alkylating agent (Scheme 20).[29] The reaction achieved a significant movement toward a greener approach by utilizing water as reaction medium under Rh-catalysis. The reaction proceeded with a variety of α-substituted allylic alcohols, delivering a series of γ-quinolinyl carbonyl derivatives.



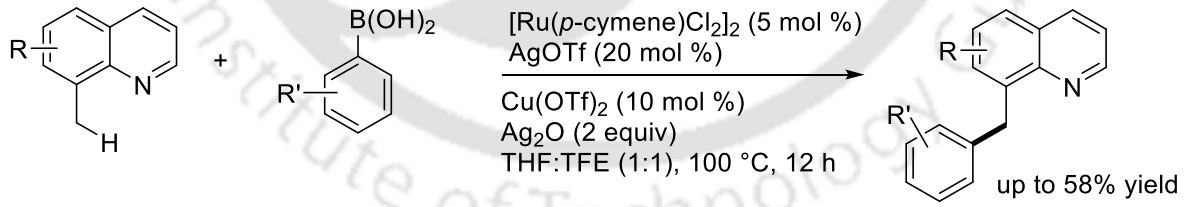
Scheme 20. Rh(III)-Catalyzed C(sp^3)-H Alkylation of 8-Methylquinoline

Samanta and co-workers disclosed direct C(sp^3)-H arylation of 8-methylquinolines under Rh(III)-catalysis (Scheme 21).[30] The reaction showcases a series of *β*-naphthol-coupled products with functional group tolerance. The authors synthesized biologically important cannabinoid CB1 receptor ligand from the obtained product.



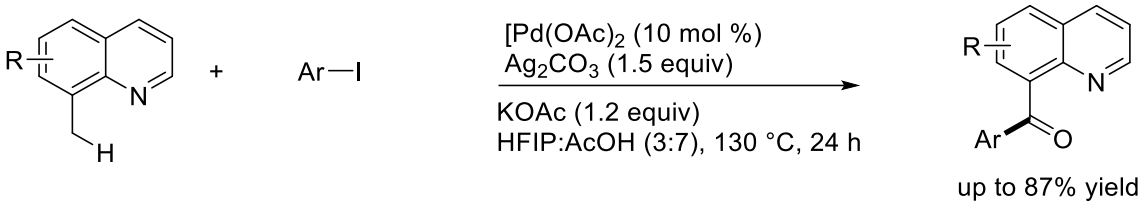
Scheme 21. C(sp^3)-H Arylation of 8-Methylquinoline with Diazo Compounds

Sharma group developed the Ru(II)-catalyzed arylation of 8-methylquinoline with boronic acid as a coupling partner (Scheme 22).[31] Selective monoarylation, gram scale preparation and post modification such as reduction, oxidation, secondary C(sp^3) arylation and amidation are the important features.



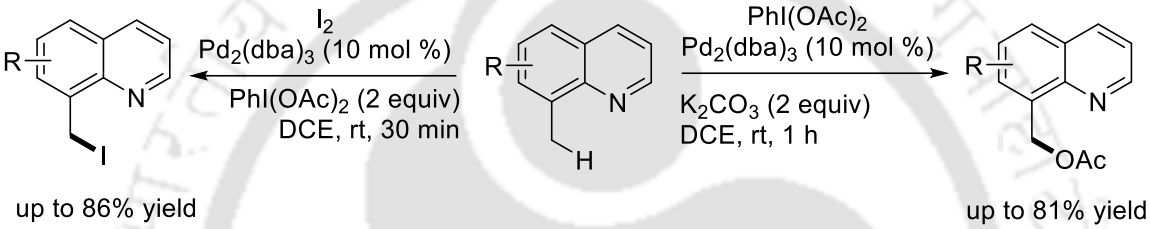
Scheme 22. Ru(II)-Catalyzed C(sp^3)-H Arylation of 8-Methylquinolines

Wang group described the Pd-catalyzed C(sp^3)-H benzoylation of 8-methylquinolines (Scheme 23).[32] The reaction exhibited a broad substrate scope and high functional group tolerance. The mechanistic experiments revealed that the reaction proceeds *via* formation of 8-benzylquinoline intermediate followed by benzyl oxidation. Oxygen incorporation into the products was originated from the water present in the reaction media.



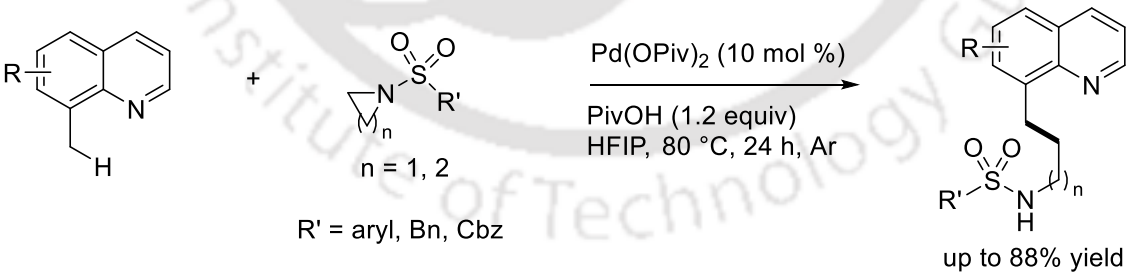
Scheme 23. Pd(II)-Catalyzed Benzoylation of 8-Methylquinolines with Aryl Iodides

Jia group reported a reagent-controlled C(sp^3)-H iodination and acetoxylation of 8-methylquinolines with I_2 and $PhI(OAc)_2$, respectively, under palladium-catalysis at room temperature (Scheme 24).[33] The reaction featured mild reaction condition with excellent functional group tolerance.



Scheme 24. Reagent-controlled C(sp^3)-H Iodination and Acetoxylation of 8-Methylquinoline

Recently, our group showed the Pd(II)-catalyzed C(sp^3)-H alkylation of 8-methylquinolines with aziridines as the alkylating source (Scheme 25).[34] The reaction proceeds *via* a sequential C-H and C-N bond functionalization to furnish γ-quinolinylpropylamines as final product. Overall, the reaction shows excellent site-selectivity and high functional group tolerance.



Scheme 25. C(sp^3)-H Alkylation of 8-Methylquinoline with Aziridines

1.2 Objective of the Thesis

Transition-metal-catalyzed site-selective C-H functionalization of quinoline scaffolds are the burgeoning field of research. Here in this chapter, we have discussed a brief and compact literature study on quinoline derivatization through C-H functionalization strategy. However, there are many useful and important articles on the quinoline modifications are present. In spite

of these advancements, there are still synthetic challenges and gaps that could lead to further research in this evolving area.

The following objectives of the thesis are listed below,

- The DG-guided C-H functionalization at the beyond C2-positions of quinolines are formidable challenge in catalytic synthetic transformation, which can be explored.
- Use of *N*-oxide as DG can help in many aspects such as easily removable, can be converted into other functional group and can act as traceless DG.
- The C-H functionalization with concomitant C-C activation is attracted great interest of research in terms of atom- and step-economy. In this view, small strained ring systems can be exploited to achieve the goal.
- The sequential C-H functionalization is not great in terms of sustainability due to consuming more time and chemicals. The C-H functionalization and annulation cascade reactions are significant approach for this purpose which can produce valuable polycyclic scaffolds.
- C6 and C7 are considered as an orphan position for the functionalization. However, with the help of a C8-DG, C7 position can be functionalized like *ortho*-C-H functionalization. In this scenario, accessing C7 position without installing DG at C8 position is a challenge and can be discussed.

1.3 References

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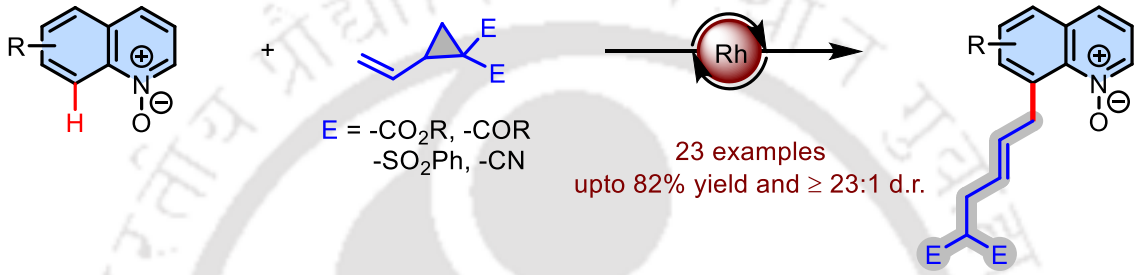
Chapter 2

C8-H Allylation of Quinoline N-Oxides with Vinylcyclopropanes



✔ C8-allylation ✔ atom economy ✔ C-H/C-C bond activation ✔ strained ring opening

Chem. Commun. **2023**, *59*, 2823.

C8-H Allylation of Quinoline *N*-Oxides with Vinylcyclopropanes

Over the past few years, quinoline core modification has been a great research interest due to its presence in a variety of functional molecules.[1] In this vein, transition-metal-catalyzed regio-selective C8-H functionalization of quinoline *N*-oxides has been demonstrated using *N*-oxide as DG.[2] Among the functionalization, allylation is a key C-C bond forming reactions as its effective modifications provide diverse synthetic applications.[3] Although, after Tsuji-Trost allylation reactions,[3a] there are numerous studies have been performed to achieve the allylation but majority of these methods comes under nucleophilic substitution reactions. Atom economy stands as the primary concern in these allylation reactions because of the loss of leaving group during the process. In this context, vinylcyclopropane (VCP), containing an olefin moiety and cyclopropane ring has played a pivotal role in synthetic organic chemistry by delivering allylated product in an atom economical way.[4] Catalytic ring opening of this 3-membered cyclopropane ring through C-C bond cleavage allows the method for maintaining atom economy. Recently, integration of C-H activation with challenging C-C cleavage created significant interest, taking advantage of multifold reactivities of these strain ring systems.[5] We thought of allylation of quinoline N-oxide knowing the fact that 8-allylquinoline has a strong effect on the treatment of hepatitis (Fig 1). Thus, development in the direct synthesis of 8-allylquinolines would be highly desirable.

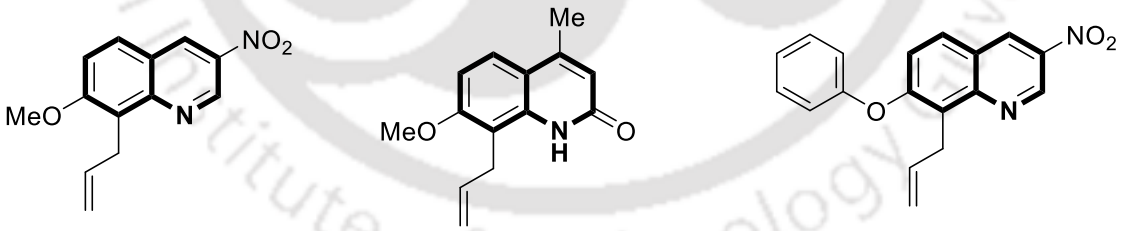
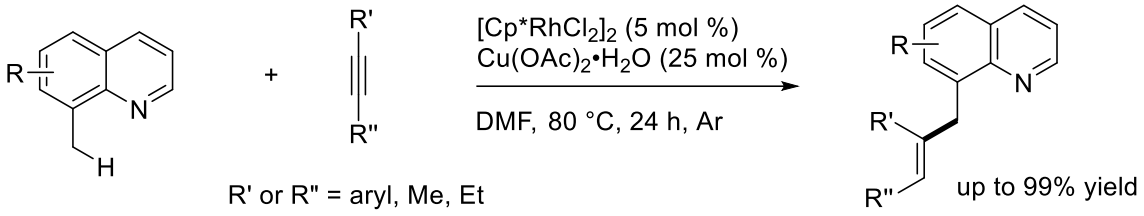


Figure 1. C8-Allylquinoline Derivatives with Hepatoprotective Effect

2.1 Literature Study

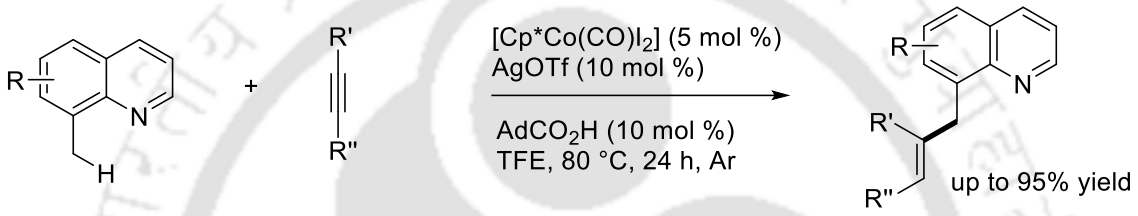
2.1.1 Synthesis of 8-Allylated Quinolines

Wang and co-workers reported C(sp^3)-H alkenylation of 8-methylquinolines with internal alkynes under Rh(III)-catalysis (Scheme 1).[6] The product is 8-allylquinoline which was found with excellent regio- and chemo-selectivities.



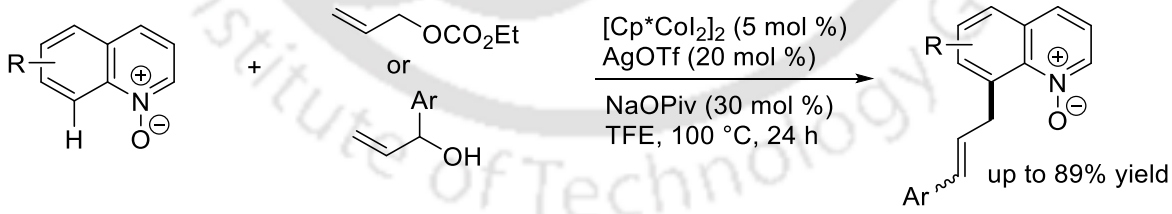
Scheme 1. C(sp^3)-H Alkenylation of 8-Methylquinolines with Internal Alkynes

Following the earlier work on C-H alkenylation of 8-methylquinolines with internal alkynes, Sundararaju and co-workers disclosed the same functionalization under less-toxic and more abundant Co(III)-catalysis (Scheme 2).[7] The authors have suggested that the reaction goes *via* base-assisted concerted metalation deprotonation (CMD) pathway.



Scheme 2. Co(III)-Catalyzed C(sp^3)-H Alkenylation of 8-Methylquinolines

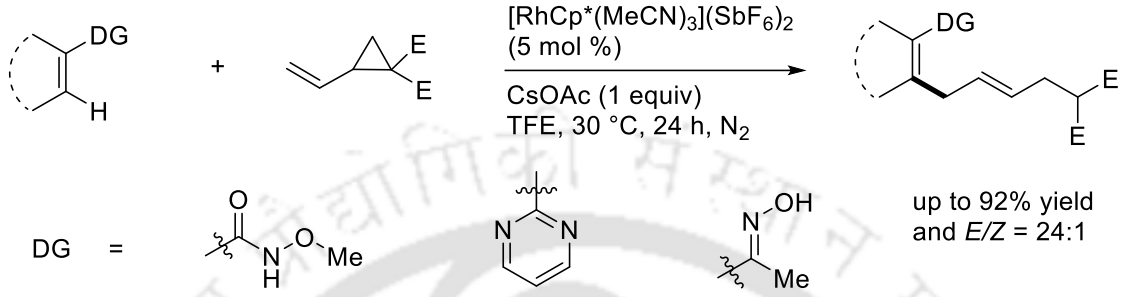
The same group reported C8-allylation of quinoline *N*-oxides using allyl carbonates or alcohols as the coupling partner under versatile Co(III)-catalysis (Scheme 3).[8] The reaction was compatible with good functional group tolerance at oxidant-free condition. Control study confirms that *β*-oxygen elimination is the key step to obtain allylated product in good to moderate yield.



Scheme 3. C8-Allylation of QNOs using Allyl Carbonates or Alcohols

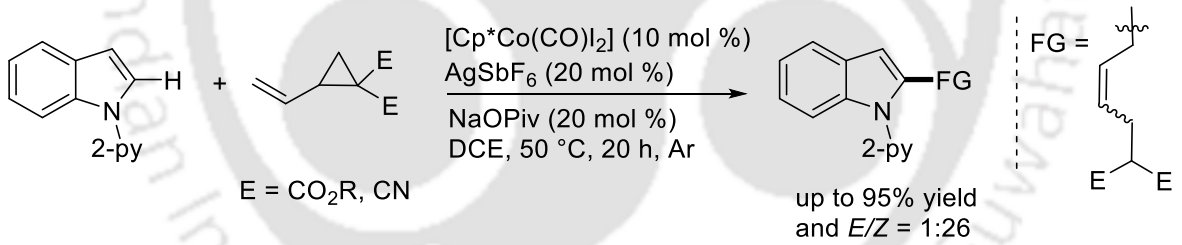
2.1.2 Vinylcyclopropane in C-H Functionalization

Wang and co-workers demonstrated allylation reaction using vinylcyclopropanes as a coupling partners *via* sequential C-H/C-C functionalization (Scheme 4).[9] The reaction sequence offers a practical route for the synthesis of allylated arenes. The reaction features excellent substrate scope and stereoselectivity with high yield.



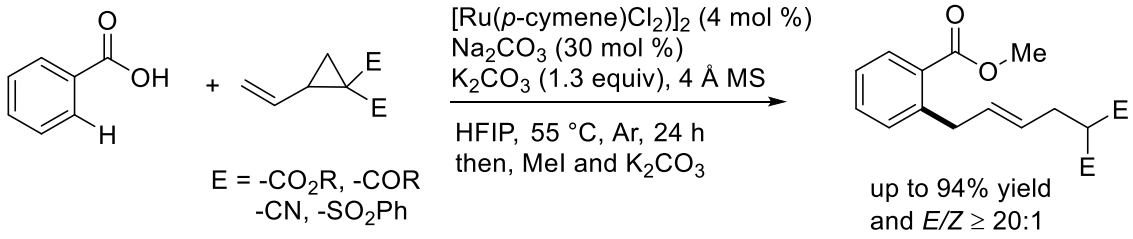
Scheme 4. DG Assisted C-H Allylation under Rh(III)-Catalysis

Later, Ackermann group developed cobalt-catalyzed C2-H allylation of indole *via* C-H/C-C functionalization with unique selectivity features (Scheme 5).[10] The efficacy of the cobalt catalyst was experienced through broad substrate scope, efficient C-H/C-C cleavage at room temperature, and less stable *Z*-selective alkenes.



Scheme 5. Co(III)-Catalyzed *Z*-Selective C2-H Allylation of Indoles

Gooßen and co-workers accomplished *ortho*-C-H allylation of aromatic acids with vinylcyclopropanes under Ru-catalysis (Scheme 6).[11] The authors studied a wide range of substrates scope with moderate to high yields and good *E/Z*-selectivities. Synthesis of *iso*-coumarin and 3,4-dihydroisocoumarin derivatives have been studied in the synthetic utility.

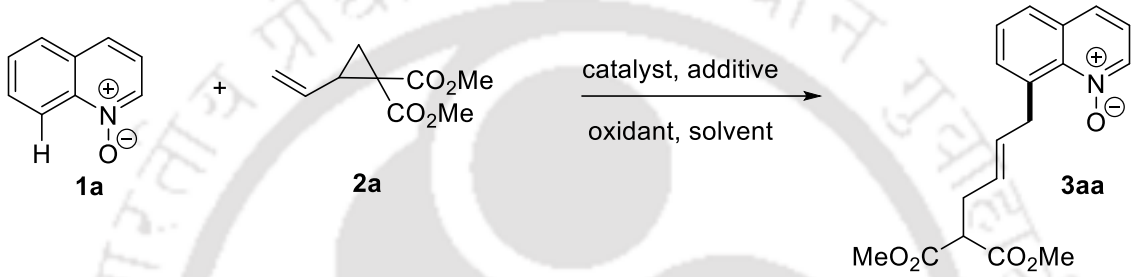


Scheme 6. *ortho*-C-H Allylation of Benzoic Acids with Vinylcyclopropanes

2.2 Present Study

Herein, we present Rh(III)-catalyzed C8-allylation of quinoline *N*-oxides with vinylcyclopropanes *via* a sequential C-H/C-C activation. Initially, the optimization studies began with quinoline *N*-oxide **1a** and dimethyl 2-vinylcyclopropane-1,1-dicarboxylate **2a** as the standard substrates in presence of various catalysts, oxidants, additives and solvents (Table 1). Delightedly, the C8-allyl product **3aa** was formed in 78% yield with 16:1 *E/Z*-selectivity

Table 1. Optimization of the Reaction Condition[a]



Entry	Catalyst system	Additive	Oxidant	Solvent	Yield (%)[b]	*E/Z*[c]
1	$[RhCp^*Cl_2]_2$/ $AgBF_4$	-	-	TFE	25	4:1
2	$[RhCp^*Cl_2]_2$/ $AgBF_4$	AcOH	-	TFE	n.d.	-
3	$[RhCp^*Cl_2]_2$/ $AgBF_4$	PivOH	-	TFE	22	6:1
4	$[RhCp^*Cl_2]_2$/ $AgBF_4$	AgOAc	-	TFE	45	11:1
5	$[RhCp^*Cl_2]_2$/$AgBF_4$	NaOAc	-	TFE	36	8:1
6	$[RhCp^*Cl_2]_2$/ $AgBF_4$	CsOAC	-	TFE	38	10:1
7	$[RhCp^*Cl_2]_2$/ $AgBF_4$	NaOPiv•H_2O	-	TFE	49	16:1
8	$[RhCp^*Cl_2]_2$/ $AgBF_4$	CsOPiv	-	TFE	12	5:1
9	**$[RhCp^*Cl_2]_2$/ $AgBF_4$**	**NaOPiv•H_2O**	**Ag_2O**	**TFE**	**78**	**16:1**
10	$[RhCp^*Cl_2]_2$/ $AgBF_4$	NaOPiv•H_2O	Ag_2CO_3	TFE	33	10:1
11	$[RhCp^*Cl_2]_2$/ $AgBF_4$	NaOPiv•H_2O	$Cu(OAc)_2$•H_2O	TFE	28	7:1

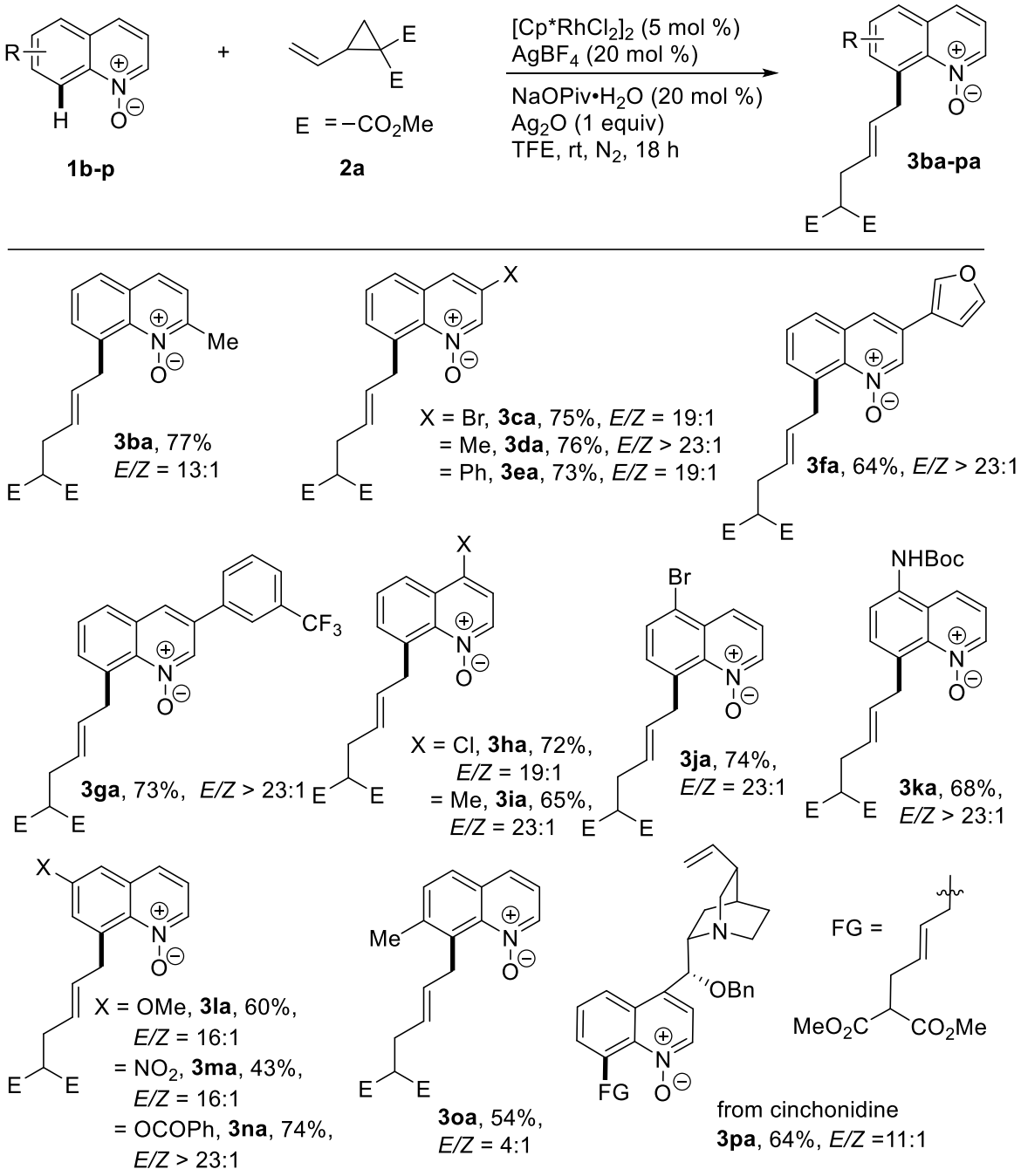
12	$[RhCp^*Cl_2]_2$/ $AgBF_4$	$NaOPiv•H_2O$	Cu_2O	TFE	30	4:1
13	$[RhCp^*Cl_2]_2$/ $AgBF_4$	$NaOPiv•H_2O$	O_2	TFE	45	3:1
14	$[RhCp^*Cl_2]_2$/ $AgSbF_6$	$NaOPiv•H_2O$	Ag_2O	TFE	63	16:1
15	$[RhCp^*Cl_2]_2$/ $AgNTf_2$	$NaOPiv•H_2O$	Ag_2O	TFE	65	8:1
16	$[RhCp^*Cl_2]_2$/ $AgBF_4$	$NaOPiv•H_2O$	Ag_2O	EtOH	trace	-
17	$[RhCp^*Cl_2]_2$/ $AgBF_4$	$NaOPiv•H_2O$	Ag_2O	HFIP	trace	-
18	$[RhCp^*Cl_2]_2$/ $AgBF_4$	$NaOPiv•H_2O$	Ag_2O	THF	trace	-
19	$[RhCp^*Cl_2]_2$/ $AgBF_4$	$NaOPiv•H_2O$	Ag_2O	toluene	n.d.	-
20	$[RhCp^*Cl_2]_2$/ $AgBF_4$	$NaOPiv•H_2O$	Ag_2O	DCE	trace	-
21[d]	$[RhCp^*Cl_2]_2$/ $AgBF_4$	$NaOPiv•H_2O$	Ag_2O	TFE	43	16:1
22[e]	$[RhCp^*Cl_2]_2$/ $AgBF_4$	$NaOPiv•H_2O$	Ag_2O	TFE	60	16:1
23[f]	$[RhCp^*Cl_2]_2$/ $AgBF_4$	$NaOPiv•H_2O$	Ag_2O	TFE	59	12:1

[a]Reaction condition: **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst (5 mol %) and silver source (20 mol %), additive (20 mol %), oxidant (0.2 mmol), solvent (1 mL), rt, N_2, 18 h. [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]24 h reaction time. [e]16 h reaction time. [f]50 °C temp. n.d. = not detected.

with reaction condition 5 mol % $[Cp^*RhCl_2]_2$, 20 mol % $AgBF_4$, 20 mol % $NaOPiv•H_2O$ and 1 equiv Ag_2O in TFE for 18 h at room temperature under a nitrogen atmosphere (entry 9, Table 1). Among the additives screened, $NaOPiv•H_2O$, AcOH, PivOH, NaOAc and CsOAc, the former gave the best result. Ag_2O was superior from the screened oxidant Ag_2CO_3, $Cu(OAc)_2•H_2O$, Cu_2O and O_2. The preferred solvent was TFE, surpassing $(CH_2Cl_2)_2$, HFIP, EtOH, THF and toluene, which produce inferior results. The combination of Rh-catalyst, additive and oxidant was essential for the high yields and superior *E*-selectivity, as demonstrated by control studies.

With the optimal reaction conditions, the scope of the reaction was investigated with substituted quinoline *N*-oxides **1b**-**p** and VCP **2a** as the model substrates (Table 2). First, the reaction of VCP **2a** with 2-Methylquinoline *N*-oxide **1b** afforded allylated product **3ba** in 77% yield and 13:1 *E/Z*-ratio. The reactions of quinoline *N*-oxides with 3-bromo **1c**, 3-methyl **1d**

Table 2. Substrate Scope of QNOs[a,b]

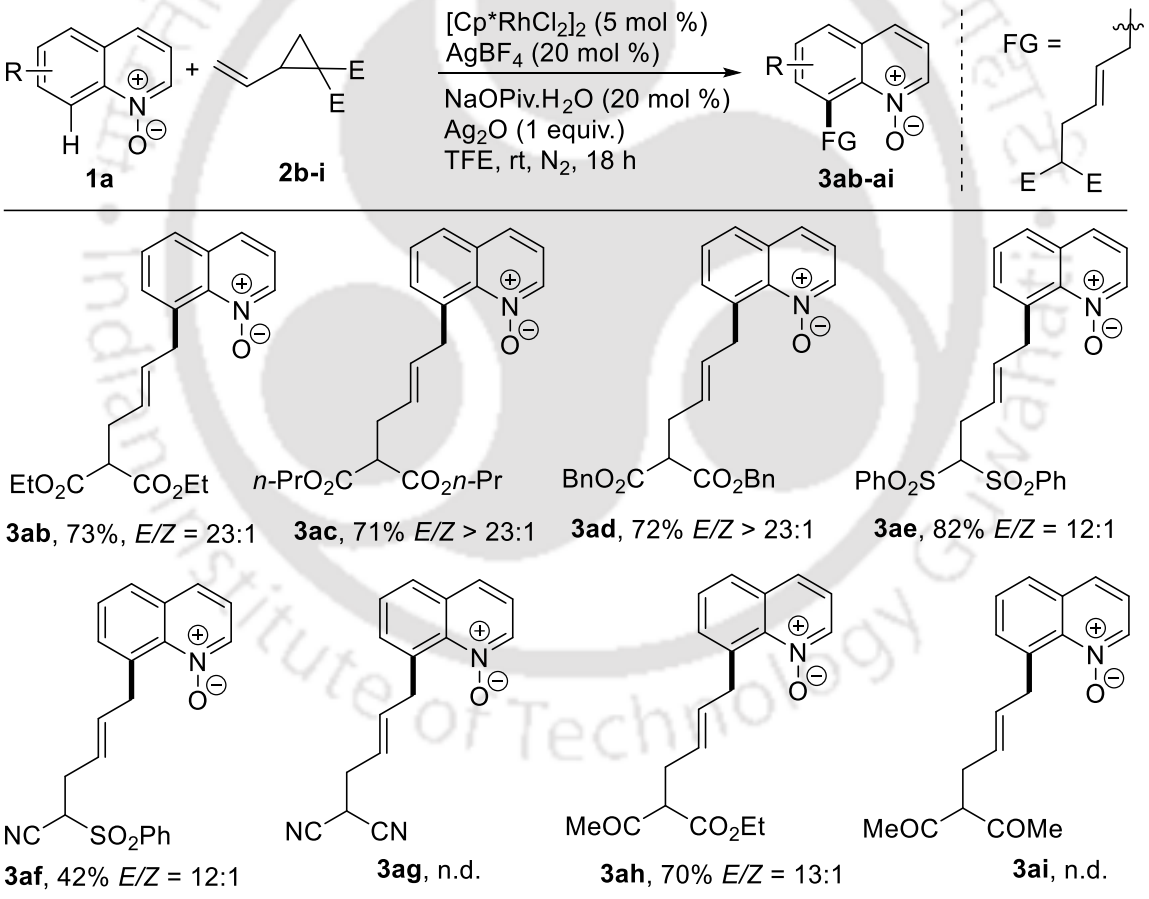


[a]Reaction condition: **1a** (0.2 mmol), **2a** (0.3 mmol), $[Cp^*RhCl_2]_2$ (5 mol %) and $AgBF_4$ (20 mol %), $NaOPiv•H_2O$ (20 mol %), Ag_2O (0.2 mmol), TFE (1 mL), rt, N_2, 18 h. [b]Isolated yield.

and 3-phenyl **1e** took place to give **3ca-ea** in 73-76% yields and ≥19:1 *E/Z*-selectivities. QNOs having aryl and het-aryl substituents at 3-position with furanyl **1f**, trifluoro **1g** group reacted to yield the allylated products **3fa** and **3ga** in 64% and 73%, respectively with >23:1 *E/Z*-selectivities. While, 4-methylquinoline *N*-oxide **1i** was coupled with VCP **2a** to produce **3ia** in

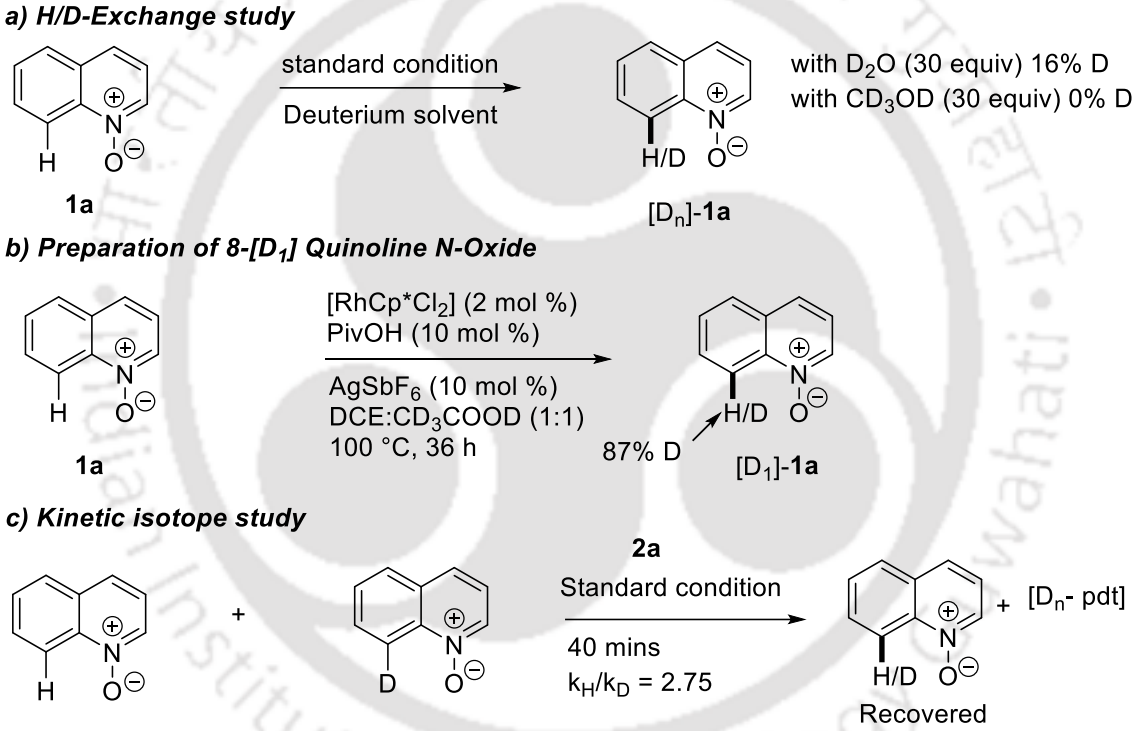
65% yield with 23:1 *E/Z*-ratio. Moreover, the halogen containing *N*-oxide substrates with 4-chloro **1h** and 5-bromo **1j** substituents were tolerated to provide **3ha** and **3ja** in 72% and 74% yields, respectively with ≥19:1 *E/Z*-selectivities. Additionally, the reactions of the substrates having amine **1k**, ether **1l** and ester **1n** functionalities, occurred to furnish **3ka**, **3la** and **3na** in 60-74% yields and ≥16:1 *E/Z*-selectivities. Furthermore, the reaction of 6-nitroquinoline *N*-oxide **1m**, having an electron-withdrawing nitro group, took place to deliver **3ma** in 43% yield with 16:1 *E/Z*-selectivity, whereas substrate containing 7-methyl group **1o** produced the allylated product **3oa** in 54% yield and 4:1 *E/Z*-ratio. Naturally occurring cinchonidine derivative **1p** was tolerated to furnish targeted allylation **3pa** in 64% yield with 11:1 *E/Z*-selectivity, illustrating the potentiality of the protocol for late-stage modification.

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



[a]Reaction condition: **1a** (0.2 mmol), **2a** (0.3 mmol), $[Cp^*RhCl_2]_2$ (5 mol %) and $AgBF_4$ (20 mol %), $NaOPiv{\bullet}H_2O$ (20 mol %), Ag_2O (0.2 mmol), TFE (1 mL), rt, N_2, 18 h. [b]Isolated yield.

Next, the scope of the method was extended to the various VCPs **2b-h**, keeping quinoline *N*-oxide **1a** as model static substrate (Table 3). The initial carboxylate variations of VCPs with ethyl **2b**, *n*-propyl **2c** and benzyl **2d** were reacted to afford **3ab-ad** in 71-73% yields and ≥23:1 *E/Z*-selectivities. An intriguing outcome was achieved when the benzenesulfonyl group (SO_2Ph) substituted VCP was investigated, producing **3ae** in 82% yield with 12:1 *E/Z*-ratio. However, the yield of the reaction between QNO **1a** and VCP **2f** was dropped to 42% in **3af**, upon replacing SO_2Ph with single carbonitrile (-CN) group. While, with two carbonitrile VCP **2g**, it was failed to produce any result, which might be due to complex formation of the substrate with catalyst. However, the excellent result was found from the reaction of VCP with methyl and ethyl esters **2h** and QNO **1a,** delivering **3ah** in 70% yield with 13:1 *E/Z*-selectivity.

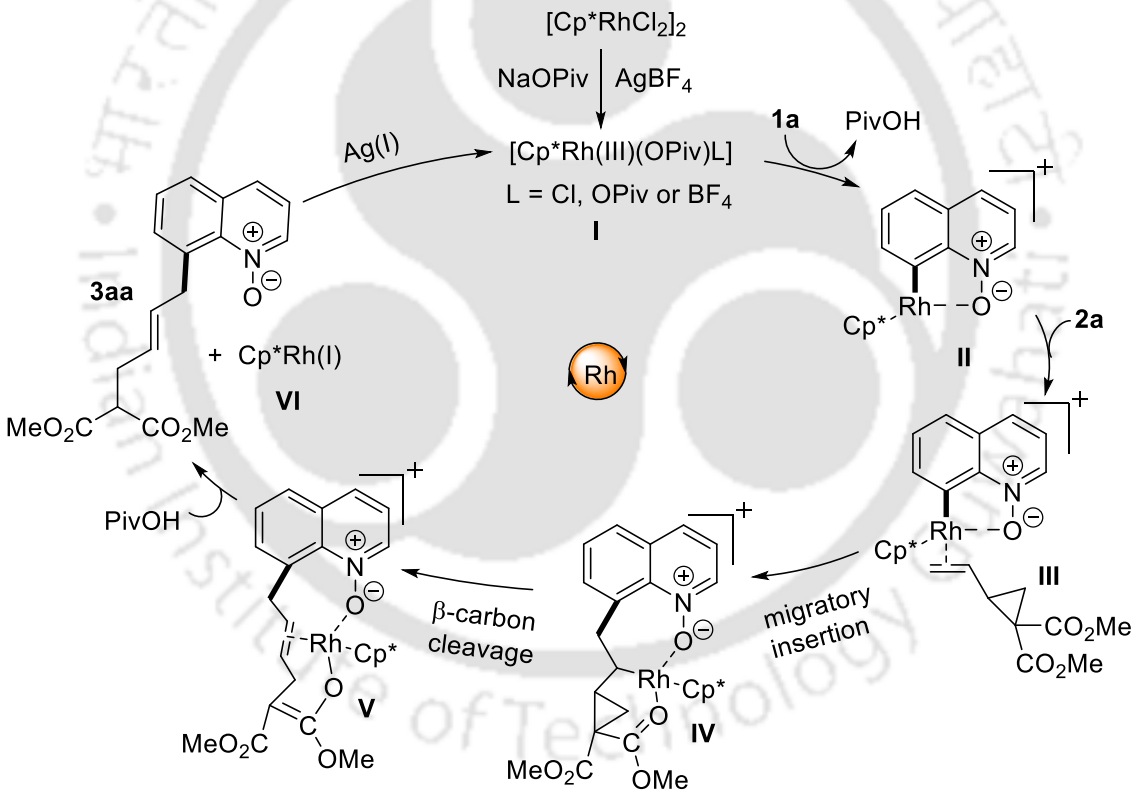


Scheme 7. Preliminary Mechanistic Investigation

To shed light on the reaction mechanism, H/D-exchange and kinetic isotope experiments were executed. No H/D scrambling was found in presence of CD_3OD co-solvent, whereas 16% D incorporation was detected in D_2O. The above results demonstrate an irreversible nature of the initial C-H activation step (Scheme 7a). Additionally, synthesis of 8-[D_1] quinoline *N*-oxide using DCE and CD_3COOD solvent mixture in 1:1 ratio as deuterium source under Rh-catalysis showed 87% D incorporation at the C8-position (Scheme 7b). Finally, kinetic isotope

experiment using QNO **1a** and [D_1]-**1a** with **2a** yielded a k_H/k_D of 2.75 (Scheme 7c), indicating the possibility of C-H activation as rate determining step.

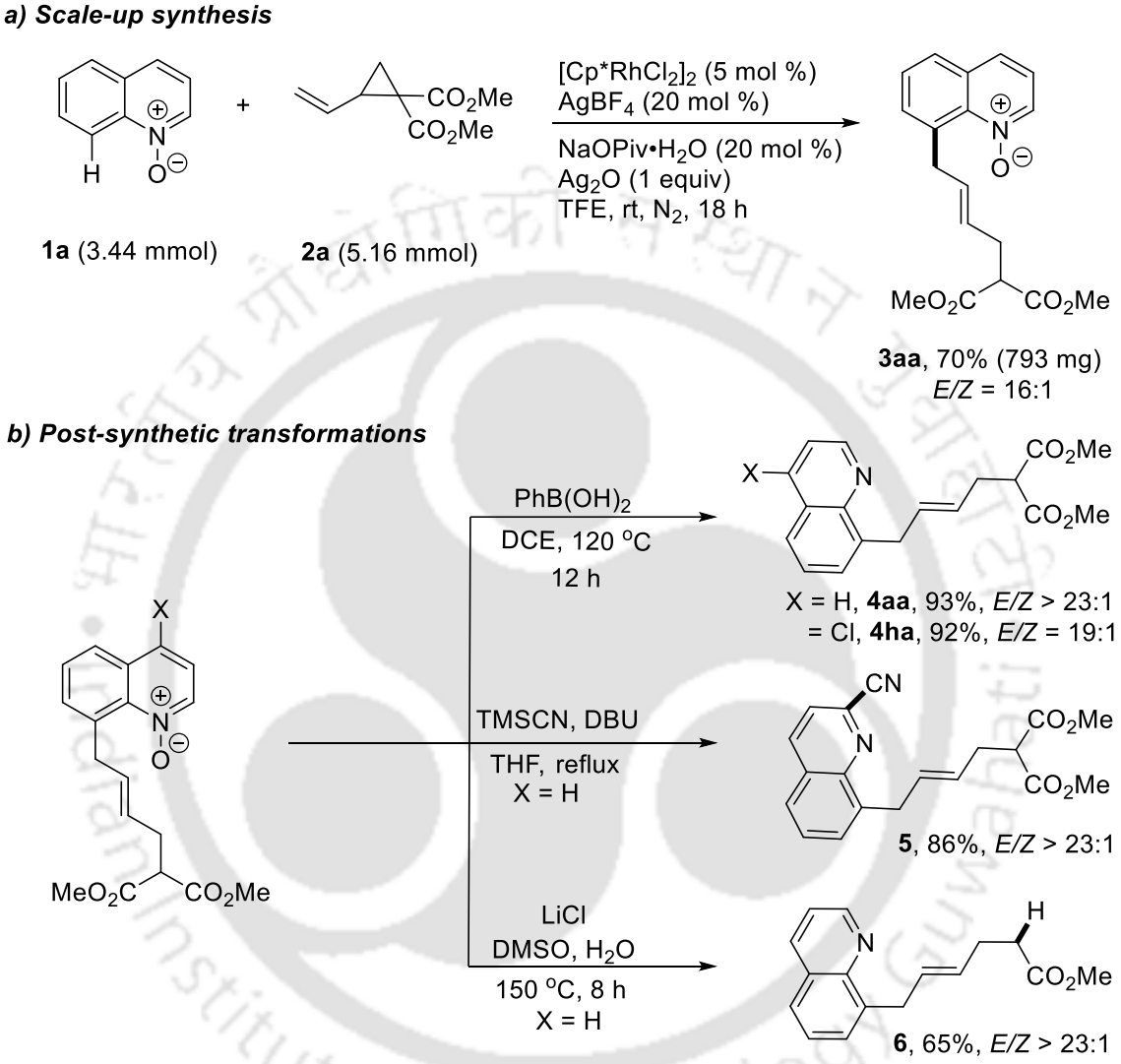
On the basis of these preliminary mechanistic investigations and previous literature studies,[2,4] a plausible mechanism is depicted as in Scheme 8. First, the active Rh(III)-species **I**, which might be generated from $[Cp^*RhCl_2]_2$ with $AgBF_4$ and NaOPiv, co-ordinate to oxygen of QNO **1a** and directs the C8-H bond activation through the formation of 5-membered rhodacycle **II**. This will coordinate with π-chelation of VCP **2a** to form **III** which undergoes 1,2-migratory insertion and produce **IV**. When the ester group of VCP and Rh-centre are co-ordinated, it facilitates energetically favoured *β*-carbon cleavage to deliver **V**, which may give our targeted product **3aa** *via* proto-demetallation and generates Rh(I)-species **VI** that upon oxidation regenerates the active Rh(III)-species **I** and thus, complete the catalytic cycle.



Scheme 8. Plausible Reaction Pathway

To demonstrate the synthetic utility of the procedure, we performed scale-up synthesis and post-synthetic transformations (Scheme 9). The scalability of method was checked with 3.44 mmol of **1a** with **2a** as the standard examples, producing allylated **3aa** in 70% yield with 16:1 *E/Z*-selectivity. It is important to note that the *E/Z*-ratio was preserved in the scale-up method, showcasing effectiveness of the procedure. Moreover, removal of *N*-oxide moiety from the

final products **3aa** and **3ha** were successful using $PhB(OH)_2$ to afford **4aa** and **4ha** in 93% and 92% yields, respectively. In addition, cyanation of **3aa** was successfully carried out by TMSCN, leading the formation **5** in 86% yield. Similarly, the Krapcho decarboxylation of **3aa** proceeds efficiently, producing **6** in 65% yield.



Scheme 9. Synthetic Utilities

In summary, we have developed an efficient, atom economic route to synthesize 8-allylquinolines employing vinylcyclopropane as the allyl source under Rh(III)-catalysis *via* sequential C-H/C-C functionalization. Excellent regio- and diastereo-selectivities at room temperature, naturally occurring cinchonidine alkaloid modification and post-synthetic utilities are the key advancements of the protocol.

2.3 Experimental Section

General Information. All the reactions were performed under nitrogen atmosphere using oil bath as heating source. Quinolines, $[RhCp^*Cl_2]_2$ (97%), $[Ru(p\text{-cymene})Cl_2]_2$, $AgSbF_6$ (99%), $AgNTf_2$ (97%), Ag_2O (99%), Ag_2CO_3 (99%), Cu_2O (($\geq$99.9%), $Cu(OAc)_2 \cdot H_2O$ (98%), PivOH (99%), AgOAc ($\geq$99.9%), $NaOPiv \cdot H_2O$ (99%), *m*-CPBA ($\geq$77%), AcOH ($\geq$99%), NaOAc ($\geq$99%), CsOAC ($\geq$99.9%), CsOPiv (98%) were purchased from Aldrich and TFE solvent was purchased from TCI chemicals and used as received. Quinoline *N*-oxides[2] and vinylcyclopropanes[12] were prepared according to the reported procedure. $[CoCp^*(CO)I_2]$ was synthesized from the reported literature.[13] SRL silica gel G/GF 254 plates were used for analytical TLC and SRL silica gel (230-400 mesh) was used for column chromatography. Bruker Avance III 600, 500 and 400 MHz spectrometers used for NMR spectra using tetramethylsilane (Me_4Si) as an internal standard. Chemical shifts (δ) and spin-spin coupling constant (*J*) are reported in parts per million (ppm) and hertz (Hz), respectively and other data are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, dd = double doublet. Melting points were determined using a Büchi B-540 apparatus and are uncorrected. IR spectra were collected on a PerkinElmer Fourier transform infrared (FTIR) spectrometer. Quadrupole time-of-flight electrospray ionization (ESI) mass spectrometer (model HAB 273) used for recording HRMS.

General Procedure for the 3-Substituted Quinolines.[14] In an oven dried sealed tube, 3-bromo-quinoline (1 mmol, 208 mg), aryl boronic acid (2 mmol), $Pd(PPh_3)_4$ (0.02 mmol, 23 mg), Na_2CO_3 (2 mmol, 212 mg), H_2O (10 µL) and toluene : ethanol (1:1, 4 mL) were stirred at 100 °C under nitrogen atmosphere. After completion (monitored by TLC), the reaction mixture was cooled to room temperature and passed through a short pad of celite using CH_2Cl_2 (20 ml). Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate as an eluent to give desired substituted quinoline.

Synthesis of *tert*-Butyl Quinolin-5-ylcarbamate.[15] To a stirred solution of 5-aminoquinoline (1 mmol, 144 mg) in ethanol (2 mL), $(Boc)_2O$ (1.1 mmol, 240 mg) was added at room temperature. The reaction was monitored by TLC and after completion, the solution was concentrated under vacuum to afford desired product. Protected aminoquinoline was used for the next step without further purification.

Synthesis of Quinolin-6-yl benzoate.[16] To a stirred solution of 6-hydroxyquinoline (1 mmol, 145 mg), 4-(dimethylamino)pyridine (0.05 mmol, 6 mg) and triethylamine (Et_3N, 3 mL) in CH_2Cl_2 (15 mL), benzoyl chloride (1 mmol, 0.14 mL) was added dropwise at room temperature. The stirring was continued and after completion, the reaction was quenched with water (5 mL). The resultant mixture was extracted using CH_2Cl_2 (2 x 20 mL) and washed with brine and water. Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by column chromatography using hexane and ethyl acetate as an eluent (80/20, v/v) to afford the desired quinoline.

General Procedure for the Synthesis of Quinoline *N*-oxide. To a stirred solution of quinoline (1 mmol) in $CHCl_3$ (3 mL), *m*-CPBA (2.5 mmol, 431 mg) was added and the reaction mixture was allowed to reflux for 4 h. Then the reaction mixture was cooled to room temperature and quenched with aqueous $NaHCO_3$ solution (5 mL). The solution was extracted using CH_2Cl_2 (3 x 10 mL) and dried over Na_2SO_4. The evaporation of the solvent gave a residue that was purified by silica gel column chromatography to afford desired *N*-oxides **1**.

General Procedure for Rh(III) Catalyzed C8 Allylation of Quinoline *N*-oxide. Quinoline *N*-oxide **1** (0.2 mmol), vinylcyclopropane **2** (0.3 mmol), $[RhCp^*Cl_2]_2$ (0.01 mmol, 6 mg), $AgBF_4$ (0.04 mmol, 7.8 mg), $NaOPiv•H_2O$ (0.04 mmol, 6 mg), Ag_2O (0.2 mmol, 46 mg) and TFE (1 mL) were stirred for 18 h at room temperature under N_2 atmosphere. After completion, the reaction mixture was extracted with EtOAc (3 x 10 mL) and was washed with saturated $NaHCO_3$ (2 x 5 mL) and water (2 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate as an eluent to afford C8-allylated quinoline *N*-oxide **3** in good to moderate yield.

Scale-up Synthesis of 3aa. Quinoline *N*-oxide **1a** (3.44 mmol, 500 mg), vinylcyclopropane **2a** (5.16 mmol, 950 mg), $[RhCp^*Cl_2]_2$ (5 mol %, 104 mg), $AgBF_4$ (0.688 mmol, 134.16 mg), $NaOPiv•H_2O$ (0.688 mmol, 98 mg), Ag_2O (0.2 mmol, 795 mg) and TFE (12 mL) were stirred for 18 h at room temperature under N_2 atmosphere. After completion, the reaction mixture was passed through a pad of celite using EtOAc. Evaporation of the solvent gave a residue which was purified by silica gel column chromatography using hexane and ethyl acetate as an eluent (40/60, v/v) to afford **3aa** in 70% (793 mg) yield.

Post-synthetic Transformations

Synthesis of 4aa and 4ha.[17b] To an oven dried sealed tube, respective quinoline *N*-oxide (0.1 mmol), phenylboronic acid (0.15 mmol, 18 mg) and 1,2-dichloroethane (1 mL) were allowed to stir for 12 h at 120 °C. After the completion of reaction, the mixture was treated with dichloromethane and washed with water (2 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue which was purified by silica gel column chromatography to afford C8-functionalized quinoline.

Synthesis of 5.[2d] To an oven dried sealed tube, **3aa** (0.1 mmol, 32 mg), TMSCN (0.12 mmol, 16 µL), DBU (0.23 mmol, 34 µL) and THF (1 mL) were allowed to stir for 12 h under reflux. The solvent was evaporated and the residue was extracted using EtOAc (2 x 5 mL) and washed with water (2 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica column chromatography using hexane and ethyl acetate as an eluent (90/10, v/v) to afford **5** in 86% yield (29 mg).

Synthesis of 6.[17a] In an oven dried round bottom flask, **3aa** (0.1 mmol, 32 mg), LiCl (0.5 mmol, 21 mg), DMSO (1 mL) and H_2O (0.5 mmol, 10 µL) were allowed to stir for 12 h at 130 °C under N_2 atmosphere. After the completion, reaction mixture was extracted EtOAc (2 x 10 mL) and washed with water (2 x 5 mL). After the evaporation of the solvent residue was purified by silica column chromatography using hexane and ethyl acetate as an eluent (90/10, v/v) to afford **6** in 65% yield (16.5 mg).

Preliminary Mechanistic Investigation

H/D-Exchange study. To a stirred solution of quinoline *N*-oxide **1a** (0.1 mmol, 14.5 mg), $[RhCp^*Cl_2]_2$ (0.005 mmol, 3 mg), $AgBF_4$ (0.02 mmol, 4 mg), $NaOPiv.H_2O$ (0.02 mmol, 2.8 mg), and Ag_2O (0.1 mmol, 23 mg) in TFE (0.5 mL), deuterated solvent (30 equiv) was added. The resulting mixture were stirred for 18 h at room temperature under N_2 atmosphere. After completion, the reaction mixture was extracted with EtOAc (3 x 10 mL) and washed with saturated $NaHCO_3$ (2 x 5 mL) and water (2 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified according to general procedure. Deuterium incorporation of the recovered starting material was confirmed by ^1H NMR.

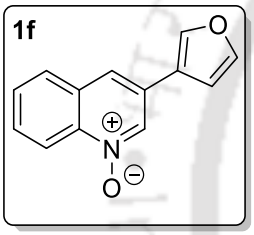
Preparation of Deuterated 8-d_1 Quinoline *N*-oxide [D_1]-1a.[18] Quinoline *N*-oxide 1a (1 mmol, 145 mg), $[RhCp^*Cl_2]_2$ (0.02 mmol, 12 mg), pivalic acid (0.1 mmol, 11 mg), $AgSbF_6$ (0.08 mmol, 28 mg) and DCE:CD_3COOD (1:1, 4 mL) were stirred for 36 h at 110 °C. The resulting

mixture was extracted with EtOAc (3 x 15 mL). Evaporation of the solvent gave a residue that was purified as described in the general procedure. The deuterium incorporation of the recovered starting material was found to be 87% as per ^{1}H NMR.

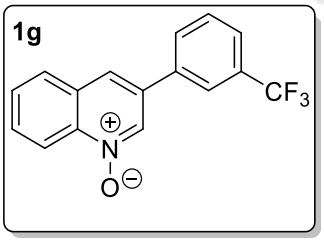
Kinetic Isotope Effect. Quinoline *N*-oxide **1a** (0.05 mmol, 7.3 mg), quinoline 1-oxide-8-d_1 [D_1]-**1a** (0.05 mmol, 7.3 mg), vinyl cyclopropane **2a** (0.15 mmol, 28 mg), $[RhCp^*Cl_2]_2$ (0.005, 3 mg), $AgBF_4$ (0.02 mmol, 4 mg), $NaOPiv.H_2O$ (0.02 mmol, 3 mg), Ag_2O (0.1 mmol, 23 mg) and TFE (0.5 mL) were stirred for 40 minutes at room temperature under N_2 atmosphere. ^{1}H NMR was taken of the recovered *N*-oxide to calculate the intermolecular k_H/k_D and it was found to be 2.75.

2.4 Characterization data

Characterization Data of Newly Synthesized Quinoline *N*-Oxides

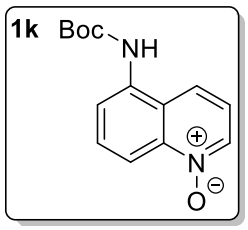


3-(Furan-3-yl)quinoline 1-oxide 1f. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.3; brown solid; mp 85-86 °C; yield 85% (179 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.70 (d, *J* = 8.5 Hz, 1H), 7.87-7.85 (m, 2H), 7.80 (s, 1H), 7.74-7.71 (m, 1H), 7.66-7.63 (m, 1H), 7.56-7.55 (m, 1H), 6.77 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8, 140.3, 139.8, 134.3, 130.5, 130.1, 129.3, 128.1, 126.8, 122.2, 122.1, 119.8, 108.4; FT-IR (neat) 2925, 1652, 1608, 1583, 1395, 1347, 1260, 1222, 1162, 874, 825, 765, 594 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{13}H_{10}NO_2$: 212.0706, found 212.0706.



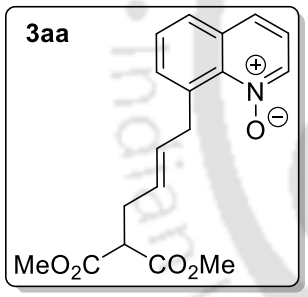
3-(3-(Trifluoromethyl)phenyl)quinoline 1-oxide 1g. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.4; brown solid; mp 183-184 °C; yield 80% (230 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.77 (d, *J* = 9 Hz, 1H), 7.96-7.91 (m, 3H), 7.84-7.78 (m, 2H), 7.74-7.65 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.8, 136.9, 134.7, 133.6, 132.2 (J_{C-F} = 32.3 Hz), 130.8, 130.4, 130.3, 130.1, 129.5, 128.6, 125.8 (J_{C-F} = 3.75 Hz),

125.0 (J_{C-F} = 271 Hz), 124.1 (J_{C-F} = 3.75 Hz), 123.7, 119.9; FT-IR (neat) 3064, 1583, 1493, 1369, 1316, 1171, 1110, 934, 766, 684 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{11}F_3NO$: 290.0787, found 290.0785.

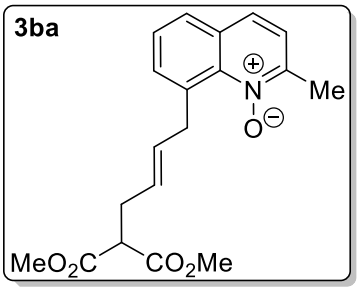


5-((*tert*-Butoxycarbonyl)amino)quinoline 1-oxide 1k. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.2; colorless solid; mp 185-186 °C; yield 77% (200 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 8.55-8.52 (m, 2H), 8.01-8.00 (m, 1H), 7.88-7.85 (m, 1H), 7.74-7.71 (m, 1H), 7.35-7.28 (m, 1H), 7.15 (s, 1H), 1.55 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.3, 142.3, 135.6, 134.2, 130.5, 124.7, 121.8, 120.4, 119.9, 115.9, 81.6, 28.4; FT-IR (neat) 3200, 2978, 1721, 1536, 1404, 1364, 1304, 1237, 1152, 1054, 879, 784 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{14}H_{17}N_2O_3$: 261.1234, found 261.1229.

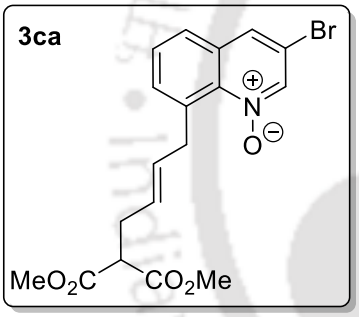
Characterization Data of the Products



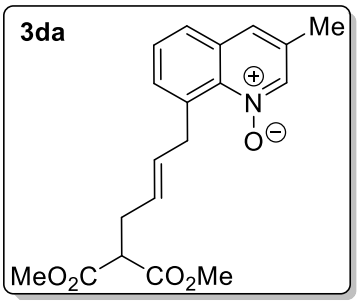
(*E*)-8-(6-Methoxy-5-(methoxycarbonyl)-6-oxohex-2-en-1-yl) quinoline 1-oxide 3aa. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.30; brown solid; mp 75-76 °C; yield 78% (51 mg); *E/Z* = 16:1 mixture of diastereomers; ^1H NMR (600 MHz, $CDCl_3$) δ 8.43 (d, *J* = 6 Hz, 1H), 7.68 (t, *J* = 9 Hz, 2H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 6.6 Hz, 1H), 7.22-7.20 (m, 1H), 5.99-5.95 (m, 1H), 5.46-5.41 (m, 1H), 4.36 (d, *J* = 6.6 Hz, 2H), 3.66 (s, 6H), 3.41 (t, *J* = 7.8 Hz, 1H), 2.60 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5, 140.6, 137.7, 135.7, 134.2, 133.0, 132.6, 128.3, 127.5, 126.8, 126.2, 120.7, 52.5, 52.0, 39.7, 32.0; FT-IR (neat) 2953, 1732, 1572, 1435, 1274, 1219, 1156, 815, 751 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{20}NO_5$: 330.1336, found 330.1337.



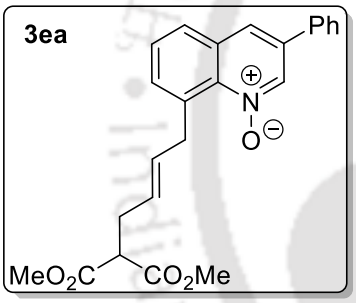
(*E*)-8-(6-Methoxy-5-(methoxycarbonyl)-6-oxohex-2-en-1-yl)-2-methylquinoline 1-oxide 3ba. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.30; brown solid; mp 99-100 °C; yield 77% (53 mg); *E/Z* = 13:1 mixture of diastereomers; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.2 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.41-7.39 (m, 2H), 7.25 (d, *J* = 8.4 Hz, 1H), 6.01-5.96 (m, 1H), 5.44-5.39 (m, 1H), 4.37 (d, *J* = 6.6 Hz, 2H), 3.63 (s, 6H), 3.39 (t, *J* = 7.8 Hz, 1H), 2.61-2.58 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5, 147.2, 140.7, 135.2, 134.5, 132.9, 131.3, 127.4, 127.3, 125.8, 125.5, 122.7, 52.4, 52.0, 39.9, 32.0, 19.3; FT-IR (neat) 2953, 1731, 1567, 1435, 1239, 1151, 1023, 821, 765 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{22}NO_5$: 344.1492, found 344.1495.



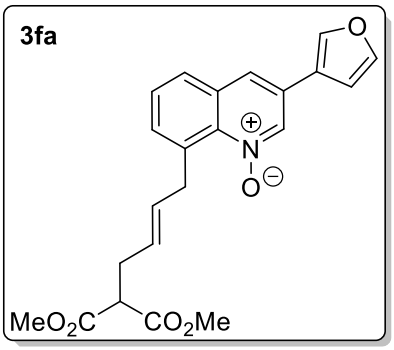
(*E*)-3-Bromo-8-(6-methoxy-5-(methoxycarbonyl)-6-oxohex-2-en-1-yl)quinoline 1-oxide 3ca. Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.30; brown solid; mp 134-135 °C; yield 75% (61 mg); *E/Z* = 19:1 mixture of diastereomers; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.79 (s, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.49 (t, *J* = 7.8, 1H), 7.41 (d, *J* = 6.6 Hz, 1H), 5.95-5.90 (m, 1H), 5.44-5.39 (m, 1H), 4.29 (d, *J* = 6.6 Hz, 2H), 3.67 (s, 6H), 3.40 (t, *J* = 7.8 Hz, 1H), 2.60 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5, 139.7, 138.8, 135.9, 133.7, 132.9, 132.4, 129.2, 128.0, 126.7, 126.5, 114.0, 52.5, 52.0, 39.4, 32.0; FT-IR (neat) 2953, 1732, 1557, 1435, 1355, 1275, 1213, 1156, 877, 764 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{19}BrNO_5$: 408.0441, found 408.0449.



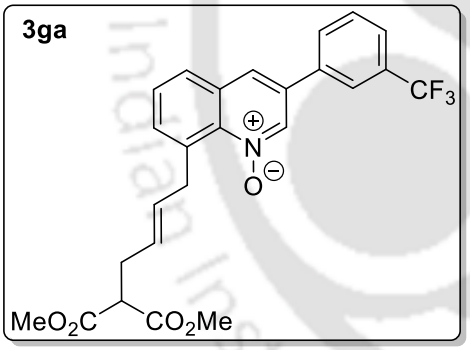
(*E*)-8-(6-Methoxy-5-(methoxycarbonyl)-6-oxohex-2-en-1-yl)-3-methylquinoline 1-oxide 3da. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.40; brown solid; mp 70-71 °C; yield 76% (52 mg); *E/Z* > 23:1 mixture of diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.57 (d, *J* = 8 Hz, 1H), 7.41-7.38 (m, 2H), 7.32 (d, *J* = 6.5 Hz, 1H), 5.98-5.92 (m, 1H), 5.44-5.38 (m, 1H), 4.33 (d, *J* = 6 Hz, 2H), 3.64 (s, 6H), 3.39 (t, *J* = 7.5 Hz, 1H), 2.58 (t, *J* = 7.0 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5, 139.0, 138.7, 135.4, 134.2, 132.3, 131.8, 130.8, 128.2, 126.8, 126.2, 126.0, 52.4, 52.0, 39.5, 32.0, 18.3; FT-IR (neat) 2953, 1727, 1579, 1434, 1214, 1149, 1025, 848, 763 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{22}NO_5$: 344.1492, found 344.1491.



(*E*)-8-(6-Methoxy-5-(methoxycarbonyl)-6-oxohex-2-en-1-yl)-3-phenylquinoline 1-oxide 3ea. Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.30; brown solid; mp 100-101 °C; yield 73% (59 mg); *E/Z* = 19:1 mixture of diastereomers; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.83 (s, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.65-7.64 (m, 2H), 7.53-7.48 (m, 3H), 7.45 (t, *J* = 7.8, 1H), 7.42 (d, *J* = 7.2 Hz, 1H), 6.03-5.98 (m, 1H), 5.49-5.44 (m, 1H), 4.39 (d, *J* = 6.6 Hz, 2H), 3.67 (s, 6H), 3.43 (t, *J* = 7.8 Hz, 1H), 2.62 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5, 139.4, 136.8, 135.7, 134.5, 134.2, 132.7, 132.5, 129.4, 129.0, 128.6, 127.7, 127.0, 126.2, 124.0, 52.5, 52.0, 39.6, 32.0; FT-IR (neat) 2952, 1731, 1580, 1434, 1217, 1152, 1022, 860, 758, 694 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{24}NO_5$: 406.1649, found 406.1653.

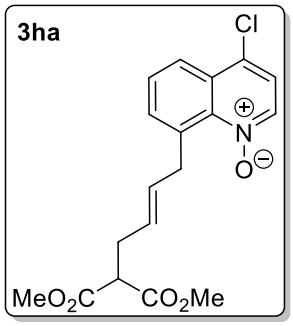


(*E*)-3-(Furan-3-yl)-8-(6-methoxy-5-(methoxycarbonyl)-6-oxohex-2-en-1-yl)quinoline 1-oxide 3fa. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.40; light brown solid; mp 144-145 °C; yield 64% (50.5 mg); *E/Z* > 23:1 mixture of diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.85 (s, 1H), 7.70-7.67 (m, 2H), 7.556 (s, 1H), 7.47 (t, *J* = 8 Hz, 1H), 7.38 (d, *J* = 7 Hz, 1H), 6.75 (s, 1H), 6.00-5.95 (m, 1H), 5.48-5.42 (m, 1H), 4.35 (d, *J* = 6.5 Hz, 2H), 3.67 (s, 6H), 3.42 (t, *J* = 8 Hz, 1H), 2.61 (t, *J* = 7 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5, 144.7, 139.8, 139.2, 136.0, 135.7, 134.1, 132.56, 132.50, 128.7, 127.4, 126.37, 126.32, 122.5, 121.8, 108.4, 52.5, 52.0, 39.5, 32.0; FT-IR (neat) 2953, 1731, 1611, 1583, 1435, 1217, 1156, 1022, 874, 761, 597 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{22}NO_6$: 396.1442, found 396.1442.

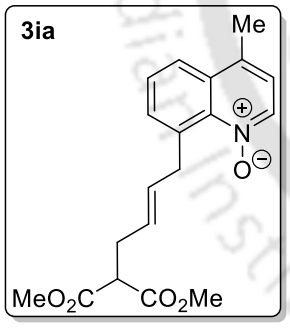


(*E*)-8-(6-Methoxy-5-(methoxycarbonyl)-6-oxohex-2-en-1-yl)-3-(3-(trifluoromethyl)phenyl)quinoline 1-oxide 3ga. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.40; grey solid; mp 134-135 °C; yield 65% (61.5 mg); *E/Z* > 23:1 mixture of diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.90 (s, 1H), 7.83-7.81 (m, 2H), 7.77 (d, *J* = 8 Hz, 1H), 7.72 (d, *J* = 8 Hz, 1H), 7.65 (t, *J* = 8 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 6.02-5.96 (m, 1H), 5.49-5.43 (m, 1H), 4.38 (d, *J* = 6.5 Hz, 2H), 3.68 (s, 6H), 3.42 (t, *J* = 7.5 Hz, 1H), 2.62 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5, 139.7, 136.6, 136.5, 135.8, 134.0, 133.2, 133.1, 132.4, 132.1 (J_{C-F} = 32.5 Hz), 130.3, 130.0, 128.9, 127.9, 126.4, 125.7 (J_{C-F} = 3.6 Hz), 124.8 (J_{C-F} = 270.9 Hz), 124.1, 123.9 (J_{C-F} = 3.9 Hz), 52.5, 52.0, 39.5, 32.0; ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.74. FT-IR (neat)

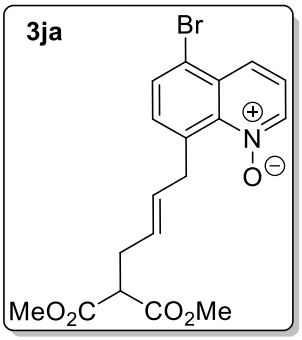
2954, 1732, 1581, 1436, 1343, 1316, 1159, 1123, 804, 763, 700 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{23}F_3NO_5$: 474.1523, found 474.1530.



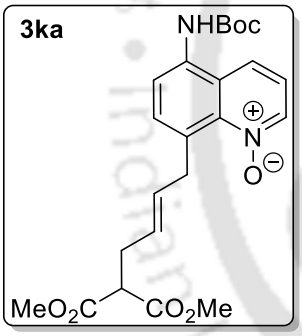
(*E*)-4-Chloro-8-(6-methoxy-5-(methoxycarbonyl)-6-oxohex-2-en-1-yl)quinoline 1-oxide 3ha. Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.30; brown solid; mp 118-119 °C; yield 72% (52.5 mg); *E/Z* = 19:1 mixture of diastereomers; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.32 (d, *J* = 6.6 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 6 Hz, 1H), 7.31 (d, *J* = 6.6 Hz, 1H), 5.97-5.92 (m, 1H), 5.45-5.40 (m, 1H), 4.34 (d, *J* = 6.6 Hz, 2H), 3.67 (s, 6H), 3.40 (t, *J* = 7.8 Hz, 1H), 2.60 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5, 141.3, 136.9, 136.4, 133.9, 133.8, 129.9, 129.8, 129.2, 126.5, 124.3, 121.1, 52.5, 52.0, 39.6, 32.0; FT-IR (neat) 2954, 1730, 1561, 1435, 1372, 1296, 1208, 1150, 757 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{19}ClNO_5$: 364.0946, found 364.0951.



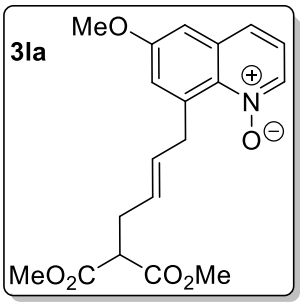
(*E*)-8-(6-Methoxy-5-(methoxycarbonyl)-6-oxohex-2-en-1-yl)-4-methylquinoline 1-oxide 3ia. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.30; brown solid; mp 58-59 °C; yield 65% (44.5 mg); *E/Z* = 23:1 mixture of diastereomers; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.32 (d, *J* = 6 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 7.2 Hz, 1H), 7.05 (d, *J* = 6 Hz, 1H), 6.00-5.95 (m, 1H), 5.44-5.39 (m, 1H), 4.37 (d, *J* = 6.6 Hz, 2H), 3.65 (s, 6H), 3.40 (t, *J* = 7.8 Hz, 1H), 2.59-2.58 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5, 140.0, 136.9, 136.2, 134.5, 134.3, 132.8, 131.7, 128.0, 126.0, 123.7, 121.6, 52.4, 52.0, 39.9, 32.0, 19.3; FT-IR (neat) 2953, 1730, 1567, 1394, 1218, 1151, 974, 830, 759 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{22}NO_5$: 344.1492, found 344.1491.



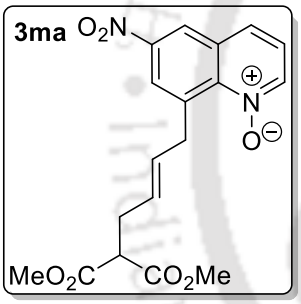
(*E*)-5-Bromo-8-(6-methoxy-5-(methoxycarbonyl)-6-oxohex-2-en-1-yl)quinoline 1-oxide 3ja. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.30; brown sticky liquid; yield 74% (60 mg); *E/Z* = 23:1 mixture of diastereomers; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.43 (d, *J* = 6 Hz, 1H), 8.08 (d, *J* = 9 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.31-7.28 (m, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 5.94-5.89 (m, 1H), 5.44-5.39 (m, 1H), 4.27 (d, *J* = 6.6 Hz, 2H), 3.66 (s, 6H), 3.39 (t, *J* = 7.8 Hz, 1H), 2.59 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.4, 141.6, 137.9, 135.8, 133.5, 132.6, 132.3, 131.4, 126.6, 125.6, 121.6, 120.8, 52.5, 51.9, 39.7, 31.9; FT-IR (neat) 2953, 1730, 1568, 1510, 1435, 1393, 1262, 850, 750 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{19}BrNO_5$: 408.0441, found 408.0446.



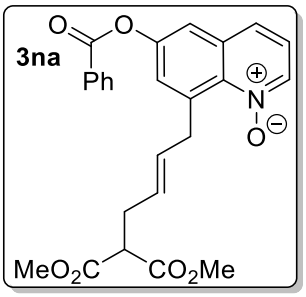
(*E*)-5-((*tert*-Butoxycarbonyl)amino)-8-(6-methoxy-5-(methoxycarbonyl)-6-oxohex-2-en-1-yl)quinoline 1-oxide 3ka. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.30; dark brown sticky liquid; yield 68% (60.5 mg); *E/Z* > 23:1 mixture of diastereomers; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34 (d, *J* = 6 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.68 (s, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.14-7.11 (m, 1H), 5.91-5.87 (m, 1H), 5.40-5.35 (m, 1H), 4.23 (d, *J* = 6 Hz, 2H), 3.64 (s, 6H), 3.37 (t, *J* = 7.8 Hz, 1H), 2.56 (t, *J* = 7.2 Hz, 2H), 1.48 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.4, 153.7, 140.8, 137.5, 134.0, 132.7, 132.5, 132.0, 127.3, 126.1, 122.9, 120.5, 120.2, 81.2, 52.4, 51.9, 39.6, 31.9, 28.3; FT-IR (neat) 3198, 2977, 1727, 1538, 1436, 1239, 1156, 1054, 881, 750 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{29}N_2O_7$: 445.1969, found 445.1977.



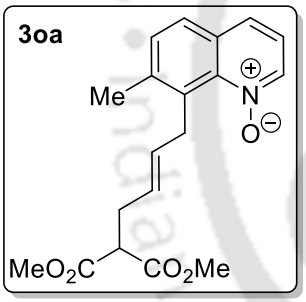
(*E*)-6-Methoxy-8-(6-methoxy-5-(methoxycarbonyl)-6-oxohex-2-en-1-yl)quinoline 1-oxide 3la. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.30; brown liquid; yield 60% (43 mg); *E/Z* = 16:1 mixture of diastereomers; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.25 (d, *J* = 4.8 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.14-7.11 (m, 1H), 7.03-7.02 (m, 1H), 6.91-6.90 (m, 1H), 5.95-5.90 (m, 1H), 5.46-5.42 (m, 1H), 4.31 (d, *J* = 6 Hz, 2H), 3.87 (s, 3H), 3.66 (s, 6H), 3.41 (t, *J* = 7.8 Hz, 1H), 2.60 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5, 158.3, 137.7, 136.5, 135.8, 134.2, 133.6, 126.6, 125.6, 124.5, 121.2, 104.8, 55.5, 52.5, 51.9, 39.5, 32.0; FT-IR (neat) 2955,1726, 1610, 1430, 1277, 1200, 1032, 831, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{22}NO_6$: 360.1442, found 360.1441.



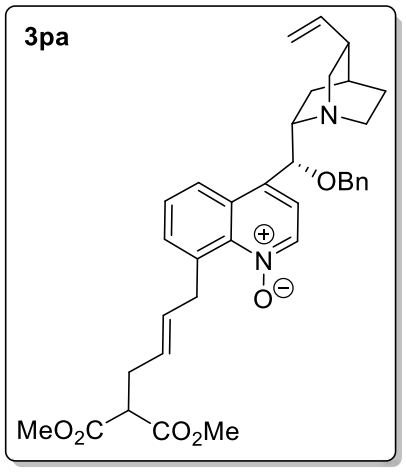
(*E*)-8-(6-Methoxy-5-(methoxycarbonyl)-6-oxohex-2-en-1-yl)-6-nitro quinoline 1-oxide 3ma. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.30; dark brown solid; mp 120-121 °C; yield 43% (32 mg); *E/Z* = 16:1 mixture of diastereomers; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.60 (d, *J* = 2.4 Hz, 1H), 8.57 (d, *J* = 6 Hz, 1H), 8.16 (d, *J* = 2.4 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.41-7.38 (m, 1H), 5.97-5.92 (m, 1H), 5.54-5.50 (m, 1H), 4.43 (d, *J* = 6.6 Hz, 2H), 3.70 (s, 6H), 3.43 (t, *J* = 7.8 Hz, 1H), 2.64 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.4, 146.3, 142.7, 140.4, 139.5, 132.3, 132.2, 128.1, 127.6, 125.0, 123.3, 122.9, 52.6, 51.8, 39.8, 31.9; FT-IR (neat) 3080, 2925, 2853, 1734, 1542, 1436, 1348, 1214, 792 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{19}N_2O_7$: 375.1187, found 375.1188.



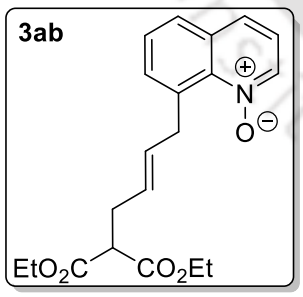
(*E*)-8-(6-Methoxy-5-(methoxycarbonyl)-6-oxohex-2-en-1-yl)-6-(2-phenylacetoxy)quinoline 1-oxide 3na. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.30; colorless liquid; yield 74% (68.5 mg); *E/Z* > 23:1 mixture of diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, *J* = 6 Hz, 1H), 8.22 (d, *J* = 8 Hz, 2H), 7.67-7.61 (m, 3H), 7.53 (t, *J* = 8 Hz, 2H), 7.29-7.29 (d, *J* = 2.5 Hz, 1H), 7.23-7.20 (m, 1H), 5.98-5.92 (m, 1H), 5.51-5.46 (m, 1H), 4.40 (d, *J* = 6.5 Hz, 2H), 3.65 (s, 6H), 3.42 (t, *J* = 7.5 Hz, 1H), 2.62 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 164.8, 149.7, 138.8, 138.5, 137.4, 134.1, 133.4, 133.2, 130.3, 129.0, 128.8, 127.2, 127.1, 126.2, 121.5, 118.1, 52.5, 51.9, 39.5, 32.0; FT-IR (neat) 3075, 3006, 1731, 1574, 1375, 1249, 1151, 1049, 1024, 750, 708 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{26}NO_7$: 450.1547, found 450.1554.



(*E*)-8-(6-Methoxy-5-(methoxycarbonyl)-6-oxohex-2-en-1-yl)-7-methylquinoline 1-oxide 3oa. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.30; brown solid; mp 65-66 °C; yield 54% (37 mg); *E/Z* = 4:1 mixture of diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, *J* = 6 Hz, 1H), 7.58 (t, *J* = 9.5 Hz, 2H), 7.37 (d, *J* = 8 Hz, 1H), 7.12 (t, *J* = 7.2 Hz, 1H), 5.98-5.93 (m, 1H), 5.36-5.28 (m, 1H), 4.38 (d, *J* = 7.2 Hz, 2H), 3.62 (s, 6H), 3.36 (t, *J* = 8 Hz, 1H), 2.56 (t, *J* = 7.5 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5, 140.9, 138.1, 133.1, 131.99, 131.90, 131.2, 126.68, 126.60, 125.2, 123.9, 119.9, 52.4, 52.1, 34.0, 32.0, 20.9; FT-IR (neat) 2953, 1730, 1557, 1435, 1229, 1151, 1023, 828, 752 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{22}NO_5$: 344.1492 , found 344.1492.

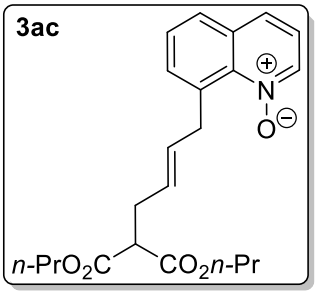


4-((*R*)-(Benzyloxy)((1S,2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl) -8-((*E*)-6-methoxy-5-(methoxycarbonyl)-6-oxohex-2-en-1-yl)quinoline 1-oxide 3pa. Analytical TLC on silica gel, 1:9 methanol/dichloromethane R_f = 0.70; light brown liquid; yield 64% (75 mg); *E/Z* = 11:1 mixture of diastereomers; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.39 (d, *J* = 6.0 Hz, 1H), 8.07 (d, *J* = 4.8 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 7.2 Hz, 1H), 7.36-7.33 (m, 3H), 7.31-7.28 (m, 3H), 6.01-5.96 (m, 1H), 5.74-5.69 (m, 1H), 5.50-5.45 (m, 1H), 5.33 (s, 1H), 4.97-4.93 (m, 2H), 4.44 (s, 2H), 4.37 (d, *J* = 6.6 Hz, 2H), 3.67 (s, 6H), 3.44-3.41 (m, 2H), 3.13-3.10 (m, 2H), 2.73-2.65 (m, 2H), 2.62 (t, *J* = 7.2 Hz, 2H), 2.33-2.31 (m, 1H), 1.84-1.73 (m, 4H), 1.56-1.52 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5, 141.1, 140.6, 137.5, 136.9, 136.6, 135.5, 134.2, 132.8, 130.4, 128.66, 128.61, 128.0, 127.8, 126.2, 122.7, 118.9, 114.9, 71.5, 60.5, 56.6, 52.69, 52.68, 52.5, 52.0, 43.2, 40.1, 39.5, 32.0, 27.8, 27.3; FT-IR (neat) 2927, 2863, 1732, 1565, 1435, 1265, 1150, 1044, 731, 700 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{35}H_{41}N_2O_6$: 585.2959, found 585.2971.

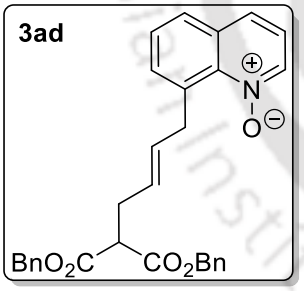


(*E*)-8-(6-Ethoxy-5-(ethoxycarbonyl)-6-oxohex-2-en-1-yl)quinoline 1-oxide 3ab. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.40; colourless liquid; yield 73% (52 mg); *E/Z* = 23:1 mixture of diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (d, *J* = 6.0 Hz, 1H), 7.67-7.62 (m, 2H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 6.5 Hz, 1H), 7.19-7.17 (m, 1H), 6.00-5.94 (m, 1H), 5.48-5.42 (m, 1H), 4.36 (d, *J* = 6.5 Hz, 2H), 4.14-4.08 (m, 4H), 3.36 (t, *J* = 7.5 Hz, 1H), 2.59 (t, *J* = 7.5 Hz, 2H), 1.18 (t, *J* = 7.5 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.1, 140.6, 137.6, 135.7, 134.0, 132.9, 132.6, 128.30, 127.4, 126.5, 126.3,

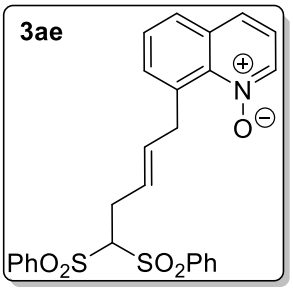
120.7, 61.3, 52.3, 39.7, 31.9, 14.1; FT-IR (neat) 2982, 2926, 1727, 1572, 1369, 1274, 1219, 1153, 1031, 815, 751 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{24}NO_5$: 358.1649, found 358.1649.



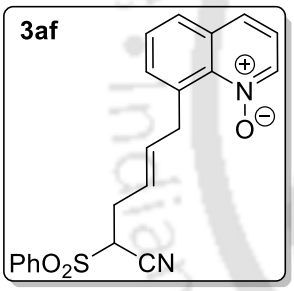
(*E*)-8-(6-Oxo-6-propoxy-5-(propoxycarbonyl)hex-2-en-1-yl) quinoline 1-oxide 3ac. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.50; colourless liquid; yield 71% (54.5 mg); *E/Z* > 23:1 mixture of diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (d, *J* = 6 Hz, 1H), 7.64 (t, *J* = 8.5 Hz, 2H), 7.44-7.38 (m, 2H), 7.18-7.15 (m, 1H), 5.98-5.92 (m, 1H), 5.46-5.40 (m, 1H), 4.33 (d, *J* = 6 Hz, 2H), 4.03-3.95 (m, 4H), 3.37 (t, *J* = 7.5 Hz, 1H), 2.58 (t, *J* = 7.0 Hz, 2H), 1.59-1.52 (m, 4H), 0.84 (t, *J* = 7.5 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.1, 140.5, 137.6, 135.6, 133.9, 132.9, 132.5, 128.2, 127.4, 126.7, 126.3, 120.6, 66.8, 52.2, 39.6, 31.8, 21.8, 10.3; FT-IR (neat) 2967, 1726, 1571, 1383, 1300, 1268, 1219, 1147, 1058, 814, 756 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{28}NO_5$: 386.1962, found 386.1967.



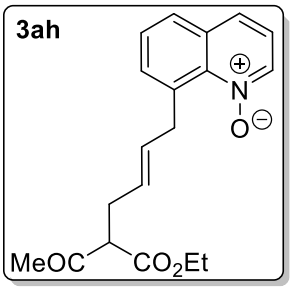
(*E*)-8-(6-(Benzyloxy)-5-((benzyloxy)carbonyl)-6-oxohex-2-en-1-yl) quinoline 1-oxide 3ad. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.40; colourless liquid; yield 72% (69.3 mg); *E/Z* > 23:1 mixture of diastereomers; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.40 (d, *J* = 6.0 Hz, 1H), 7.66-7.62 (m, 2H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 6.6 Hz, 1H), 7.30-7.28 (m, 6H), 7.25-7.23 (m, 4H), 7.18-7.16 (m, 1H), 6.00-5.95 (m, 1H), 5.45-5.40 (m, 1H), 5.08 (d, *J* = 3 Hz, 4H), 4.33 (d, *J* = 6.6 Hz, 2H), 3.50 (t, *J* = 7.8 Hz, 1H), 2.65 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.7, 140.6, 137.6, 135.6, 135.4, 134.3, 132.9, 132.6, 128.5, 128.3, 128.2, 128.1, 127.4, 126.5, 126.0, 120.7, 67.0, 52.3, 39.6, 31.9; FT-IR (neat) 3033, 2922, 1729, 1571, 1455, 1217, 1145, 973, 813,749, 696 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{30}H_{28}NO_5$: 482.1962, found 482.1965.



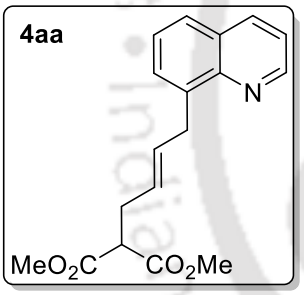
(*E*)-8-(5,5-bis(Phenylsulfonyl)pent-2-en-1-yl)quinoline 1-oxide 3ae. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.30; light yellow liquid; yield 82% (81 mg); *E/Z* = 12:1 mixture of diastereomers; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.42 (d, *J* = 6 Hz, 1H), 7.92-7.91 (m, 4H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.64-7.61 (m, 2H), 7.54-7.46 (m, 5H), 7.40 (d, *J* = 7.2 Hz, 1H), 7.24-7.21 (m, 1H), 5.89-5.84 (m, 1H), 5.40-5.36 (m, 1H), 4.45 (t, *J* = 6 Hz, 1H), 4.27 (d, *J* = 6.6 Hz, 2H), 2.86 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.6, 138.1, 137.7, 135.6, 135.3, 134.6, 133.4, 132.7, 129.8, 129.7, 128.4, 127.9, 126.7, 121.6, 120.9, 113.8, 57.8, 39.8, 30.2; FT-IR (neat) 3060, 2923, 1660, 1573, 1447, 1329, 1155, 1078, 750, 687, 553 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}NO_5S_2$: 494.1090, found 494.1097.



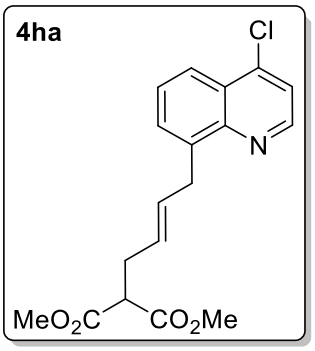
(*E*)-8-(5-Cyano-5-(phenylsulfonyl)pent-2-en-1-yl)quinoline 1-oxide 3af. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.40; colourless liquid; yield 42% (32 mg); *E/Z* = 12:1 mixture of diastereomers; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.41 (d, *J* = 6.0 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 2H), 7.75-7.73 (m, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.62 (t, *J* = 7.8 Hz, 2H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 7.2 Hz, 1H), 7.22-7.20 (m, 1H), 6.21-6.16 (m, 1H), 5.41-5.36 (m, 1H), 4.37 (d, *J* = 6 Hz, 2H), 3.92 (dd, J = 10.8, 4.2 Hz, 1H), 2.92-2.87 (m, 1H), 2.58-2.53 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.6, 138.1, 137.7, 135.7, 135.0, 134.6, 133.3, 132.7, 129.8, 129.1, 128.4, 127.7, 126.6, 124.2, 120.9, 84.0, 39.7, 29.0; FT-IR (neat) 2923, 2853, 1712, 1465, 1275, 1260, 1157, 1082 750 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{19}N_2O_3S$: 379.1111, found 379.1112.



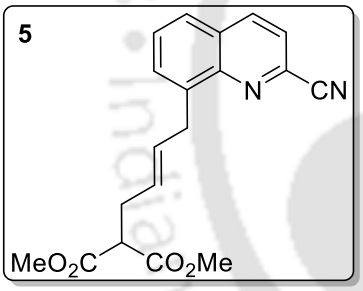
(*E*)-8-(5-(Ethoxycarbonyl)-6-oxohept-2-en-1-yl)quinoline 1-oxide 3ah. Analytical TLC on silica gel, 7:3 ethyl acetate/hexane R_f = 0.35; colourless liquid; yield 70% (46 mg); *E/Z* = 13:1 mixture of diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, *J* = 6 Hz, 1H), 7.68-7.64 (m, 2H), 7.46 (t, *J* = 8 Hz, 1H), 7.40 (d, *J* = 7 Hz, 1H), 7.21-7.18 (m, 1H), 5.99-5.93 (m, 1H), 5.42-5.37 (m, 1H), 4.34 (d, *J* = 7.5 Hz, 2H), 4.13-4.09 (m, 2H), 3.46 (t, *J* = 7.5 Hz, 1H), 2.56-2.52 (m, 2H), 2.17 (s, 3H), 1.18 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.0, 169.4, 140.6, 137.6, 135.6, 134.0, 133.0, 132.6, 128.3, 127.5, 126.5, 126.4, 120.7, 61.3, 59.8, 39.7, 31.3, 29.2, 14.1; FT-IR (neat) 2981, 2922, 1711, 1572, 1423, 1383, 1300, 1217, 1151, 1015, 815, 757 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{22}NO_4$: 328.1543, found 328.1547.



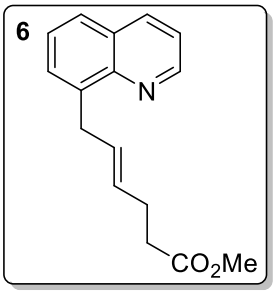
Dimethyl (*E*)-2-(4-(44uinoline-8-yl)but-2-en-1-yl)malonate 4aa. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.30; light brown liquid; yield 78% (24.5 mg); *E/Z* > 23:1 mixture of diastereomers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93-8.92 (m, 1H), 8.14-8.12 (m, 1H), 7.69-7.66 (m, 1H), 7.52-7.44 (m, 2H), 7.41-7.38 (m, 1H), 5.95-5.88 (m, 1H), 5.56-5.49 (m, 1H), 4.00 (d, *J* = 6.8 Hz, 2H), 3.66 (s, 6H), 3.43 (t, *J* = 7.6 Hz, 1H), 2.63 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 149.5, 146.6, 139.4, 136.4, 132.5, 128.8, 128.5, 126.9, 126.5, 126.3, 121.0, 52.5, 52.0, 34.1, 32.0; FT-IR (neat) 3004, 2952, 1731, 1497, 1434, 1275, 1149, 1025, 971, 793, 750 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{20}NO_4$: 314.1387, found 314.1384.



Dimethyl (*E*)-2-(4-(4-chloroquinolin-8-yl)but-2-en-1-yl)malonate 4ha. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.30; light brown liquid; yield 77% (26.8 mg); *E/Z* = 19:1 mixture of diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76-8.74 (m, 1H), 8.09-8.05 (m, 1H), 7.54-7.51 (m, 2H), 7.47-7.43 (m, 1H), 5.90-5.85 (m, 1H), 5.54-5.48 (m, 1H), 3.97 (d, *J* = 4.5 Hz, 2H), 3.65 (s, 6H), 3.42 (t, *J* = 7.5 Hz, 1H), 2.62 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.4, 148.7, 147.4, 142.8, 139.8, 132.2, 129.7, 127.4, 127.1, 126.5, 122.5, 121.1, 52.4, 51.8, 34.3, 31.9; FT-IR (neat) 2953, 1732, 1584, 1489, 1435, 1386, 1230, 1149, 971, 763 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{19}ClNO_4$: 348.0997, found 348.0992.



Dimethyl (*E*)-2-(4-(2-cyanoquinolin-8-yl)but-2-en-1-yl) malonate 5. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.30; light brown liquid; yield 75% (25.5 mg); *E/Z* > 23:1 mixture of diastereomers; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.4 Hz, 1H), 7.74-7.73 (m, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.62-7.60 (m, 2H), 5.86-5.82 (m, 1H), 5.58-5.54 (m, 1H), 3.97 (d, *J* = 7.2 Hz, 2H), 3.68 (s, 6H), 3.44 (t, *J* = 7.8 Hz, 1H), 2.63 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5, 146.6, 140.5, 137.7, 132.5, 131.8, 130.4, 129.5, 128.9, 127.5, 126.1, 123.3, 117.9, 52.6, 51.8, 33.9, 31.9. FT-IR (neat) 2924, 2235, 1731, 1434, 1261, 1150, 971, 841, 765 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{19}H_{18}NaN_2O_4$: 361.1159, found 361.1160.



Methyl (*E*)-6-(46uinoline-8-yl)hex-4-enoate 6. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.50; colorless liquid; yield 68% (17.5 mg); *E/Z* > 23:1 mixture of diastereomers; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.94 (d, *J* = 2.4 Hz 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 6.6 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.41-7.39 (m, 1H), 5.88-5.84 (m, 1H), 5.59-5.54 (m, 1H), 4.01 (d, *J* = 6.6 Hz, 2H), 3.63 (s, 3H), 2.40-2.36 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.8, 149.5, 146.6, 139.6, 136.5, 130.2, 129.7, 128.9, 128.5, 126.5, 126.3, 121.0, 51.6, 34.2, 34.1, 28.0; FT-IR (neat) 2949, 2915, 1732, 1596, 1497, 1435, 1365, 1151, 970, 826, 793 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{18}NO_2$: 256.1332, found 256.1331.

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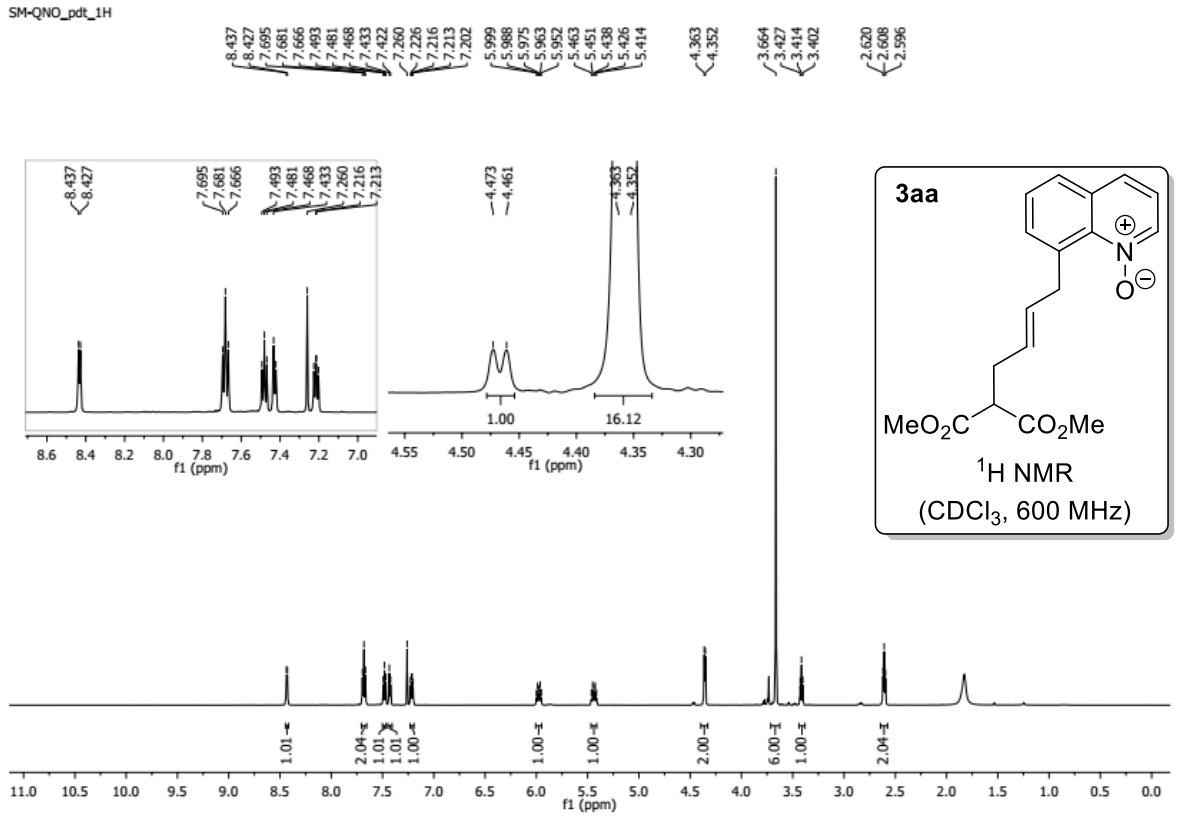
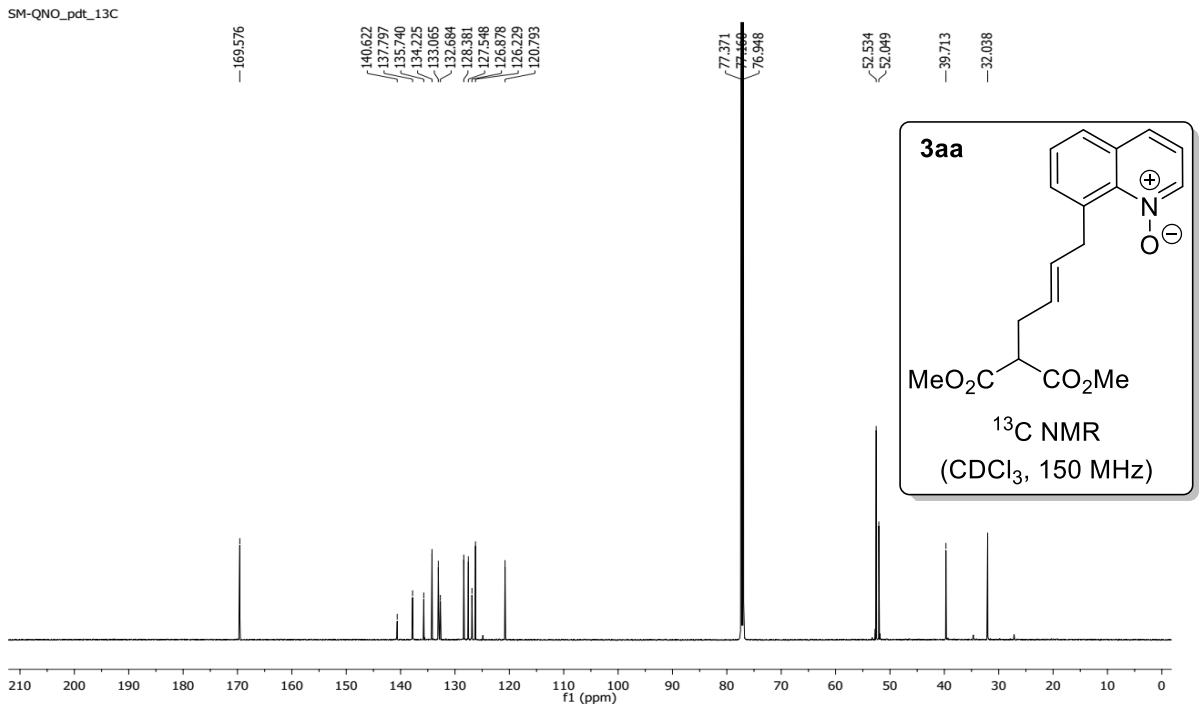
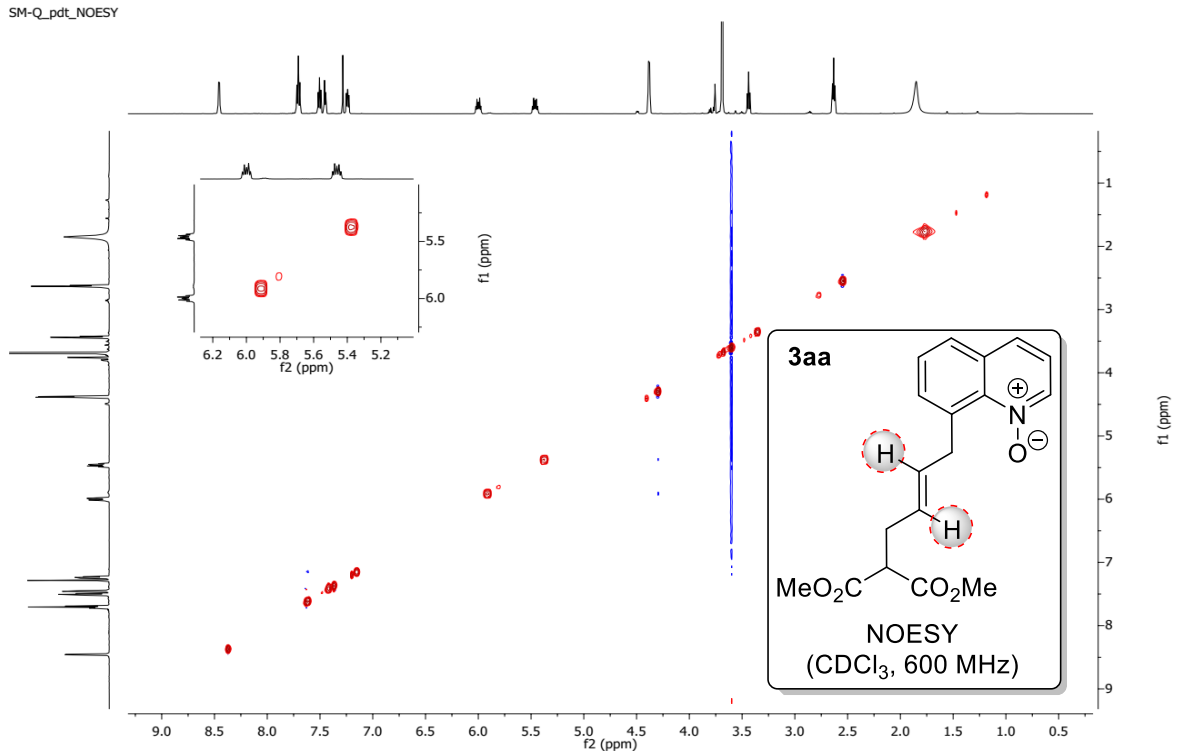
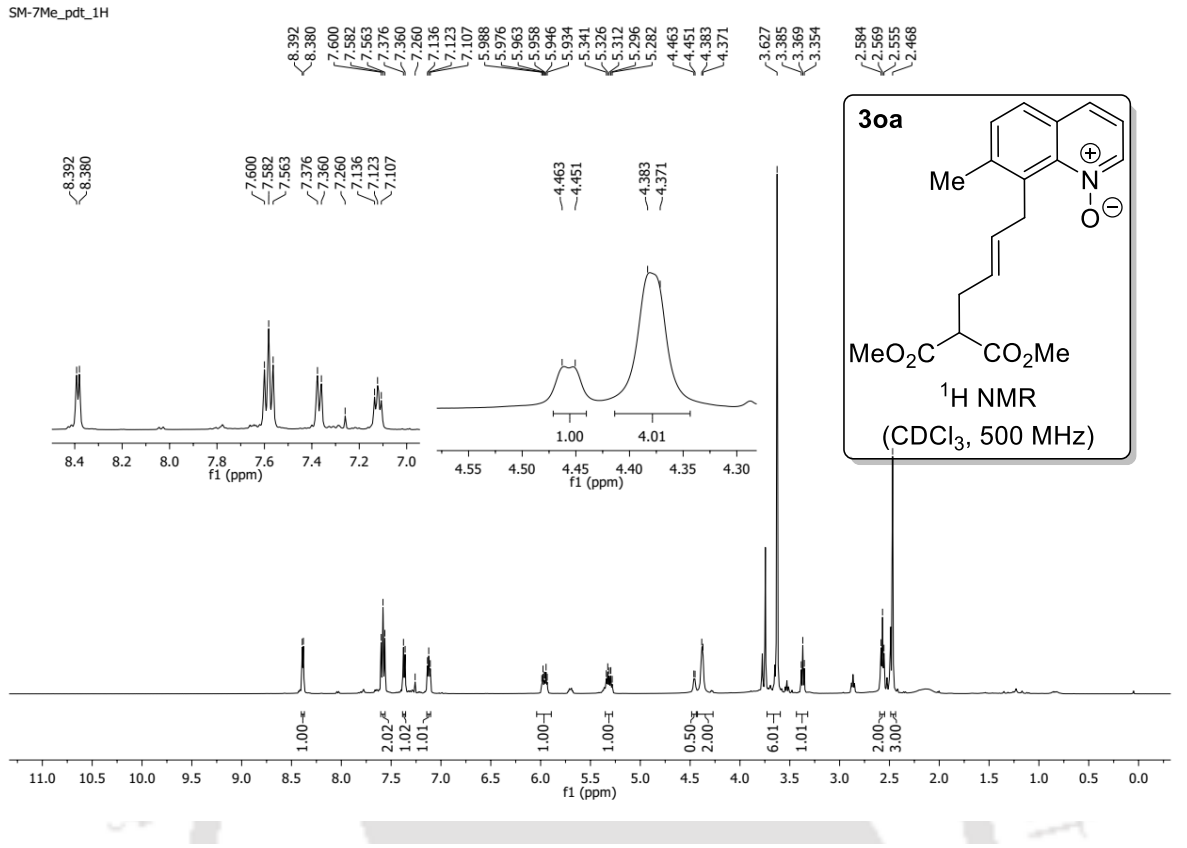
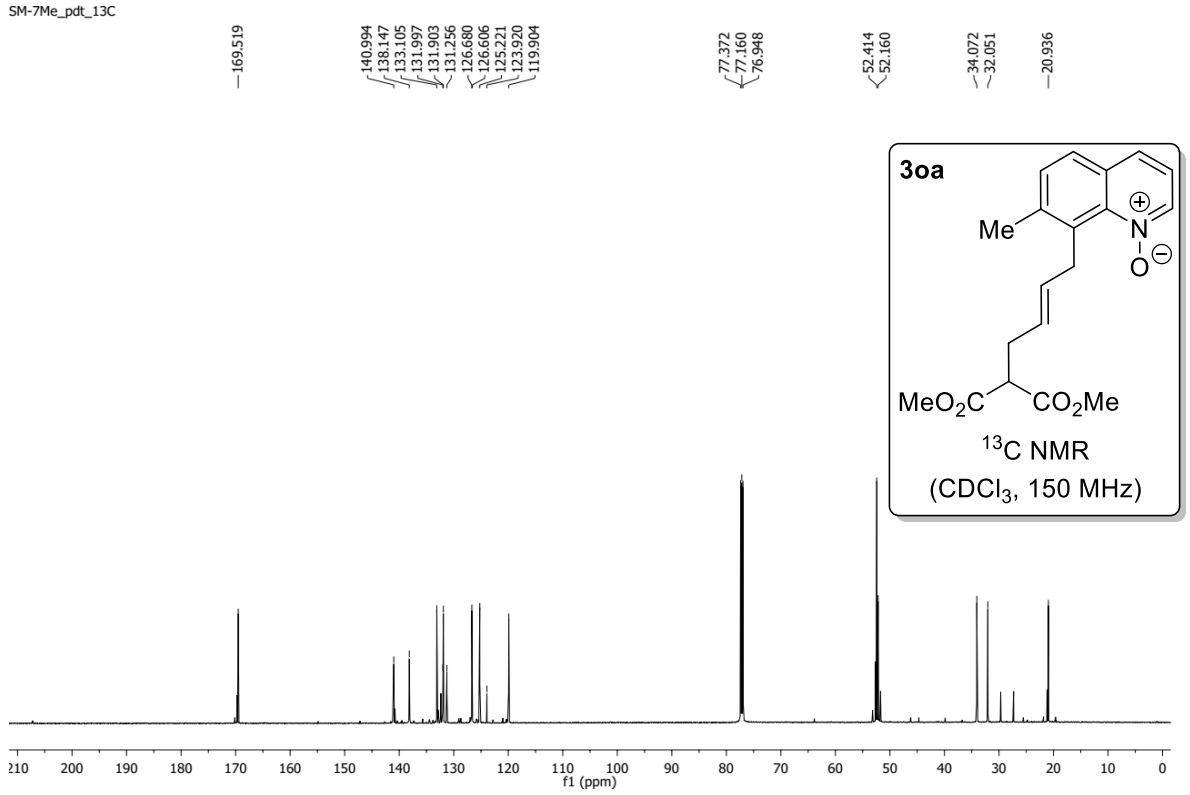
2.6 Selected NMR Spectra

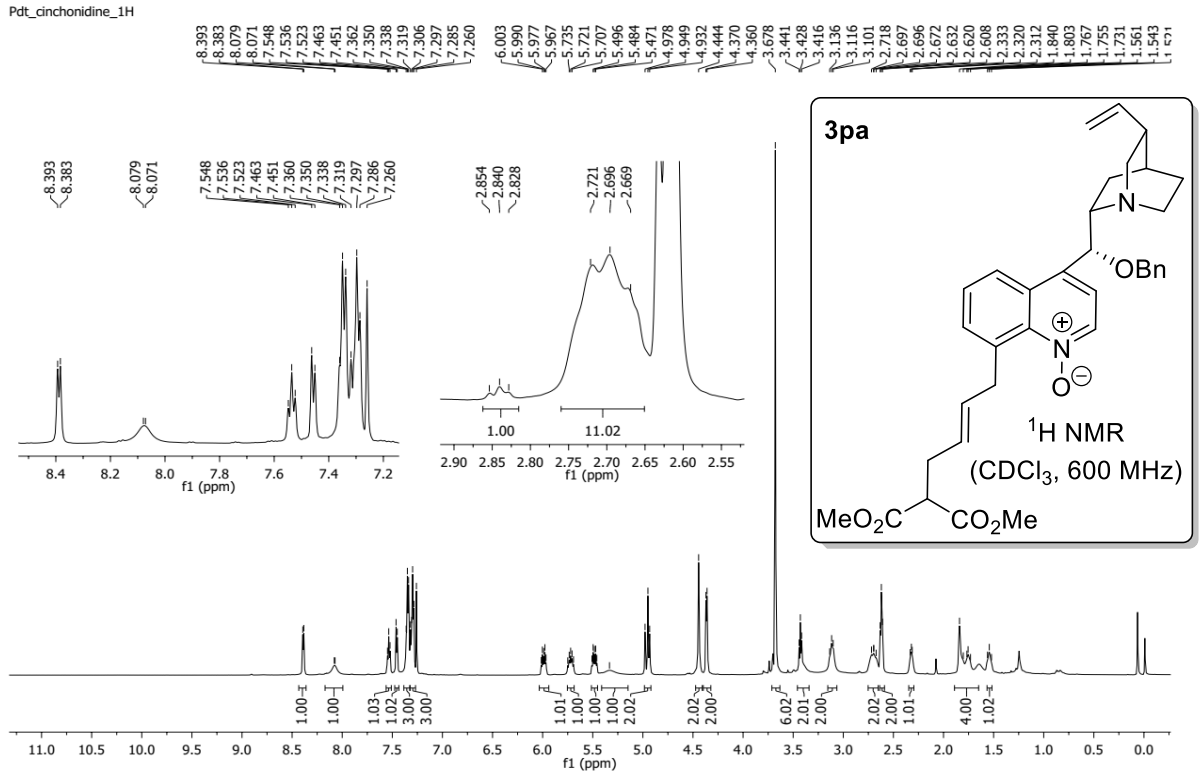


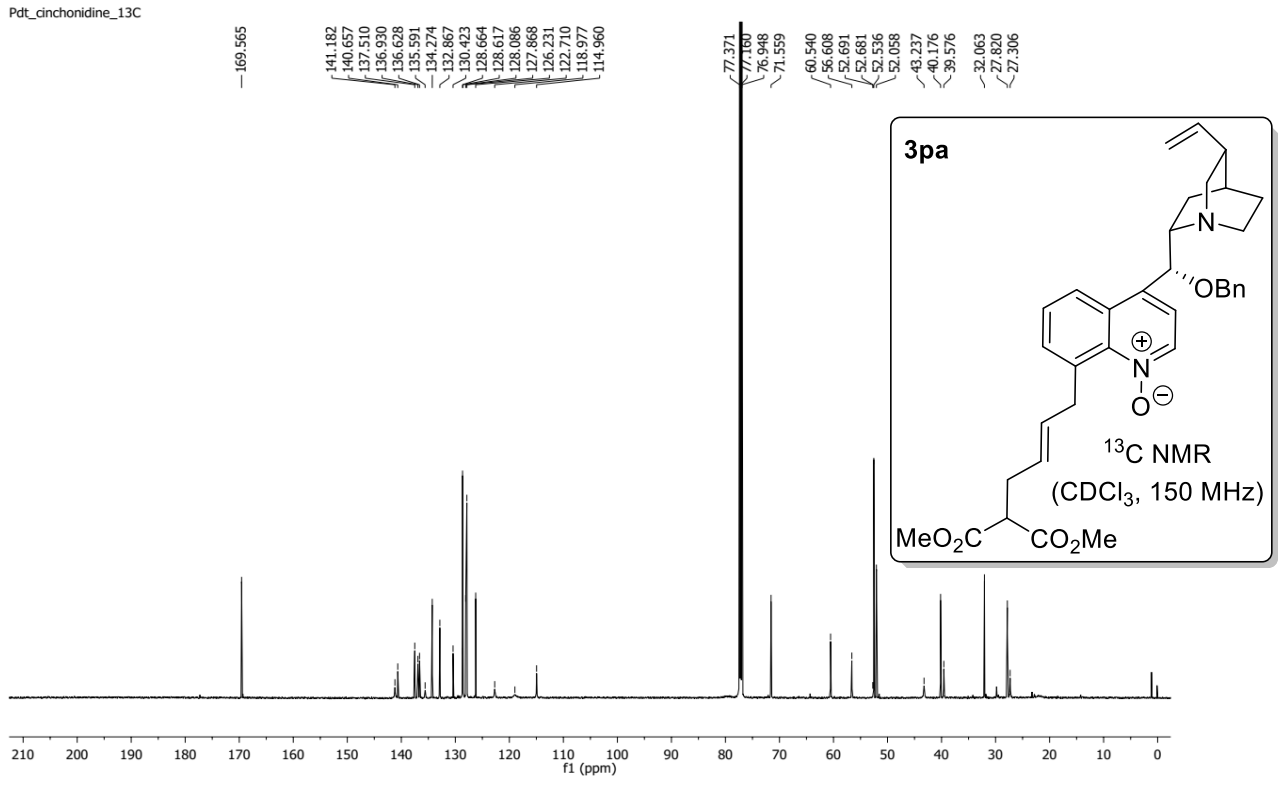


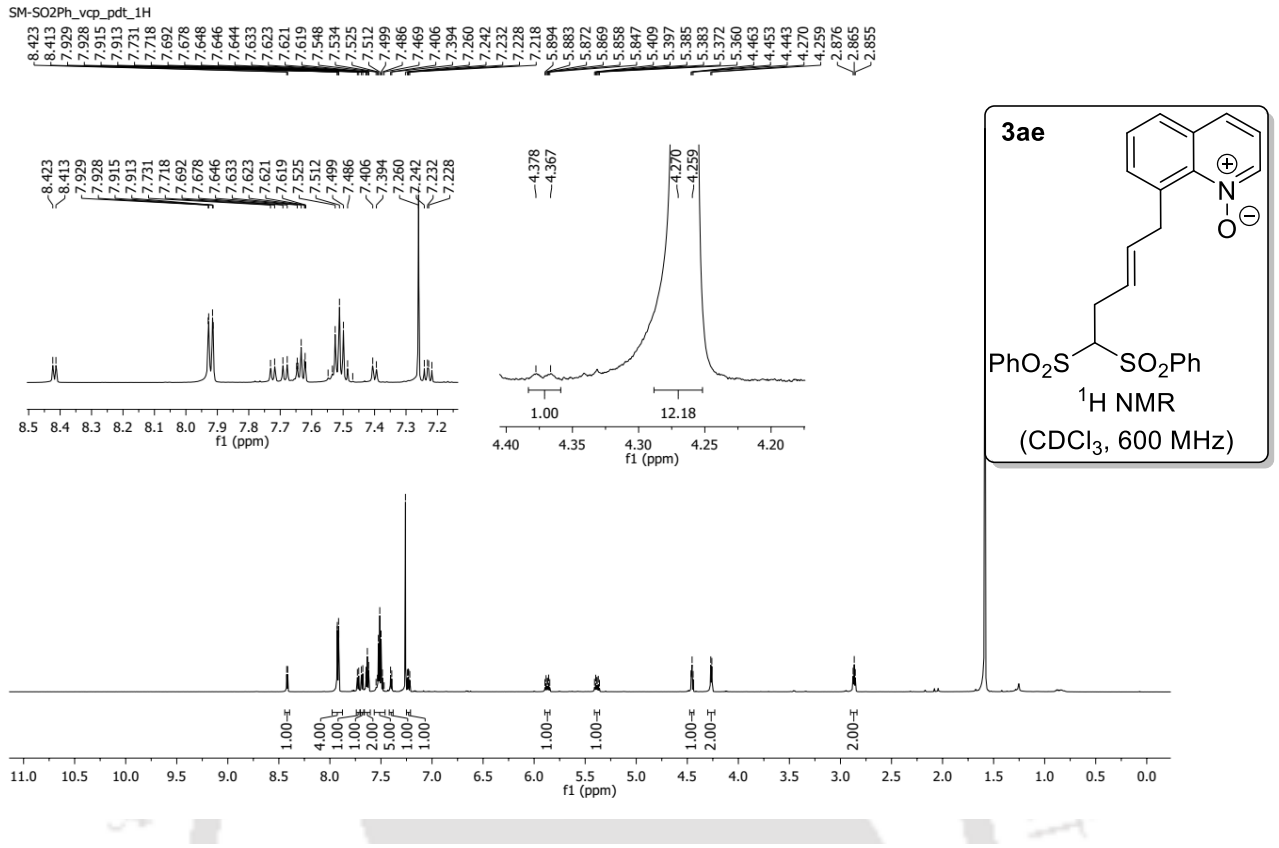


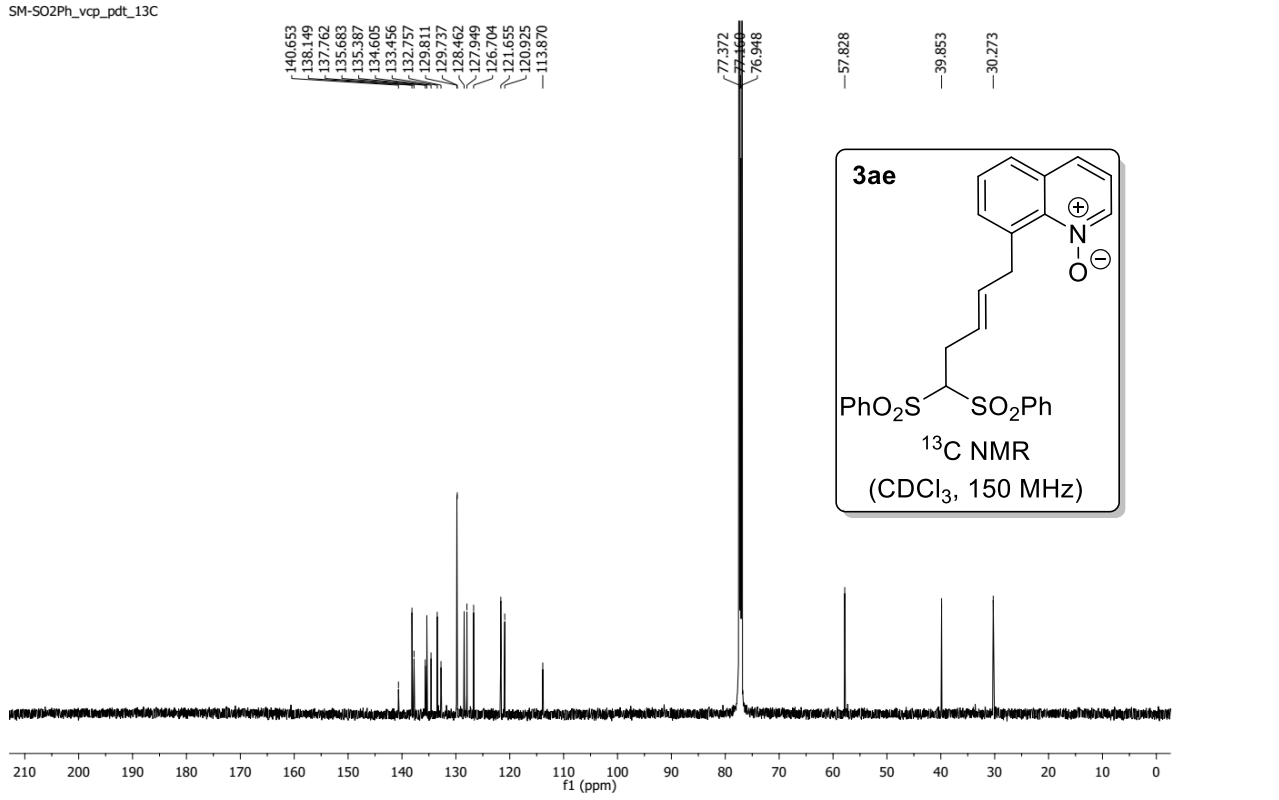






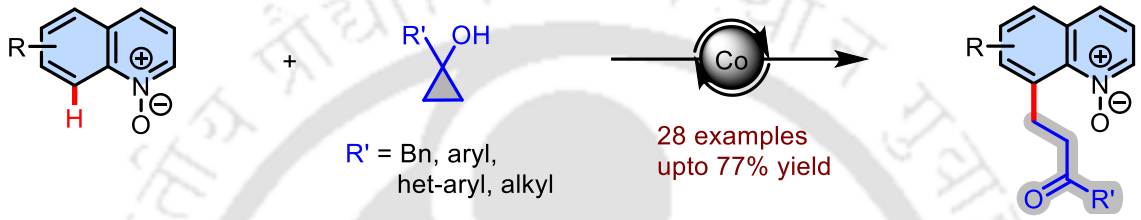






Chapter 3

C8-Alkylation of Quinolines with Cyclopropanols



✔ C8-alkylation ✔ versatile cobalt catalysis ✔ drug mutation ✔ substrate scope

Org. Lett. **2023**, *25*, 7805.

C8-Alkylation of Quinolines with Cyclopropanols

Substituted quinolines are essential building blocks in the field of drug discovery and material sciences.[1] As a result, synthetic modification of these compounds has been recognized as an important research topic. In the previous chapter, we have demonstrated an atom economical route for C8-H allylation of quinoline *N*-oxide utilizing vinylcyclopropane as coupling partner under Rh(III)-catalysis. Later, we have realized the use of expensive catalyst is the primary obstacle in the path of sustainability. A detailed literature study on the C8-H functionalization has just discovered us that most of these reactions have used rare second and third row transition-metal-catalysts (Rh, Ir, Pd, Ru etc.).[2] Whereas, first-row transition-metal-catalysis is fascinating to the chemists due to their low toxicity and high abundant nature. Thus, our recent focus has been shifted towards quinoline functionalization with less toxic metal catalysis in view of economic and sustainable approach.[3] In continuation of our previous interest in C-H/C-C functionalization using strained ring system, here, we have introduced cyclopropanol (Cyp) as new alkylating agent to meet the synthetic diversities. Recently, C8-alkylation of quinoline has been the subject of intensive investigation due to their potential applications (Figure 1).[4]

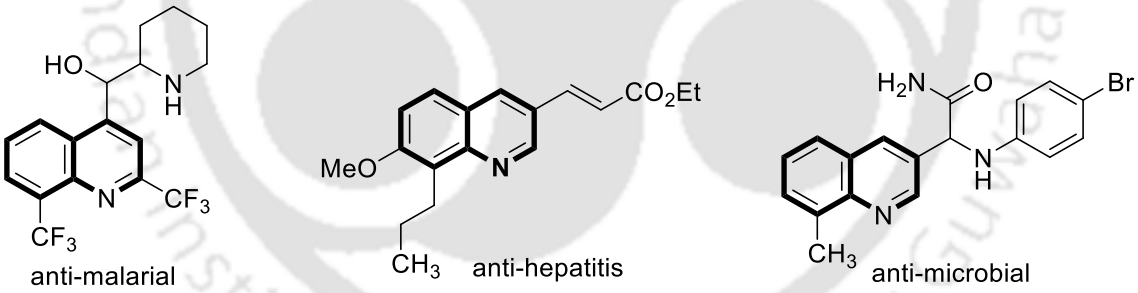


Figure 1. Selected Examples of Bioactive C8-Alkyl Quinoline Derivatives

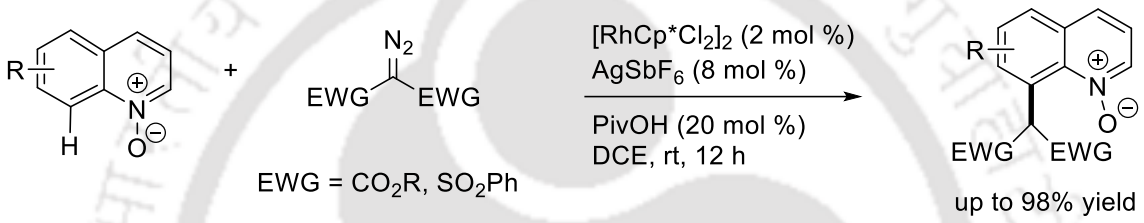
Cyclopropanols offer a unique alkylation strategy producing *β*-substituted ketones *via* C-C bond cleavage.[5] However, the notable progress has been made on cyclopropanols often focused on the *ortho*-C-H activation, while the distal C-H alkylation using cyclopropanol is rarely studied. Thus, to minimize the requirement of heavy metal-catalysis and silver-based oxidants and to promote the novelty and sustainability, exploration of comparatively abundant and less hazardous oxidants and catalyst would be desirable.[6] In this context, the recently studied high-valent Co-complex has been evolved as versatile, robust and less-expensive catalyst for C-H functionalization reactions by Kanai/Matsunaga, Glorius, Ellman, Shi and along with other

groups.[7] Given the intriguing reactivity Co-catalyst, we aim to combine quinoline *N*-oxide with cyclopropanol to explore a new approach for constructing C8-alkylated quinolines.

3.1 Literature Study

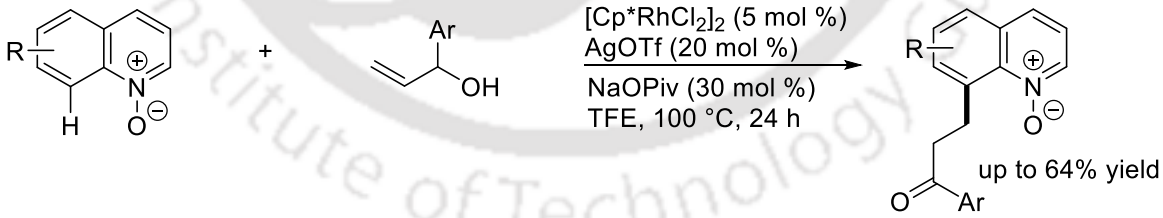
3.1.1 C8-Alkylation of Quinolines

Chang and co-workers developed *N*-oxide-directed C8-alkylation using diazo carbonyl compounds with QNOs under Rh(III)-catalysis (Scheme 1).[4a] The synthesis of 8-alkylated compounds was designed at room temperature with a wide range of varied substrates, including carbamate, siloxy, acetoxy, acetal, aldehyde, ketone and ester groups in moderate to high yields.



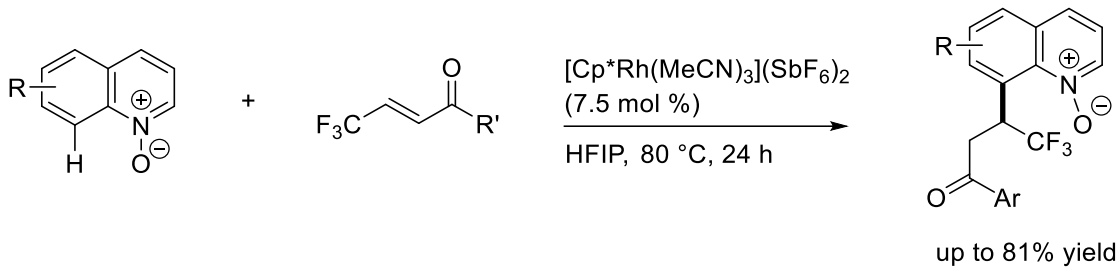
Scheme 1. Rh(III)-Catalyzed C8-Alkylation of QNOs with Diazo Malonates

A $[RhCp^*Cl_2]_2$ catalyzed C8-alkylation of QNO with allyl alcohol has been accomplished by Sundararaju group (Scheme 2).[8] The DFT studies and experimental results unveiled *β*-hydride elimination over *β*-hydroxy elimination by Cp*Rh(III)-catalyst to afford the targeted *β*-aryl ketones.



Scheme 2. C8 Alkylation of Quinoline *N*-Oxides using Allyl Alcohols

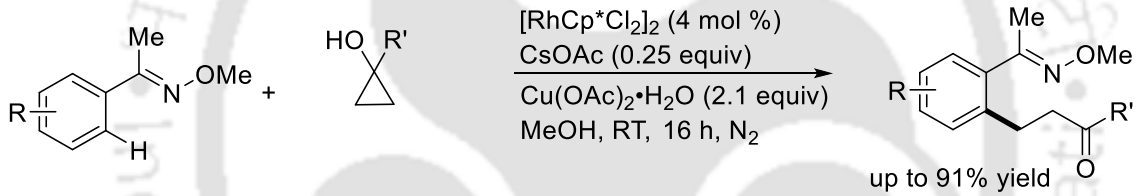
Lee group demonstrated a Rh(III)-catalyzed conjugate addition of *β*-CF_3-enones with QNOs to produce CF_3 embedded *β*-aryl ketones (Scheme 3).[9] The reaction proceeded in good yield for aryl, alky and hetero-aryl vinyl ketones. However, with the electron-deficient aryl vinyl ketones exhibited comparatively lower yields.



Scheme 3. C8-Alkylation of QNOs with *α,β*-Unsaturated Ketones under Rh(III)-Catalysis

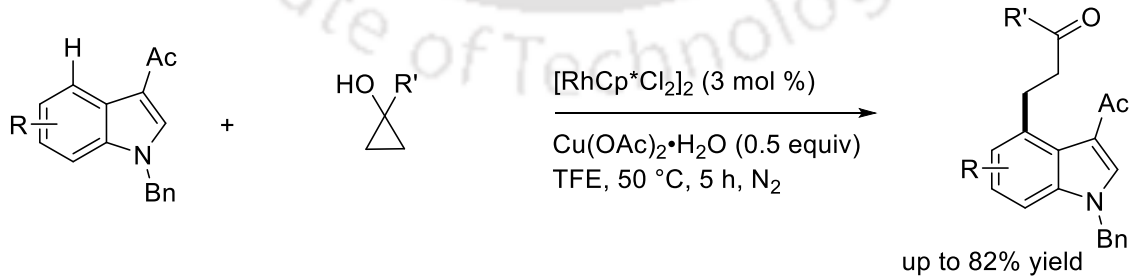
3.1.2 Ring Opening Reactions of Cyclopropanols

Li and co-workers established a combination of C-H bond activation with ring opening of cyclopropanols under Rh(III)-catalysis for the first time (Scheme 4).[5a] The reaction ensured broad substrate scope, regioselectivity and functional group tolerance under mild conditions. Both oxime ethers and *N*-pyrimidylindoles proved to be arene substrates for the developed protocol.



Scheme 4. Rh(III)-Catalyzed *ortho*-Alkylation of Arenes with Cyclopropanols

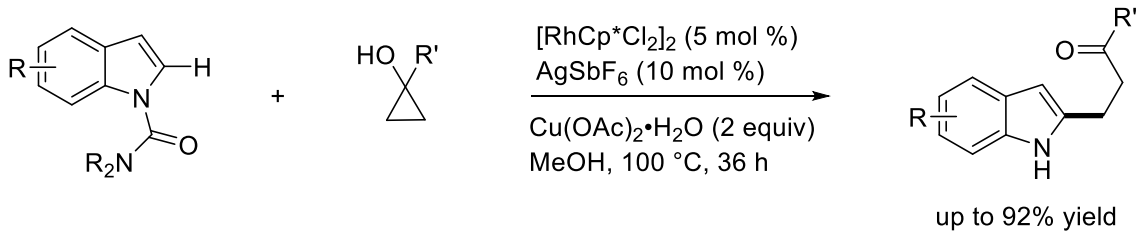
Our group developed weak chelation-guided C4-alkylation of indoles utilizing the strain cyclopropanol ring as an alkylating agent (Scheme 5).[10] The reaction supported numerous functional group tolerances and wide substrate scope. Important practical features include post-synthetic amendments and late-stage functionalization.



Scheme 5. C4-Selective Alkylation of Indoles using Cyclopropanols

Anbarasan and co-workers reported a synthetic method for synthesizing C2-alkylated NH-free indoles employing cyclopropanol under Rh-catalysis (Scheme 6).[11] The room temperature

reaction condition allows variety of C2-alkylated quinoline synthesis in good yield. A *N*,*N*-dialkylcarbamoyl group was used as a traceless directing group in the procedure.



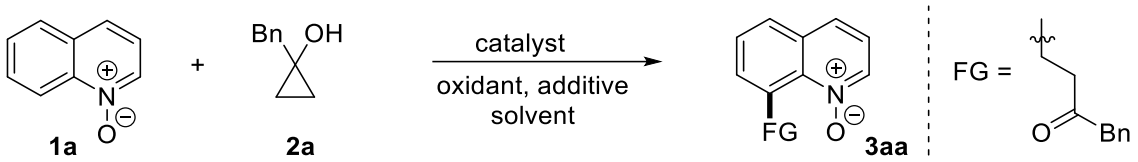
Scheme 6. C2-Alkylation of Indoles Using *N*,*N*-Dialkylcarbamoyl as Traceless DG

3.2 Present Study

This chapter describes C8-alkylation strategy using quinoline *N*-oxides with cyclopropanols using [Cp*Co(CO)I_2] as versatile catalyst. Initially, we commenced the optimization studies taking quinoline *N*-oxide **1a** and 1-benzylcyclopropan-1-ol **2a** as model substrates (Table 1). Gratifyingly, the reaction proceeded to produce C8-alkylated product **3aa** in 75% yield in 15 mol % of [Cp*Co(CO)I_2] and 1 equiv of $Cu(OAc)_2$•H_2O in 2,2,2-trifluoroethanol (TFE) for 5 h at 70 °C under argon (entry 1, Table 1). Further screening of different oxidants other than $Cu(OAc)_2$•H_2O, such as $Mn(OAc)_3$•$2H_2O$, $K_2S_2O_8$, BQ, CuO were failed to yielded the best result. In addition, additives such as NaOPiv·H_2O, NaOAc, AcOH and $AdCO_2H$ showed inferior results. Solvent screening showed TFE is the best compared to MeOH, $(CH_2Cl_2)_2$, HFIP, *t*-AmOH and CH_3CN. Moreover cobalt-sources such as [Cp*Co$(CH_3CN)_3$]$(SbF_6)_2$, $Co(OAc)_2$ and $Co(acac)_2$ were failed to catalyze the reaction. Control experiments confirmed that the combination of [Cp*Co(CO)I_2] and $Cu(OAc)_2$•H_2O was crucial to accomplish the C8-alkylation.

Having the optimized reaction conditions, we scrutinized the reaction scope using diversely substituted quinoline *N*-oxides **1b**-**p** with cyclopropanol **2a** as representative substrate (Table 2). The QNO substrate having 2-methyl substitution **1b** afforded alkylated product **3ba** in 77% yield. Further, alkylation of 3-substituted quinoline substrate bearing furanyl **1c,** methyl **1d** and trifluoromethylphenyl **1e** underwent smoothly, providing targeted products **3ca-ea** in 68-74% yield. Moreover, transitioning to halogen bearing quinoline *N*-oxides with 4-chloro **1f** and 5-bromo **1h** were tolerated to afford **3fa** and **3ha** in 60% and 74% yields, respectively. Similarly, the reaction between cyclopropanol **2a** with 4-methyl **1g** and 5-phenyl **1i** substituted quinoline *N*-oxides were amenable to deliver alkylated products **3ga** and **3ia** in 73% and 72% yields,

Table 1. Optimization of Reaction Conditions[a]

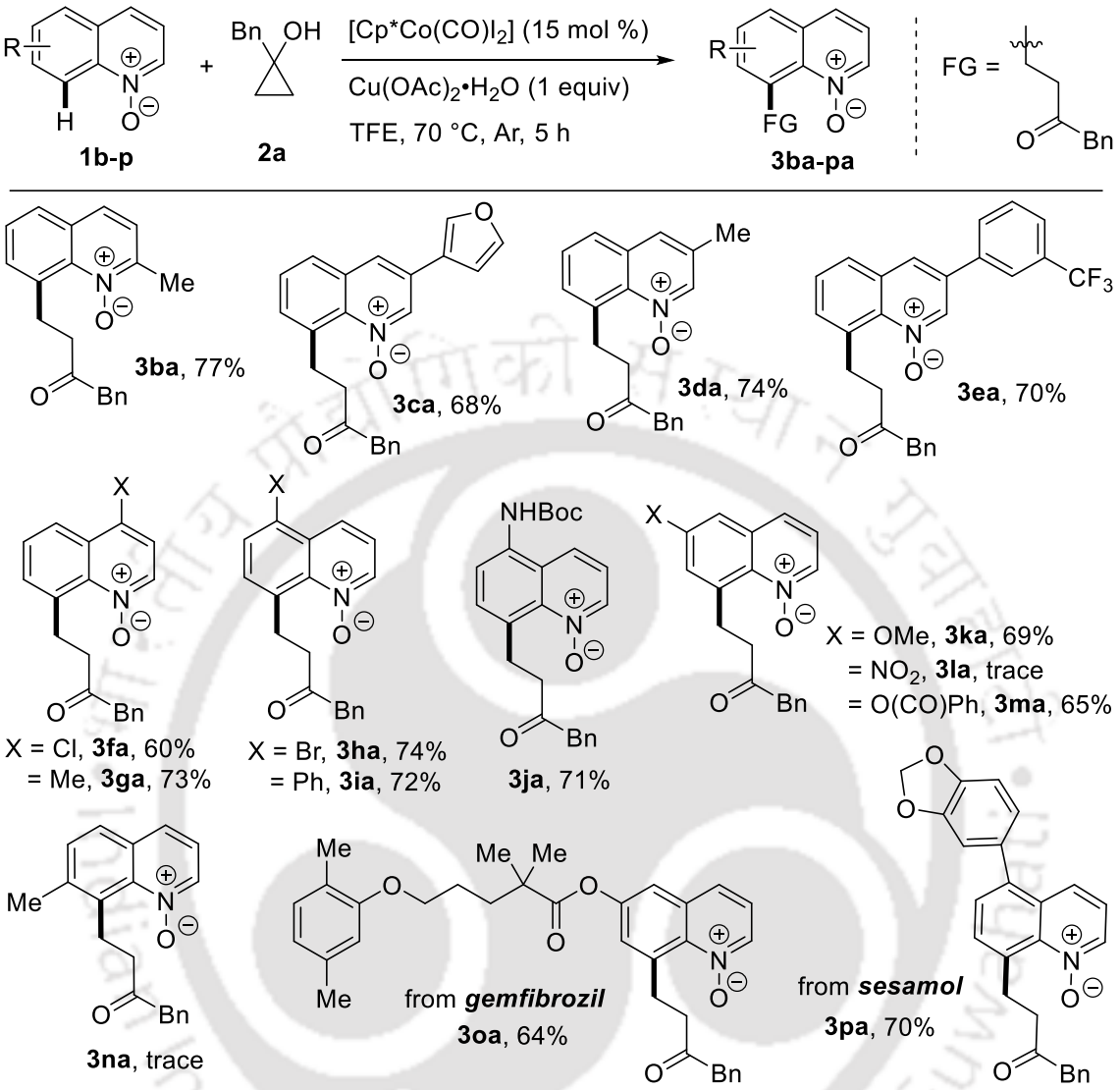


1a **2a** **3aa**

Entry	Catalyst	Oxidant	Solvent	Yield (%)[b]
1	**[Cp*Co(CO)I$_2$]**	**Cu(OAc)$_2$•H$_2$O**	**TFE**	**75**
2	[CoCp*(CO)I$_2$]	Mn(OAc)$_3$•2H$_2$O	TFE	32
3	[CoCp*(CO)I$_2$]	$K_2S_2O_8$	TFE	n.d.
4	[CoCp*(CO)I$_2$]	BQ	TFE	12
5	[CoCp*(CO)I$_2$]	CuO	TFE	15
6	[CoCp*(CO)I$_2$]	Cu(OAc)$_2$•H$_2$O	TFE	11
7	[CoCp*(CO)I$_2$]	Cu(OAc)$_2$•H$_2$O	TFE	n.d.
8	[CoCp*(CO)I$_2$]	Cu(OAc)$_2$•H$_2$O	TFE	trace
9	[CoCp*(CO)I$_2$]	Cu(OAc)$_2$•H$_2$O	TFE	trace
10	[Cp*Co(CO)I$_2$]	Cu(OAc)$_2$•H$_2$O	MeOH	n.d.
11	[Cp*Co(CO)I$_2$]	Cu(OAc)$_2$•H$_2$O	DCE	trace
12	[Cp*Co(CO)I$_2$]	Cu(OAc)$_2$•H$_2$O	HFIP	63
13	[Cp*Co(CO)I$_2$]	Cu(OAc)$_2$•H$_2$O	*t*AmOH	n.d.
14	[Cp*Co(CO)I$_2$]	Cu(OAc)$_2$•H$_2$O	CH_3CN	n.d.
15	[Cp*Co(CO)I$_2$]	Cu(OAc)$_2$•H$_2$O	TFE:HFIP (1:1)	67
16	Co(OAc)$_2$	Cu(OAc)$_2$•H$_2$O	TFE	n.d.
17	Co(acac)$_2$	Cu(OAc)$_2$•H$_2$O	TFE	n.d.
18	[Cp*Co(CH_3CN)$_3$](SbF$_6$)$_2$	Cu(OAc)$_2$•H$_2$O	TFE	trace
19[c]	[Cp*Co(CO)I$_2$]	Cu(OAc)$_2$•H$_2$O	TFE	32
20[d]	[Cp*Co(CO)I$_2$]	Cu(OAc)$_2$•H$_2$O	TFE	37
21[e]	[Cp*Co(CO)I$_2$]	Cu(OAc)$_2$•H$_2$O	TFE	15
22[f]	[Cp*Co(CO)I$_2$]	Cu(OAc)$_2$•H$_2$O	TFE	21
23[g]	[Cp*Co(CO)I$_2$]	Cu(OAc)$_2$•H$_2$O	TFE	55

[a]Reaction condition: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (15 mol %), oxidant (0.2 mmol), TFE (1 mL), 70 ˚C, Ar, 5 h. [b]Isolated yield. [c]0.5 equiv of oxidant. [d]1.5 equiv of oxidant. [e]At 100 °C temperature. [f]O_2 atmosphere. [g]10 mol% catalyst was used. n.d. = not detected.

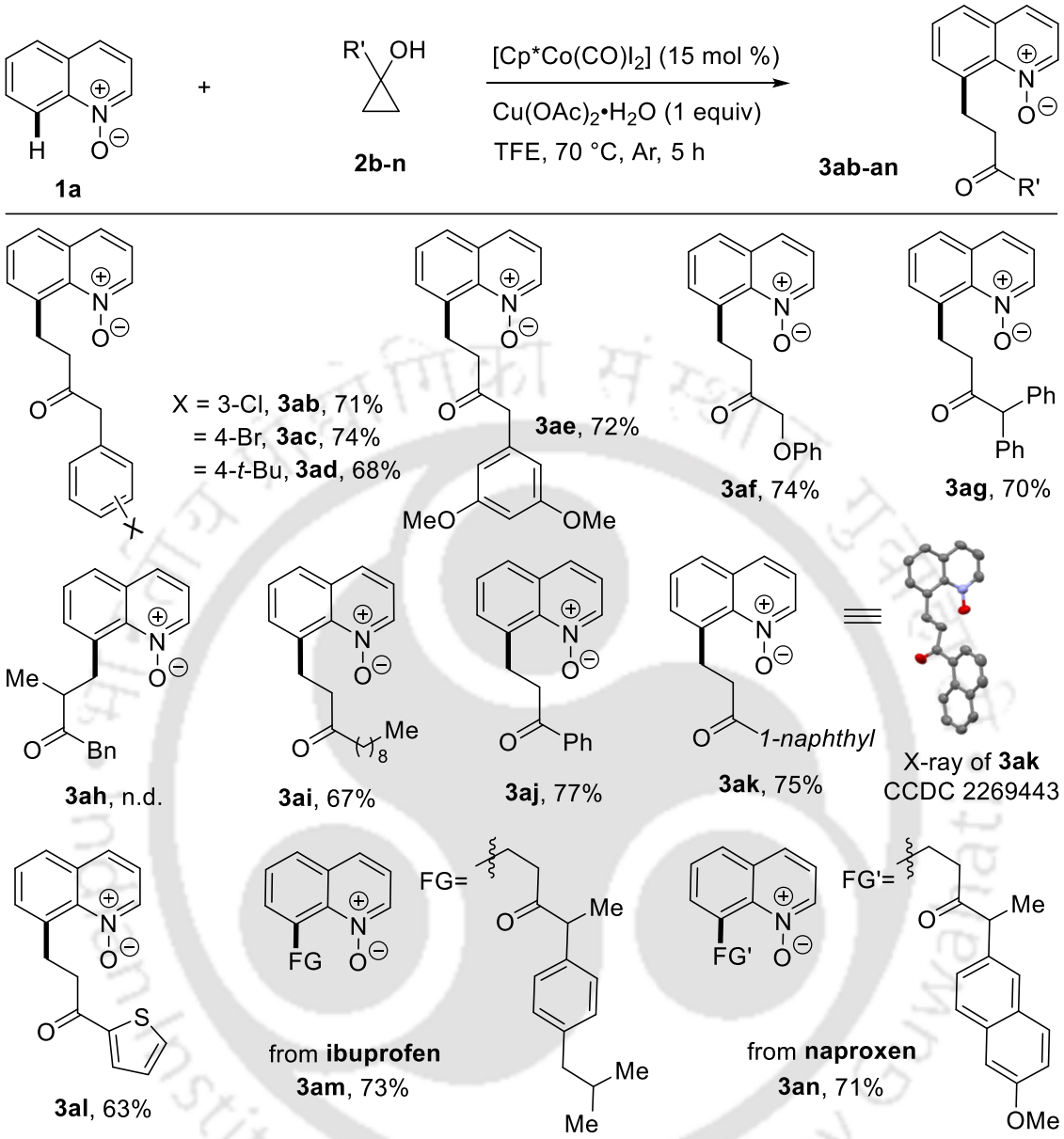
Table 2. Substrates Scope of QNOs[a,b]



[a]Reaction condition: **1a** (0.2 mmol), **2a** (0.4 mmol), [Cp*Co(CO)I_2] (15 mol %), Cu(OAc)$_2$•H_2O (0.2 mmol), TFE (1 mL), 70 ˚C, Ar, 5 h. [b]Isolated yield.

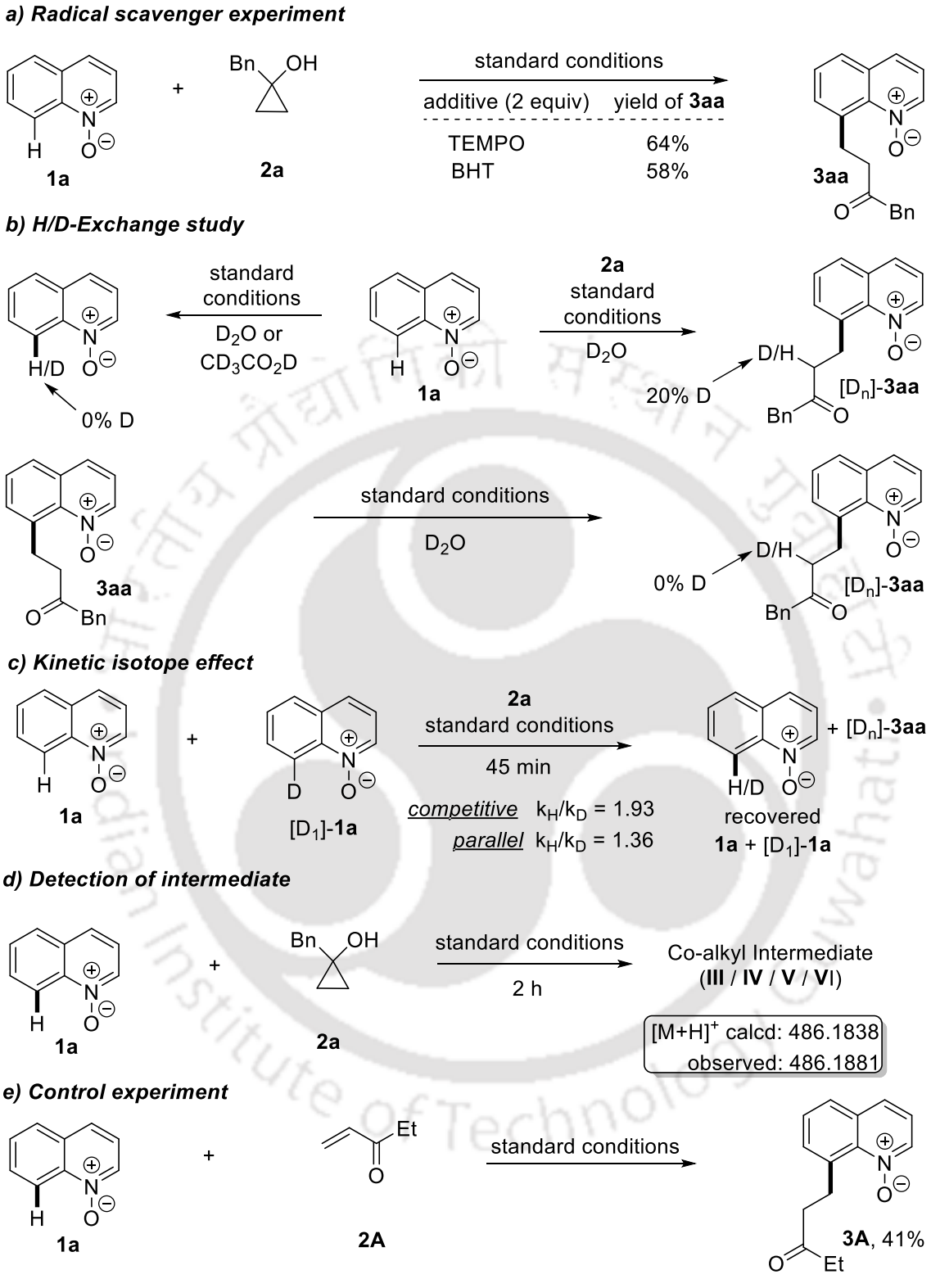
respectively. Furthermore, the alkylation of QNO substrates with amine **1j**, ether **1k** and ester **1m** functionalities were successful, producing **3ja**, **3ka** and **3ma** in 65-71% yields. While, the electron-withdrawing effect of nitro group has been observed for 6-nitroquinoline *N*-oxide **1l**, resulting alkylation in trace amount. A similar outcome was noted for 7-methylquinoline *N*-oxide **1n**, although, it could be steric hinderance in the coupling region. In addition, gemfibrozil and sesamol tethered QNO **1o** and **1p** participated efficiently in the alkylation to give **3oa** and **3pa** in 64% and 70% yields, respectively, representing the potentiality against the bio-active compounds for late-stage modifications.

Table 3. Substrates Scope of Cyclopropanols[a,b]



[a]Reaction condition: **1a** (0.2 mmol), **2a** (0.4 mmol), [Cp*Co(CO)I_2] (15 mol %), Cu(OAc)$_2$•H_2O (0.2 mmol), TFE (1 mL), 70 ˚C, Ar, 5 h. [b]Isolated yield.

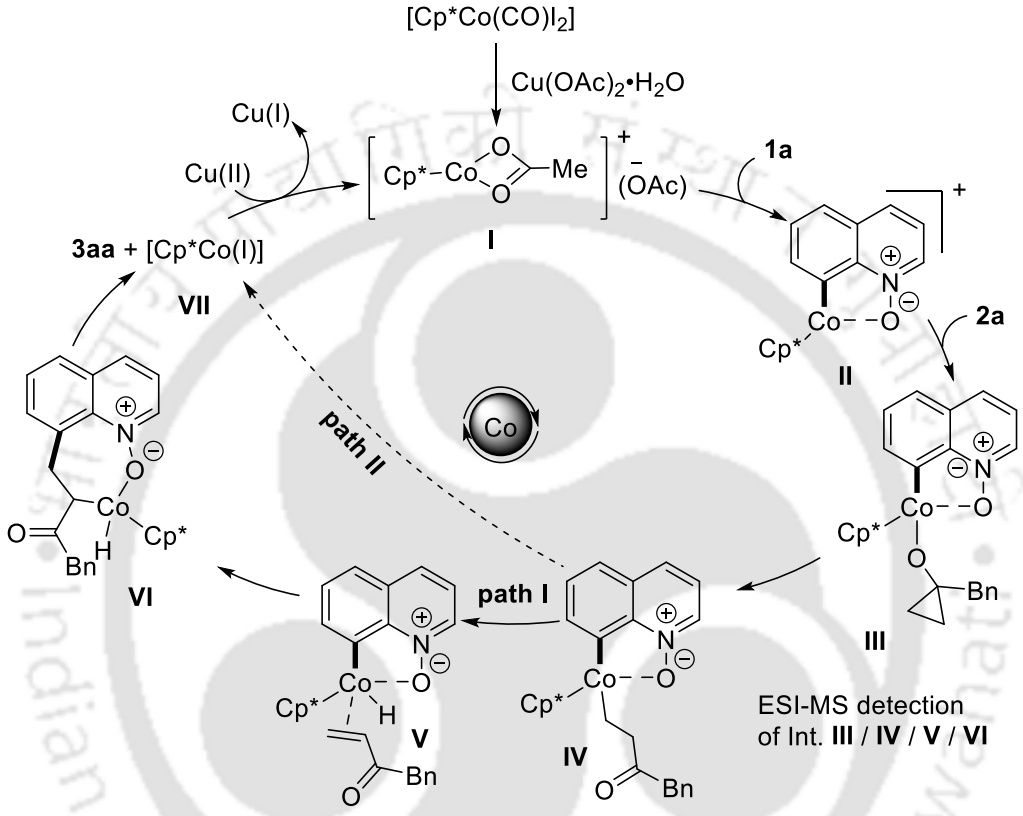
The reaction was further extended to comprise the variation of cyclopropanols including benzyl, alkyl, aryl and (hetero)aryl substituents **2b-n** with quinoline *N*-oxide **1a** as model substrate (Table 3). Substrates having substitution at benzyl ring of cyclopropanol with 3-chloro **2b**, 4-bromo **2c** and 4-*tert*-butyl **2d** successfully coupled to produce **3ab-ad** in 68-74% yields, whereas, 3,5-dimethoxy Cyp **2e** delivered **3ae** in 72% yield. Further, 1-phenoxymethyl **2f** and diphenylmethyl **2g** cyclopropanols proved to be viable in furnishing the selective alkylation at C8-position, giving **3af** and **3ag** in 74% and 70% yields, respectively. However,



Scheme 7. Preliminary Mechanistic Investigation

cyclopropanol with methyl substitution at the cyclopropane ring **2h** was failed to perform C8-alkylation due to steric hindrance. Although, long alkyl chain 1-nonyl derived cyclopropanol **2i** delivered **3ai** in 67% yield. Moreover, the aryl and het-aryl substituted cyclopropanols such

as phenyl **2j**, 1-naphthyl **2k** and 2-thienyl **2l** undergo alkylation effortlessly to furnish **3aj-al** in 63-77% yields. A single crystal X-ray analysis established the structure of **3ak** (CCDC 2269443). Further, nonsteroidal anti-inflammatory drugs ibuprofen and naproxen embedded cyclopropanols **2m** and **2n** underwent reaction with QNO **1a** to deliver **3am** and **3an** in 73% and 71% yields, respectively, illustrating the synthetic versatility of the protocol.

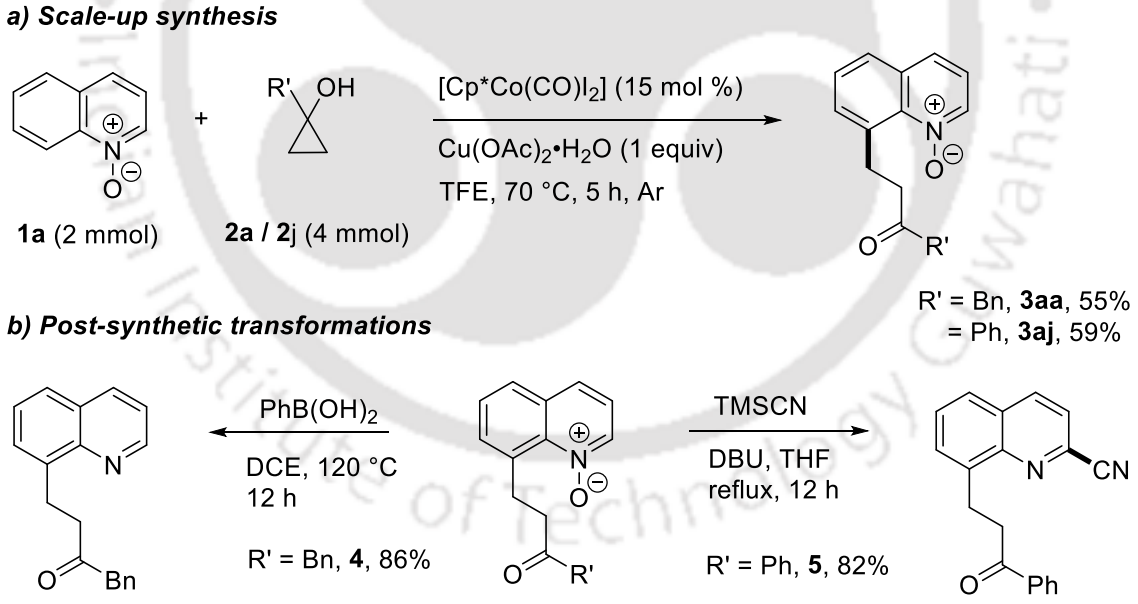


Scheme 8. Plausible Reaction Pathway

To elucidate reaction pathway, a set of preliminary investigations were performed. At first, C8-alkylation was made in presence of radical scavengers like 2,2,6,6-tetramethyl-piperidine 1-oxyl (TEMPO) and butylated hydroxytoluene (BHT) with the standard substrate **1a** and **2a** (Scheme 7a). No significant decrement in **3aa** yield, ruled out the possibility of a radical pathway. Moreover, the H/D-exchange reactions using D_2O or CD_3CO_2D co-solvent exhibit no deuteration in absence of **2a**, however, its presence allows the 20% deuteration at α-keto position of the isolated [D_n]-**3aa** (Scheme 7b). The above results indicate that the reaction may occur *via* an olefin intermediate formation. Post coupling H/D scrambling experiment provided an additional support to the statement as no deuteration was found in **3aa**. The kinetic isotope experiments, competitive and parallel, using **1a** and [D1]-**1a** with **2a** yielded a k_H/k_D of 1.93 and 1.36, respectively, precluding C-H bond cleavage as rate determining step (Scheme 7c). In

addition, the formation of Co(III)-alkyl species was verified by the HRMS analysis of the reaction mixture (Scheme 7d). A successful control experiment between QNO **1a** and ethyl vinyl ketone **2A**, validates the presence of olefin intermediate during the course of reaction (Scheme 7e).

These mechanistic experiments and literature precedents[4,5] suggest that [Cp*Co(CO)I_2] with $Cu(OAc)_2$•H_2O may generate the active Co(III)-species **I**, which ultimately activate the C8-H bond of quinoline *N*-oxide **1a** *via* 5-membered metallacycle to produce **II** (Scheme 8). Coordination of cyclopropanol **2a** can produce **III**, which can endure the *β*-carbon cleavage to provide the Co-alkyl species **IV**. The *β*-Hydride elimination followed by 1,2-migratory insertion may generate **VI** (path *I*). Reductive elimination of **VI** can achieve the C8-alkation successfully, providing **3aa** and reduced Co(I)-species **VII** which can be oxidized by Cu(II) regenerate the active Co(III)-catalyst **I**. An alternative path from **IV** can be drawn to yield the **3aa** *via* C-C reductive elimination (path II), which may be unlikely due to (*i*) no product detection with cyclopropanol **2h** (Table 3), (*ii*) deuteration at *α*-keto position (Scheme 7b) and (*iii*) successful reaction between **1a** and **2A** (Scheme 7e).



Scheme 9. Synthetic Utilities

The scalability of the procedure was investigated by taking QNO **1a** with cyclopropanol **2a** and **2j** as the representative substrates (Scheme 9a). The alkylation occurred to afford **3aa** and **3aj** in 55% and 59% yields, respectively. Moreover, the products were transformed into diverse quinoline scaffolds to highlight the post synthetic utilities. For example, the reaction using

$PhB(OH)_2$ and TMSCN led to the formation of **4** and **5** in 86% yield and 82% yield, respectively (Scheme 9b).

In conclusion, we have shown C8-alkylationof quinoline *N*-oxides with cyclopropanols as alkyl surrogates under Co(III)-catalysis. The significant advantages of the protocol include cyclopropanol as the alkyl source, substrate scope, site-selectivity, cobalt catalysis, and mutation of natural products and drug molecules, making this method a valuable and practical contribution to the chemical synthesis.

3.3 Experimental Section

General Information. All the heating reaction were performed under Ar atmosphere using an oil bath. Quinolines, $Co(OAc)_2$ (99.99%), $Co(acac)_2$ (97%), CuO (≥99.9%), $Cu(OAc)_2•H_2O$ (98%), $Mn(OAc)_3•2H_2O$ (97%), 1,4-benzoquinone (BQ) (≥98%), $K_2S_2O_8$ (≥99%), $NaOPiv•H_2O$ (99%), NaOAc (≥99%), AcOH (≥99%), $AdCO_2H$ (99%) and *m*-CPBA (≥77%) of Aldrich, TFE of TCI chemicals and ethyl vinyl ketone (97%) of Alfa Aesar were used as received. Methanol (MeOH), *tert*-amyl alcohol, 1,2-dichloroethane and acetonitrile were dried prior to use as per the procedure. Quinolines,[12] quinoline *N*-oxides[4] and cyclopropanols[5] were prepared according to the reported procedure. $[Cp^*Co(CO)I_2]$ and $[Cp^*Co(CH_3CN)_3](SbF_6)_2$ were synthesized from the reported literature.[7b] SRL silica gel G/GF 254 plates were used for analytical TLC and SRL silica gel (230-400 mesh) was used for column chromatography. Bruker Avance III 600, 500 and 400 MHz spectrometers used for NMR spectra with tetramethylsilane (Me_4Si) as an internal standard. Chemical shifts (δ) and spin-spin coupling constant (*J*) are reported in parts per million (ppm) and hertz (Hz), respectively and other data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet. Melting points were determined using a Büchi B-540 apparatus and are uncorrected. FT-IR spectra were collected on a PerkinElmer Fourier transform infrared spectrometer. Q-TOF ESI-MS instrument was used for recording HRMS. Single crystal X-ray data was 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 SHELXT (Göttingen, Germany).

General Procedure for the Synthesis of Cyclopropanol. To a solution of ester (5.0 mmol) in THF (10 mL), $Ti(i\text{-}PrO)_4$ (7 mmol, 1.4 equiv) was added under Ar atmosphere and the resultant mixture was stirred for 5 min. Ethylmagnesium bromide (2.8 equiv) was added dropwise at 0 °C. The black solution was allowed to warm to room temperature and the stirring was continued

for an additional 8 h. Sulfuric acid (2.0 M, 5 mL) was added at 0 °C to quench the reaction. The reaction mixture was then extracted with diethyl ether (3 x 20 mL) and 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 by silica gel column chromatography using hexane and ethyl acetate as an eluent to give the cyclopropanol **2**.

General Procedure for Co(III) Catalyzed C8-Alkylation of Quinoline *N*-Oxides. Quinoline *N*-oxide **1** (0.2 mmol), cyclopropanol **2** (0.4 mmol), [Cp*Co(CO)I_2] (0.03 mmol, 14 mg) and $Cu(OAc)_2 \cdot H_2O$ (0.2 mmol, 40 mg) were stirred in TFE (1 mL) for 5 h at 70 °C under argon atmosphere. After completion, the reaction mixture was passed through a short pad of celite using EtOAc (40 mL). The combined organic layer was washed with saturated $NaHCO_3$ (2 x 5 mL) and water (2 x 5 mL). Drying and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate as an eluent to afford C8 alkylated quinoline *N*-oxide **3**.

Scale-up Synthesis of 3aa and 3aj. Quinoline *N*-oxide **1** (2 mmol), cyclopropanol **2** (4 mmol), [Cp*Co(CO)I_2] (0.3 mmol, 140 mg), $Cu(OAc)_2 \cdot H_2O$ (2 mmol, 400 mg) and TFE (10 mL) were subjected to the above described general procedure to produce **3aa** and **3aj** in 55% yield (319 mg) and 59% yield (327 mg), respectively.

Post-synthetic Transformations

Synthesis of 4.[13] 8-(3-Oxo-4-phenylbutyl)quinoline 1-oxide **3aa** (0.2 mmol, 58 mg) and phenylboronic acid (0.3 mmol, 36 mg) were stirred in 1,2-dichloroethane (2 mL) for 12 h at 120 °C in a sealed tube. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (1 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue which was purified by silica gel column chromatography to afford C8-functionalized quinoline **4** in 86% yield.

Synthesis of 5.[14] 8-(3-Oxo-3-phenylpropyl)quinoline 1-oxide **3aj** (0.2 mmol, 54 mg), TMSCN (0.24 mmol, 32 µL) and DBU (0.46 mmol, 68 µL) were stirred in THF (2 mL) for 12 h under reflux. The solvent was evaporated and the residue was extracted using EtOAc (2 x 10 mL) and washed with water (2 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica column chromatography using hexane and ethyl acetate as an eluent (90/10, v/v) to afford **5** in 82% yield.

Mechanistic Investigation

Radical Scavenger Experiment. To a solution of quinoline *N*-oxide **1a** (0.2 mmol, 29 mg), 1-benzylcyclopropan-1-ol **2a** (0.4 mmol, 60 mg), [Cp*Co(CO)I_2] (0.030 mmol, 14 mg) and $Cu(OAc)_2 \cdot H_2O$ (0.2 mmol, 40 mg) in TFE (1 mL), TEMPO or BHT (0.4 mmol) was added. The resulting mixture was stirred for 5 h at 70 °C under argon atmosphere. The reaction mixture was cooled to room temperature and passed through celite pad using EtOAc (30 mL). Evaporation of the solvent gave a residue that was purified according to general procedure.

H/D-Exchange Study Without 2a. To a solution of quinoline *N*-oxide **1a** (0.2 mmol, 29 mg), [Cp*Co(CO)I_2] (0.030 mmol, 14 mg) and $Cu(OAc)_2 \cdot H_2O$ (0.2 mmol, 40 mg) in TFE (1 mL), D_2O (30 equiv) was added. The resulting mixture were stirred for 5 h at 70 °C under argon atmosphere. The reaction mixture was cooled to room temperature and passed through celite pad using EtOAc (30 mL). Evaporation of the solvent gave a residue that was purified by silica gel chromatography and deuterium incorporation of the recovered starting material was confirmed by ^{1}H NMR.

H/D-Exchange Study with 2a. To a solution of quinoline *N*-oxide **1a** (0.2 mmol, 29 mg), 1-benzylcyclopropan-1-ol **2a** (0.4 mmol, 60 mg), [Cp*Co(CO)I_2] (0.030 mmol, 14 mg), and $Cu(OAc)_2 \cdot H_2O$ (0.2 mmol, 40 mg) in TFE (1 mL), D_2O (30 equiv) was added. The resulting mixture was stirred for 5 h at 70 °C under argon atmosphere. The purification was performed according to the general procedure and [D_n]-**3aa** was determined with ^{1}H NMR.

Competitive Kinetic Isotope Experiment. Quinoline *N*-oxide **1a** (0.1 mmol, 14 mg), 8-[D_1] quinoline 1-oxide [D_1]-**1a** (0.1 mmol, 14 mg), 1-benzylcyclopropan-1-ol **2a** (0.4 mmol, 60 mg), [Cp*Co(CO)I_2] (0.030 mmol, 14 mg) and $Cu(OAc)_2 \cdot H_2O$ (0.2 mmol, 40 mg) were stirred in TFE (1 mL) for 45 minutes at 70 °C under argon atmosphere. ^{1}H NMR was taken of the recovered quinoline *N*-oxide to calculate the intermolecular k_H/k_D, which was found to be 1.93.

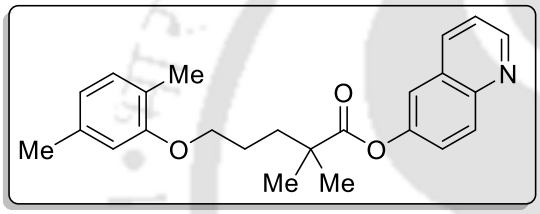
Parallel Kinetic Isotope Experiment. Two round bottom flasks were charged with quinoline *N*-oxide **1a** or [D_1]-**1a** (0.1 mmol, 14 mg), 1-benzylcyclopropan-1-ol **2a** (0.4 mmol, 60 mg), [Cp*Co(CO)I_2] (0.030 mmol, 14 mg), $Cu(OAc)_2 \cdot H_2O$ (0.2 mmol, 40 mg) and TFE (1 mL) and stirred for 45 minutes at 70 °C under argon atmosphere. Recovery of starting quinoline *N*-oxide was performed as described in the general procedure. The KIE value was determined to be k_H/k_D = 1.36 on the basis of ^{1}H NMR analysis.

Detection of Intermediate. Quinoline *N*-oxide **1a** (0.1 mmol, 14 mg), 1-benzylcyclopropan-1-ol **2a** (0.2 mmol, 30 mg), [Cp*Co(CO)I_2] (0.015 mmol, 7 mg) and $Cu(OAc)_2 \cdot H_2O$ (0.1 mmol, 20 mg) were stirred in TFE (0.5 mL) for 2 h at 70 °C under argon atmosphere. The HRMS analysis of the crude reaction mixture: (ESI) *m/z* $[M+H]^+$ calcd for $C_{29}H_{33}CoNO_2$ [Co(III)-alkyl species D]: 486.1838, found 486.1881.

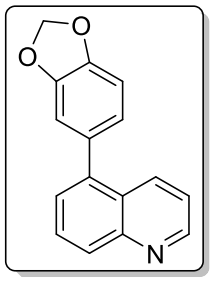
Control Experiment. Quinoline *N*-oxide **1a** (0.2 mmol, 29 mg), ethyl vinyl ketone **2A** (0.4 mmol, 34 mg), [Cp*Co(CO)I_2] (0.030 mmol, 14 mg) and $Cu(OAc)_2 \bullet H_2O$ (0.2 mmol, 40 mg) were stirred in TFE (1 mL) under inert argon atmosphere for 5h at 70 °C. The purification and characterization were performed according to the general procedure.

3.4 Characterization Data

Characterization Data of Newly Synthesized Quinolines



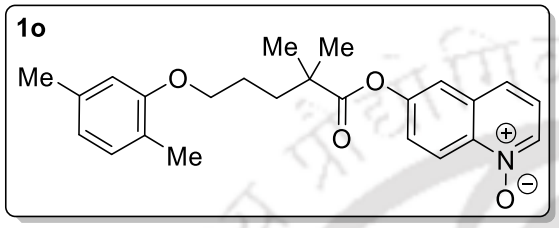
Quinolin-6-yl 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoate. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.35; brown liquid; yield 70% (263 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.90-8.89 (m, 1H), 8.12 (d, *J* = 9.0 Hz, 1H), 8.10-8.08 (m, 1H), 7.495-7.491 (m, 1H), 7.41-7.39 (m, 2H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 6.64 (s, 1H), 4.02 (t, *J* = 5.4 Hz, 2H), 2.30 (s, 3H), 2.19 (s, 3H), 1.97-1.91 (m, 4H), 1.42 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.4, 156.9, 150.2, 148.9, 146.3, 136.6, 135.8, 131.0, 130.5, 128.6, 124.9, 123.7, 121.6, 120.9, 118.4, 112.1, 67.8, 42.6, 37.2, 25.4, 25.3, 21.5, 15.9; FT-IR (neat) 2924, 1749, 1501, 1261, 1208, 1144, 1119, 1100, 1045, 803 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{28}NO_3$: 378.2064, found 378.2084.



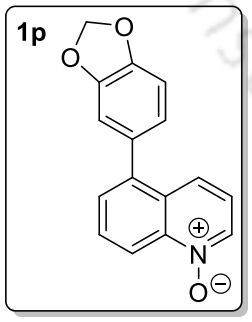
5-(Benzo[d][1,3]dioxol-5-yl)quinoline. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.35; light brown solid; mp 115-116 °C; yield 86% (214 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92-8.91 (m, 1H), 8.28 (d, *J* = 8.5 Hz, 1H), 8.11 (d, *J* = 8.0 Hz,

1H), 7.75-7.71 (m, 1H), 7.48 (d, *J* = 7.0 Hz, 1H), 7.37-7.34 (m, 1H), 6.96-6.90 (m, 3H), 6.05 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.3, 148.6, 147.8, 147.4, 140.2, 134.5, 133.3, 129.0, 128.9, 127.3, 127.0, 123.6, 121.1, 110.6, 108.5, 101.4; FT-IR (neat) 2888, 1571, 1503, 1485, 1466, 1225, 1036, 933, 897, 797, 732 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{12}NO_2$: 250.0863, found 250.0878.

Characterization Data of Newly Synthesized Quinoline *N*-Oxides



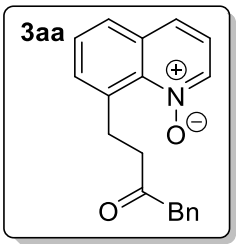
6-((5-(2,5-Dimethylphenoxy)-2,2-dimethyl pentanoyl)oxy)quinoline 1-oxide 1o. Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.20; brown sticky liquid; yield 72% (283 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.76 (d, *J* = 9.6 Hz, 1H), 8.52 (d, *J* = 6.0 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.55-7.54 (m, 1H), 7.43-7.41 (m, 1H), 7.32-7.29 (m, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 6.63 (s, 1H), 4.01 (t, *J* = 6.0 Hz, 2H), 2.30 (s, 3H), 2.17 (s, 3H), 1.96-1.89 (m, 4H), 1.41 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.1, 156.9, 150.9, 139.5, 136.6, 135.5, 131.3, 130.5, 125.77, 125.72, 123.7, 121.9, 121.8, 121.0, 119.0, 112.1, 67.7, 42.7, 37.2, 25.4, 25.2, 21.5, 15.9; FT-IR (neat) 2923, 1749, 1570, 1508, 1453, 1367, 1265, 1196, 1105, 1045, 802, 733, 586 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{28}NO_4$: 394.2013, found 394.2023.



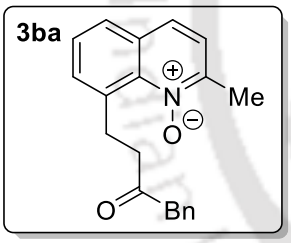
5-(Benzo[d][1,3]dioxol-4-yl)quinoline 1-oxide 1p. Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.25; brown solid; mp 178-179 °C; yield 85% (225 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, *J* = 8.8 Hz, 1H), 8.55 (d, *J* = 6.0 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.78-7.74 (m, 1H), 7.56 (d, *J* = 6.8 Hz, 1H), 7.26-7.22 (m, 1H), 6.95-6.87 (m, 3H), 6.05 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.9, 147.7, 142.2, 140.9, 135.5, 132.5, 129.9, 129.6, 129.5, 124.8, 123.7, 120.6, 119.1, 110.5, 108.6, 101.5; FT-IR (neat) 2921, 1753,

1567, 1502, 1487, 1434, 1398, 1223, 1035, 917, 783, 729 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{12}NO_3$: 266.0812, found 266.0820.

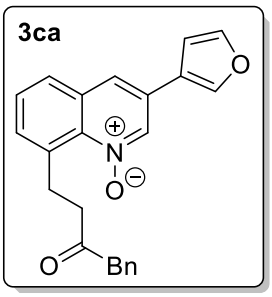
Characterization Data of the Products



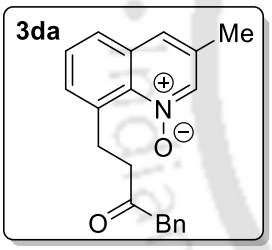
8-(3-Oxo-4-phenylbutyl)quinoline 1-oxide 3aa. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.35; brown thick liquid; yield 75% (43 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, *J* = 6.5 Hz, 1H), 7.69-7.67 (m, 2H), 7.49 (d, *J* = 6.0 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.24-7.21 (m, 3H), 7.18-7.15 (m, 1H), 7.14 (d, *J* = 7.5 Hz, 2H), 3.76 (t, *J* = 7.5 Hz, 2H), 3.70 (s, 2H), 3.08 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.0, 140.9, 137.7, 135.8, 134.49, 134.42, 132.7, 129.5, 128.6, 128.3, 127.8, 127.0, 126.8, 120.7, 50.2, 45.5, 31.7; FT-IR (neat) 2923, 1709, 1571, 1299, 1221, 1032, 814, 752, 699 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{18}NO_2$: 292.1332, found 292.1331.



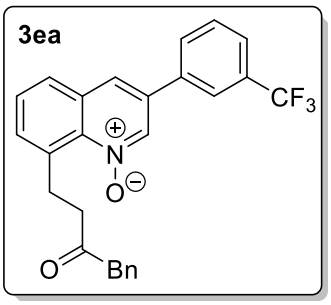
2-Methyl-8-(3-oxo-4-phenylbutyl)quinoline 1-oxide 3ba. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.30; light brown solid; mp 108-109 °C; yield 77% (47 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.45 (d, *J* = 7.0 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.25-7.24 (m, 1H), 7.21 (t, *J* = 7.5 Hz, 2H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 7.0 Hz, 2H) 3.76 (t, *J* = 7.5 Hz, 2H), 3.68 (s, 2H), 3.09 (t, *J* = 7.0 Hz, 2H), 2.62 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.1, 147.1, 141.2, 135.4, 134.5, 134.3, 131.5, 129.5, 128.5, 127.7, 127.3, 126.8, 125.5, 122.7, 50.2, 45.6, 32.0, 19.4; FT-IR (neat) 3027, 1707, 1567, 1437, 1327, 1240, 1033, 830, 700 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{20}NO_2$: 306.1489, found 306.1483.



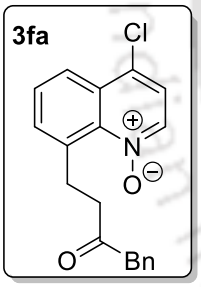
3-(Furan-3-yl)-8-(3-oxo-4-phenylbutyl)quinoline 1-oxide 3ca. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.50; brown solid; mp 107-108 °C; yield 68% (48.5 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.608-8.605 (m, 1H), 7.85 (s, 1H), 7.695-7.693 (m, 1H), 7.67-7.66 (m, 1H), 7.569-7.564 (m, 1H), 7.43-7.42 (m, 2H), 7.23 (t, *J* = 7.8 Hz, 2H), 7.17 (t, *J* = 7.8 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 2H), 6.76-6.75 (m, 1H), 3.75 (t, *J* = 7.2 Hz, 2H), 3.70 (s, 2H), 3.08 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.0, 144.7, 139.7, 139.6, 135.89, 135.87, 134.4, 133.9, 132.6, 129.6, 128.7, 128.6, 127.7, 126.8, 126.3, 122.5, 121.8, 108.4, 50.2, 45.4, 31.6; FT-IR (neat) 2926, 1711, 1582, 1496, 1342, 1219, 1161, 1023, 874, 761, 701, 597 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{20}NO_3$: 358.1438, found 358.1449.



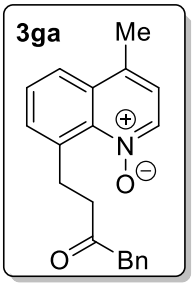
3-Methyl-8-(3-oxo-4-phenylbutyl)quinoline 1-oxide 3da. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.25; brown solid; mp 50-51 °C; yield 74% (45 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.60-7.56 (m, 1H), 7.45 (s, 1H), 7.39 (d, *J* = 5.0 Hz, 2H), 7.23 (t, *J* = 7.5 Hz, 2H), 7.19-7.15 (m, 1H), 7.14 (d, *J* = 7.0 Hz, 2H), 3.73 (t, *J* = 7.5 Hz, 2H), 3.69 (s, 2H), 3.06 (t, *J* = 7.5 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.1, 139.1, 139.0, 135.6, 134.4, 133.3, 132.5, 130.9, 129.6, 128.6, 128.3, 127.1, 126.8, 126.5, 50.1, 45.5, 31.7, 18.3; FT-IR (neat) 2923, 1709, 1580, 1366, 1322, 1215, 1041, 993, 849, 763, 698 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{20}NO_2$: 306.1489, found 306.1498.



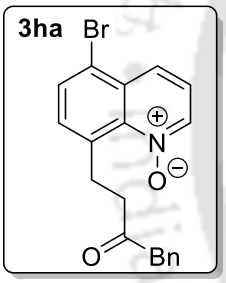
8-(3-Oxo-4-phenylbutyl)-3-(3-(trifluoromethyl)phenyl) quinoline 1-oxide 3ea. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.50; brown solid; mp 160-161 °C; yield 70% (61 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.696-8.693 (m, 1H), 7.90 (s, 1H), 7.83-7.81 (m, 2H), 7.76-7.75 (m, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.51-7.47 (m, 2H), 7.23 (t, *J* = 7.8 Hz, 2H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.15-7.13 (m, 2H), 3.78 (t, *J* = 7.2 Hz, 2H), 3.71 (s, 2H), 3.10 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.9, 140.1, 136.6, 136.3, 135.9, 134.6, 134.4, 133.0, 132.5, 132.1 (J_{C-F} = 32.5 Hz), 130.3, 130.1, 129.5, 128.9, 128.6, 128.1, 126.8, 125.8 (J_{C-F} = 3.9 Hz), 124.8 (J_{C-F} = 270.6 Hz), 124.1, 123.9 (J_{C-F} = 3.9 Hz), 50.3, 45.3, 31.6. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.74; FT-IR (neat) 3065, 1712, 1584, 1441, 1342, 1249, 1156, 1116, 1078, 796, 689 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{21}F_3NO_2$: 436.1519, found 436.1533.



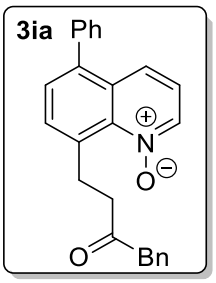
4-Chloro-8-(3-oxo-4-phenylbutyl)quinoline 1-oxide 3fa. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.30; brown thick liquid; yield 60% (39 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 6.4 Hz, 1H), 8.12-8.08 (m, 1H), 7.55 (d, *J* = 5.6 Hz, 2H), 7.32 (d, *J* = 6.4 Hz, 1H), 7.23-7.15 (m, 3H), 7.14-7.09 (m, 2H), 3.75 (t, *J* = 7.2 Hz, 2H), 3.68 (s, 2H), 3.06 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.8, 138.9, 136.5, 135.4, 134.2, 129.9, 129.5, 129.2, 128.6, 126.8, 124.6, 121.0, 50.3, 45.0, 31.7; FT-IR (neat) 2924, 1711, 1651, 1559, 1495, 1372, 1298, 1218, 822, 758, 700 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{17}ClNO_2$: 326.0942, found 326.0928.



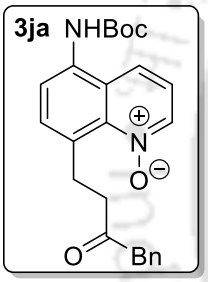
4-Methyl-8-(3-oxo-4-phenylbutyl)quinoline 1-oxide 3ga. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.40; brown thick liquid; yield 73% (44.5 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.35 (d, *J* = 6.0 Hz, 1H), 7.81-7.80 (m, 1H), 7.51-7.47 (m, 2H), 7.22 (t, *J* = 7.8 Hz, 2H), 7.16 (t, *J* = 7.2 Hz, 1H), 7.13 (d, *J* = 7.2 Hz, 2H), 7.08 (d, *J* = 6.0 Hz, 1H), 3.79 (t, *J* = 7.2 Hz, 2H), 3.69 (s, 2H), 3.09 (t, *J* = 7.2 Hz, 2H), 2.62 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.1, 137.0, 136.4, 134.4, 134.3, 131.8, 129.6, 128.5, 128.1, 126.8, 124.0, 121.5, 50.2, 45.5, 32.1, 19.3; FT-IR (neat) 2924, 1709, 1652, 1569, 1451, 1397, 1303, 1207, 1099, 1048, 830, 770, 700 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{20}NO_2$: 306.1489, found 306.1495.



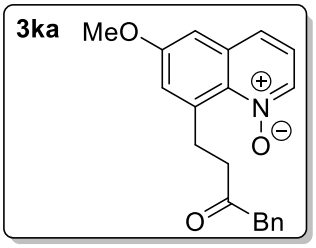
5-Bromo-8-(3-oxo-4-phenylbutyl)quinoline 1-oxide 3ha. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.40; brown thick liquid; yield 74% (54.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (d, *J* = 6.0 Hz, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.32-7.29 (m, 2H), 7.21-7.18 (m, 2H), 7.16-7.09 (m, 3H), 3.71-3.67 (m, 4H), 3.06 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.7, 141.9, 137.9, 135.9, 134.2, 134.1, 132.3, 131.5, 129.5, 128.5, 126.8, 126.0, 121.5, 121.1, 50.3, 44.8, 31.8; FT-IR (neat) 2924, 1709, 1567, 1510, 1394, 1264, 1207, 842, 744, 699 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{17}BrNO_2$: 370.0437, found 370.0444.



8-(3-Oxo-4-phenylbutyl)-5-phenylquinoline 1-oxide 3ia. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.45; brown thick liquid; yield 72% (52.8 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46-8.45 (m, 1H), 7.73-7.71 (m, 1H), 7.52-7.45 (m, 4H), 7.39-7.36 (m, 3H), 7.24-7.22 (m, 2H), 7.19-7.13 (m, 4H), 3.80 (t, *J* = 7.2 Hz, 2H), 3.73 (s, 2H), 3.14 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.1, 141.4, 140.2, 139.1, 137.4, 135.0, 134.4, 133.8, 131.3, 130.0, 129.6, 129.1, 128.7, 128.63, 128.61, 128.1, 126.8, 125.4, 120.3, 50.2, 45.5, 32.1; FT-IR (neat) 2925, 1709, 1567, 1494, 1401, 1253, 1032, 751, 700 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{22}NO_2$: 368.1645, found 368.1652.

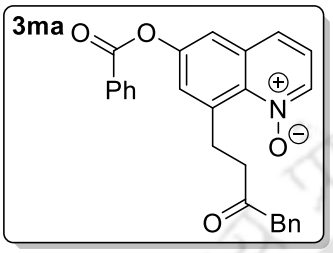


5-((*tert*-Butoxycarbonyl)amino)-8-(3-oxo-4-phenylbutyl)quinoline 1-oxide 3ja. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.40; brown thick liquid; yield 71% (57.8 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.42 (d, *J* = 6.0 Hz, 1H), 7.76 (d, *J* = 9.0 Hz, 1H), 7.69 (d, *J* = 7.2 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.25-7.21 (m, 3H), 7.19-7.16 (m, 1H), 7.15 (d, *J* = 7.8 Hz, 2H), 6.65 (bs, 1H), 3.71-3.68 (m, 4H), 3.03 (t, *J* = 7.2 Hz, 2H), 1.53 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.9, 153.5, 141.5, 137.6, 134.4, 133.9, 132.6, 129.6, 128.6, 127.5, 126.8, 122.9, 120.5, 120.0, 81.5, 50.2, 45.5, 31.8, 28.4; FT-IR (neat) 2976, 1709, 1536, 1366, 1240, 1155, 1055, 881, 738, 698 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{27}N_2O_4$: 407.1965, found 407.1976.

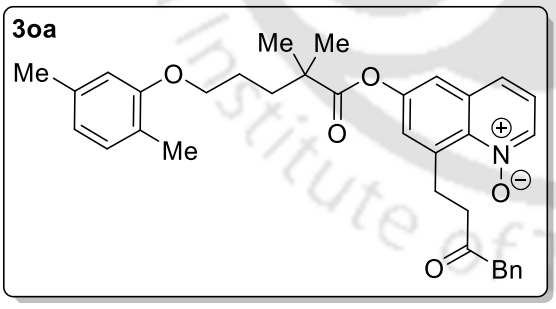


6-Methoxy-8-(3-oxo-4-phenylbutyl)quinoline 1-oxide 3ka. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.35; thick liquid; yield 69% (44.2

mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (d, *J* = 6.0 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 2H), 7.19-7.14 (m, 4H), 7.11 (s, 1H), 6.93 (s, 1H), 3.88 (s, 3H), 3.71-3.69 (m, 4H), 3.06 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.9, 158.3, 137.8, 136.7, 135.9, 134.4, 134.3, 129.6, 128.6, 126.8, 126.1, 126.0, 121.2, 105.4, 55.6, 50.1, 45.3, 31.8; FT-IR (neat) 2924, 1613, 1463, 1371, 1315, 1201, 1033, 839, 799, 745 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{20}NO_3$: 322.1438, found 322.1448.

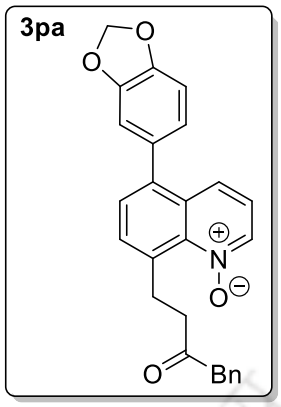


6-(Benzoyloxy)-8-(3-oxo-4-phenylbutyl)quinoline 1-oxide 3ma. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.35; brown solid; mp 115-116 °C; yield 65% (53.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, *J* = 6.0 Hz, 1H), 8.22 (d, *J* = 8.0 Hz, 2H), 7.69-7.62 (m, 3H), 7.54 (t, *J* = 8.0 Hz, 2H), 7.366-7.361 (m, 1H), 7.24-7.21 (m, 3H), 7.17-7.14 (m, 3H), 3.76 (t, *J* = 7.0 Hz, 2H), 3.70 (s, 2H), 3.12 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.7, 164.8, 149.5, 139.1, 138.5, 137.5, 134.3, 134.1, 133.5, 130.4, 129.6, 129.0, 128.9, 128.8, 128.6, 126.9, 126.6, 121.5, 118.5, 50.2, 45.0, 31.7; FT-IR (neat) 2937, 1738, 1577, 1451, 1371, 1250, 1154, 1050, 1024, 706 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{22}NO_4$: 412.1543, found 412.1557.

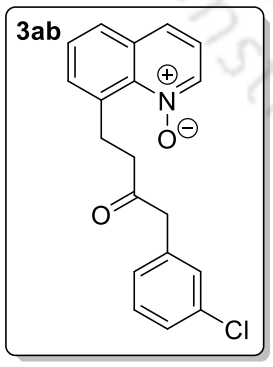


6-((5-(2,5-Dimethylphenoxy)-2,2-dimethylpentanoyl)oxy)-8-(3-oxo-4-phenylbutyl)quinoline 1-oxide 3oa. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.35; brown solid; mp 115-116 °C; yield 64% (69 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 6.0 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.38-7.37 (m, 1H), 7.24-7.14 (m, 7H), 7.00 (d, *J* = 7.2 Hz, 1H), 6.67-6.63 (m, 2H), 4.00 (t, *J* = 5.2 Hz, 2H), 3.73-3.69 (m, 4H), 3.08 (t, *J* = 7.2 Hz, 2H), 2.29 (s, 3H), 2.16 (s, 3H), 1.95-1.88 (m, 4H), 1.40 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.6, 176.0, 156.9, 149.6, 139.0, 138.4, 137.3, 136.6, 134.3, 133.5, 130.5, 129.6, 128.7, 128.6, 126.9, 126.3, 123.7, 121.4, 120.9, 118.2, 112.1, 67.7,

50.1, 45.2, 42.7, 37.2, 31.8, 25.4, 25.2, 21.5, 15.9; FT-IR (neat) 2923, 1748, 1716, 1664, 1581, 1454, 1376, 1259, 1101, 1045, 971, 803, 699 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{34}H_{38}NO_5$: 540.2744, found 540.2758.

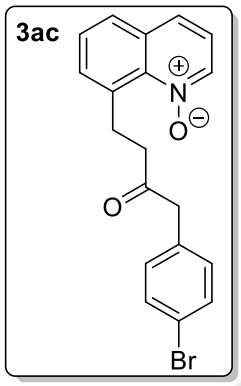


5-(Benzo[d][1,3]dioxol-4-yl)-8-(3-oxo-4-phenylbutyl)quinoline 1-oxide 3pa. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.40; brown solid; mp 115-116 °C; yield 70% (57.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 6.0 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 7.2 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.25-7.22 (m, 2H), 7.19-7.13 (m, 4H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.84-6.80 (m, 2H), 6.04 (s, 2H), 3.78 (t, *J* = 7.2 Hz, 2H), 3.72 (s, 2H), 3.12 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.1, 147.9, 147.6, 141.4, 139.7, 137.4, 134.9, 134.4, 133.8, 132.8, 131.5, 129.6, 129.1, 128.6, 126.8, 125.3, 123.6, 120.3, 110.4, 108.6, 101.5, 50.2, 45.5, 32.0; FT-IR (neat) 2923, 1709, 1488, 1401, 1225, 1035, 918, 813, 730, 699 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{22}NO_4$: 412.1543, found 412.1553.

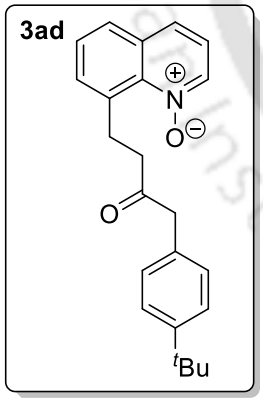


8-(4-(3-Chlorophenyl)-3-oxobutyl)quinoline 1-oxide 3ab. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.35; dark brown solid; mp 70-71 °C; yield 71% (46.2 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.42-8.41 (m, 1H), 7.70-7.68 (m, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.48-7.44 (m, 2H), 7.24-7.22 (m, 1H), 7.16-7.13 (m, 2H), 7.11 (s, 1H), 7.03-7.00 (m, 1H), 3.77 (t, *J* = 7.2 Hz, 2H), 3.67 (s, 2H), 3.09 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.1, 137.8, 136.2, 135.6, 134.5, 134.3, 132.7, 129.7, 128.3, 128.0, 127.8,

127.1, 126.9, 120.6, 49.5, 45.7, 31.8; FT-IR (neat) 2939, 1713, 1572, 1476, 1424, 1300, 1220, 1079, 1033, 816, 758, 684 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{17}ClNO_2$: 326.0942, found 326.0946.

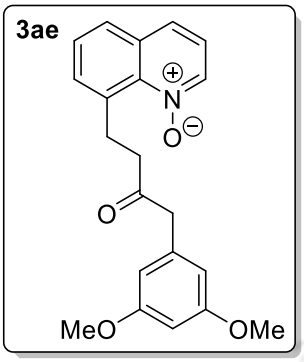


8-(4-(4-Bromophenyl)-3-oxobutyl)quinoline 1-oxide 3ac. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.35; brown solid; mp 90-91 °C; yield 74% (54.7 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 8.41 (d, *J* = 6.0 Hz, 1H), 7.69-7.65 (m, 2H), 7.46-7.41 (m, 2H), 7.31-7.29 (m, 2H), 7.24-7.22 (m, 1H), 6.97-6.95 (m, 2H), 3.75 (t, *J* = 7.2 Hz, 2H), 3.64 (s, 2H), 3.08 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.3, 137.7, 135.5, 134.4, 133.1, 132.7, 131.6, 131.2, 128.3, 127.9, 126.8, 120.9, 120.7, 49.5, 45.4, 31.9; FT-IR (neat) 2926, 1710, 1572, 1488, 1300, 1221, 1012, 815, 757 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{17}BrNO_2$: 370.0437, found 370.0447.

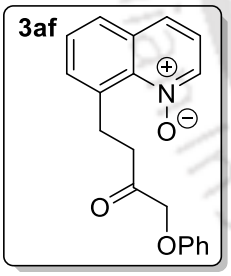


8-(4-(4-(*tert*-Butyl)phenyl)-3-oxobutyl)quinoline 1-oxide 3ad. Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.45; brown thick liquid; yield 68% (47.3 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 8.44 (d, *J* = 6.0 Hz, 1H), 7.69-7.66 (m, 2H), 7.50 (d, *J* = 6.0 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.27-7.26 (m, 2H), 7.23-7.21 (m, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 3.77 (t, *J* = 7.2 Hz, 2H), 3.67 (s, 2H), 3.09 (t, *J* = 7.2 Hz, 2H), 1.27 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.3, 149.6, 141.1, 137.7, 136.0, 134.4, 132.7, 131.4, 129.2, 128.3, 127.7, 126.8, 125.5, 120.7, 49.6, 45.6, 34.5, 31.7, 31.4; FT-IR (neat) 2960, 1708, 1572, 1514,

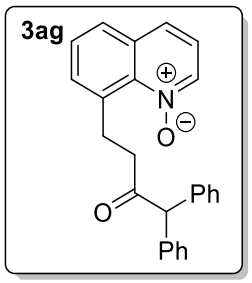
1384, 1300, 1221, 1035, 817, 758 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{26}NO_2$: 348.1958, found 348.1966.



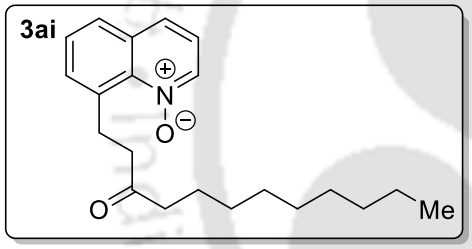
8-(4-(3,5-Dimethoxyphenyl)-3-oxobutyl)quinoline 1-oxide 3ae. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.30; brown thick liquid; yield 72% (50.6 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.42 (d, *J* = 6.0 Hz, 1H), 7.66 (t, *J* = 9.6 Hz, 2H), 7.47-7.46 (m, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.22-7.20 (m, 1H), 6.29-6.26 (m, 3H), 3.75 (t, *J* = 7.2 Hz, 2H), 3.72 (s, 6H), 3.62 (s, 2H), 3.08 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.8, 160.8, 141.0, 137.6, 136.5, 135.8, 134.4, 132.7, 128.3, 127.8, 126.7, 120.7, 107.5, 99.2, 55.3, 50.6, 45.3, 31.8; FT-IR (neat) 2933, 1709, 1595, 1461, 1429, 1299, 1205, 1152, 1065, 817, 758 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{22}NO_4$: 352.1543, found 352.1546.



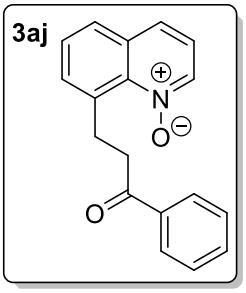
8-(3-Oxo-4-phenoxybutyl)quinoline 1-oxide 3af. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.30; dark brown solid; mp 62-63 °C; yield 74% (45.3 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 6.0 Hz, 1H), 7.72-7.67 (m, 2H), 7.54-7.52 (m, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.25-7.21 (m, 3H), 6.93 (t, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 2H), 4.59 (s, 2H), 3.83 (t, *J* = 7.2 Hz, 2H), 3.19 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.8, 157.9, 141.0, 137.7, 135.6, 134.4, 132.8, 129.6, 128.4, 128.0, 126.9, 121.5, 120.8, 114.7, 72.8, 42.6, 31.2; FT-IR (neat) 3063, 2926, 1727, 1598, 1572, 1494, 1383, 1299, 1220, 1063, 816, 753, 691 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{18}NO_3$: 308.1281, found 308.1287.



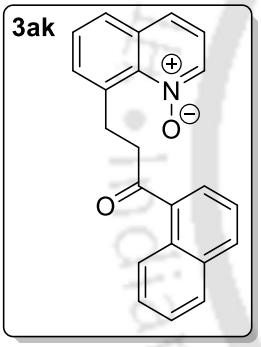
8-(3-Oxo-4,4-diphenylbutyl)quinoline 1-oxide 3ag. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.50; brown solid; mp 110-111 °C; yield 70% (51.5 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.40 (d, *J* = 6.0 Hz, 1H), 7.68-7.65 (m, 2H), 7.51 (d, *J* = 6.6 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.32-7.29 (m, 1H), 7.22-7.18 (m, 5H), 7.17-7.15 (m, 2H), 7.14-7.12 (m, 4H), 5.16 (s, 1H), 3.80 (t, *J* = 7.2 Hz, 2H), 3.18 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.2, 140.9, 138.5, 137.7, 135.6, 134.7, 132.7, 129.1, 129.0, 128.8, 128.5, 128.3, 127.7, 127.3, 127.0, 126.9, 120.6, 64.2, 46.1, 31.9; FT-IR (neat) 2926, 1714, 1573, 1494, 1451, 1300, 1221, 1081, 1032, 750, 702 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{22}NO_2$: 368.1645, found 368.1653.



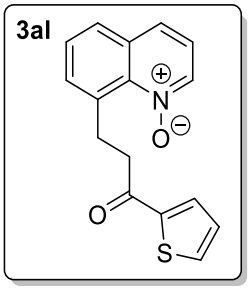
8-(3-Oxododecyl)quinoline 1-oxide 3ai. Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.50; brown thick liquid; yield 67% (43.8 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, *J* = 6.0 Hz, 1H), 7.69 (d, *J* = 7.5 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.52 (d, *J* = 6.5 Hz, 1H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.25-7.22 (m, 1H), 3.76 (t, *J* = 7.5 Hz, 2H), 2.99 (t, *J* = 7.5 Hz, 2H), 2.40 (t, *J* = 7.5 Hz, 2H), 1.56-1.50 (m, 2H), 1.22 (s, 12H), 0.86 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.2, 138.0, 136.2, 134.3, 132.7, 128.3, 127.8, 127.0, 120.5, 46.2, 43.0, 31.9, 31.8, 29.5, 29.3, 23.9, 22.7, 14.2; FT-IR (neat) 2923, 2853, 1707, 1571, 1423, 1381, 1300, 1221, 816, 758 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{30}NO_2$: 328.2271, found 328.2248.



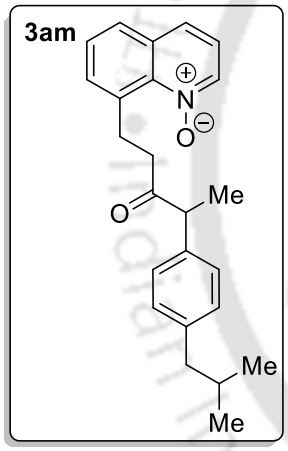
8-(3-Oxo-3-phenylpropyl)quinoline 1-oxide 3aj. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.40; brown thick liquid; yield 77% (42.7 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.46 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 7.2 Hz, 2H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 7.2 Hz, 1H), 7.60 (d, *J* = 7.2 Hz, 1H), 7.51-7.47 (m, 2H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.25-7.22 (m, 1H), 3.94 (t, *J* = 7.8 Hz, 2H), 3.59 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.1, 137.9, 137.2, 136.2, 134.5, 132.9, 132.7, 128.5, 128.47, 128.40, 128.3, 127.9, 126.9, 120.6, 42.5, 32.3; FT-IR (neat) 3061, 2929, 1681, 1572, 1448, 1383, 1299, 1221, 1032, 819, 743, 690 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{16}NO_2$: 278.1176, found 278.1170.



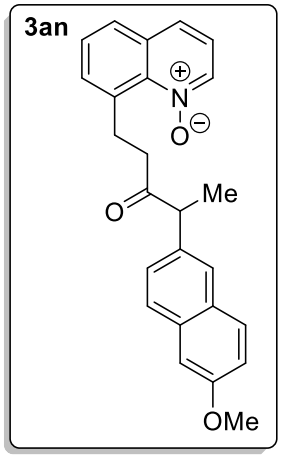
8-(3-(Naphthalen-1-yl)-3-oxopropyl)quinoline 1-oxide 3ak. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.35; light brown solid; mp 167-168 °C; yield 75% (49.2 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.62 (d, *J* = 8.4 Hz, 1H), 8.45 (d, *J* = 6.0 Hz, 1H), 7.99 (d, *J* = 7.2 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 6.6 Hz, 1H), 7.56-7.54 (m, 1H), 7.51-7.48 (m, 1H), 7.47-7.42 (m, 2H), 7.22-7.20 (m, 1H), 4.01 (t, *J* = 7.8 Hz, 2H), 3.67 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.3, 141.2, 137.6, 136.16, 136.12, 134.3, 134.0, 132.8, 132.4, 130.3, 128.4, 128.3, 128.1, 127.88, 127.81, 126.6, 126.3, 126.0, 124.5, 120.7, 45.8, 32.8; FT-IR (neat) 2925, 1674, 1572, 1508, 1423, 1299, 1221, 1099, 806, 782 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{18}NO_2$: 328.1332, found 328.1343.



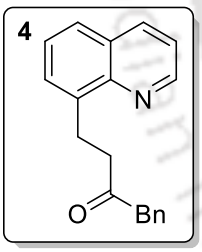
8-(3-Oxo-3-(thiophen-2-yl)propyl)quinoline 1-oxide 3al. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.40; brown thick liquid; yield 63% (35.6 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (d, *J* = 6.0 Hz, 1H), 7.87-7.86 (m, 1H), 7.72-7.68 (m, 2H), 7.60-7.57 (m, 2H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.26-7.22 (m, 1H), 7.09-7.07 (m, 1H), 3.94 (t, *J* = 7.5 Hz, 2H), 3.52 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3, 144.6, 141.1, 137.7, 135.8, 134.6, 133.4, 132.8, 132.6, 128.4, 128.2, 127.9, 126.9, 120.7, 43.2, 32.8; FT-IR (neat) 3083, 2926, 1654, 1572, 1414, 1298, 1220, 1031, 818, 752 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{14}NO_2S$: 284.0740, found 284.0744.



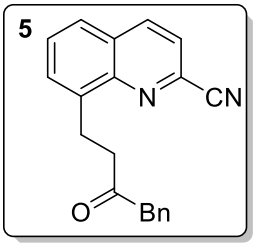
8-(4-(4-Isobutylphenyl)-3-oxopentyl)quinoline 1-oxide 3am. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.45; brown thick liquid; yield 73% (52.7 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 6.0 Hz, 1H), 7.65-7.60 (m, 2H), 7.43-7.37 (m, 2H), 7.18-7.15 (m, 1H), 6.97 (d, *J* = 7.6 Hz, 2H), 6.92 (d, *J* = 8.0 Hz, 2H), 3.92-3.86 (m, 1H) 3.75 (q, *J* = 7.2 Hz, 1H), 3.55-3.49 (m, 1H), 3.06-2.99 (m, 1H), 2.96-2.88 (m, 1H), 2.34 (d, *J* = 7.2 Hz, 2H), 1.81-1.71 (m, 1H), 1.33 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.7, 141.0, 140.2, 137.7, 137.5, 135.9, 134.3, 132.6, 129.4, 128.2, 127.6, 126.5, 120.5, 52.6, 45.1, 44.2, 31.7, 30.2, 22.5, 17.4; FT-IR (neat) 2953, 1708, 1571, 1422, 1383, 1300, 1222, 818, 757 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{28}NO_2$: 362.2115, found 362.2120.



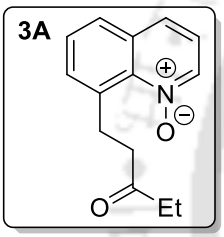
8-(4-(6-Methoxynaphthalen-2-yl)-3-oxopentyl)quinoline 1-oxide 3an. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.35; brown liquid; yield 71% (54.7 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25-8.23 (m, 1H), 7.54-7.49 (m, 2H), 7.46-7.40 (m, 3H), 7.37-7.35 (m, 1H), 7.31 (t, *J* = 7.6 Hz, 1H) 7.11-7.05 (m, 2H), 7.01-6.97 (m, 2H), 3.96-3.85 (m, 5H), 3.50-3.44 (m, 1H), 3.05-3.01 (m, 2H), 1.41 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.3, 157.5, 140.7, 137.3, 135.4, 135.3, 134.3, 133.4, 132.4, 129.3, 128.9, 128.0, 127.6, 127.1, 126.54, 126.52, 126.4, 120.3, 118.8, 105.6, 55.4, 53.1, 44.0, 31.9, 17.2; FT-IR (neat) 2932, 1706, 1604, 1572, 1389, 1300, 1265, 1219, 1162, 1030, 816, 755 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{24}NO_3$: 386.1751, found 386.1755.



1-Phenyl-4-(quinolin-8-yl)butan-2-one 4. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.45; light yellow thick liquid; yield 86% (47.3 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.89-8.88 (m, 1H), 8.13-8.11 (m, 1H), 7.67-7.65 (m, 1H), 7.53 (d, *J* = 7.2 Hz, 1H), 7.43-7.40 (m, 1H), 7.39 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.27-7.24 (m, 2H), 7.21-7.18 (m, 1H), 7.14-7.12 (m, 2H), 3.67 (s, 2H), 3.50 (t, *J* = 7.8 Hz, 2H), 3.01 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.1, 149.4, 146.8, 139.7, 136.5, 134.4, 129.59, 129.56, 128.7, 128.5, 126.9, 126.5, 126.4, 121.0, 50.3, 43.0, 26.5; FT-IR (neat) 3028, 2928, 1709, 1595, 1496, 1363, 1078, 792, 697 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{18}NO$: 276.1383, found 276.1388.



8-(3-Oxo-4-phenylbutyl)quinoline-2-carbonitrile 5. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.35; thick liquid; yield 82% (49.2 mg); ^{1}H NMR (400 MHz, $CDCl_3$) 8.31 (d, *J* = 8.4 Hz, 1H), 8.11-8.08 (m, 2H), 7.80 (d, *J* = 6.8 Hz, 1H), 7.77-7.75 (m, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.64-7.60 (m, 1H), 7.58-7.54 (m, 1H), 7.51-7.47 (m, 2H), 3.67 (t, *J* = 8.0 Hz, 2H), 3.48 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.0, 147.0, 141.1, 138.0, 136.8, 133.2, 132.6, 131.5, 129.6, 129.1, 128.8, 128.5, 126.4, 123.3, 118.0, 40.2, 27.5; FT-IR (neat) 3063, 2925, 2234, 1681, 1597, 1500, 1449, 1375, 1204, 972, 842, 766, 742, 690 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{15}N_2O$: 287.1179, found 287.1192.



8-(3-Oxopentyl)quinoline 1-oxide 3A. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.35; brown liquid; yield 41% (18 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.45 (d, *J* = 6.0 Hz, 1H), 7.71-7.68 (m, 2H), 7.53-7.52 (m, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.23 (dd, *J* = 8.4, 6.0 Hz, 1H), 3.77 (t, *J* = 7.2 Hz, 2H), 3.00 (t, *J* = 7.8 Hz, 2H), 2.45 (q, *J* = 7.2 Hz, 2H), 1.03 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.5, 141.1, 137.7, 136.3, 134.3, 132.8, 128.4, 127.8, 126.9, 120.7, 45.9, 36.0, 31.9, 7.93; FT-IR (neat) 2926, 1707, 1573, 1382, 1300, 1220, 820, 757 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{14}H_{16}NO_2$: 230.1176, found 230.1180.

Crystal Data and Structure Refinement for 3ak

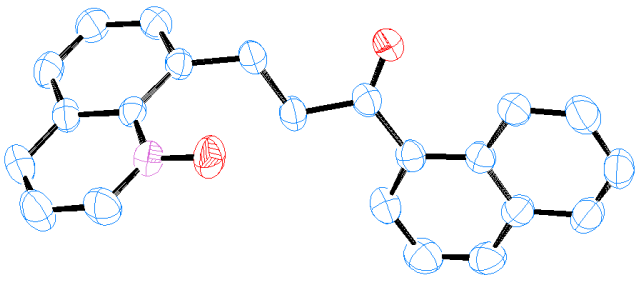


Figure S1. ORTEP diagram of 8-(3-(naphthalen-1-yl)-3-oxopropyl)quinoline 1-oxide **3ak** with 50% ellipsoid (CCDC 2269443). H-Atoms are omitted for clarity.

Identification code	**3ak**
Empirical formula	'C22 H17 N O2'
Formula weight	327.36
Crystal habit, colour	colourless
Crystal size, mm^3	0.27 x 0.25 x 0.21
Temperature, *T*/K	297 K
Wavelength, λ/Å	0.71073
Crystal system	'Triclinic'
Space group	'P -1'
Unit cell dimensions	a = 7.6175 (5) Å b = 10.6597 (7) Å c = 11.1516 (7) Å α = 74.020 (2) β = 70.640 (2) γ = 80.418 (2)
Volume, *V*/$Å^3$	818.47 (9)
Z	2
Calculated density, g cm^{-3}	1.328
Absorption coefficient, μ/mm^{-1}	0.085
F(000)	344
θ range for data collection	1.992 to 24.998°
Limiting indices	$-9 \leq h \leq 9, -12 \leq k \leq 12, -13 \leq l \leq 13$
Reflection collected / unique	2877/2510
Completeness to θ	100% (θ = 24.998°)
Absorption correction	None
Max. and min. transmission	0.982 and 0.977
Refinement method	'SHELXL-2016/6'
Data / restraints / parameters	2877/0/226
Goodness–of–fit on F^2	1.538
Final *R* indices [*I*>2sigma(*I*)]	R1 = 0.0587, wR2 = 0.1776
R indices (all data)	R1 = 0.0638, wR2 = 0.1825

3.5 References

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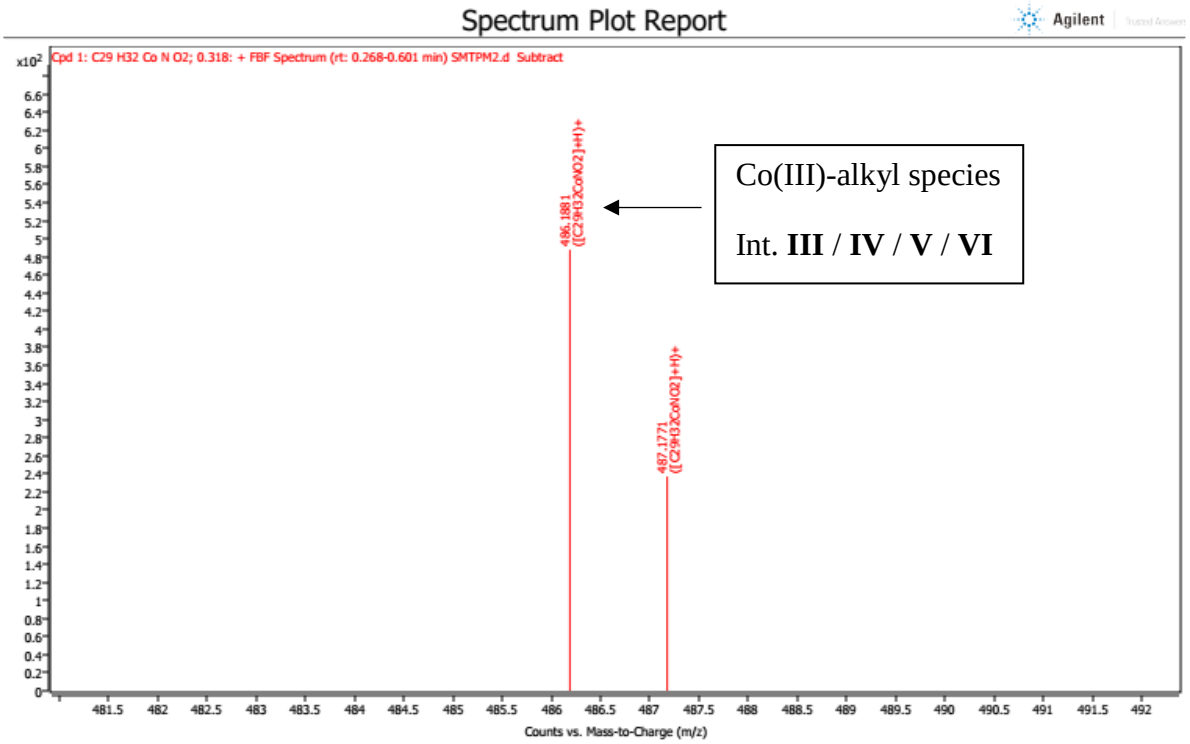
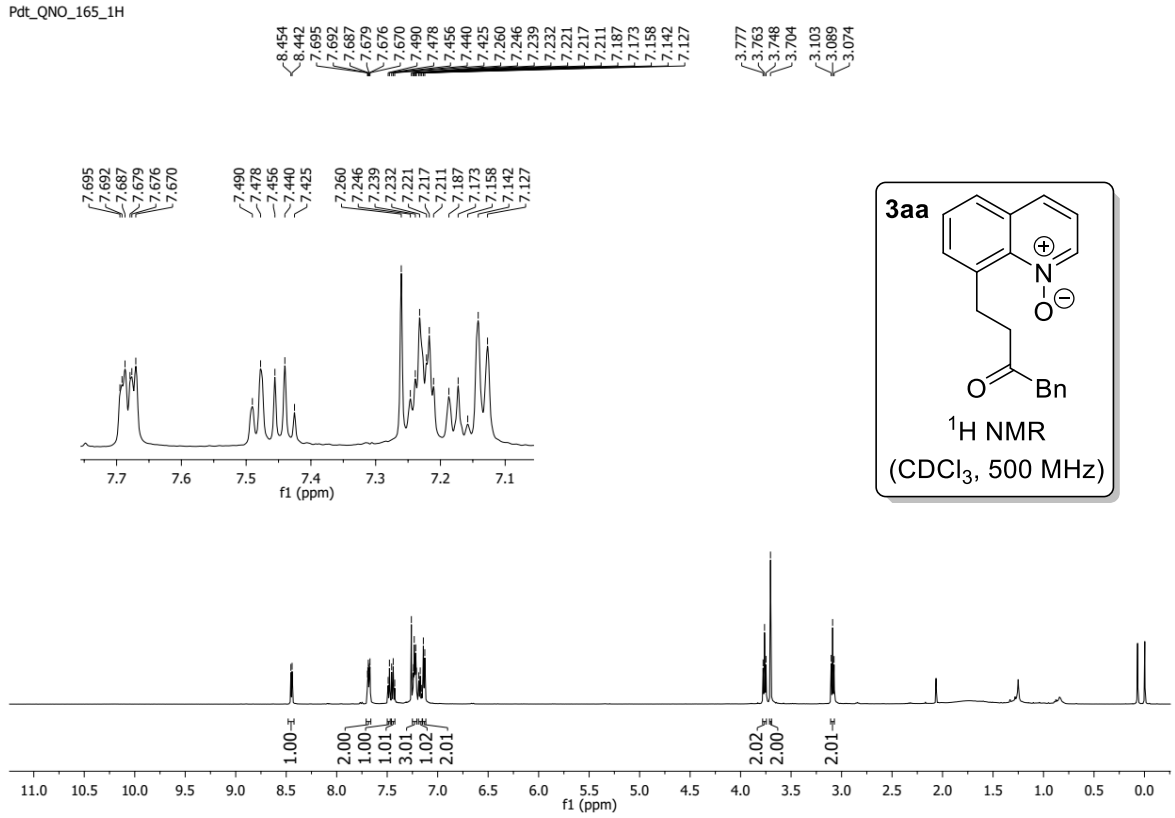
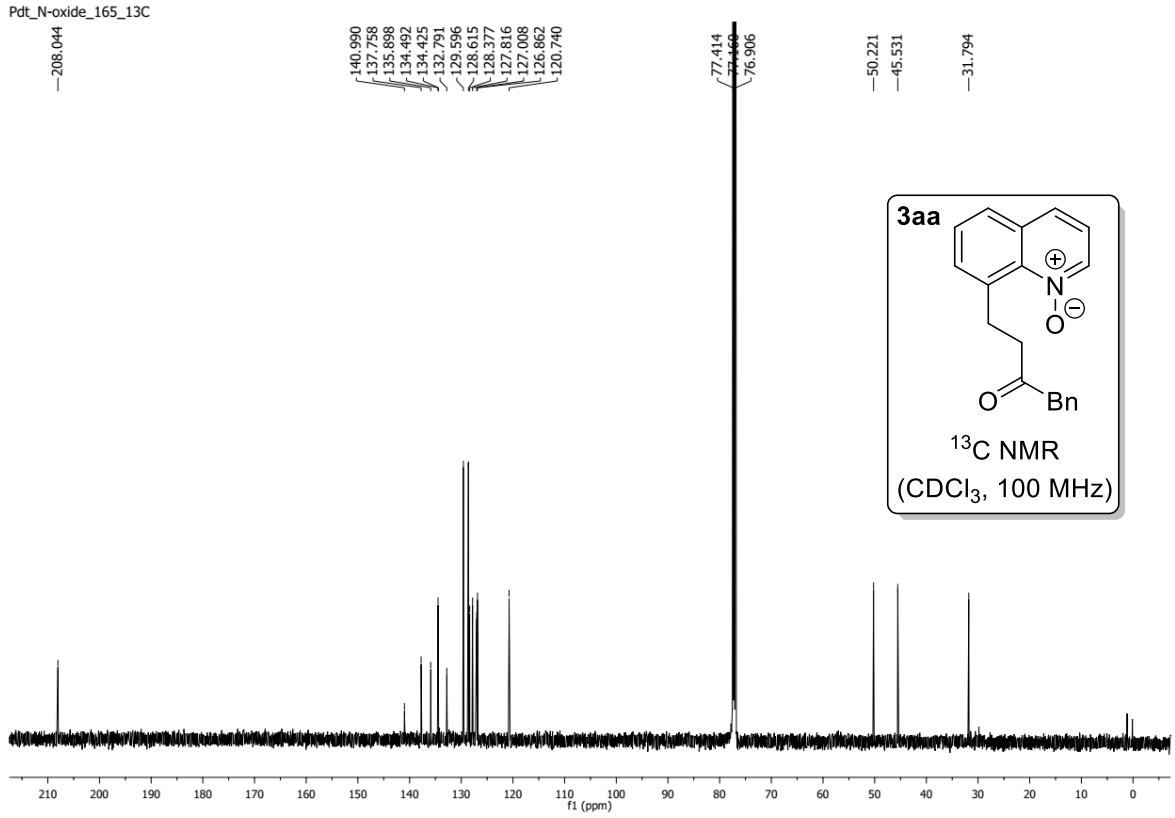
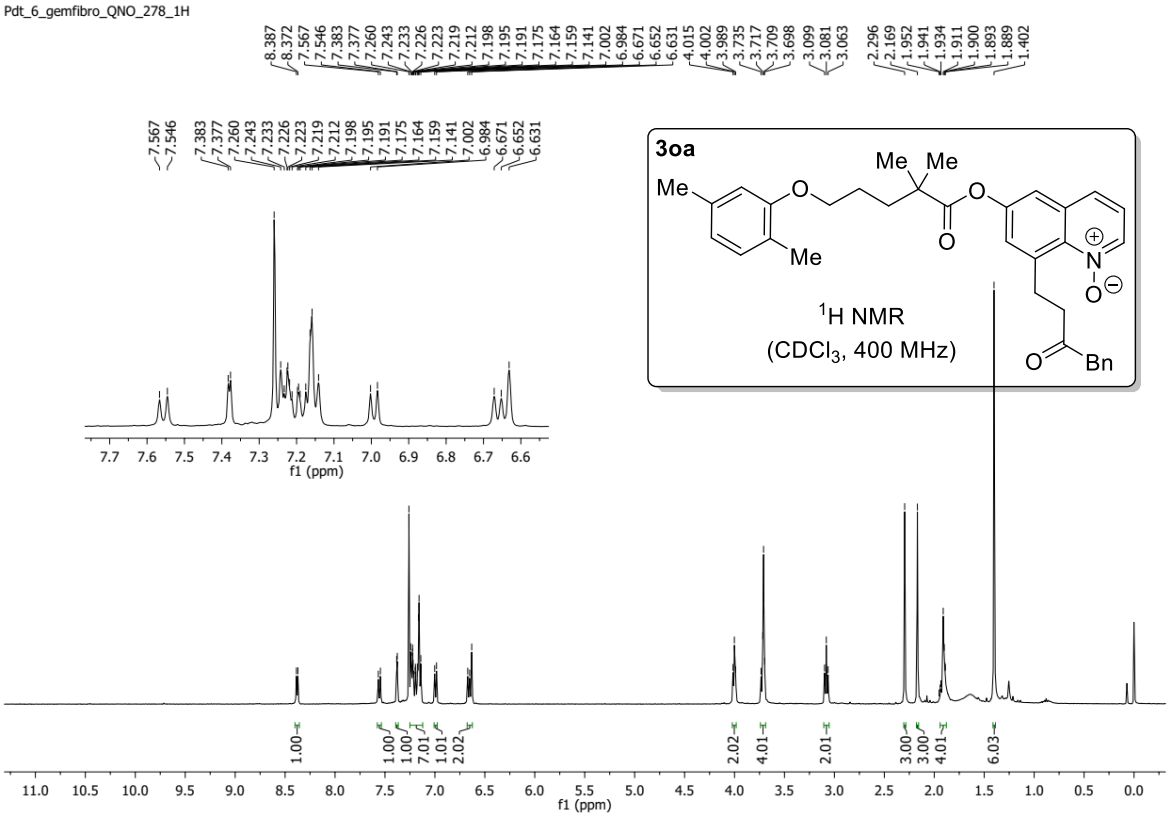
3.6 ESI-MS Spectrum of Radical Trapping Experiment

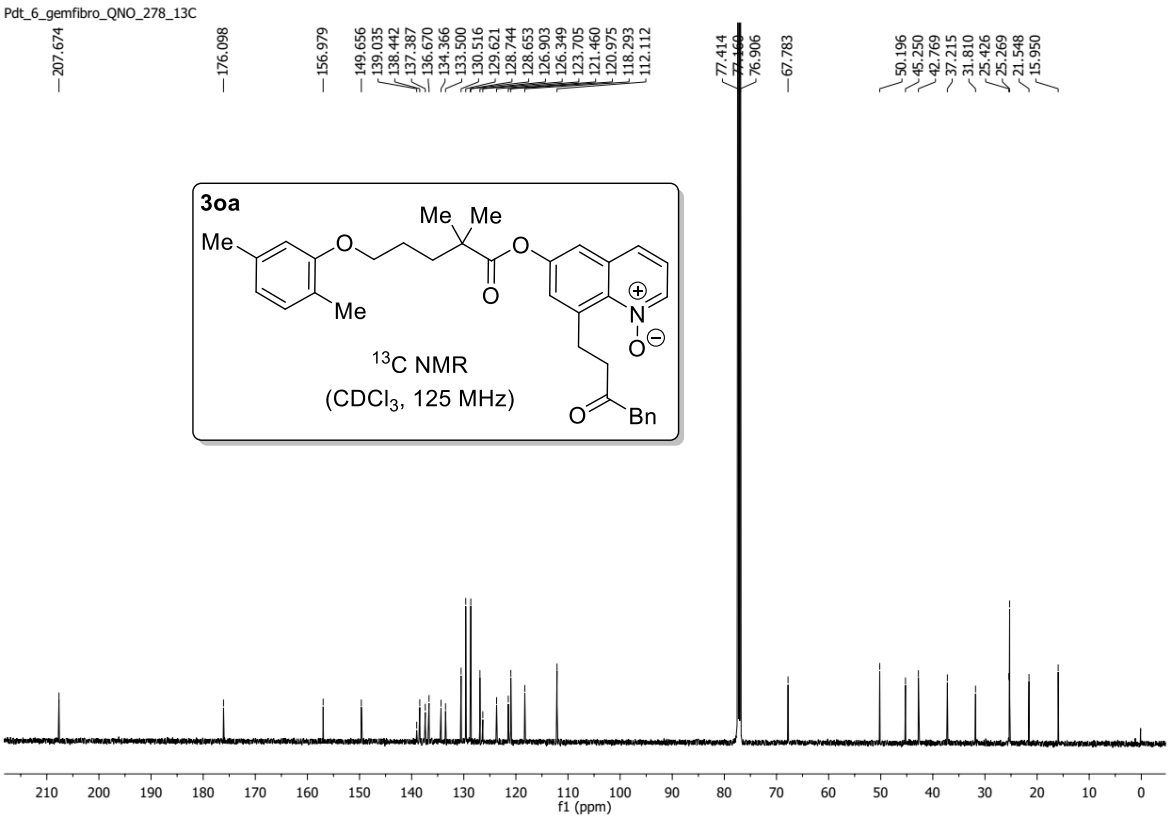


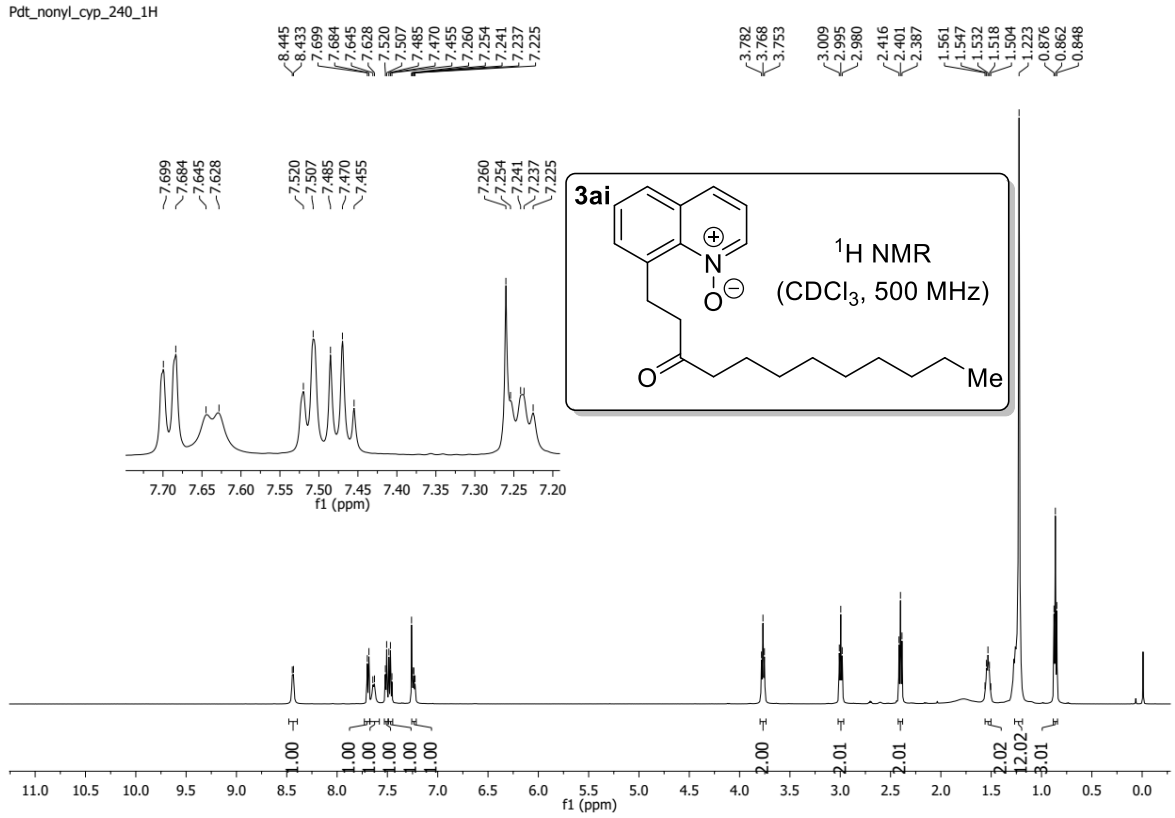
3.7 Selected NMR Spectra

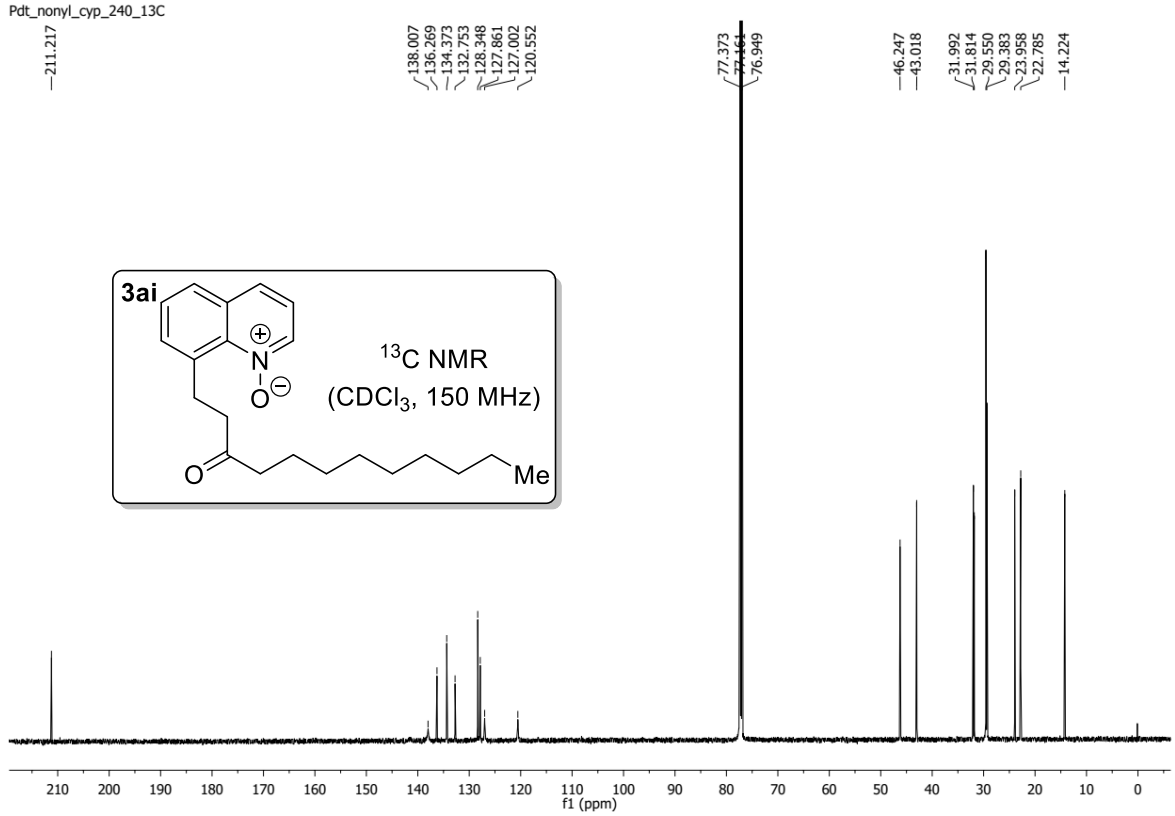


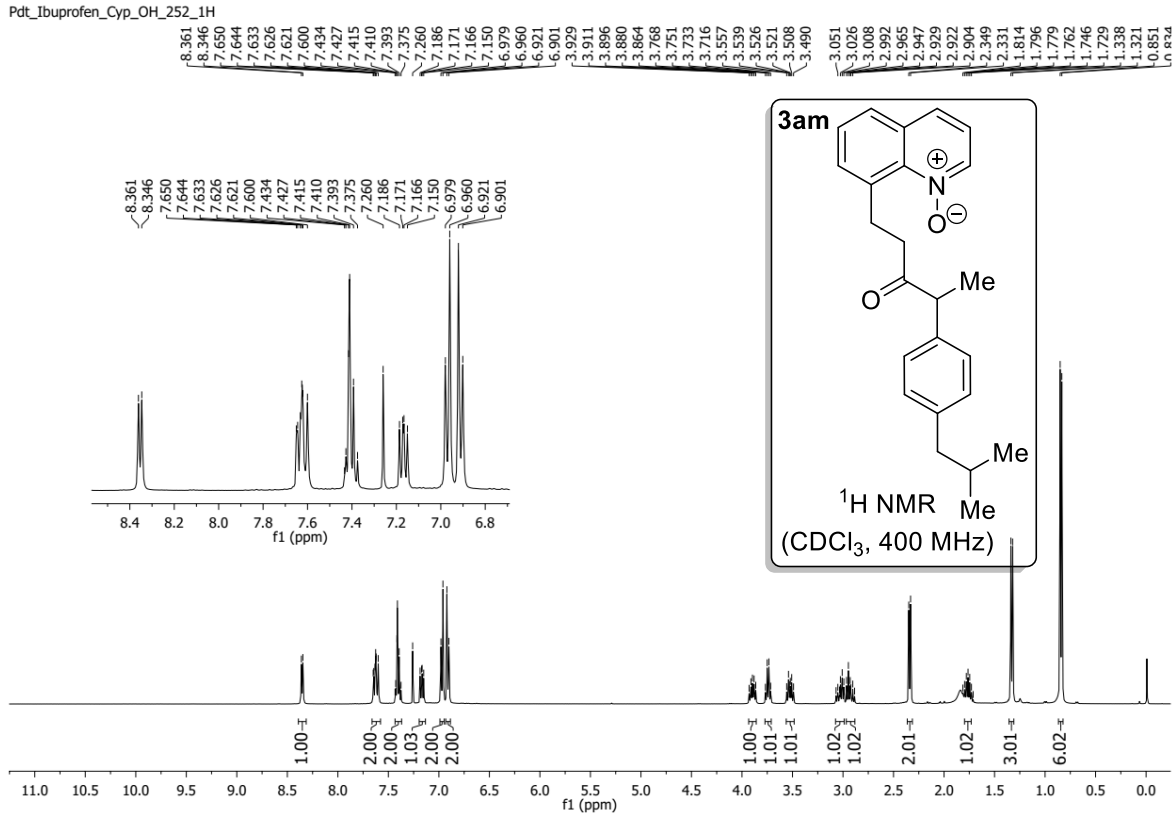


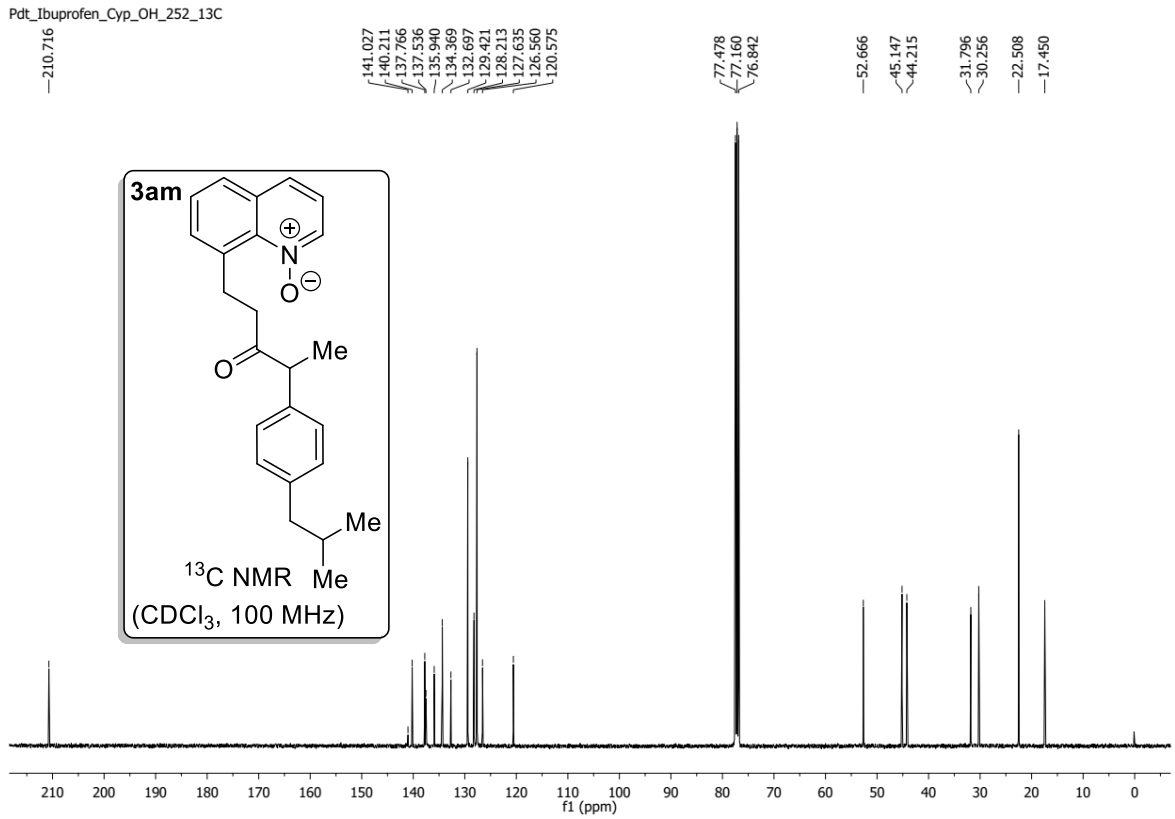






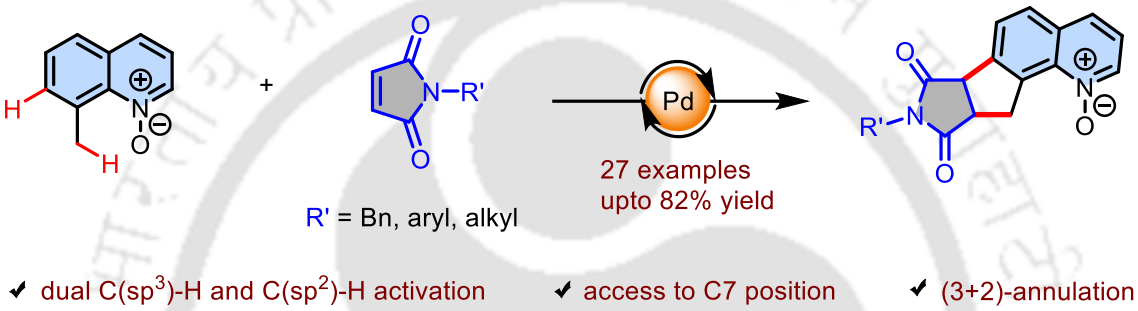






Chapter 4

Dual C(sp^3)-H and C(sp^2)-H Activation of 8-Methylquinoline N-Oxides



Org. Lett. **2024**, *26*, 7560.

Dual C(sp^3)-H and C(sp^2)-H Activation of 8-Methylquinoline *N*-Oxides

The site-selective C-H functionalization has been identified as significant approach for the quinoline functionalization in organic synthesis.[1] The advancements is due to its presence in natural products, pharmaceuticals and material sciences among others.[2] Over the years, thus substantial progress, especially on the C2- and C8-H functionalizations of quinoline have been observed, largely exploiting *N*-oxide as DG. Whereas, research focused on the activation of benzenoid C-H bonds (mainly C6 and C7) are rarely known.[1a] This scarcity may be attributed to their lower electrophilicity and the geometrical inaccessibility of the DG on the ring nitrogen to these C-H bonds. With these challenges, Dong group acknowledged Pd/NBE Catellani reaction and opted for C6-functionalization using 5-iodoquinoline as starting material.[3a] While, Shi group developed C7-functionalization by installing -NHPiv group as DG at C8 position.[3b] However, these studies showed with limited examples and expressed a lack of comprehensive exploration for the full substrate scope study. On a contrary, quinoline functionalization with a less reactive C(sp^3)-H bond has attracted considerable attention for the construction of a wide variety of C8-quinoline derivatives.[4] Although these reactions were evolved separately but our objective is to synthesize polycyclic structural frameworks by combining C(sp^3)-H and C7-H functionalization in a relay process. Moreover, these C7-functionalized quinolines have widespread application in anti-parasitic treatment (Figure 1). Recently, the dual C-H functionalization and annulation offers a sustainable and economical path for the construction of complex molecular entitites.[5] Along this line, maleimides are versatile coupling partner for C-H functionalization/annulation[6] with their widespread applications[7] in pharmaceutical and medicinal sciences. Recent works on dual C-H functionalization/annulation using maleimide have been demonstrated by Yu,[6a] Chatani[6b] and Jeganmohan[6c] group, achieved a diverse bi-/tri-cyclic scaffolds *via* under Pd-catalysis. Owing to our continuous efforts, we questioned whether 8-methylquinolines with maleimide can serve as an alternative route to dual C-H functionalization and annulation by accessing C7-H bond, which is considered as an orphan position since it remains largely unexplored till date. Here, we have found that the native nitrogen atom of quinoline acts as strong chelating DG and produced alkylation or alkenylaion *via* [C(sp^3)-Pd] protonation or β-hydride elimination, respectively (Scheme 7-9). Thus, we

converted the starting 8-methylquinoline to its *N*-oxide variant to beat the above challenges in relay C-H reaction.

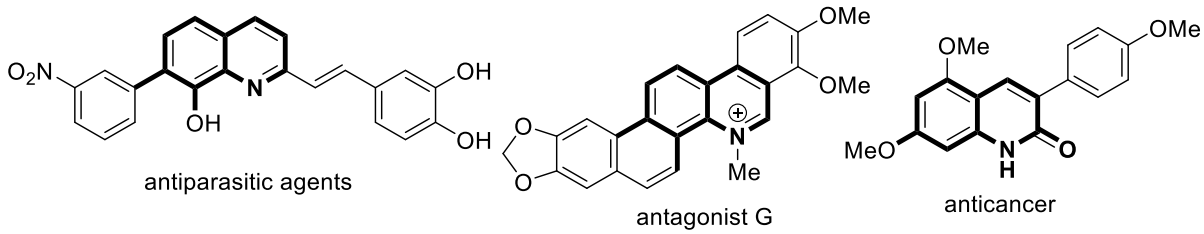
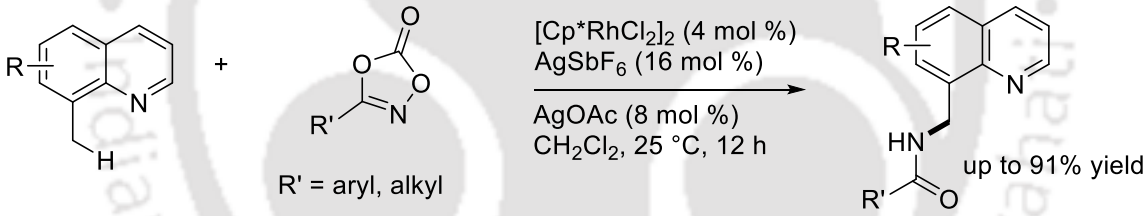


Figure 1. Examples of Biologically Important C7-Functionalized Quinoline Derivatives

4.1 Literature Study

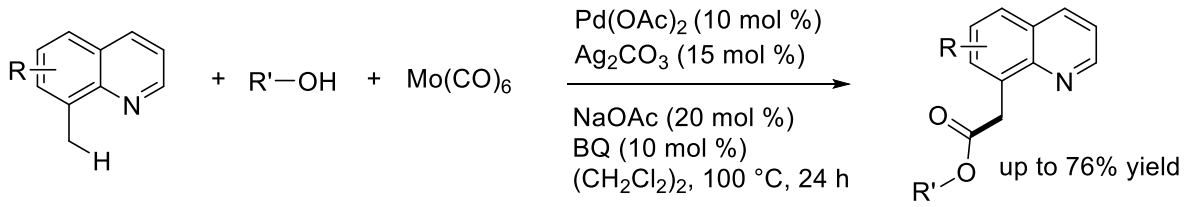
4.1.1 C(sp^3)-H functionalization of 8-Methylquinolines

Li and co-workers disclosed dioxazolone as amidation source in the Rh(III)-catalyzed C(sp^3)-H amidation of 8-methylquinolines (Scheme 1).[8] Dioxazolone moiety with 3-phenyl and -alkyl substituents worked well. Overall, the amidated derivatives were synthesized in good yields at room temperature.



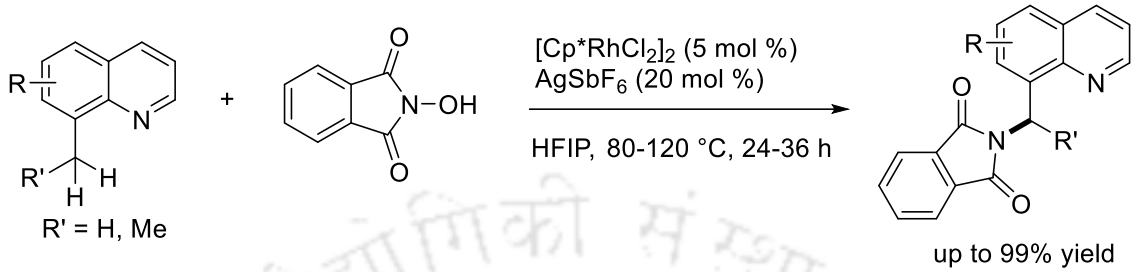
Scheme 1. Rh(III)-Catalyzed C(Sp^3)-H Amidation of 8-Methylquinolines

Our group showed three-component C(sp^3)-H alkoxycarbonylation of 8-methylquinonlines utilizing alcohols and crystalline molybdenumhexacarbonyl as CO source (Scheme 2).[4d] The method proved effective with a variety of alcohols and 8-methlquinolines. Its wide functional group tolerance and the late-stage natural product modifications highlight its practical advantages.



Scheme 2. Pd(II)-Catalyzed Alkoxycarbonylation of 8-Methylquinolines

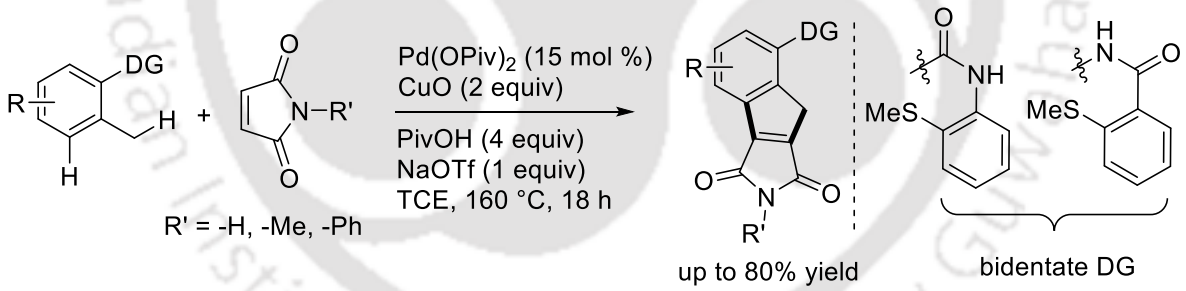
Sharma and co-workers reported a C-H amidation of 8-methylquinolines with *N*-hydroxy phthalimides under Rh(III)-catalysis (Scheme 3).[9] An in-situ exchange of HFIP with the hydroxyl group of *N*-hydroxy phthalimides renders it as an effective amidating agent, providing the targeted amidated products in good yields and regioselectivity.



Scheme 3. Rh(III)-Catalyzed C(sp^3-H)-Amidation using *N*-Hydroxy Phthalimides

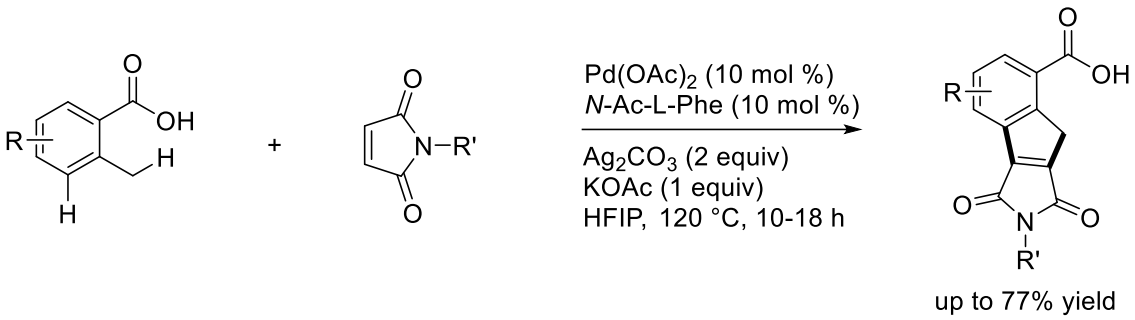
4.1.2 Maleimides as a Coupling Partner

Chatani group accomplished dual C-H functionalization of arenes bearing N, S-bidentate chelating auxiliary DG with maleimides under Pd(II)-catalysis (Scheme 4).[10] The authors showed [3+2]-annulation of aromatic amides *via* the irreversible activation of both the *ortho*-benzylic and meta C-H bonds. In order to proceed the reaction, both N-H and S-Me moieties from both the benzamide and anilide-type DG must be present.



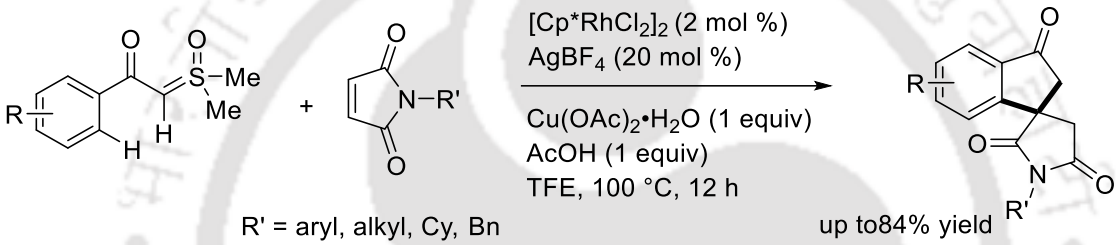
Scheme 4. Site-selective [3+2]-Annulation *via* Benzylic and meta C-H Bond Activation

Later, a palladium-catalyzed [3+2]-annulation of benzoic acids with maleimides has been demonstrated, leading to tricyclic heterocyclic molecules in a high atom- and step-economical manner (Scheme 5).[11] The reaction uses an external mono-protected amino acid (MPAA) ligand which was crucial for this dual C-H functionalization. Further, the decarboxylation and esterification were carried out in the post-synthetic modification of the free carboxylic acid group of observed products.



Scheme 5. Ligand-enabled [3+2] Annulation of Aromatic Acids with Maleimides

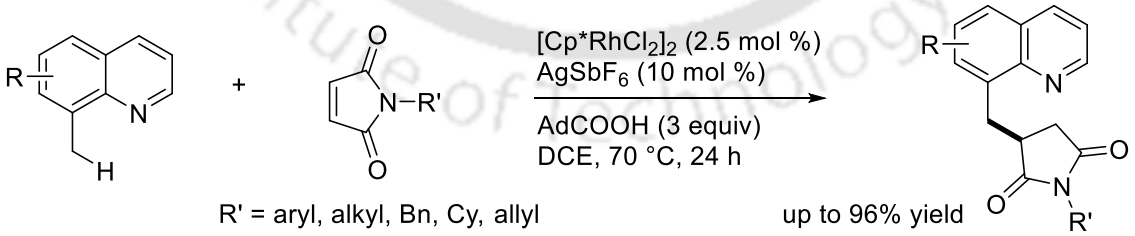
Lee and co-workers developed [4+1]-annulation of sulfoxonium ylides with maleimides under Rh(III)-catalysis (Scheme 6).[12] The reaction provides biologically intriguing various spiroindanonylpyrroline-2,5-dione derivatives in good to moderate yields.



Scheme 6. Rh(III)-Catalyzed [4+1] Annulation of Sulfoxonium Ylides

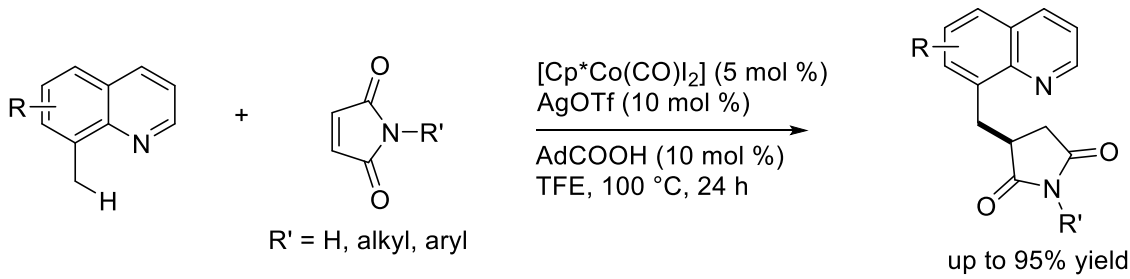
4.1.3 Reactivity of 8-Methylquinolines with Maleimides in C-H Activation

A benzylic C-H alkylation of 8-methylquinolines has been achieved with maleimides under Rh(III)-catalysis through C(sp^3)-H bond activation (Scheme 7).[13] The furnished alkylated quinoline derivatives were obtained in excellent yields. The mechanistic studies showed that C-H cleavage step is reversible and not the rate determining step.



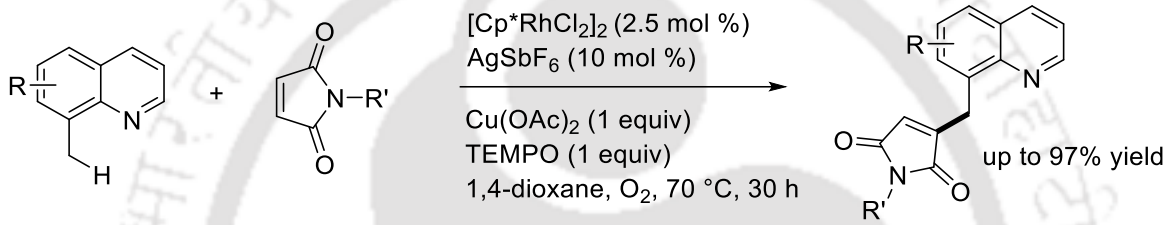
Scheme 7. Rh(III)-Catalyzed C(sp^3)-H Alkylation of 8-Methylquinolines with Maleimides

Sharma group reported the same benzylic C-H alkylation of 8-methylquinolines with maleimides under Co(III)-catalysis (Scheme 8).[14] The authors highlighted its significance by showing that the protocol is compatible for NH-free maleimides and secondary C(sp^3)-H alkylation with comparable yields.



Scheme 8. Co(III)-Catalyzed C(sp^3)-H Alkylation of 8-Methylquinolines

Zhao group disclosed C(sp^3)-H alkenylation of 8-methylquinolines with maleimides under Rh(III)-catalysis (Scheme 9).[15] A combination of $Cu(OAc)_2$, TEMPO, and molecular oxygen has been used as oxidant. A broad range of derivatives were synthesized in moderate to excellent yields.

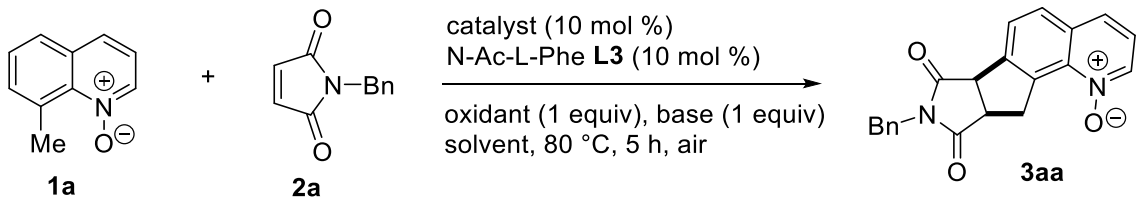


Scheme 9. Rh(III)-Catalyzed Alkenylation of 8-Methylquinolines

4.2 Present Study

Herein, we report the two-fold functionalization of C(sp^3)-H and C7-H of 8- methylquinoline *N*-oxides employing maleimide to obtain tetracyclic frameworks. At the outset, we started the optimization studies by taking quinoline *N*-oxide **1a** and 1-benzylpyrrolidine-2,5-dione **2a** as representative examples (Table 1). Delightfully, the substrates were reacted to produce [3+2]-annulated **3aa** in 82% yield when it was stirred with 10 mol % [$Pd(OAc)_2$], 10 mol % *N*-acetyl-L-phenylalanine as ligand, 1 equiv $K_2S_2O_8$ and 1 equiv NaOAc in HFIP at 80 °C for 5 h under air. Among the oxidants screened, Ag_2CO_3, AgOAc, Ag_2O, $Cu(OAc)_2$, BQ, O_2 and $K_2S_2O_8$, the latter yielded the best results. In a set of bases examined, NaOAc, KOAc, CsOAc, Na_2CO_3 and K_2CO_3, NaOAc afforded superior results compared to others. Although, HFIP and TFE both the solvent responded well, yet we choose HFIP as the best due to the cleaner reaction profile. In contrast, the other solvents such as THF, $(CH_2Cl_2)_2$, CH_3CN and toluene were failed to serve as effective reaction medium. Yield of final product **3aa** was drastically reduced to 28% when $Pd(TFA)_2$ was used instead of $Pd(OAc)_2$.

Table 1. Optimization of the Reaction Conditions[a]



Entry	Catalyst	Base	Oxidant	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$	NaOAc	Ag_2CO_3	HFIP	72
2	$Pd(OAc)_2$	KOAc	Ag_2CO_3	HFIP	52
3	$Pd(OAc)_2$	CsOAc	Ag_2CO_3	HFIP	60
4	$Pd(OAc)_2$	Na_2CO_3	Ag_2CO_3	HFIP	48
5	$Pd(OAc)_2$	K_2CO_3	Ag_2CO_3	HFIP	20
6	$Pd(OAc)_2$	-	$K_2S_2O_8$	HFIP	41
7	$Pd(OAc)_2$	NaOAc	AgOAc	HFIP	51
8	$Pd(OAc)_2$	NaOAc	Ag_2O	HFIP	35
9	$Pd(OAc)_2$	NaOAc	$Cu(OAc)_2$	HFIP	44
10	$Pd(OAc)_2$	NaOAc	BQ	HFIP	27
11	**$Pd(OAc)_2$**	**NaOAc**	**$K_2S_2O_8$**	**HFIP**	**82**
12[c]	$Pd(OAc)_2$	NaOAc	O_2	HFIP	43
13	$Pd(OAc)_2$	NaOAc	-	HFIP	32
14	$Pd(OAc)_2$	NaOAc	$K_2S_2O_8$	TFE	74
15	$Pd(OAc)_2$	NaOAc	$K_2S_2O_8$	THF	trace
16	$Pd(OAc)_2$	NaOAc	$K_2S_2O_8$	DCE	n.d.
17	$Pd(OAc)_2$	NaOAc	$K_2S_2O_8$	CH_3CN	n.d.
18	$Pd(OAc)_2$	NaOAc	$K_2S_2O_8$	toluene	n.d.
19	$Pd(TFA)_2$	NaOAc	$K_2S_2O_8$	HFIP	28
20[d]	$Pd(OAc)_2$	NaOAc	$K_2S_2O_8$	HFIP	22
21[e]	$Pd(OAc)_2$	NaOAc	$K_2S_2O_8$	HFIP	40

[a]Reaction condition: **1a** (0.2 mmol), **2a** (0.24 mmol), catalyst (10 mol %), *N*-Ac-L-Phe **L3** (10 mol %), base (0.2 mmol), oxidant (0.2 mmol), solvent (1 mL), 80 °C, 5 h, air. [b]Isolated yield. [c]Balloon used. [d]At 100 °C. [e]At 50 °C. n.d. = not detected.

We next investigated the role of ligand in our reaction procedure. It has been observed that the monoprotected amino acids (MPAA) **L1-5** enabled the [3+2]-annulation efficiently, while

L3 produced the best result. However, among the amino acid ligands, L-proline **L6** was futile. In a similar way, reactions with other ligands like pyridines **L7-10** and phosphines **L11-12** displayed inferior results (Figure 2). It was perceived from the optimization studies that a combination of [$Pd(OAc)_2$], ligand, oxidant, base and solvent was essential for the annulation.

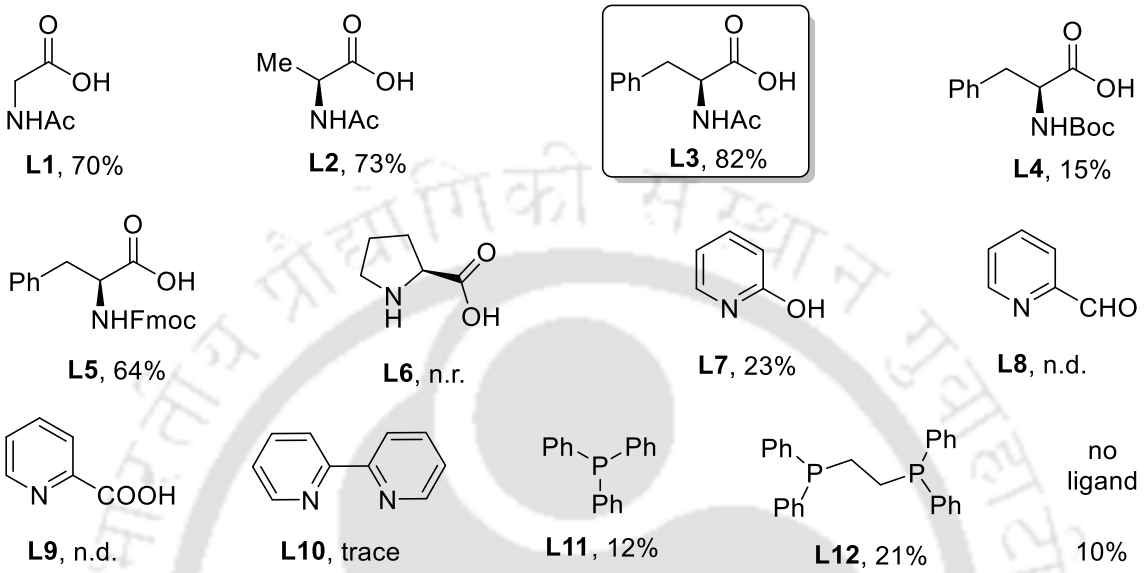
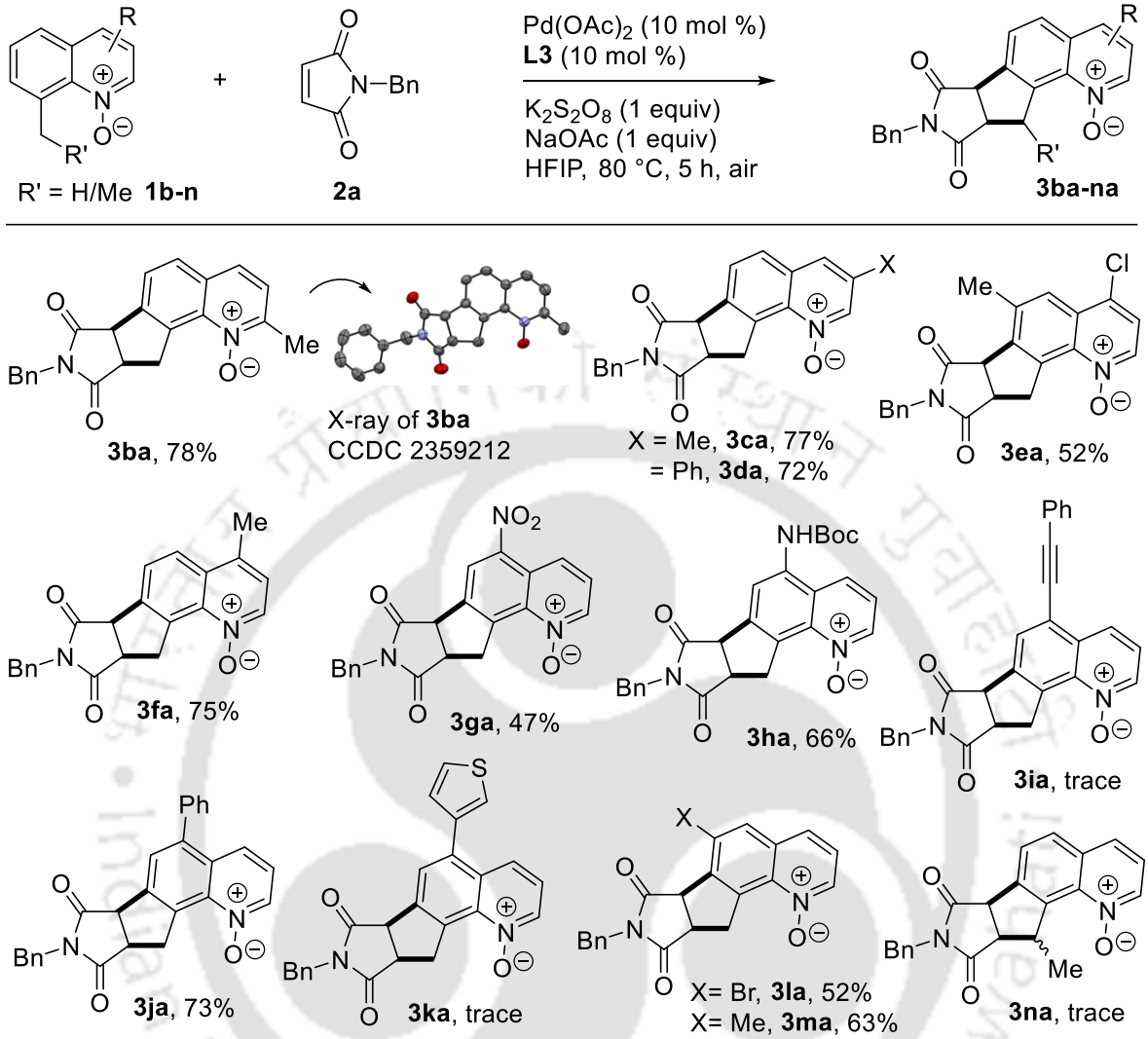


Figure 2. Ligand Optimization under Standard Reaction Condition

With the established optimized conditions, the scope of the procedure was examined for a set of 8-methylquinoline *N*-oxides **1b-n** utilizing 1-benzylpyrrolidine-2,5-dione **2a** as a standard substrate (Table 2). The 2-methyl QNO **1b** furnished annulated **3ba** in 78% yield, and the structure was confirmed by the single crystal X-ray analysis (CCDC 2359212). Notably, the substitution at 3-position of QNO with methyl **1c** and phenyl **1d** substituents underwent annulation to give **3ca** and **3da** in 77% and 72% yields, respectively. Moreover, 4-chloro 6,8-dimethyl QNO **1e** furnished **3ea** in 52% yield. In contrast, QNO **1f** bearing 4,8-dimethyl substituents reacted to give **3fa** in 75% yield. Further, the substrate **1g** having strong electron withdrawing 5-NO_2 group afforded **3ga** with slightly lower yield in 47%. The reaction of 5-subtituted quinoline derivates bearing amine **1h** and phenyl **1j** groups were amenable to deliver **3ha** and **3ja** in 66% and 73% yields, respectively. However, 5-alkynyl **1i** and 5-thiophenyl **1k** QNO substrates showed no desired outcomes, indicating a possible complex formation with Pd-catalyst. Nevertheless, the QNOs with 6-bromo **1l** and 6-methyl **1m** groups furnished **3la** and **3ma** in 52% and 63% yields, respectively. Finally, to introduce the asymmetricity into the annulated product, we tried a secondary C-H functionalization through 8-ethyl QNO **1n**, which produced trace result due to steric hindrance at the initial C-H functionalization site.

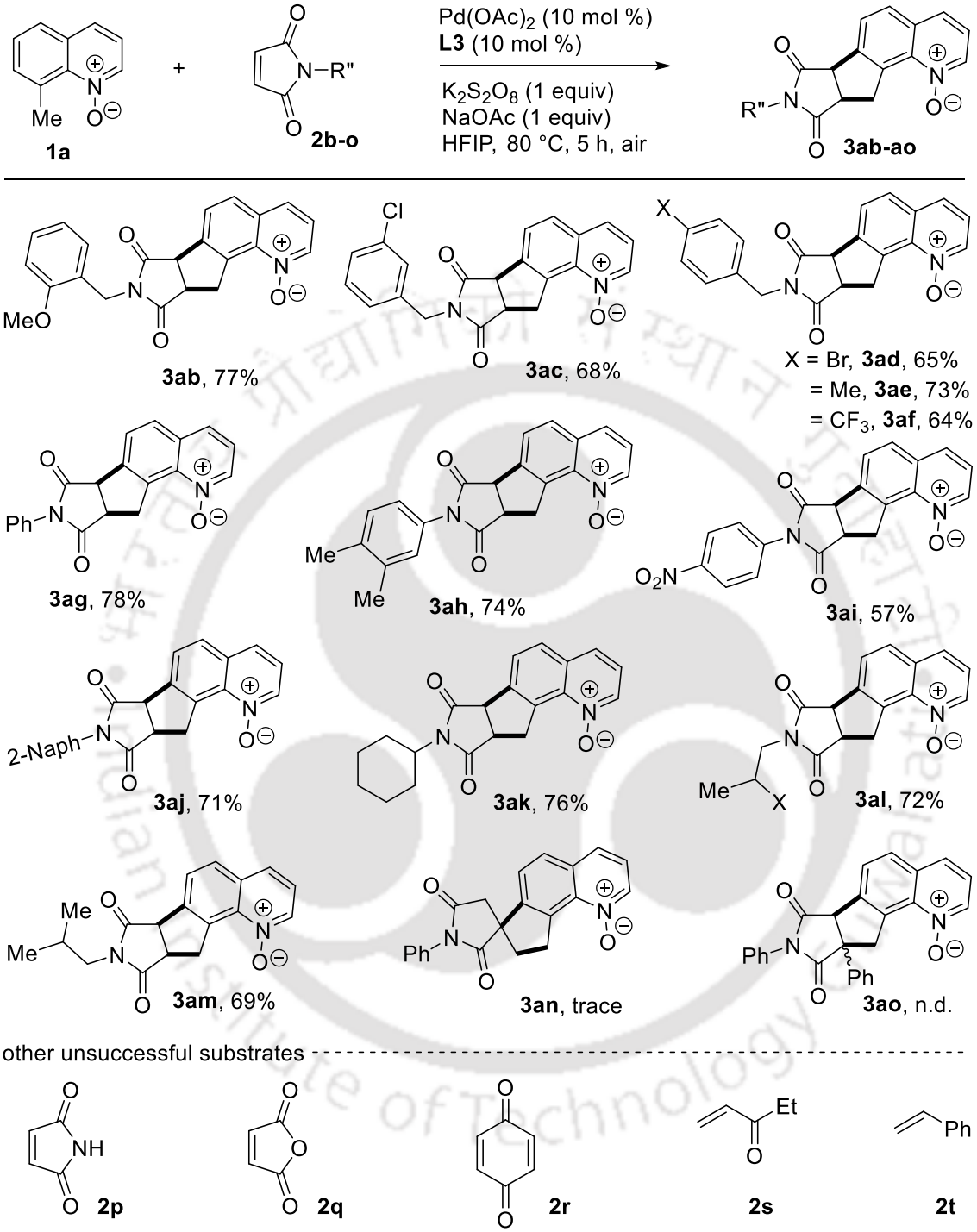
Table 2. Substrate Scope of QNOs[a,b]



[a]Reaction condition: **1a** (0.2 mmol), **2a** (0.24 mmol), $Pd(OAc)_2$ (10 mol %), **L3** (10 mol %), NaOAc (0.2 mmol), $K_2S_2O_8$ (0.2 mmol), HFIP (1 mL), 80 °C, air, 5 h. [b]Isolated yield.

Next, we shifted our attention to test the generality of the reaction scope employing diversely substituted maleimides **2b-m** with 8-methylquinoline *N*-oxide **1a** as the model substrate (Table 3). As apparent, regardless of the electronic effect, *N*-substituted maleimides were smoothly transformed into the desired products in good yields. Now starting with *N*-benzyl maleimides with 2-methoxy **2b**, 3-chloro **2c**, 4-bromo **2d**, 4-methyl **2e** and 4-trifluoromethyl **2f** groups were coupled with QNO **1a** to produce **3ab-af** in 64-77% yields. A pertinent result was obtained from the reactions of QNO **1a** and *N*-phenylmaleimides having electron donating and withdrawing substituents, affording **3ag-ai** in 57-78% yield. Moreover, 2-naphthyl maleimide

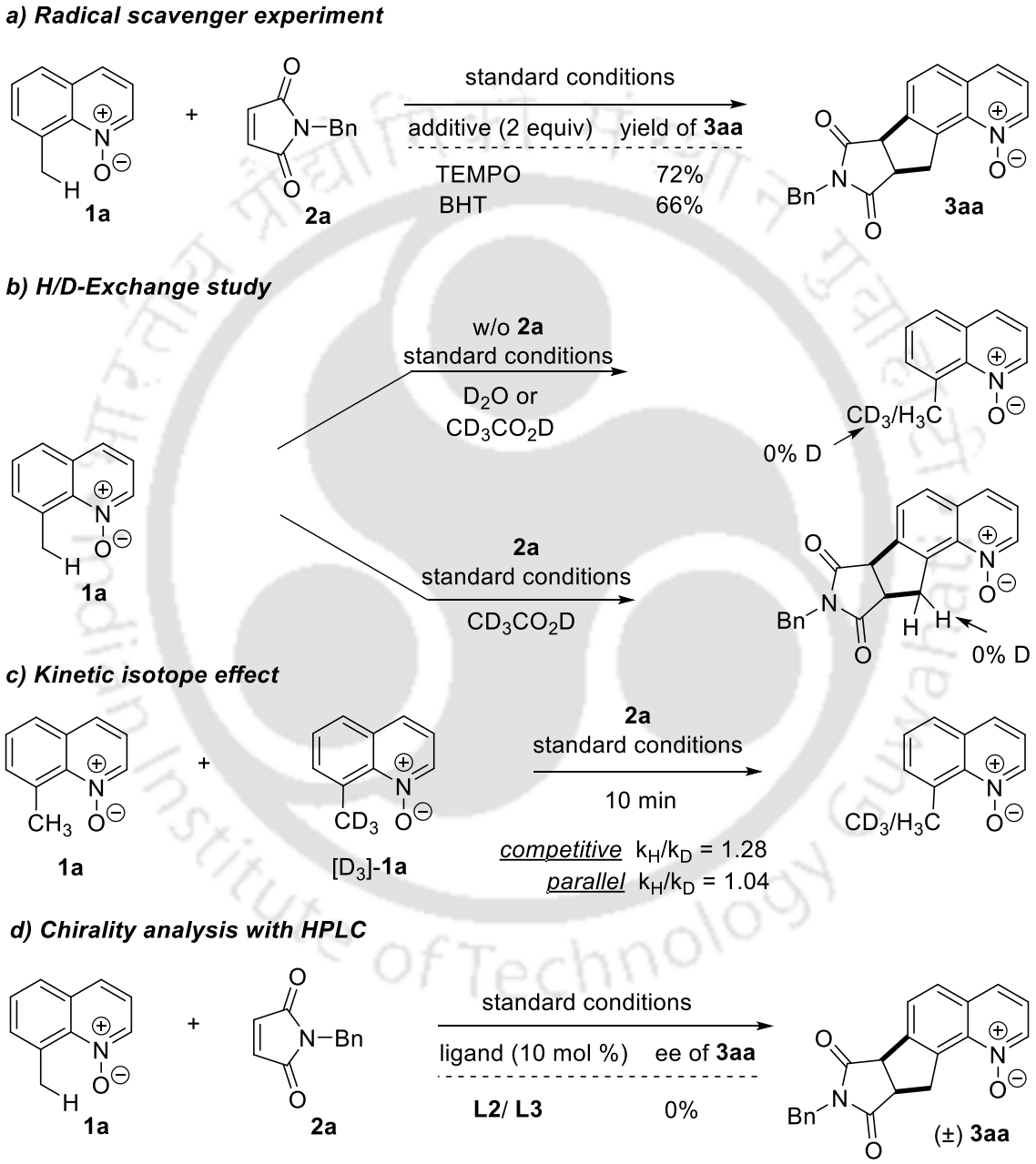
Table 3. Substrate Scope of Maleimides[a,b]



[a]Reaction condition: **1a** (0.2 mmol), **2a** (0.24 mmol), $Pd(OAc)_2$ (10 mol %), **L3** (10 mol %), NaOAc (0.2 mmol), $K_2S_2O_8$ (0.2 mmol), HFIP (1 mL), 80 °C, air, 5 h. [b]Isolated yield.

2j was tolerated to yield **3aj** in 71%. Besides the *N*-benzyl and -aryl, the reaction was tested with *N*-alkyl maleimides. The reactions were compatible with cyclohexyl **2k**, n-propyl **2l** and

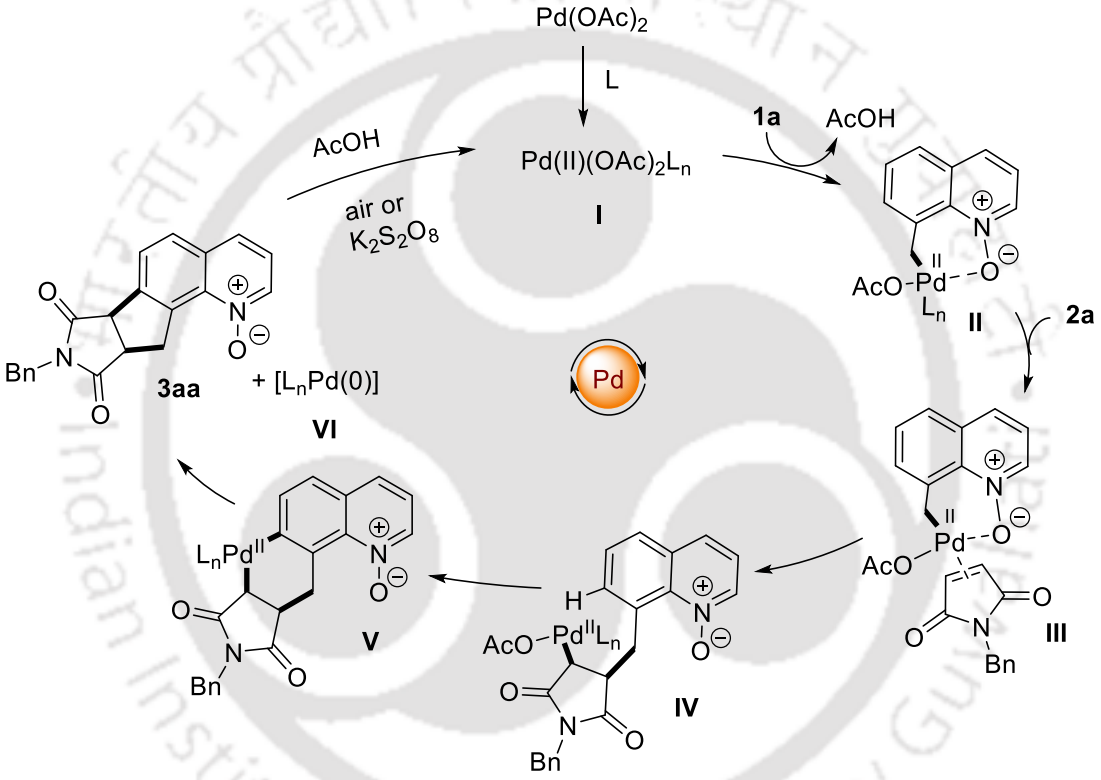
iso-butyl **2m** maleimides, delivering **3ak-am** in 69-76% yields. On a contrary, 3-substituted methylene **2n** and phenyl **2o** maleimides did not take part in the reaction. In a similar fashion, with other electron deficient coupling partners such as non-substituted maleimide **2p**, maleic anhydride **2q**, benzoquinone **2r**, ethyl vinyl ether **2s** and styrene **2t** were unsuccessful in yielding the desired coupled products.



Scheme 10. Preliminary Mechanistic Investigation

To get insight of the reaction mechanism, the radical trapping experiments employing QNO **1a** with maleimide **2a** were performed utilizing TEMPO and BHT (Scheme 10a). As the reaction proceeded without affecting reaction yield significantly, it ruling out the involvement

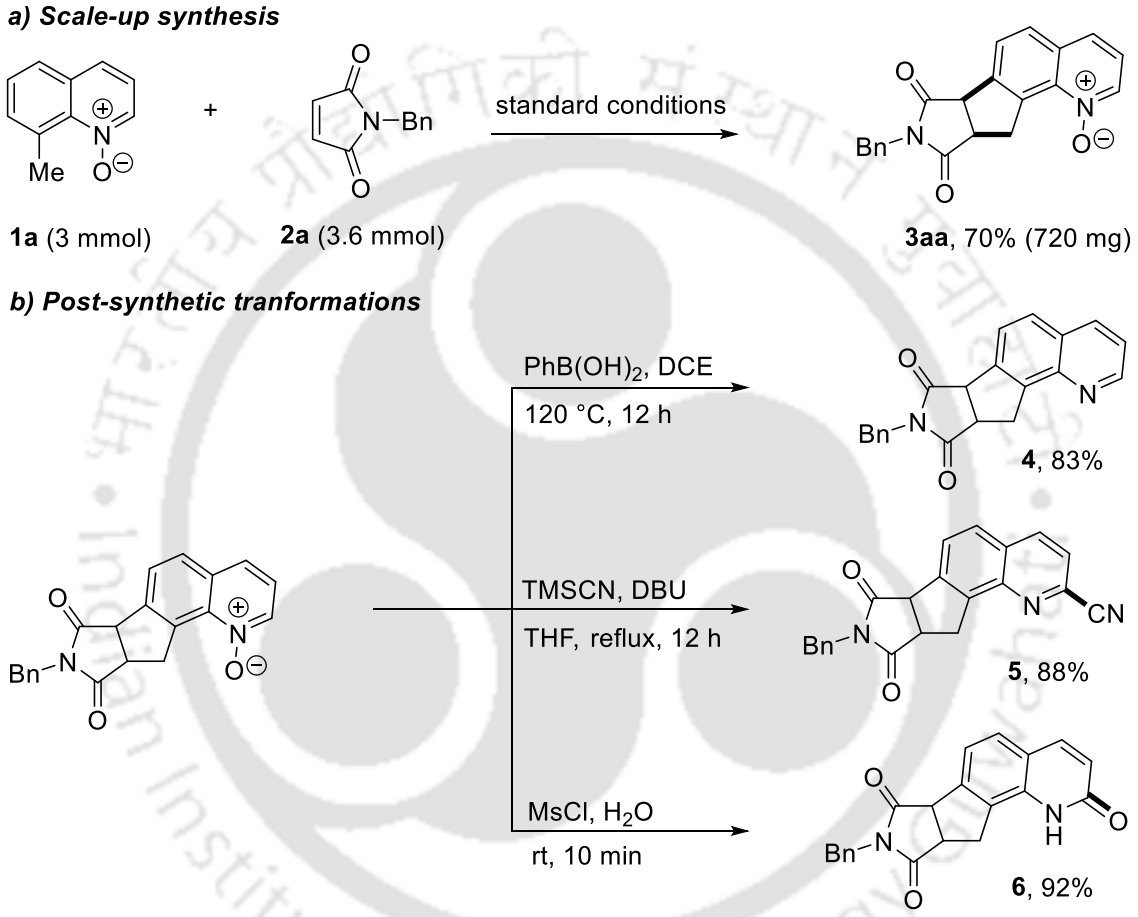
of radical pathway. In addition, the H/D-exchange reaction using D_2O or CD_3CO_2D as co-solvent showed no deuteration in both the recovered substrates **1a** and **3aa**, respectively, indicating the irreversibility of C-H activation step (Scheme 10b). Moreover, the kinetic isotope experiments using **1a** and [D_3]-**1a** with **2a** yielded k_H/k_D of 1.28 and 1.04 in competitive and parallel study, respectively, proposing C-H activation is a less probable rate-determining step (Scheme 10c). To shed light on the stereochemical aspects, the reaction of **1a** and **2a** was carried out with chiral ligands **L2** and **L3** (Scheme 10d). The HPLC results confirmed that the reaction involves in racemic fashion under standard reaction condition.



Scheme 11. Plausible Reaction Pathway

Experimental results and literature precedents[6] proposed that an active Pd(II)L_n **I** can activate the C(sp^3)-H bond of 8-methylquinoline *N*-oxide **1** to generate the 6-membered palladacycle **II** (Scheme 11). Subsequent coordination and 1,2-migratory insertion of maleimide **2** can produce **IV**. Here the most anticipated C7-H activation happens and leads to the formation of **V**, which undergoes reductive elimination to give the target product **3** and Pd(0) species **VI**. Oxidation of Pd-species regenerates the active Pd(II)-catalyst **I** to complete the catalytic cycle.

To showcase practicality, the scale up reaction using **1a** with **2a** was investigated and the annulation took place to yield **3aa** in 70% (Scheme 12a). Further, a set of post-modification reactions can be performed (Scheme 12b). For instances, *N*-oxide removal and C2-cyanation of **3aa** can be achieved using $PhB(OH)_2$ and TMSCN to deliver **4** and **5** in 83% yield and 88% yield, respectively. Moreover, transformation of **3aa** into biologically significant quinolone **6** was found in 92% yield.



Scheme 12. Synthetic Utilities

In summary, we have demonstrated the Pd(II)-catalyzed dual C-H functionalization and subsequent functionalization of $C(sp^3)$-H and $C(sp^2)$-H bonds of 8-methylquinoline *N*-oxides using maleimide as the relaying coupling partner. The key practical aspects include observed selectivity to access C7-H bond and two-fold C-H functionalization. Notably, post-synthetic transformations and substrate scope along with functional group tolerance highlight the versatility of the protocol.

4.3 Experimental Section

General Information. All the reactions were performed under air using oil bath as heating source unless stated. Quinolines, mines, maleic anhydride (99%), maleimide, Ag_2CO_3 (99%), AgOAc (99%), Ag_2O (99%), $Cu(OAc)_2$ (98%), *p*-benzoquinone (BQ) (≥98%), $K_2S_2O_8$ (≥99%), NaOAc (≥99%), KOAc (≥99%), CsOAc (99%), Na_2CO_3 (99%), K_2CO_3 (99%) and *m*-CPBA (≥77%) of Aldrich, HFIP and TFE of TCI chemicals, and quinolines of BLD pharm were used as received. Quinolines[4] and $[Cp^*Co(CO)I_2]$[16] were synthesized using the reported literature. SRL silica gel G/GF 254 plates were used for analytical TLC and SRL silica gel (100-200 and 230-400 mesh) was used for column chromatography. Bruker Avance III 600, 500 and 400 MHz spectrometers used for NMR spectra with tetramethylsilane (Me_4Si) as an internal standard. Chemical shifts (δ) and spin-spin coupling constants (*J*) are reported in parts per million (ppm) and hertz (Hz), respectively, and other data are reported as follows: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet. Melting points were determined using a Büchi B-540 apparatus and are uncorrected. FT-IR spectra were collected on a PerkinElmer Fourier transform infrared spectrometer. Q-TOF ESI-MS instrument was used for recording mass spectrum (HRMS). Single crystal X-ray data was collected on Agilent Supernova equipped with a CCD area detector using Mo/Kα radiation and the structure was solved by direct method using SHELXT. HPLC analysis was carried out using Waters-2489 with YMC Chiral ART Cellulose-SC column using iso-propanol and hexane as eluent.

General Procedure for the Synthesis of Maleimide.[18] To a clear solution of amine (2 mmol) in AcOH (3 mL), maleic anhydride was added portion-wise. The resultant mixture was stirred for 6 h at 130 °C and poured into a beaker (100 mL) and ice was added into it. The excess of acid was quenched using aqueous $NaHCO_3$ until the effervescence stops. The reaction mixture was extracted with EtOAc (2 x 30 mL), dried (Na_2SO_4) and evaporated to give a residue that was purified by silica gel column chromatography using hexane and EtOAc as an eluent to give maleimide **2**.

Pd(II)-Catalyzed (3+2)-Annulation of 8-Methylquinoline *N*-Oxides with Maleimides. In a pressure tube, quinoline *N*-oxide **1** (0.2 mmol), maleimide **2** (0.24 mmol), $Pd(OAc)_2$ (0.02 mmol, 4.4 mg), *N*-acetyl-L-phenylalanine **L3** (0.02 mmol, 4 mg), $K_2S_2O_8$ (0.2 mmol, 55 mg), NaOAc (0.2 mmol, 16.4 mg) and HFIP (1 mL) were stirred for 5 h at 80 °C under air. The reaction mixture was passed through a short pad of celite using MeOH and EtOAc (1:9, 30

mL) as eluent. Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using MeOH and 1,2-dichloromethane as an eluent to afford the annulated quinoline *N*-oxide **3**.

Scale-up Synthesis of 3aa. 8-Methylquinoline *N*-oxide **1a** (3 mmol, 478 mg), *N*-benzylmaleimide **2a** (3.6 mmol, 674 mg), $Pd(OAc)_2$ (0.3 mmol, 60 mg), *N*-Acetyl-L-phenylalanine **L3** (0.3 mmol, 62 mg), $K_2S_2O_8$ (3 mmol, 810 mg), NaOAc (3 mmol, 246 mg) and HFIP (10 mL) were subjected to the reaction conditions described in the general procedure to afford **3aa** in 70% (720 mg) yield.

Post-synthetic Transformations

Synthesis of 4.[19] Compound **3aa** (0.2 mmol, 69 mg) and phenylboronic acid (0.3 mmol, 36 mg) were stirred in 1,2-dichloroethane (2 mL) for 12 h at 120 °C in a pressure tube. The reaction mixture was diluted using CH_2Cl_2 (20 mL) and washed with water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue, which was purified by silica gel column chromatography using hexane and EtOAc as an eluent (90/10, v/v) to afford **4** in 83% (55 mg) yield.

Synthesis of 5.[20] Compound **3aa** (0.2 mmol, 69 mg), TMSCN (0.24 mmol, 32 µL) and DBU (0.46 mmol, 68 µL) were stirred in THF (2 mL) for 12 h under reflux. The solvent was evaporated and the residue was extracted using EtOAc (2 x 20 mL). The organic layer was washed with water (2 x 5 mL) and dried (Na_2SO_4). Evaporation of the solvent gave a residue that was purified by silica column chromatography using hexane and EtOAc as an eluent (80/20, v/v) to afford **5** in 88% (62 mg) yield.

Synthesis of 6.[21] To stirred solution of **3aa** (0.2 mmol, 69 mg) in H_2O (1 mL), MsCl was added dropwise at room temperature. After 10 mins, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and organic layer was washed with brine (5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica column chromatography using hexane and EtOAc as an eluent (50/50, v/v) to afford **6** in 92% (63 mg) yield.

Mechanistic Investigation

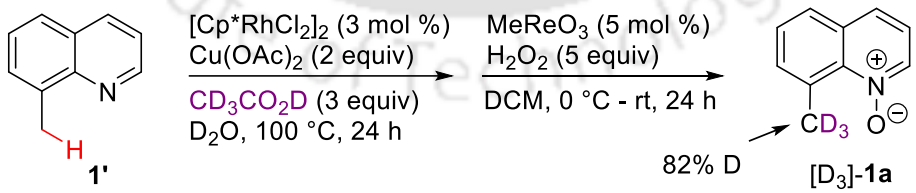
Radical Scavenger Experiments. To a solution of 8-methylquinoline 1-oxide **1a** (0.2 mmol, 32 mg), 1-benzyl-1H-pyrrole-2,5-dione **2a** (0.24 mmol, 45 mg), $Pd(OAc)_2$ (0.02 mmol, 4.5 mg), *N*-acetyl-L-Phe **L3** (0.02 mmol, 4 mg), $K_2S_2O_8$ (0.2 mmol, 54 mg) and NaOAc (0.2 mmol,

16 mg) in HFIP (1 mL), TEMPO/BHT (0.4 mmol) was added and the resulting mixture was stirred for 5 h at 80 °C under air in pressure tube. The reaction mixture was passed through a short pad of celite using MeOH and EtOAc (1:9, 30 mL). Evaporation of the solvent gave a residue that was purified according to general procedure.

H/D-Exchange Study without 2a. To a solution of 8-methylquinoline 1-oxide **1a** (0.2 mmol, 32 mg), $Pd(OAc)_2$ (0.02 mmol, 4.5 mg), *N*-acetyl-L-Phe **L3** (0.02 mmol, 4 mg), $K_2S_2O_8$ (0.2 mmol, 54 mg) and NaOAc (0.2 mmol, 16 mg) in HFIP (1 mL), D_2O (6 mmol, 109 µL) or CD_3COOD (6 mmol, 344 µL) was added and the resulting mixture were stirred for 5 h at 80 °C in pressure tube under air. The reaction mixture was passed through short celite pad using MeOH and EtOAc (1:9, 30 mL). Evaporation of the solvent gave a residue that was purified according to general procedure. The recovered starting material **1a** from D_2O (29 mg, 91%) and CD_3COOD (28 mg, 88%) has been analyzed using 400 MHz ^{1}H NMR and no deuterium incorporation was observed.

H/D-Exchange Study with 2a. To a solution of 8-methylquinoline 1-oxide **1a** (0.2 mmol, 32 mg), 1-benzyl-1H-pyrrole-2,5-dione **2a** (0.24 mmol, 45 mg), $Pd(OAc)_2$ (0.02 mmol, 4.5 mg), *N*-Acetyl-L-Phe **L3** (0.02 mmol, 4 mg), $K_2S_2O_8$ (0.2 mmol, 54 mg) and NaOAc (0.2 mmol, 16 mg) in HFIP (1 mL), D_2O (6 mmol, 109 µL) was added and the resulting mixture was stirred for 5 h at 80 °C under air in pressure tube. The purification was performed according to the general procedure. The starting *N*-oxide **1a** (13.7 mg, 43% recovered) and **3aa** were isolated (31 mg, 46% yield) and analyzed using 400 MHz ^{1}H NMR and no deuterium incorporation was observed.

Preparation of 8-(Methyl-d$_3$)quinoline 1-oxide [D$_3$]-1a.[4d]



Step 1. 8-Methylquinoline **1a** (1.2 mmol, 173 mg), $[RhCp^*Cl_2]_2$ (0.036 mmol, 22 mg), CD_3COOD (3.6 mmol, 205 µL), $Cu(OAc)_2$ (2.4 mmol, 436 mg) and D_2O (4 mL) were stirred at 100 °C for 24 h. The reaction mixture was passed through short pad of celite using EtOAc (40 mL). Evaporation of the solvent gave a residue that was used for the next step without further purification.

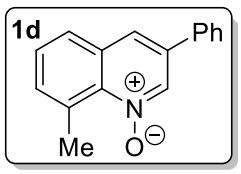
Step 2. The above residue was dissolved in CH_2Cl_2 (4 mL) and treated with $MeReO_3$ (0.06 mmol, 15 mg). The resultant mixture was cooled to 0 °C and treated with 30% H_2O_2 (2 mmol, 68 µL) dropwise for the period of 10 minutes under stirring. Then, the reaction mixture was allowed to warm up to room temperature and the stirring continued for an additional 24 h, quenched with MnO_2 (1 mg). The reaction mixture was diluted with CH_2Cl_2 (5 mL) and passed through a short pad of celite using CH_2Cl_2 (10 mL). Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane/EtOAc (50/50, v/v). The 400 MHz ^{1}H NMR analysis of [D_3]-**1a** showed 82% of deuterium incorporation.

Competitive Kinetic Isotope Experiment. 8-Methylquinoline 1-oxide **1a** (0.1 mmol, 16 mg), 8-(methyl-d_3)quinoline 1-oxide [D_3]-**1a** (0.1 mmol, 16 mg), 1-benzyl-1H-pyrrole-2,5-dione **2a** (0.24 mmol, 45 mg), $Pd(OAc)_2$ (0.02 mmol, 4.5 mg), *N*-acetyl-L-Phe **L3** (0.02 mmol, 4 mg), $K_2S_2O_8$ (0.2 mmol, 54 mg) and NaOAc (0.2 mmol, 16 mg) were stirred in HFIP (1 mL) at 80 °C for 10 min in pressure tube under air. The quinoline *N*-oxide **1a**/[D_3]-**1a** (24 mg, 76% recovered) was analyzed 400 MHz ^{1}H NMR and found k_H/k_D = 1.28.

Parallel Kinetic Isotope Experiment. Two pressures tubes were separately charged with 8-methylquinoline 1-oxide **1a** (0.1 mmol, 16 mg) or 8-(methyl-d_3)quinoline 1-oxide [D_3]-**1a** (0.1 mmol, 16 mg), 1-benzyl-1H-pyrrole-2,5-dione **2a** (0.24 mmol, 45 mg), $Pd(OAc)_2$ (0.02 mmol, 4.5 mg), *N*-acetyl-L-Phe **L3** (0.02 mmol, 4 mg), $K_2S_2O_8$ (0.2 mmol, 54 mg) and NaOAc (0.2 mmol, 16 mg), HFIP (1 mL) was added and stirred at 80 °C for 10 min. The KIE value was determined to be k_H/k_D = 1.04 based on the ^{1}H NMR analysis of **1a**/[D_3]-**1a** (23.5 mg, 74% recovered).

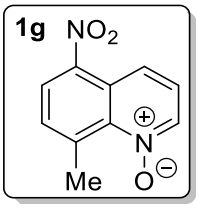
4.4 Characterization Data

Characterization Data of Newly Synthesized Quinoline *N*-oxides

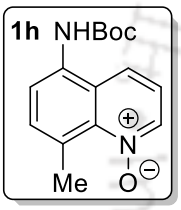


8-Methyl-3-phenylquinoline 1-oxide 1d. Analytical TLC on silica gel, 1:1 EtOAc/hexane R_f = 0.4; colourless solid; mp 99-100 °C; yield 52% (122 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71-8.70 (m, 1H), 7.81-7.80 (m, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.65-7.62 (m, 2H), 7.53-7.49 (m, 2H), 7.47-7.39 (m, 3H), 3.21 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.1, 136.5, 135.6, 134.3, 133.5, 133.22, 132.27, 129.3, 128.9, 128.4, 127.0, 126.9, 124.0, 24.8; FT-

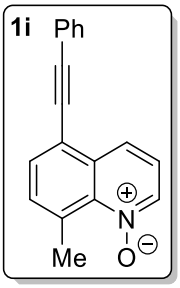
IR (neat) 3040, 2923, 1582, 1494, 1365, 1220, 1200, 756, 695 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{14}NO$: 236.1070, found 236.1065.



8-Methyl-5-nitroquinoline 1-oxide 1g. Analytical TLC on silica gel, 3:2 EtOAc/hexane R_f = 0.3; brown solid; mp 119-120 °C; yield 48% (98 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 6 Hz, 1H), 8.40 (d, *J* = 8.8 Hz, 1H), 8.19 (d, *J* = 8 Hz, 1H), 7.50 (d, *J* = 8 Hz, 1H), 7.41 (dd, *J* = 8.8, 6 Hz, 1H), 3.24 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.9, 141.9, 141.8, 138.0, 131.1, 125.7, 125.5, 123.5, 120.7, 26.1; FT-IR (neat) 2927, 1712, 1567, 1511, 1400, 1332, 1272, 1218, 1087, 809, 736 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{10}H_9N_2O_3$: 205.0608, found 205.0611.

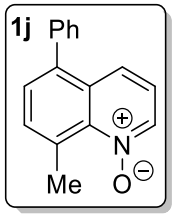


5-((*tert*-Butoxycarbonyl)amino)-8-methylquinoline 1-oxide 1h. Analytical TLC on silica gel, EtOAc/hexane R_f = 0.3; thick liquid; yield 84% (230 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 6.4 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.68 (d, *J* = 8 Hz, 1H), 7.38 (d, *J* = 8 Hz, 1H), 7.19-7.16 (m, 1H), 6.85 (bs, 1H), 3.11 (s, 3H), 1.52 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.6, 141.6, 137.3, 133.0, 131.9, 130.3, 127.2, 122.9, 120.3, 81.2, 28.3, 24.9; FT-IR (neat) 3283, 2928, 1723, 1536, 1367, 1241, 1158, 1054, 882, 748 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{15}H_{19}N_2O_3$: 275.1390, found 275.1400.

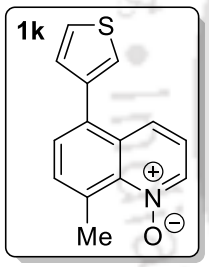


8-Methyl-5-(phenylethynyl)quinoline 1-oxide 1i. Analytical TLC on silica gel, 4:1 EtOAc/hexane R_f = 0.4; brown solid; mp 79-80 °C; yield 62% (160 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.44 (d, *J* = 6.0 Hz, 1H), 8.29 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 7.2 Hz, 1H), 7.62-7.60 (m, 2H), 7.41-7.39 (m, 4H), 7.29 (t, *J* = 7.8 Hz, 1H), 3.20 (s, 3H); ^{13}C NMR (150

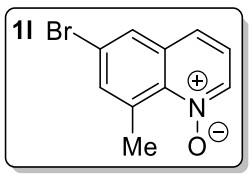
MHz, $CDCl_3$) δ 137.7, 136.8, 134.5, 132.8, 132.5, 132.0, 131.6, 128.8, 128.5, 125.0, 122.6, 121.1, 120.2, 95.5, 85.8, 25.4; FT-IR (neat) 3400, 2926, 1669, 1566, 1400, 1261, 1207, 929, 805, 754, 690 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{14}NO$: 260.1070, found 260.1074.



8-Methyl-5-phenylquinoline 1-oxide 1j. Analytical TLC on silica gel, 3:2 EtOAc/hexane R_f = 0.3; brown solid; mp 88-89 °C; yield 78% (183 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 8.43-8.41 (m, 1H), 7.70-7.68 (m, 1H), 7.50-7.43 (m, 4H), 7.39-7.36 (m, 3H), 7.13-7.09 (m, 1H), 3.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.8, 139.2, 139.1, 137.1, 132.88, 132.85, 131.0, 129.9, 128.8, 128.5, 127.9, 125.0, 120.3, 25.2; FT-IR (neat) 2926, 1668, 1568, 1400, 1257, 1197, 810, 748, 703, 602 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{14}NO$: 236.1070, found 236.1080.

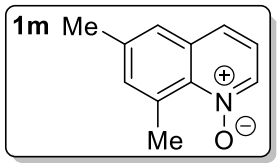


8-Methyl-5-(thiophen-3-yl)quinoline 1-oxide 1k. Analytical TLC on silica gel, 4:1 EtOAc/hexane R_f = 0.5; brown solid; mp 109-110 °C; yield 74% (178 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 8.43-8.42 (m, 1H), 7.84-7.82 (m, 1H), 7.48-7.46 (m, 1H), 7.43 (s, 2H), 7.35-7.34 (m, 1H), 7.20-7.19 (m, 1H), 7.15 (dd, *J* = 8.8, 6.0 Hz, 1H), 3.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.0, 139.6, 137.3, 134.2, 133.2, 133.0, 131.4, 129.3, 129.1, 126.2, 125.0, 124.4, 120.6, 25.3; FT-IR (neat) 3094, 2925, 1570, 1409, 1279, 1247, 1198, 1045, 844, 787, 745, 678 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{14}H_{12}NOS$: 242.0634, found 242.0640.



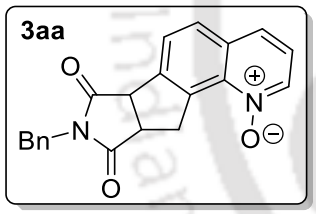
6-Bromo-8-methylquinoline 1-oxide 1l. Analytical TLC on silica gel, 4:1 EtOAc/hexane R_f = 0.5; brown solid; mp 98-99 °C; yield 52% (124 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 8.38-8.37 (m, 1H), 7.81-7.80 (m, 1H), 7.54-7.50 (m, 2H), 7.21 (dd, *J* = 8.4, 6.0 Hz,

1H), 3.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.2, 137.5, 135.9, 133.4, 128.5, 125.26, 125.21, 122.1, 121.7, 24.7; FT-IR (neat) 3414, 3111, 2926, 1568, 1427, 1365, 1294, 1210, 1193, 856, 813, 747 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{10}H_9BrNO$: 237.9862, found 237.9872.

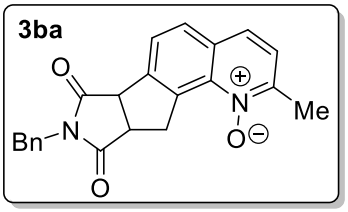


6,8-Dimethylquinoline 1-oxide 1m. Analytical TLC on silica gel, 4:1 EtOAc/hexane R_f = 0.5; brown solid; mp 59-60 °C; yield 60% (104 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35-8.33 (m, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.40 (s, 1H), 7.25 (s, 1H), 7.14 (dd, *J* = 8.4, 6.0 Hz, 1H), 3.15 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.9, 138.0, 136.67, 135.63, 133.2, 132.6, 126.1, 125.7, 120.6, 24.7, 21.0; FT-IR (neat) 3380, 2925, 1619, 1578, 1431, 1373, 1284, 1206, 1055, 852, 818, 744 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{11}H_{12}NO$: 174.0913, found 174.0923.

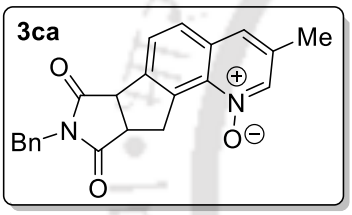
Characterization Data of the Products



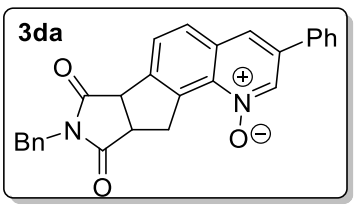
8-Benzyl-7,9-dioxo-6b,7,8,9,9a,10-hexahydropyrrolo[3',4':4,5] cyclopenta[1,2-h]quinoline 1-oxide 3aa. Analytical TLC on silica gel, 4:1 EtOAc/hexane R_f = 0.3; dark brown solid; mp 180-181 °C; yield 82% (56 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, *J* = 6.0 Hz, 1H), 7.81 (d, *J* = 8 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.31-7.29 (m, 2H), 7.26-7.20 (m, 4H), 4.63-4.53 (m, 3H), 4.43 (d, *J* = 8.5 Hz, 1H), 4.39-4.33 (m, 1H), 3.75-3.71 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 176.5, 140.4, 139.5, 136.9, 135.5, 134.8, 132.0, 128.8, 128.68, 128.65, 127.9, 126.2, 125.7, 121.3, 52.0, 43.7, 42.6, 38.1; FT-IR (neat) 2924, 1698, 1564, 1423, 1394, 1255, 1158, 1011, 818, 734, 700 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{17}N_2O_3$: 345.1234, found 345.1239.



8-Benzyl-2-methyl-7,9-dioxo-6b,7,8,9,9a,10-hexahydro-pyrrolo[3',4':4,5]cyclopenta[1,2-h]quinoline 1-oxide 3ba. Analytical TLC on silica gel, 4:1 EtOAc/hexane R_f = 0.3; light brown solid; mp 210-211 °C; yield 78% (56 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.5 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.30-7.21 (m, 6H), 4.63-4.55 (m, 3H), 4.43-4.36 (m, 2H), 3.74-3.70 (m, 1H), 2.63 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0, 176.7, 147.0, 140.3, 139.6, 135.5, 134.4, 130.8, 128.8, 128.66, 128.63, 127.8, 125.4, 124.7, 123.3, 51.9, 43.7, 42.6, 38.2, 18.7; FT-IR (neat) 3008, 1701, 1434, 1394, 1275,1260, 1172, 839, 764, 750 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{19}N_2O_3$: 359.1390, found 359.1395.

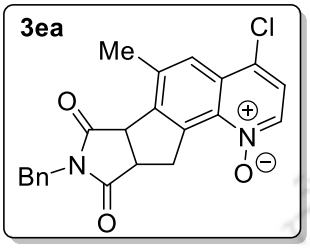


8-Benzyl-3-methyl-7,9-dioxo-6b,7,8,9,9a,10-hexahydro-pyrrolo[3',4':4,5]cyclopenta[1,2-h]quinoline 1-oxide 3ca. Analytical TLC on silica gel, 4:1 EtOAc/hexane R_f = 0.3; light brown solid; mp 230-231 °C; yield 77% (55 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.45 (s, 1H), 7.31-7.28 (m, 2H), 7.27-7.21 (m, 3H), 4.63-4.49 (m, 3H), 4.41 (d, *J* = 8.4 Hz, 1H), 4.36-4.29 (m, 1H), 3.75-3.69 (m, 1H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0, 176.6, 139.3, 138.2, 137.6, 135.5, 134.6, 131.77, 131.70, 128.65, 128.64, 128.1, 127.9, 125.9, 125.6, 51.9, 43.8, 42.6, 37.9, 18.5; FT-IR (neat) 3425, 2925, 1699, 1572, 1432, 1392, 1253, 1156, 750, 699 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{19}N_2O_3$: 359.1390, found 359.1402.

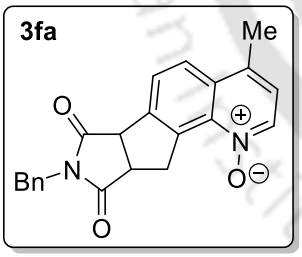


8-Benzyl-7,9-dioxo-3-phenyl-6b,7,8,9,9a,10-hexahydro-pyrrolo[3',4':4,5]cyclopenta[1,2-h]quinoline 1-oxide 3da. Analytical TLC on silica gel, 3:2 EtOAc/hexane R_f = 0.3; yellow solid; mp 258-259 °C; yield 72% (61 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.84-7.78 (m, 3H), 7.63-7.61 (m, 2H), 7.54-7.44 (m, 3H), 7.32-7.30 (m,

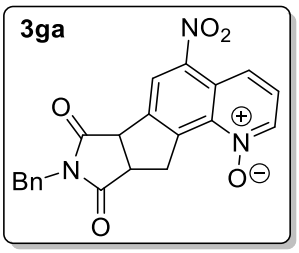
2H), 7.27-7.26 (m, 1H), 7.24-7.23 (m, 2H), 4.65-4.54 (m, 3H), 4.45-4.35 (m, 2H), 3.78-3.73 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 176.5, 140.1, 138.2, 136.1, 135.5, 135.4, 135.2, 134.8, 131.8, 129.4, 129.1, 129.0, 128.7, 128.6, 127.9, 126.9, 126.0, 123.7, 52.0, 43.8, 42.6, 38.01; FT-IR (neat) 2925, 1694, 1572, 1498, 1398, 1365, 1275, 1159, 750, 696 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{21}N_2O_3$: 421.1547, found 421.1543.



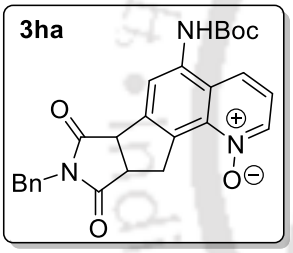
8-Benzyl-4-chloro-6-methyl-7,9-dioxo-6b,7,8,9,9a,10-hexahydropyrrolo[3',4':4,5]cyclopenta[1,2-h]quinoline 1-oxide 3ea. Analytical TLC on silica gel, 3:2 EtOAc/hexane R_f = 0.35; brown solid; mp 160-161 °C; yield 52% (41 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.26 (d, *J* = 6.6 Hz, 1H), 7.91 (s, 1H), 7.35-7.33 (m, 2H), 7.29-7.27 (m, 3H), 7.25-7.23 (m, 1H), 4.65-4.59 (m, 2H), 4.58-4.56 (m, 1H), 4.44-4.42 (m, 2H), 3.79-3.75 (m, 1H), 2.83 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.5, 175.7, 141.3, 138.7, 135.7, 135.4, 129.3, 128.8, 128.7, 128.0, 125.7, 121.4, 51.8, 43.6, 42.7, 38.5, 20.6; FT-IR (neat) 2925, 1702, 1559, 1393, 1353, 1275, 1260, 749, 710 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{18}ClN_2O_3$: 393.1000, found 393.1004.



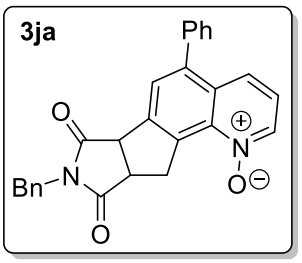
8-Benzyl-4-methyl-7,9-dioxo-6b,7,8,9,9a,10-hexahydro-pyrrolo[3',4':4,5]cyclopenta[1,2-h]quinoline 1-oxide 3fa. Analytical TLC on silica gel, 4:1 EtOAc/hexane R_f = 0.3; brown solid; mp 90-92 °C; yield 75% (54 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.33 (d, *J* = 6.0 Hz, 1H), 7.87-7.84 (m, 2H), 7.32-7.30 (m, 2H), 7.27-7.23 (m, 3H), 7.07 (d, *J* = 6.6 Hz, 1H), 4.62-4.56 (m, 3H), 4.44-4.36 (m, 2H), 3.75-3.72 (m, 1H), 2.61 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.0, 176.6, 140.1, 138.9, 136.3, 135.5, 135.3, 134.8, 131.2, 128.7, 128.6, 127.9, 125.39, 125.33, 122.0, 51.8, 43.7, 42.6, 38.3, 19.0; FT-IR (neat) 2985, 1702, 1561, 1394, 1275, 1260, 1164, 764, 750 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{19}N_2O_3$: 359.1390, found 359.1399.



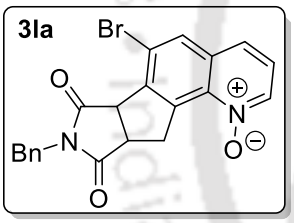
8-Benzyl-5-nitro-7,9-dioxo-6b,7,8,9,9a,10-hexahydro-pyrrolo[3',4':4,5]cyclopenta[1,2-h]quinoline 1-oxide 3ga. Analytical TLC on silica gel, 1:19 DCM/methanol R_f = 0.5; yellow solid; mp 190-191 °C; yield 47% (37 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.47 (d, *J* = 6.0 Hz, 1H), 8.35 (d, *J* = 9.2 Hz, 1H), 7.43 (dd, *J* = 8.8, 6 Hz, 1H), 7.35-7.32 (m, 2H), 7.30-7.26 (m, 3H), 4.65-4.60 (m, 2H), 4.56-4.55 (m, 1H), 4.48-4.40 (m, 2H), 3.782-3.76 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.1, 175.3, 146.5, 142.0, 140.0, 138.6, 137.5, 135.1, 128.9, 128.7, 128.1, 125.2, 124.0, 123.2, 120.8, 51.5, 43.4, 42.9, 39.2; FT-IR (neat) 2925, 1703, 1526, 1397, 1339, 1262, 1171, 816, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{16}N_3O_5$: 390.1084, found 390.1096.



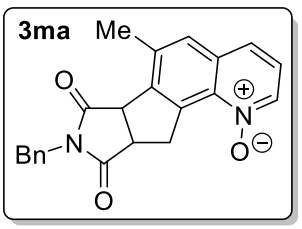
8-Benzyl-5-((tert-butoxycarbonyl)amino)-7,9-dioxo-6b,7,8,9,9a,10-hexahydropyrrolo[3',4':4,5]cyclopenta[1,2-h]quinoline 1-oxide 3ha. Analytical TLC on silica gel, 1:19 DCM/methanol R_f = 0.3; brown solid; mp 125-126 °C; yield 66% (60 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 6.0 Hz, 1H), 8.08 (s, 1H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.34-7.31 (m, 2H), 7.28-7.26 (m, 1H), 7.25-7.22 (m, 3H), 6.71 (s, 1H), 4.63-4.55 (m, 2H), 4.52-4.47 (m, 1H), 4.42 (d, *J* = 8.4 Hz, 1H), 4.36-4.28 (m, 1H), 3.74-3.68 (m, 1H), 1.54 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0, 176.3, 153.1, 140.5, 140.1, 139.9, 136.9, 135.5, 134.0, 131.1, 128.8, 128.6, 127.9, 120.9, 120.2, 119.8, 81.7, 52.1, 43.6, 42.7, 38.2, 28.2; FT-IR (neat) 2980, 2927, 1704, 1538, 1498, 1393, 1260, 1157, 764, 750 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{26}N_3O_5$: 460.1867, found 460.1860.



8-Benzyl-7,9-dioxo-5-phenyl-6b,7,8,9,9a,10-hexahydro-pyrrolo[3',4':4,5]cyclopenta[1,2-h]quinoline 1-oxide 3ja. Analytical TLC on silica gel, 4:1 EtOAc/hexane R_f = 0.35; brown solid; mp 245-246 °C; yield 73% (61 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 6.0 Hz, 1H), 7.77 (s, 1H), 7.72 (d, *J* = 8.8 Hz, 1H), 7.52-7.46 (m, 3H), 7.40-7.37 (m, 2H), 7.34-7.31 (m, 2H), 7.28-7.23 (m, 3H), 7.16 (dd, *J* = 8.8, 6 Hz, 1H), 4.65-4.56 (m, 3H), 4.46-4.39 (m, 2H), 3.78-3.72 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0, 176.4, 141.7, 140.0, 139.8, 138.4, 136.7, 135.5, 133.9, 130.8, 129.9, 128.7, 128.65, 128.64, 128.2, 127.9, 126.3, 125.1, 120.9, 52.0, 43.7, 42.7, 38.4; FT-IR (neat) 2926, 1702, 1400, 1346, 1260, 1171, 872, 749, 701 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{21}N_2O_3$: 421.1547, found 421.1543.

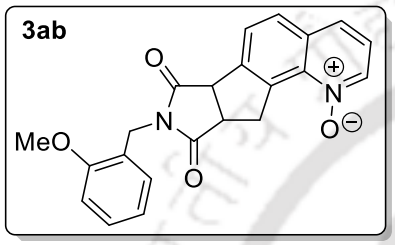


8-Benzyl-6-bromo-7,9-dioxo-6b,7,8,9,9a,10-hexahydro-pyrrolo[3',4':4,5]cyclopenta[1,2-h]quinoline 1-oxide 3la. Analytical TLC on silica gel, 4:1 EtOAc/hexane R_f = 0.35; brown solid; mp 190-191 °C; yield 52% (44 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.38 (d, *J* = 6.0 Hz, 1H), 7.99 (s, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.39-7.37 (m, 2H), 7.30-7.26 (m, 3H), 7.25-7.23 (m, 2H), 4.67-4.61 (m, 3H), 4.59-4.54 (m, 1H), 4.341-4.37 (m, 1H), 3.80-3.76 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.9, 174.5, 140.0, 138.5, 137.2, 137.0, 135.4, 132.9, 131.6, 129.0, 128.7, 128.0, 124.9, 122.4, 121.2, 53.2, 43.3, 42.8, 39.6; FT-IR (neat) 2926, 1704, 1551, 1432, 1392, 1355, 1275, 1260, 1174, 764, 750 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{16}BrN_2O_3$: 423.0339, found 423.0332.

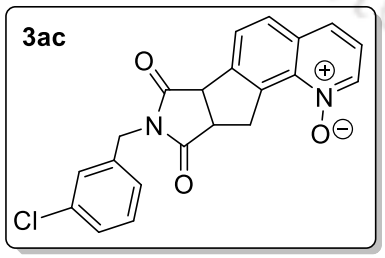


8-Benzyl-6-methyl-7,9-dioxo-6b,7,8,9,9a,10-hexahydro-pyrrolo[3',4':4,5]cyclopenta[1,2-h]quinoline 1-oxide 3ma. Analytical TLC on silica gel, 4:1

EtOAc/hexane R_f = 0.3; whitish brown solid; mp 178-179 °C; yield 63% (45 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 6.0 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.53 (s, 1H), 7.35-7.32 (m, 2H), 7.30-7.27 (m, 2H), 7.25-7.24 (m, 1H), 7.17 (dd, *J* = 8.4, 5.6 Hz, 1H), 4.66-4.61 (m, 2H), 4.57-4.54 (m, 1H), 4.46-4.43 (m, 2H), 3.79-3.72 (m, 1H), 2.77 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.7, 176.0, 140.2, 138.1, 137.4, 136.2, 135.5, 135.0, 132.2, 128.78, 128.70, 128.5, 127.9, 125.5, 121.3, 52.0, 43.7, 42.6, 38.5, 20.3; FT-IR (neat) 2925, 1701, 1567, 1432, 1394, 1275, 1261, 1176, 764, 750 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{19}N_2O_3$: 359.1390, found 359.1395.

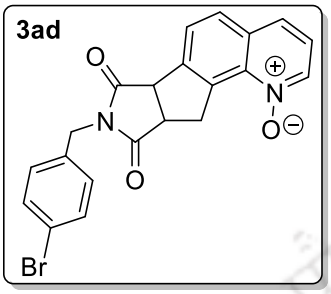


8-(2-Methoxybenzyl)-7,9-dioxo-6b,7,8,9,9a,10-hexahydro-pyrrolo[3',4':4,5]cyclopenta[1,2-h]quinoline 1-oxide 3ab. Analytical TLC on silica gel, 4:1 EtOAc/hexane R_f = 0.3; light brown solid; mp 125-126 °C; yield 77% (58 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, *J* = 6.0 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.69 (d, *J* = 8.5 Hz, 1H), 7.23 (dd, *J* = 8.5, 6 Hz, 1H), 7.17 (t, *J* = 8 Hz, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 6.79-6.75 (m, 2H), 4.71-4.56 (m, 3H), 4.45 (d, *J* = 8.5 Hz, 1H), 4.40-4.34 (m, 1H), 3.78-3.74 (m, 1H), 3.68 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 176.5, 157.0, 140.7, 139.6, 136.9, 134.9, 132.0, 128.8, 128.7, 128.6, 126.1, 125.8, 123.0, 121.3, 120.3, 110.4, 55.2, 51.9, 43.7, 38.1; FT-IR (neat) 3386, 2936, 1774, 1699, 1602, 1563, 1493, 1395, 1247, 1158, 1115, 1011, 829, 751 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{19}N_2O_4$: 375.1339, found 375.1347.

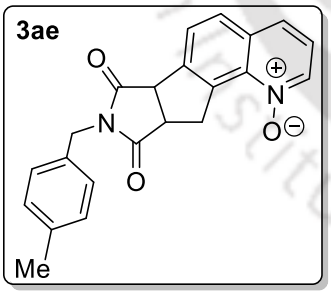


8-(3-Chlorobenzyl)-7,9-dioxo-6b,7,8,9,9a,10-hexahydro-pyrrolo[3',4':4,5]cyclopenta[1,2-h]quinoline 1-oxide 3ac. Analytical TLC on silica gel, 4:1 EtOAc/hexane R_f = 0.35; brown solid; mp 130-131 °C; yield 68% (51 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, *J* = 6 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.76 (d, *J* = 8 Hz, 1H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.27-7.16 (m, 5H), 4.59-4.52 (m, 3H), 4.46 (d, *J* = 8.5 Hz, 1H), 4.39-4.33

(m, 1H), 3.78-3.73 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.8, 176.4, 140.3, 139.5, 137.3, 137.0, 134.8, 134.4, 132.1, 129.9, 128.9, 128.6, 128.2, 126.8, 126.4, 125.6, 121.4, 52.0, 43.8, 42.0, 38.0; FT-IR (neat) 2927, 1773, 1701, 1564, 1423, 1394, 1343, 1256, 1158, 1011, 946, 829, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{16}ClN_2O_3$: 379.0844, found 379.0850.

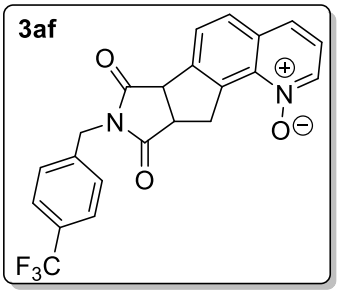


8-(4-Bromobenzyl)-7,9-dioxo-6b,7,8,9,9a,10-hexahydro-pyrrolo[3',4':4,5]cyclopenta[1,2-h]quinoline 1-oxide 3ad. Analytical TLC on silica gel, 4:1 EtOAc/hexane R_f = 0.3; light brown solid; mp 205-206 °C; yield 65% (55 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (d, *J* = 5 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.38-7.36 (m, 2H), 7.25-7.22 (m, 1H), 7.19 (d, *J* = 8 Hz, 2H), 4.57-4.50 (m, 3H), 4.44 (d, *J* = 8.5 Hz, 1H), 4.40-4.34 (m, 1H), 3.76-3.71 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.8, 176.4, 140.3, 139.5, 137.1, 134.8, 134.4, 132.1, 131.8, 130.5, 128.9, 126.5, 125.6, 122.1, 121.4, 52.0, 43.7, 42.0, 38.1; FT-IR (neat) 2927, 1701, 1564, 1488, 1393, 1341, 1258, 1158, 1012, 829, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{16}BrN_2O_3$: 423.0339, found 423.0340.

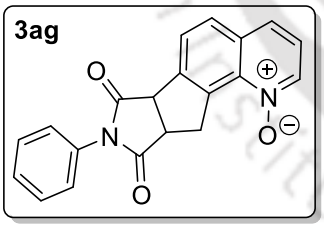


8-(4-Methylbenzyl)-7,9-dioxo-6b,7,8,9,9a,10-hexahydro-pyrrolo[3',4':4,5]cyclopenta[1,2-h]quinoline 1-oxide 3ae. Analytical TLC on silica gel, 4:1 EtOAc/hexane R_f = 0.35; brown solid; mp 205-206 °C; yield 73% (52 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, *J* = 6.0 Hz, 1H), 7.82 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 8 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.23-7.19 (m, 3H), 7.06 (d, *J* = 7.5 Hz, 2H), 4.59-4.51 (m, 3H), 4.41-4.33 (m, 2H), 3.74-3.69 (m, 1H), 2.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0, 176.5, 140.5, 139.6, 137.7, 136.9, 134.8, 132.6, 132.0, 129.3, 128.8, 128.7, 126.2, 125.7, 121.3, 52.0, 43.7, 42.4, 38.0, 21.1; FT-IR (neat) 3407, 2925, 1698, 1564, 1517, 1424, 1394, 1341, 1306, 1256,

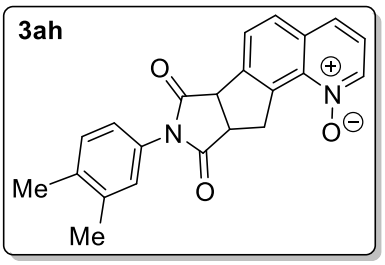
1158, 1011, 829, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{19}N_2O_3$: 359.1390, found 359.1399.



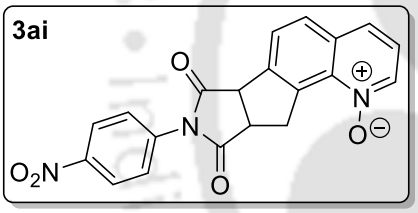
7,9-Dioxo-8-(4-(trifluoromethyl)benzyl)-6b,7,8,9,9a,10-hexahydropyrrolo[3',4':4,5]cyclopenta[1,2-h]quinoline 1-oxide 3af. Analytical TLC on silica gel, 4:1 EtOAc/hexane R_f = 0.3; light brown solid; mp 212-213 °C; yield 64% (53 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, *J* = 6 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.69 (d, *J* = 8 Hz, 1H), 7.51 (d, *J* = 8 Hz, 2H), 7.41 (d, *J* = 7.5 Hz, 2H), 7.24 (dd, *J* = 8, 6 Hz, 1H), 4.68-4.61 (m, 2H), 4.59-4.54 (m, 1H), 4.46 (d, *J* = 8 Hz, 1H), 4.41-4.35 (m, 1H), 3.78-3.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.8, 176.4, 140.1, 139.6, 139.2, 137.0, 134.8, 132.1, 130.3 (J_{C-F} = 32.3 Hz), 128.98, 128.95, 126.2, 125.7 (J_{C-F} = 3.75 Hz), 125.6, 125.0 (J_{C-F} = 270.5 Hz), 121.4, 52.0, 43.8, 42.1, 38.1; ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.68; FT-IR (neat) 2933, 1774, 1701, 1619, 1564, 1422, 1394, 1323, 1256, 1158, 1112, 1066, 1018, 943, 829, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{16}F_3N_2O_3$: 413.1108, found 413.1116.



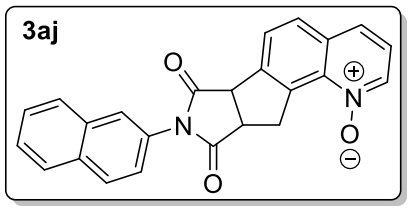
7,9-Dioxo-8-phenyl-6b,7,8,9,9a,10-hexahydropyrrolo[3',4':4,5]-cyclopenta[1,2-h]quinoline 1-oxide 3ag. Analytical TLC on silica gel, 4:1 EtOAc /hexane R_f = 0.3; light brown solid; mp 225-226 °C; yield 78% (52 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.45 (d, *J* = 6.6 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.44-7.41 (m, 2H), 7.37-7.35 (m, 1H), 7.27-7.24 (m, 2H), 7.23-7.21 (m, 2H), 4.73-4.69 (m, 1H), 4.61 (d, *J* = 8.4 Hz, 1H), 4.48-4.43 (m, 1H), 3.94-3.90 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.4, 175.8, 140.4, 139.6, 137.0, 135.0, 132.1, 131.7, 129.1, 128.9, 128.6, 126.3, 126.2, 125.7, 121.4, 52.0, 43.8, 38.5; FT-IR (neat) 2924, 1709, 1564, 1497, 1377, 1275, 1259, 1185, 764, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{15}N_2O_3$: 331.1077, found 331.1078.



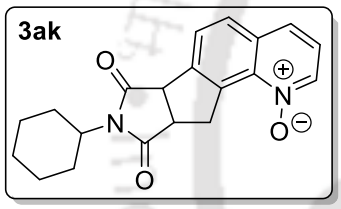
8-(3,4-Dimethylphenyl)-7,9-dioxo-6b,7,8,9,9a,10-hexahydropyrrolo[3',4':4,5]cyclopenta[1,2-h]quinoline 1-oxide 3ah. Analytical TLC on silica gel, 4:1 EtOAc/hexane R_f = 0.3; light brown solid; mp 209-210 °C; yield 74% (53 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (d, *J* = 6.5 Hz, 1H), 7.88 (d, *J* = 8 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.27-7.24 (m, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 6.94-6.90 (m, 2H), 4.71-4.66 (m, 1H), 4.58 (d, *J* = 8.5 Hz, 1H), 4.47-4.41 (m, 1H), 3.91-3.87 (m, 1H), 2.24 (d, *J* = 7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 176.0, 140.6, 139.6, 137.7, 137.5, 137.0, 135.0, 132.1, 130.2, 129.2, 128.9, 127.3, 126.4, 125.8, 123.7, 121.4, 52.0, 43.8, 38.5, 19.7, 19.5; FT-IR (neat) 2924, 1708, 1564, 1504, 1421, 1377, 1257, 1191, 817, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{19}N_2O_3$: 359.1390, found 359.1397.



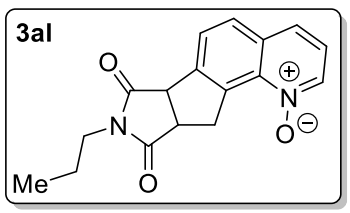
8-(4-Nitrophenyl)-7,9-dioxo-6b,7,8,9,9a,10-hexahydro-pyrrolo[3',4':4,5]cyclopenta[1,2-h]quinoline 1-oxide 3ai. Analytical TLC on silica gel, 4:1 EtOAc/hexane R_f = 0.25; brown solid; mp 228-229 °C; yield 57% (43 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (d, *J* = 6 Hz, 2H), δ 8.30-8.28 (m, 2H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.83 (d, *J* = 8 Hz, 1H), 7.74 (d, *J* = 8 Hz, 1H), 7.56-7.53 (m, 2H), 7.28 (dd, *J* = 8.5, 6 Hz, 1H), 4.75-4.70 (m, 1H), 4.65 (d, *J* = 8.5 Hz, 1H), 4.51-4.45 (m, 1H), 3.98-3.94 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6, 175.0, 146.9, 139.9, 139.5, 137.2, 135.0, 132.2, 129.2, 126.8, 126.6, 125.6, 124.3, 121.6, 51.9, 43.8, 38.6; FT-IR (neat) 2925, 1715, 1595, 1565, 1523, 1341, 1725, 1259, 1177, 848, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{14}N_3O_5$: 376.0928, found 376.0933.



8-(Naphthalen-2-yl)-7,9-dioxo-6b,7,8,9,9a,10-hexahydropyrrolo[3',4':4,5]cyclopenta[1,2-h]quinoline 1-oxide 3aj. Analytical TLC on silica gel, 4:1 EtOAc/hexane R_f = 0.3; light brown solid; mp 120-121 °C; yield 71% (54 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.46 (d, *J* = 6 Hz, 1H), 7.90 (dd, *J* = 11.4, 9 Hz, 2H), 7.85-7.83 (m, 1H), 7.82-7.80 (m, 2H), 7.74-7.71 (m, 2H), 7.52-7.47 (m, 2H), 7.32-7.30 (m, 1H), 7.28-7.25 (m, 2H), 4.77-4.73 (m, 1H), 4.66 (d, *J* = 8.4 Hz, 1H), 4.51-4.46 (m, 1H), 3.99-3.96 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.5, 176.0, 140.4, 139.6, 137.0, 135.0, 133.0, 132.8, 132.2, 129.09, 129.06, 129.03, 128.1, 127.7, 126.9, 126.6, 126.2, 125.8, 125.5, 123.6, 121.4, 52.0, 43.9, 38.5; FT-IR (neat) 2926, 1708, 1600, 1565, 1509, 1471, 1377, 1257, 1178, 1013, 817, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{17}N_2O_3$: 381.1234, found 381.1236.

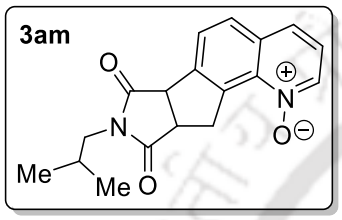


8-Cyclohexyl-7,9-dioxo-6b,7,8,9,9a,10-hexahydropyrrolo-[3',4':4,5]cyclopenta[1,2-h]quinoline 1-oxide 3ak. Analytical TLC on silica gel, 4:1 EtOAc/hexane R_f = 0.35; light brown solid; mp 153-154 °C; yield 76% (51 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 6 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.27-7.22 (m 1H), 4.56-4.49 (m, 1H), 4.38-4.30 (m, 2H), 3.95-3.87 (m, 1H), 3.68-3.63 (m, 1H), 2.14-2.00 (m, 2H), 1.79-1.75 (m, 2H), 1.63-1.59 (m, 1H), 1.50-1.44 (m, 2H), 1.32-1.11 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.4, 177.0, 141.1, 139.5, 137.1, 134.8, 132.0, 128.7, 126.8, 125.7, 121.2, 51.9, 51.7, 43.3, 38.3, 28.7, 28.6, 25.79, 25.75, 24.9; FT-IR (neat) 2931, 2856, 1694, 1564, 1369, 1304, 1257, 1197, 1154, 1011, 830, 750 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{21}N_2O_3$: 337.1547, found 337.1550.

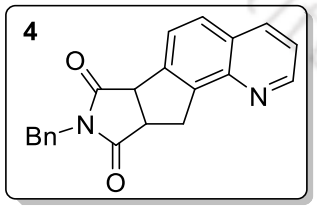


7,9-Dioxo-8-propyl-6b,7,8,9,9a,10-hexahydropyrrolo-[3',4':4,5]cyclopenta[1,2-h]quinoline 1-oxide 3al. Analytical TLC on silica gel, 3:2

EtOAc/hexane R_f = 0.3; light brown solid; mp 155-156 °C; yield 72% (43 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 6.0 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.23 (dd, *J* = 8.4, 6.0 Hz, 1H), 4.59 (d, *J* = 19.6 Hz, 1H), 4.42-4.32 (m, 2H), 3.75-3.69 (m, 1H), 3.42 (t, *J* = 7.2 Hz, 2H), 1.57-1.48 (m, 2H), 0.79 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.4, 176.9, 140.7, 139.6, 136.9, 134.8, 132.0, 128.8, 126.2, 125.7, 121.3, 51.9, 43.6, 40.6, 38.2, 20.9, 11.1; FT-IR (neat) 3385, 2963, 2934, 1771, 1696, 1564, 1399, 1363, 1255, 1202, 1130, 1011, 830, 750, cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}N_2O_3$: 297.1234, found 297.1238.

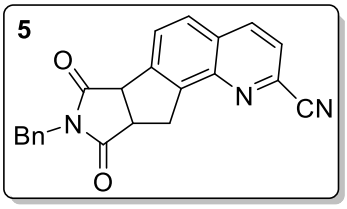


8-Isobutyl-7,9-dioxo-6b,7,8,9,9a,10-hexahydropyrrolo-[3',4':4,5]cyclopenta[1,2-h]quinoline 1-oxide 3am. Analytical TLC on silica gel, 3:2 EtOAc/hexane R_f = 0.25; light brown solid; mp 171-172 °C; yield 69% (43 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (d, *J* = 6 Hz, 1H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.27-7.23 (m, 1H), 4.59-4.54 (m, 1H), 4.43 (d, *J* = 8 Hz, 1H), 4.40-4.34 (m, 1H), 3.76-3.71 (m, 1H), 3.30-3.26 (m, 2H), 2.00-1.91 (m, 1H), 0.79 (d, *J* = 7 Hz, 3H), 0.74 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.6, 177.1, 140.9, 139.5, 137.1, 134.7, 132.0, 128.8, 126.7, 125.7, 121.3, 51.8, 46.1, 43.5, 38.2, 26.9, 19.9, 19.8; FT-IR (neat) 2960, 1773, 1698, 1563, 1400, 1258, 1205, 1154, 1133, 1011, 830, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{19}N_2O_3$: 311.1390, found 311.1398.

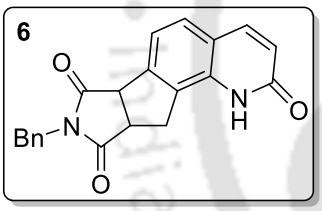


8-Benzyl-9a,10-dihydropyrrolo[3',4':4,5]cyclopenta[1,2-h]quinoline-7,9(6bH,8H)-dione 4. Analytical TLC on silica gel, 1:9 EtOAc/hexane R_f = 0.35; light brown solid; mp 157-158 °C; yield 83% (55 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94-8.93 (m, 1H), 8.19-8.16 (m, 1H), 7.76 (s, 2H), 7.44-7.41 (m, 1H), 7.32-7.29 (m, 2H), 7.27-7.21 (m, 3H), 4.63-4.53 (m, 3H), 4.02-3.97 (m, 1H), 3.90-3.80 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.2, 176.8, 150.5, 145.1, 139.6, 138.2, 136.4, 135.5, 128.66, 128.63, 128.49, 128.43, 127.9, 123.3, 121.3, 53.1, 43.7, 42.6, 33.3. FT-IR (neat) 2929, 1775, 1701, 1507, 1430,

1392, 1342, 1171, 834, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{17}N_2O_2$: 329.1285, found 329.1271.



8-Benzyl-7,9-dioxo-6b,7,8,9,9a,10-hexahydropyrrolo-[3',4':4,5]cyclopenta[1,2-h]quinoline-2-carbonitrile 5. Analytical TLC on silica gel, 1:4 EtOAc/hexane R_f = 0.3; light brown solid; mp 227-228 °C; yield 88% (62 mg); ^{1}H NMR (500 MHz, CDCl3) δ 8.32 (d, *J* = 8.5 Hz, 1H), 7.91 (d, *J* = 8.5 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.32-7.30 (m, 2H), 7.26-7.23 (m, 3H), 4.64-4.56 (m, 3H), 4.02-3.95 (m, 1H), 3.90-3.83 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.8, 176.2, 145.2, 140.8, 140.2, 137.7, 135.4, 133.6, 128.9, 128.7, 128.6, 128.2, 127.9, 126.2, 123.6, 117.4, 53.1, 43.5, 42.7, 33.3. FT-IR (neat) 2928, 2233, 1775, 1702, 1507, 1432, 1395, 1343, 1275, 1171, 857, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{16}N_3O_2$: 354.1237, found 354.1243.



8-Benzyl-1,6b,9a,10-tetrahydropyrrolo[3',4':4,5]cyclopenta-[1,2-h]quinoline-2,7,9(8H)-trione 6. Analytical TLC on silica gel, 4:1 EtOAc/hexane R_f = 0.35; colourless sticky solid; yield 92% (63 mg); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.46 (s, 1H), 7.97 (d, *J* = 9.5 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.32-7.25 (m, 4H), 7.20-7.18 (m, 2H), 6.55-6.53 (m, 1H), 4.62-4.53 (m, 3H), 4.00-3.96 (m, 1H), 3.48 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.4, 176.6, 162.2, 140.5, 140.4, 135.9, 135.4, 128.4, 127.8, 127.4, 127.3, 127.0, 121.7, 119.0, 118.1, 52.1, 43.4, 41.6, 31.9. FT-IR (neat) 3400, 2924, 2853, 2256, 1655, 1048, 1023, 995, 823, 761 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{17}N_2O_3$: 345.1234, found 345.1239.

Crystal Data and Structure Refinement for 3ba

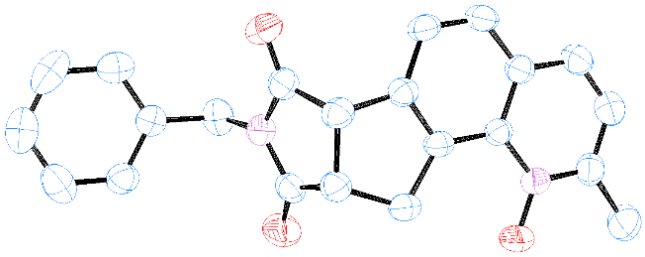


Figure S1. ORTEP diagram of 8-benzyl-2-methyl-7,9-dioxo-6b,7,8,9,9a,10-hexahydro-pyrrolo[3',4':4,5]cyclopenta[1,2-h]quinoline 1-oxide **3ba** with 50% ellipsoid (CCDC 2359212). H-Atoms are omitted for clarity.

Identification code	**3ba**
Empirical formula	'C22 H18 N2 O3'
Formula weight	358.38
Crystal habit, colour	Needle, colorless
Crystal size, mm^3	0.26 x 0.24 x 0.23
Temperature, *T*/K	293 K
Wavelength, λ/Å	0.71073
Crystal system	'Monoclinic'
Space group	' P 1 21/c 1'
Unit cell dimensions	a = 11.2422 (5) Å b = 8.4429 (5) Å c = 18.7490 (9) Å α = 90 β = 96.352 (4) γ = 90
Volume, *V*/$Å^3$	1768.67 (16)
Z	4
Calculated density, g cm^{-3}	1.346
Absorption coefficient, μ/mm^{-1}	0.091
F(000)	752
θ range for data collection	2.186 to 25.496°
Limiting indices	$-8 \leq h \leq 13$, $-6 \leq k \leq 10$, $-21 \leq l \leq 22$
Reflection collected / unique	2157/3292

Completeness to θ	99.9% (θ = 25.496°)
Absorption correction	None
Max. and min. transmission	0.979 and 0.977
Refinement method	'SHELXL-2019/1'
Data / restraints / parameters	3292/0/245
Goodness−of−fit on F^2	1.178
Final *R* indices [*I*>2sigma(*I*)]	R1 = 0.0617, wR2 = 0.1857
R indices (all data)	R1 = 0.0969, wR2 = 0.2107

4.5 References

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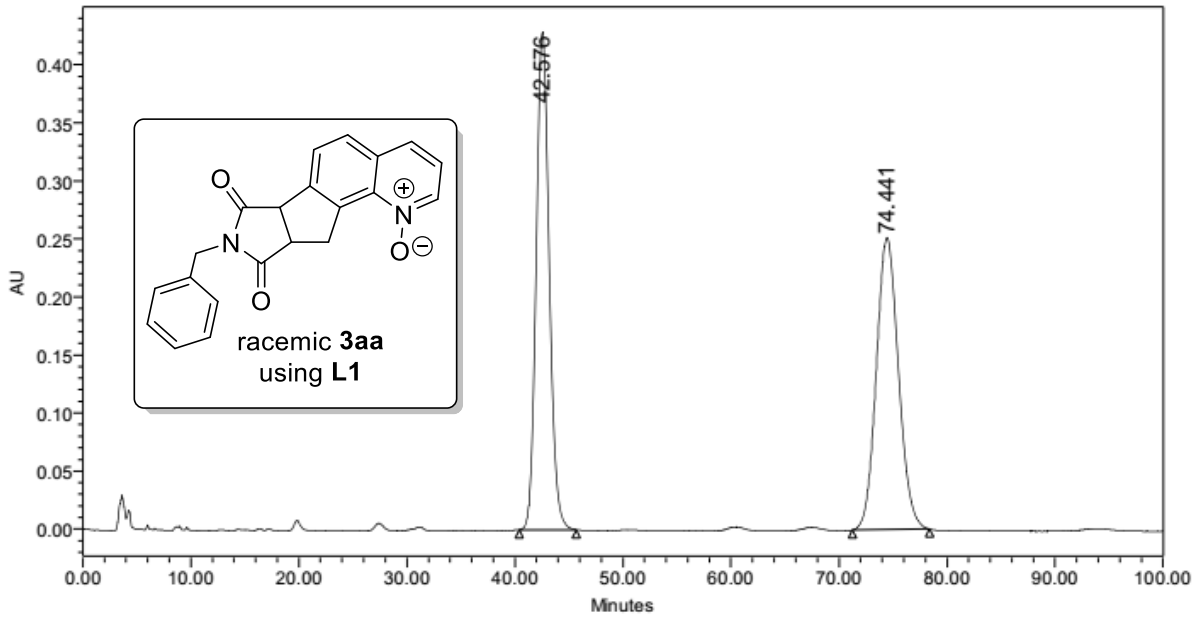
4.6 HPLC Chromatograms



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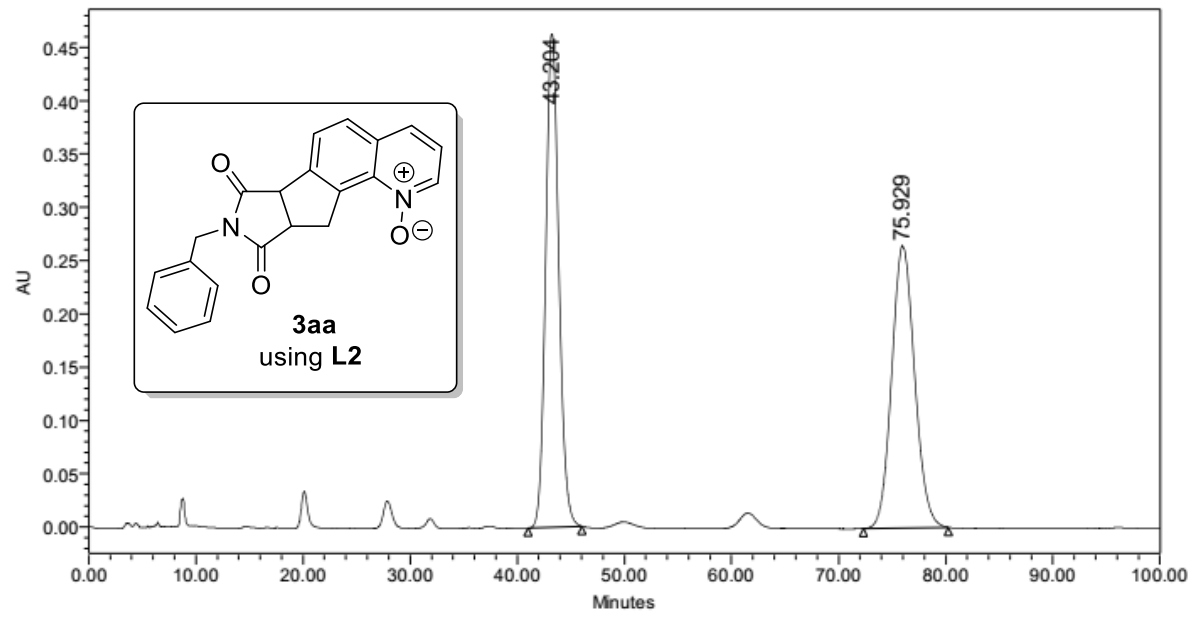

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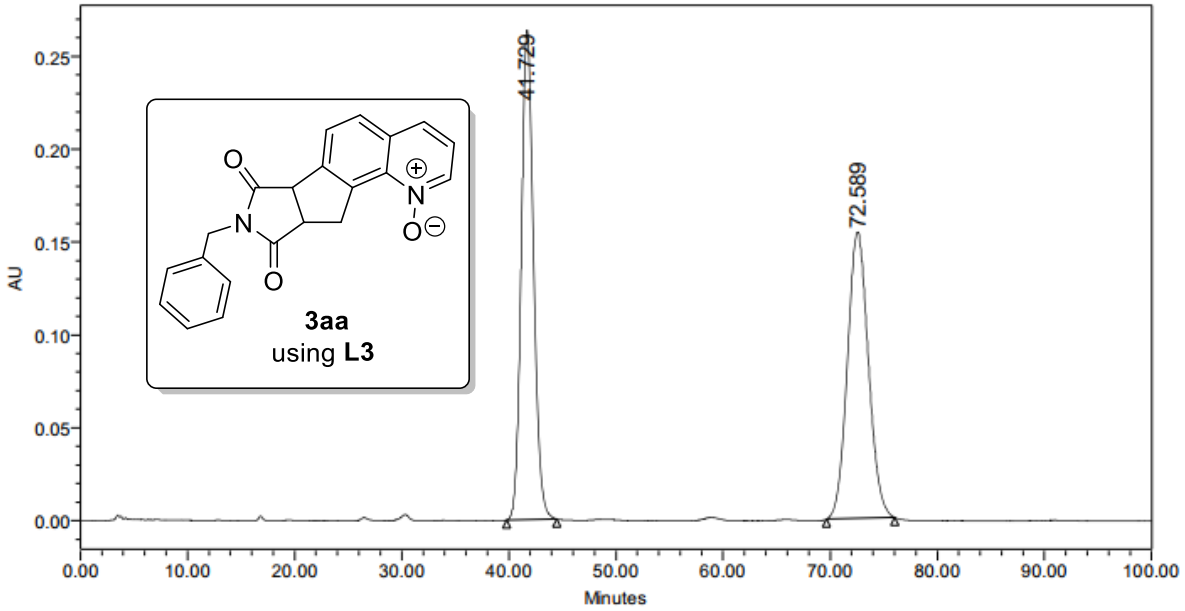

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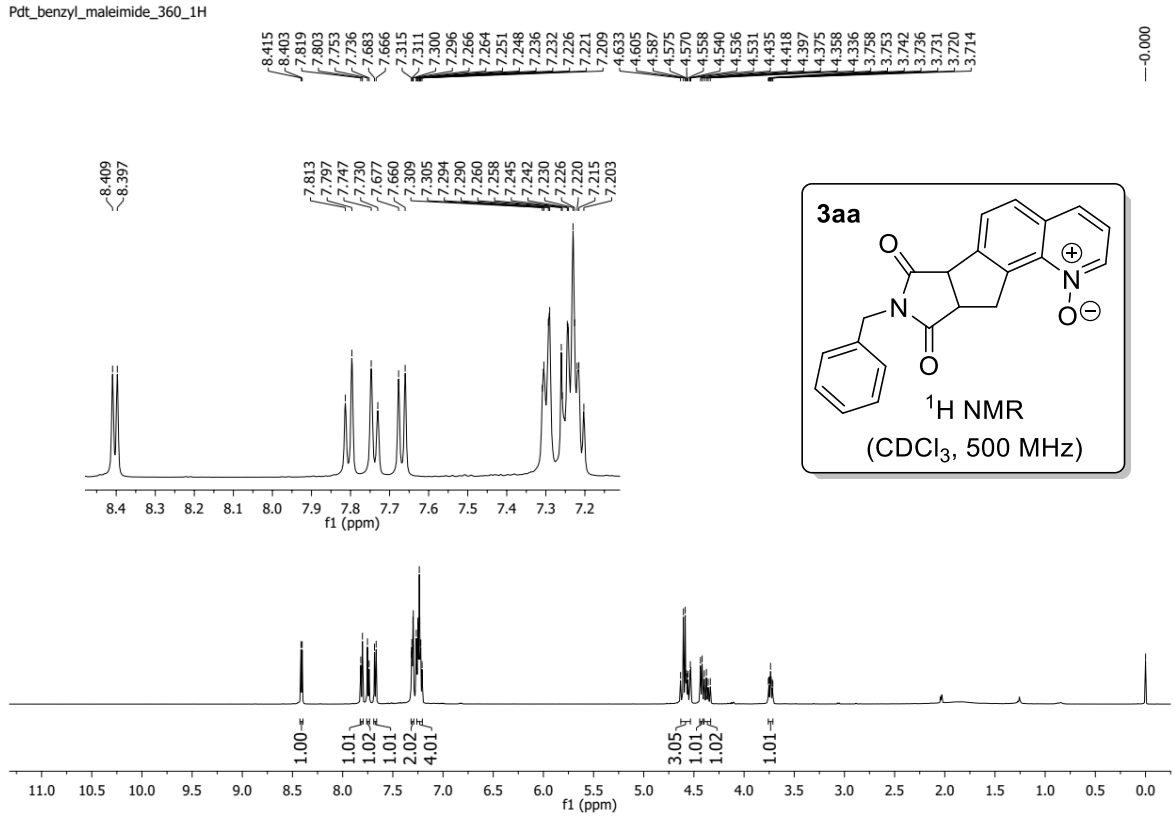
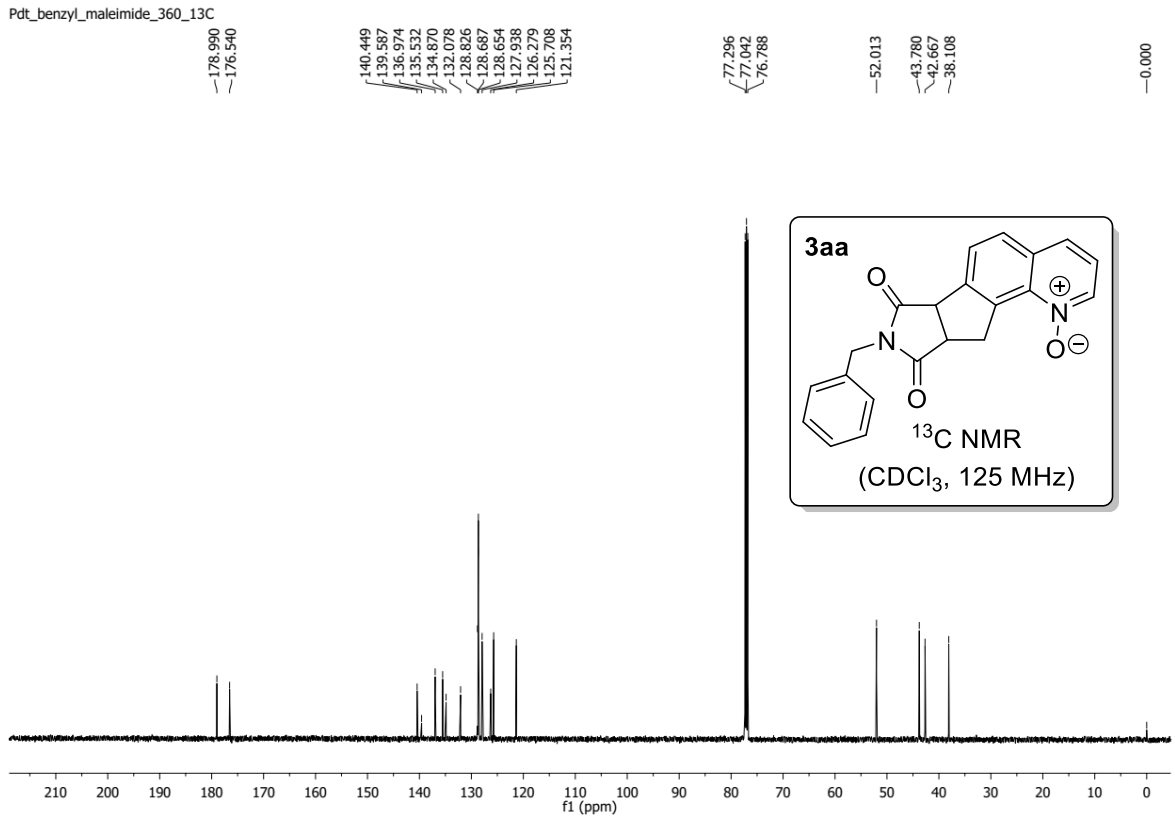
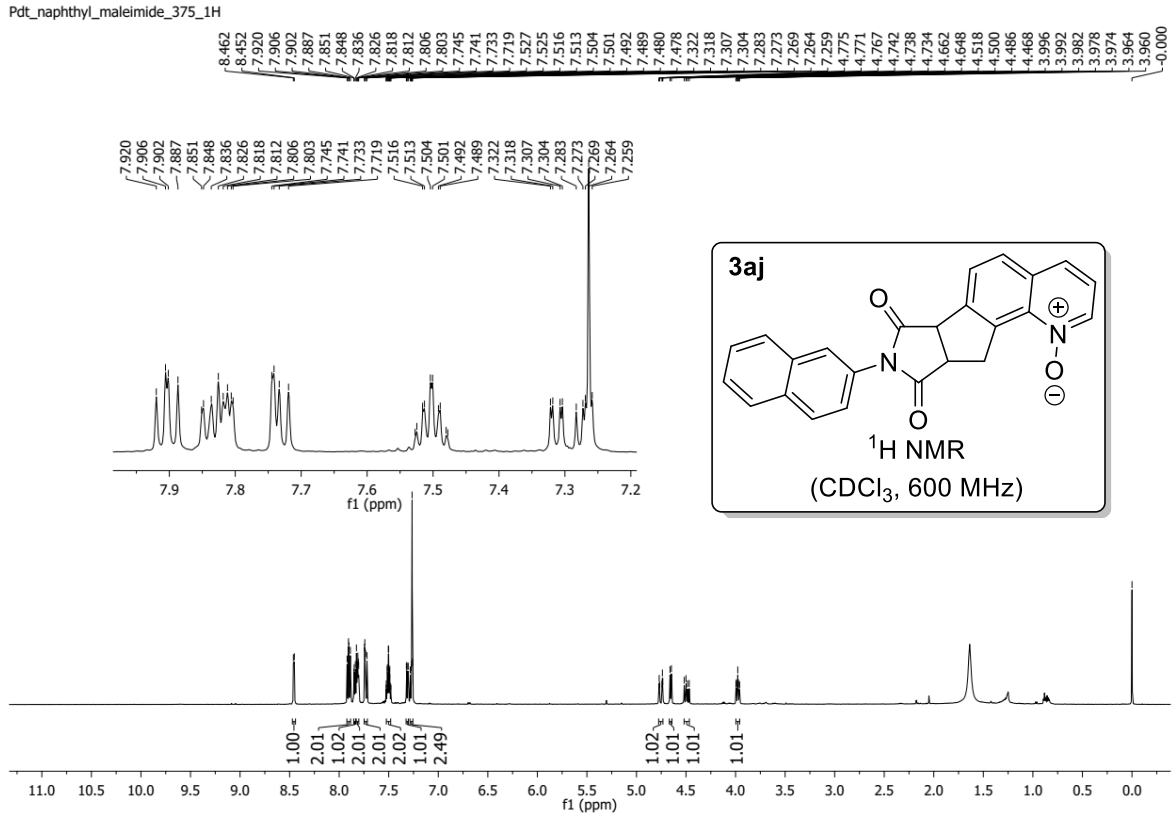
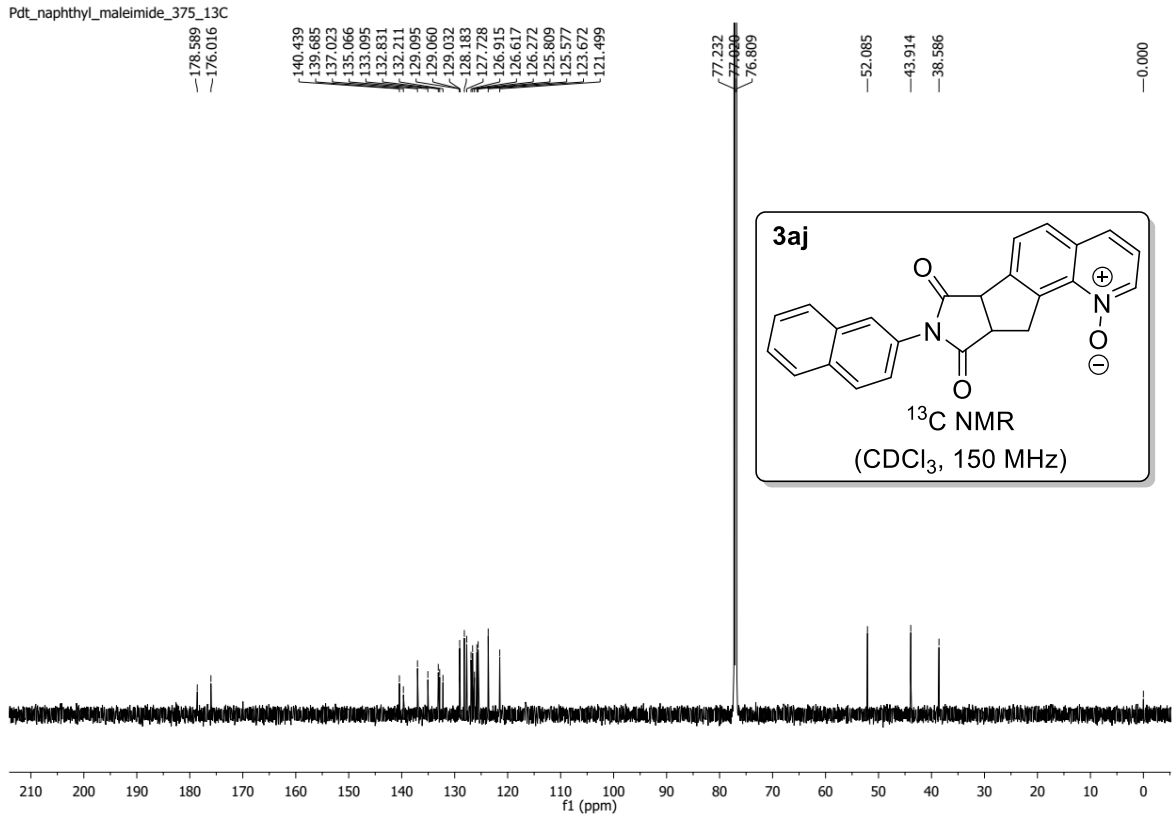
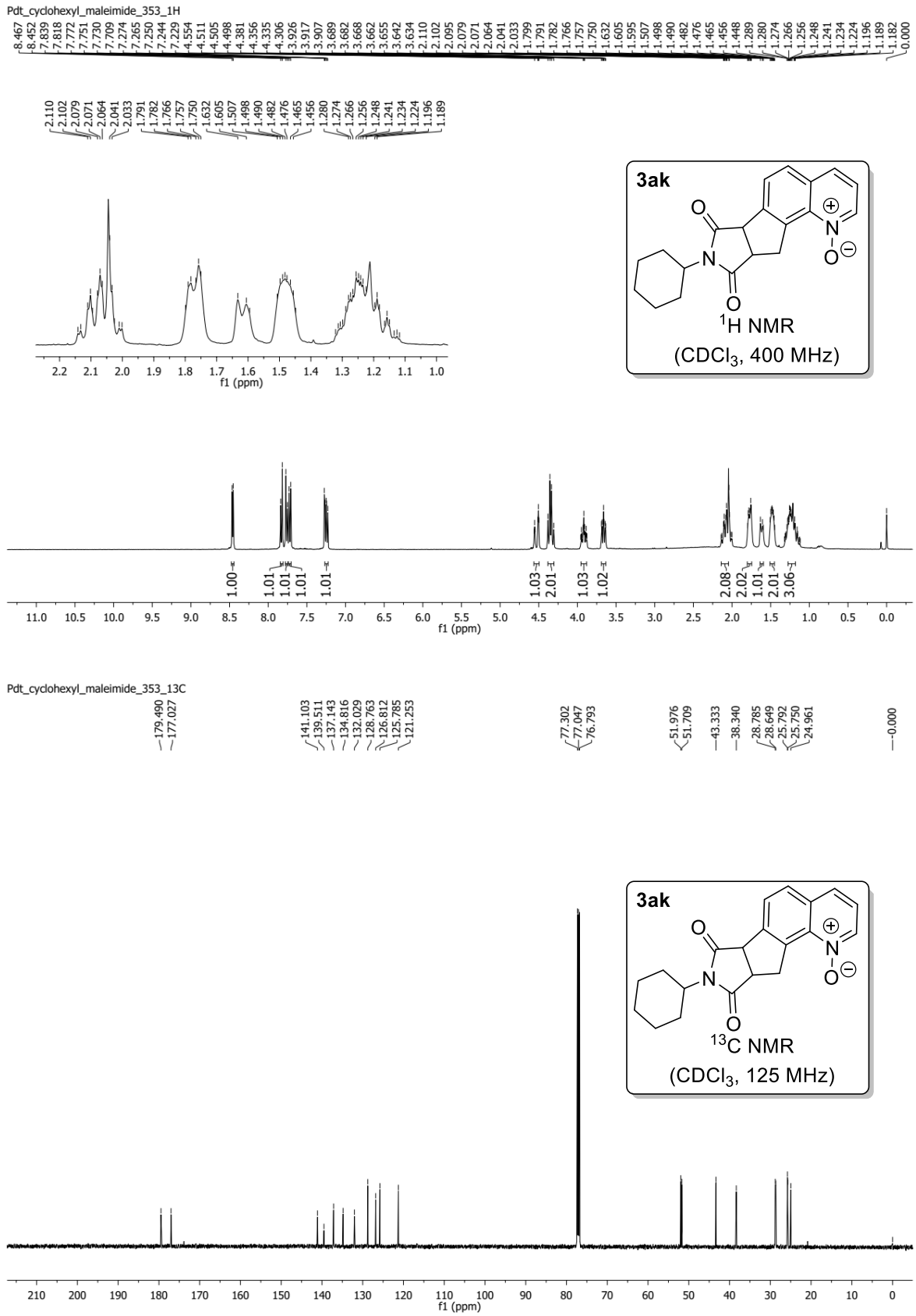
4.7 Selected NMR Spectra



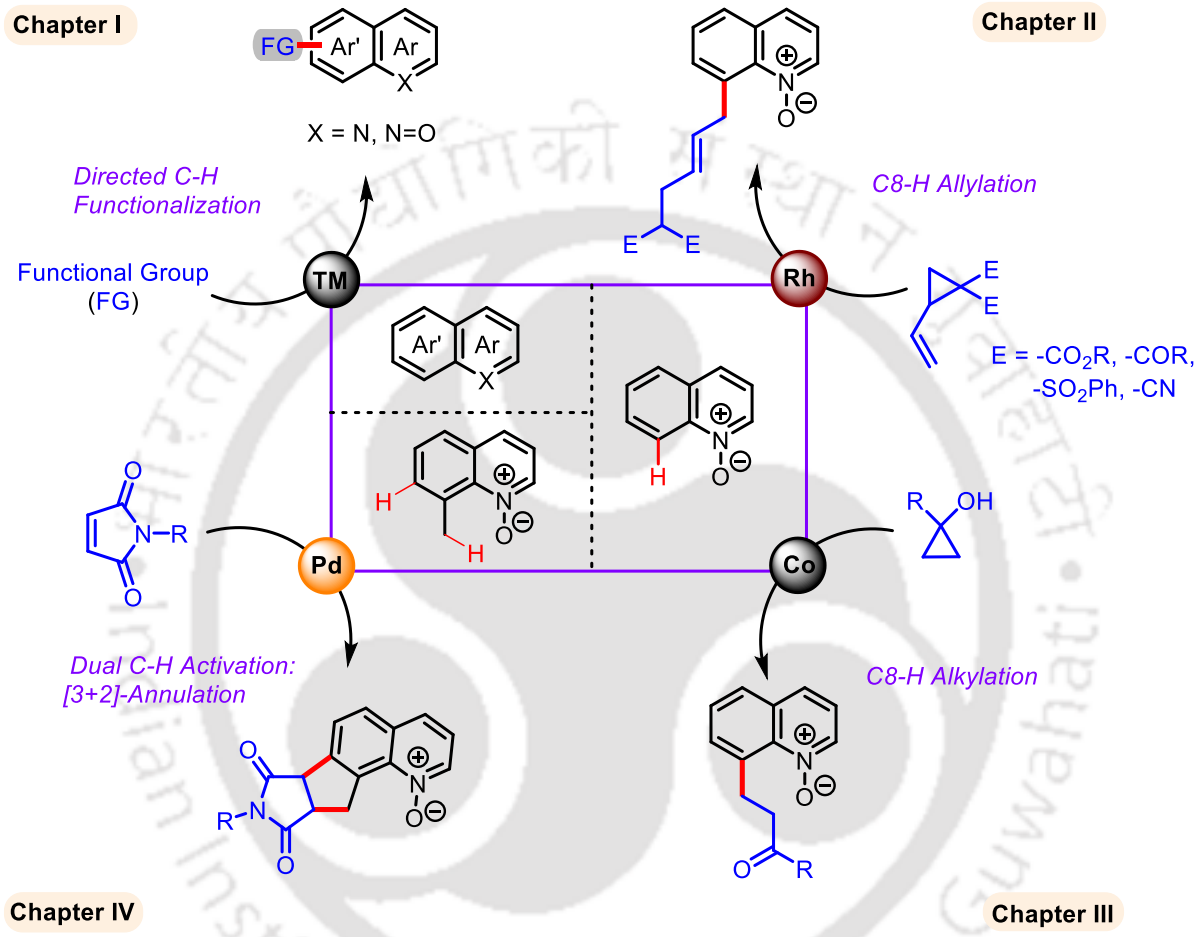








Thesis Overview



Summary

In chapter I, we have discussed the work towards the development of transition-metal-catalyzed C-H functionalization of quinolines different coupling partners. All the seven distinct C-H bonds have been functionalized. However, majority of these methods target the C2-position due to its accessibility and acidic nature. A seminal number of regioselective methods has been found to achieve the C8-H functionalization of QNOs *via* formation of a key five-membered metallacycle intermediate. Remote C-H functionalization of other positions remains a challenge and therefore was less documented.

In chapter II, we have described C8-selective allylation of quinoline *N*-oxides employing VCPs as the allyl source using Rh(III)-catalysis at room temperature. This reaction provides an atom economical route for direct synthesis of C8-allylquinolines which exhibit hepato-protective effect. The sequential C–H and C–C activation, substrate scope, regio- and diastereo-selectivities and late-stage cinchonidine alkaloid mutation are the major findings of the protocol.

In chapter III, we have demonstrated C8-alkylation of quinoline *N*-oxides employing cyclopropanol as alkyl surrogates under versatile Co(III) catalysis. The protocol offers *β*-quinoline substituted quinolines of importance. Mechanistic part was well supported by the control experiments studies and HRMS intermediate detection. The use of less expensive and abundant Cp*Co(III)-catalysis, cyclopropanol as the source and mutation of bioactive molecules make this method a valuable and practical addition to chemical synthesis.

In chapter IV, we have developed ligand enabled Pd(II)-catalyzed dual C(sp^3)-H and C(sp^2)-H activation of 8-methylquinoline *N*-oxide. 8-Methylquinoline substrate was designed to its *N*-oxide variant for dual C(sp3)-H and a sequential C7-H bond functionalization. The reaction was studied with other coupling partners whereas maleimide came out to be suitable partner. The [3 + 2]-annulation, access to the C7-H bond, substrate scope and post-synthetic transformations are the important practical features.

List of Publications

1. **S. Mandal**, P. Karjee, S. Saha and T. Punniyamurthy. Directed C8–H Allylation of Quinoline *N*-Oxides with Vinyl-cyclopropanes *via* Sequential C-H/C-C Activation. *Chem. Commun.* **2023**, *59*, 2823.
2. S. Basak, T. Paul, **S. Mandal**, P. Karjee, Maniya V. N. and T. Punniyamurthy. Transition-Metal-Catalyzed Directed C8-H Carbon-Carbon Bond Formation in Quinolines and 1,2,3,4-Tetrahydroquinolines. *Synthesis* **2023**, *55*, 3454.
3. S. Saha, B. Debnath, K. Talukdar, P. Karjee, **S. Mandal** and T. Punniyamurthy. Cascade C-H Activation/Annulation of Sulfoxonium Ylides with Vinyl Cyclopropanes: Access to Cyclopropane-Fused α-Tetralones. *Org. Lett.* **2023**, *25*, 3352.
4. P. Karjee, **S. Mandal**, B. Debnath, N. Namdev and T. Punniyamurthy. Expedient (3+3)-Annulation of *in Situ* Generated Azaoxyallyl Cations with Diaziridines. *Chem. Commun.* **2023**, *59*, 8270.
5. **S. Mandal**, T. Paul, P. Karjee, M. Barman and T. Punniyamurthy. Site-Selective C8-Alkylation of Quinolines with Cyclopropanols: Merging C-H/C-C Bond Activation. *Org. Lett.* **2023**, *25*, 7805.
6. P. Karjee, B. Debnath, **S. Mandal**, S. Saha and T. Punniyamurthy. One-pot C-N/C-C Bond Formation and Oxidation of Donor-acceptor Cyclopropanes with Tetrahydroisoquinolines: Access to Benzo-fused Indolizines. *Chem. Commun.* **2024**, *60*, 4068.
7. M. Barman, M. Mishra, **S. Mandal** and T. Punniyamurthy. Palladium Catalysis Enabled Sequential C(sp^3)-H/C-C Activation: Access to Vinyl γ-Lactams. *Org. Lett*. **2024**, *26*, 3722.
8. **S. Mandal**, M. Barman, B. Debnath and T. Punniyamurthy. Dual C(sp^3)-H and C(sp^2)-H Activation of 8-Methylquinoline *N*-Oxides: A Route to Access C7-H Bond. *Org. Lett*. **2024**, *26*, 7560.
9. P. Karjee, T. A. Shah, **S. Mandal**, B. Debnath and T. Punniyamurthy. Recent Advancement on Ring Expansion of Bicyclic Diaziridines to Access *N*-Heterocyclic Compounds. *Eur. J. Org. Chem.* **2025**, *28*, e202401057.
10. M. Barman, **S. Mandal**, Maniya V. N. and T. Punniyamurthy. Palladium-Catalyzed Directed Alkenylation of Alkyl Amides with Unactivated Alkenes: Access to γ-Alkenyl γ-Lactams. *Org. Lett*. **2025**, *27*, 2913.
11. S. Basak, T. Paul, **S. Mandal**, M. Barman, Maniya V. N. and T. Punniyamurthy. Transition-metal-catalyzed auxiliary assisted C-H functionalization using vinylcyclopropanes and cyclopropanols. *Chem. Commun*. **2025**, *61*, 6055.

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

Conference Attended

1. **Participated** in 28th National Symposium in Chemistry (CRSI NSC-28) by IIT Guwahati - March, 2022.
2. Scientifique: **Poster Presentation** on "Directed C8–H Allylation of Quinoline *N*-Oxides with Vinyl-cyclopropanes *via* Sequential C-H/C-C Activation" at RIC Integration 2023 by IIT Guwahati-May, 2023.
3. **Poster Presentation** on "Directed C8-H Allylation of Quinoline *N*-Oxides with Vinylcyclopropanes *via* Sequential C-H/C-C Activation" at CRSI NSC-31 by NIT Rourkela - July, 2023.
4. **Poster Presentation** on "Site-Selective C8-Alkylation of Quinolines with Cyclopropanols: Merging C-H/C-C Bond Activation" at CRSI NSC-32 by BITS Pilani - Feb, 2024.
5. **Poster Presentation** on "Dual C(sp^3)-H and C(sp^2)-H Activation of 8-Methylquinoline *N*-Oxides: A Route to Access C7-H Bond" at FICS 2024 by IIT Guwahati - Dec, 2024.