Studies Towards C-C and C-N Bond Formation using Strained Rings: A Probe for Heterocycle Formation

A Thesis Submitted

in Partial Fulfilment of the Requirements

for the Degree of

Doctor of Philosophy in Chemistry

By

Pallab Karjee

Roll No. 186122022

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

My Parents

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

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

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

Guwahati
January 2024

Pallab Karjee

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

CERTIFICATE

This is to certify that Mr. Pallab Karjee has been working under my supervision since July 2018. I am forwarding his thesis entitled "*Studies Towards C-C and C-N Bond Formation using Strained Rings: A Probe for Heterocycle Formation*" being submitted for the Ph.D. degree of this institute. I certify that he has fulfilled all the requirements according to the rules of this institute, and regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

Guwahati
January 2024

Prof. Tharmalingam Punniyamurthy
Supervisor

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God bless you all!

Pallab Karjee

List of Abbreviations

Å	angstrom (10^{-8} cm)
BHT	2,6-di-*tert*-butyl-4-methylphenol
Bn	benzyl
BQ	benzoquinone
CCDC	cambridge crystallographic data center
CDC	cross dehydrogenative coupling
DAC	donor-acceptor cyclopropane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIPEA	*N*,*N*-diisopropylethylamine
DMSO	dimethylsulfoxide
DMF	*N*,*N*-dimethylformamide
DTBP	di-*tert*-butyl peroxide
EDG	electron donating group
equiv	equivalent
ESI	electrospray ionization
EWG	electron wthdrawing group
FT-IR	Fourier transform infrared spectroscopy
HFIP	hexafluoroisopropanol
het	heterocyclic
HRMS	high-resolution mass spectrometry
Hz	hertz
LG	leaving group
m/z	mass to charge ratio
mp	melting point
MHz	megahertz
NMR	nuclear magnetic resonance
Ns	4-nitrobenzenesulfony
ORTEP	oak ridge thermal ellipsoid plot
R_f	retardation factor

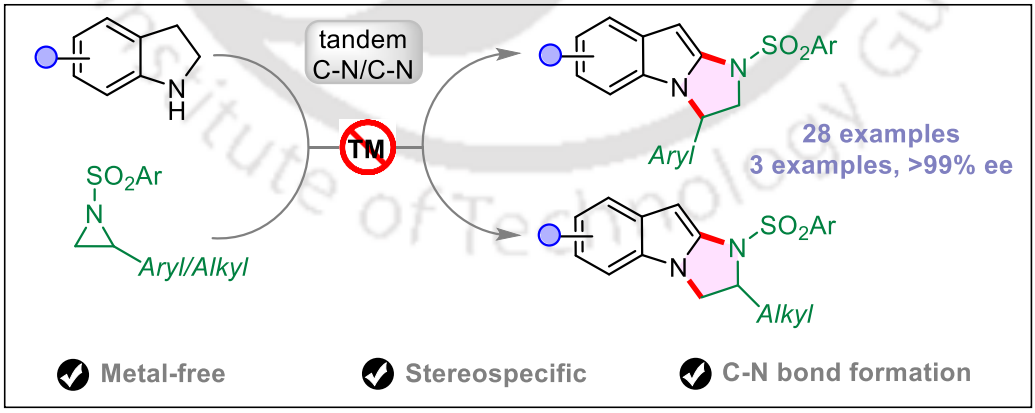
r.t.	room temperature
SET	single-electron transfer
TBHP	*tert*-butyl hydroperoxide
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TFE	2,2,2-trifluoroethanol
Tf	trifluoromethanesulfonyl
THIQ	1,2,3,4-tetrahydroisoquinoline
Ts	toluenesulfonyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TM	transition metal
μL	microliter

Abstract

The thesis is organized into four chapters. The initial chapter delineates a tandem C–N bond formation for the oxidative annulation of indolines with aziridines, utilizing a combination of DDQ and NaOCl under ambient conditions. The second chapter addresses the annulative coupling of donor-acceptor cyclopropanes with cyclic secondary amines, employing $Ni(OTf)_2$ and visible light-assisted eosin Y catalysis for tandem C–N and C–C bond formation. The third chapter focuses on the coupling of cyclic secondary amines with donor-acceptor cyclopropanes using MgI_2 and $Mn(OAc)_3•2H_2O$, leading to the synthesis of fused indolizine derivatives. The fourth chapter showcases an efficient annulation of *in situ* formed azaoxyallyl cations with diaziridines, yielding 1,2,4-triazines at room temperature.

Chapter I. Stereospecific Oxidative Coupling of Indolines with Aziridines

In recent decades, the advancement of C-H functionalization in indoles has experienced notable growth, attributed to the widespread occurrence of indole frameworks in numerous bioactive molecules. Aziridines have proven to be valuable tools in *N*-heterocycle synthesis through tandem C-N bond formation. The exploration of synthetic strategies involving these two heterocyclic units holds potential as a viable route for accessing fused structural scaffolds. This chapter elucidates an oxidative annulative coupling of indolines with *N*-sulfonyl aziridines, achieving the synthesis of imidazoindoles under ambient conditions through the utilization of a combination of DDQ and NaOCl (Scheme 1).

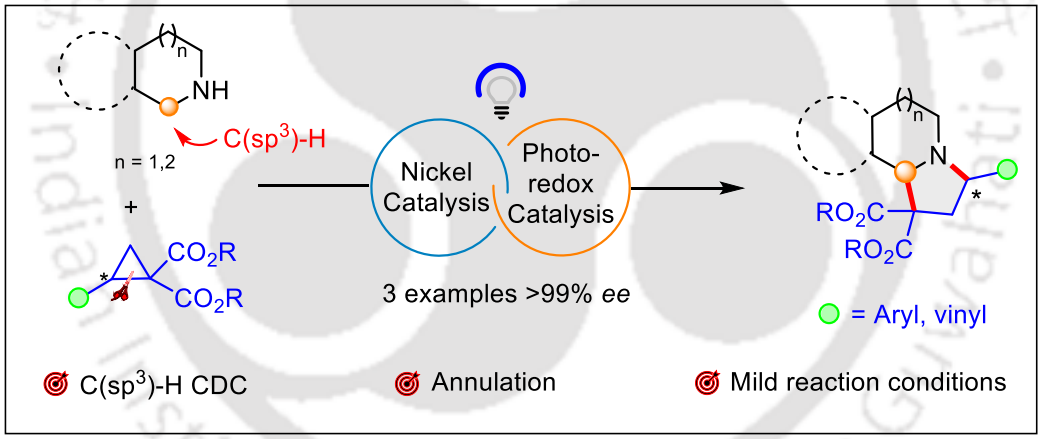


J. Org. Chem. **2020**, *85*, 8261.

Scheme 1. Metal Free Annulation of Indolines with Aziridines

Chapter II. Stereospecific Coupling of Donor-Acceptor Cyclopropanes with Cyclic Secondary Amines

The compelling biological and medicinal properties of pyrrolidine alkaloids, which are characterized by their privileged structural frameworks, have elicited substantial interest. Consequently, the pursuit of proficient synthetic methodologies for constructing pyrrolidine structural scaffolds is of considerable significance. In this context, cyclic secondary amines play a crucial role in organic synthesis and hold significant importance in various chemical and biological contexts. Moreover, donor-acceptor cyclopropanes, with their unique reactivity and versatile applications, contribute to the field of organic synthesis. In this chapter, we have established the stereospecific annulation of donor-acceptor cyclopropanes with cyclic secondary amines, catalyzed by the readily available first-row $Ni(OTf)_2$, followed by visible light eosin Y catalysis to facilitate the cross-dehydrogenative coupling (CDC) for the construction of fused pyrrolidines (Scheme 2).



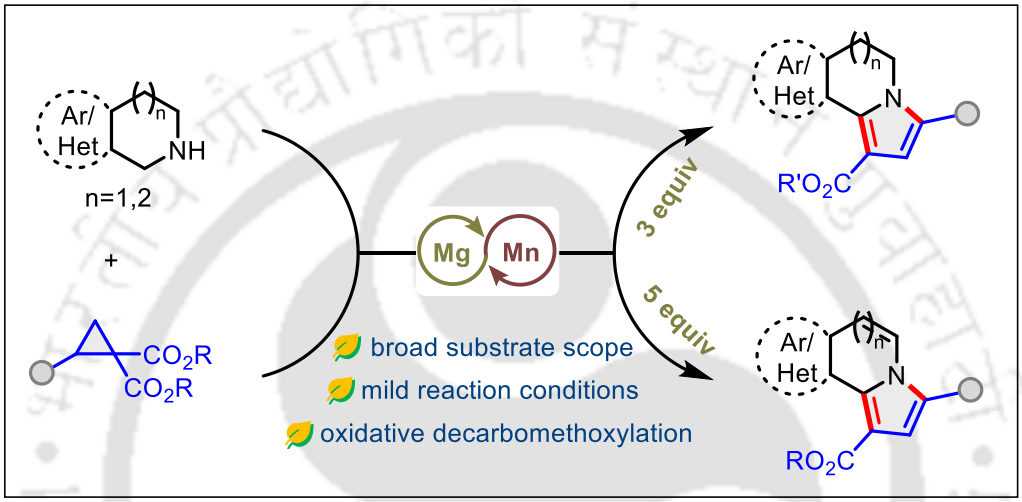
Chem. Commun. **2022**, *58*, 8670.

Scheme 2. Ni(II)/Photoredox-Catalyzed Synthesis of Fused Pyrrolidines

Chapter III. Oxidative Coupling of Donor-Acceptor Cyclopropanes with Cyclic Secondary Amines

Aza heterocycles represent essential structural motifs within a diverse array of natural products and pharmaceutical compounds. Within this domain, indolizine alkaloids emerge as privileged scaffolds, pervasive in various potent natural products, bioactive molecules, and pharmacophores. This chapter demonstrates the oxidative cyclopentannulation of donor acceptor cyclopropanes

with cyclic secondary amines, leading to the synthesis of indolizines (Scheme 3). The reaction entails oxidative cross-dehydrogenative coupling (CDC) for carbon-carbon bond formation. Key practical aspects encompass the utilization of commercially available MgI_2 for the ring opening of cyclopropanes with amines and $Mn(OAc)_3 \cdot 2H_2O$ for the oxidative annulation. The substrate scope, mild reaction conditions and the incorporation of natural product mutagenesis are the important practical features.

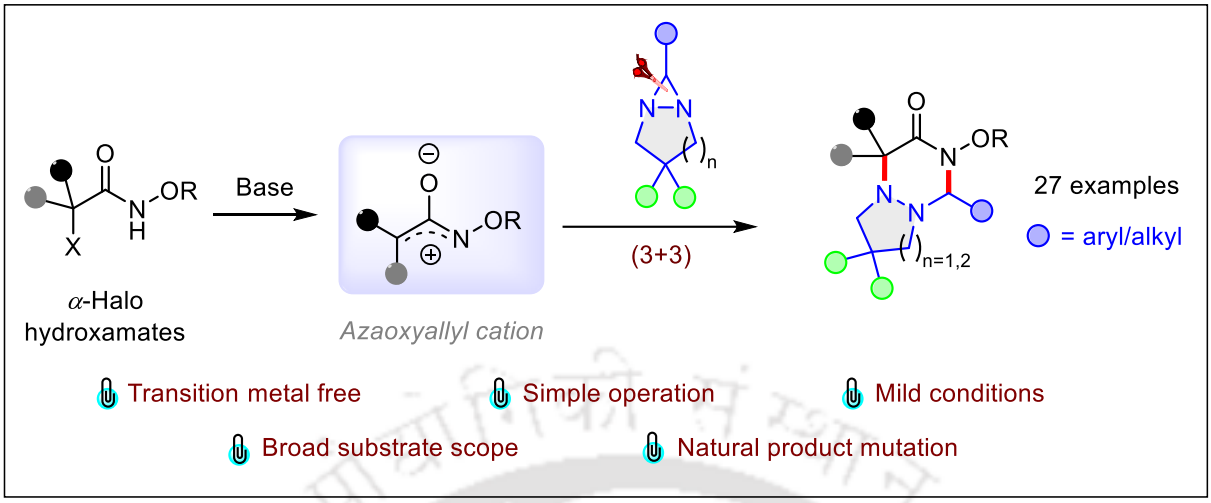


Chem. Commun. **2024**, *60*, 4068.

Scheme 3. Synthesis of Fused Indolizines

Chapter IV. Annulation of *in situ* Generated Azaoxyallyl Cations with Diaziridines

1,2,4-Triazines frequently serve as pivotal structural motifs in a wide assembly of natural products, bioactive compounds, and agrochemicals. Thus, the development of effective synthetic methods for their construction, employing readily accessible and simple building blocks increase enthusiasm among chemists. Three-membered ring systems, owing to their intrinsic ring strain and staple architecture, paving way to construct a variety of synthetic transformations. In this context, diaziridines have recently emerged as three-membered ring 1,3-dipolar systems featuring two nitrogen atoms. Moreover, due to the ease of availability and high reactivity of α-halohydroxamates, they experienced remarkable growth as optimal three-atom synthons (C-C-N) for constructing *N*-heterocycles. This chapter unveils a room temperature transition-metal free base-mediated annulation of α-halohydroxamates with diaziridines for the synthesis of 1,2,4-triazines (Scheme 4).



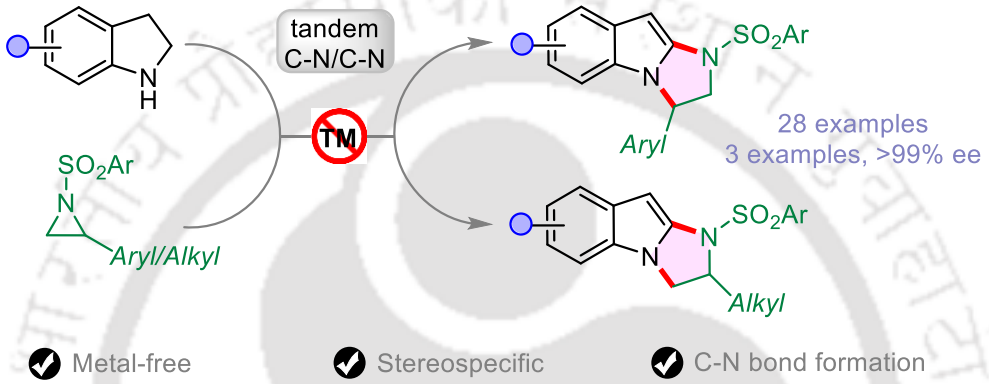
Chem. Commun. **2023**, *59*, 8270.

Scheme 4. Base-Mediated Synthesis of 1,2,4-Triazines

Contents

Chapter I

Stereospecific Oxidative Coupling of Indolines with Aziridines



J. Org. Chem. **2020**, *85*, 8261.

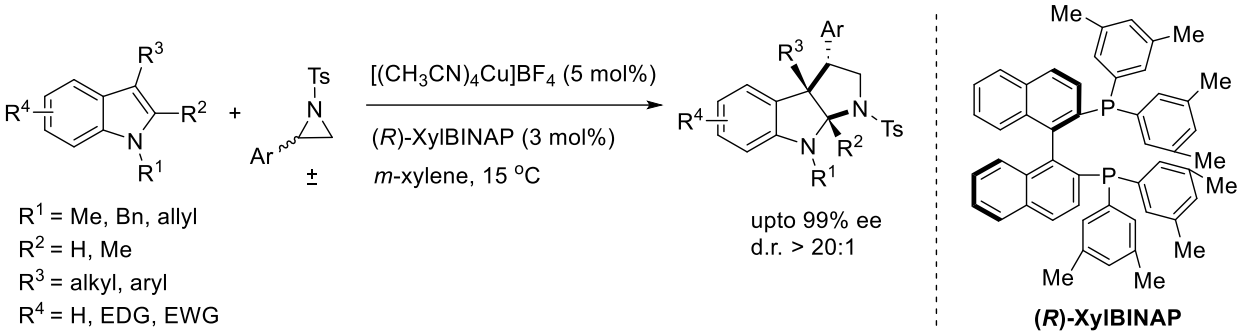
Stereospecific Oxidative Coupling of Indolines with Aziridines

The formation of C-N bonds[1] has garnered significant attention due to the prevalence of aza-heterocycles in pharmaceuticals, functional materials, and natural products.[2] Within this domain, the functionalization of C-H bonds in indoles[3] has demonstrated remarkable expansion, driven by the abundant prevalence of indole frameworks in a myriad of bioactive molecules. Among these, imidazoindolines stand out as privileged structures due to their intriguing biological properties.[4] Efficient and stereospecific syntheses of these fused frameworks, using atom- and step-economical approaches,[5] hold substantial value. Small-ring heterocycles, characterized by their inherent ring strain and staple architecture, readily undergo ring scissoring. Consequently, they serve as versatile building blocks for constructing diverse heterocycles.[6] In this context, aziridines emerge as valuable tools for contemporary *N*-heterocycle synthesis via tandem C-N bond formation.[7,8] Consequently, development of synthetic strategies with these two heterocyclic units can lead a potential route to access fused structural scaffolds. Recently, NaOCl has been explored as an effective reagent for the oxidation for organic substrates, amidation of amines and C-N coupling of 3-alkylindoles with amino esters.[9] This, chapter describes an oxidative annulative coupling of indolines with *N*-sulfonyl aziridines. By employing a combination of DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) and NaOCl (sodium hypochlorite), we achieve the synthesis of imidazoindoles under ambient conditions. Notably, this approach offers substrate scope, selectivity, and transition-metal-free C-N bond formation as key features.

1.1 Literature Study

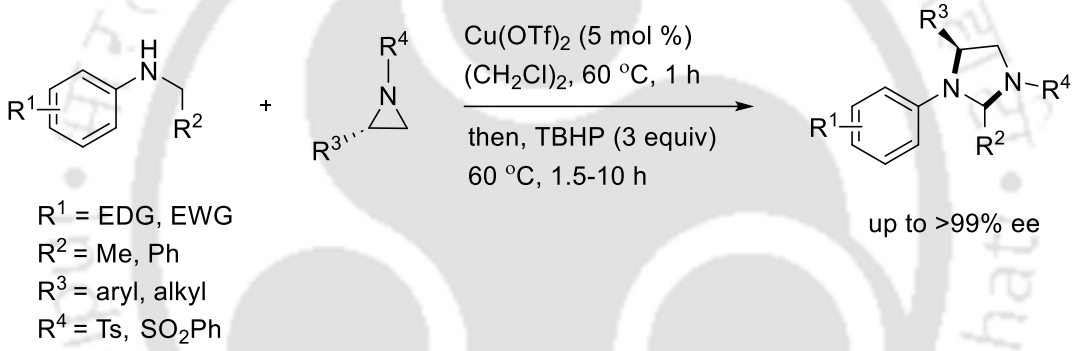
1.1.1 Metal-Catalyzed Annulation of Aziridines

Yang and co-workers described the asymmetric Lewis acid catalysed (3+2)-annulation of indoles with 2-aryl-*N*-tosylaziridines for the construction of pyrroloindolines (Scheme 1).[10] This method proceeds *via* regioselective ring opening of aziridines followed by cyclization. Utilizing this methodology, a diverse array of uniquely substituted chiral pyrroloindolines, each containing multiple adjacent stereogenic centers, were readily synthesized under mild conditions with high yield and exceptional stereoselectivity.



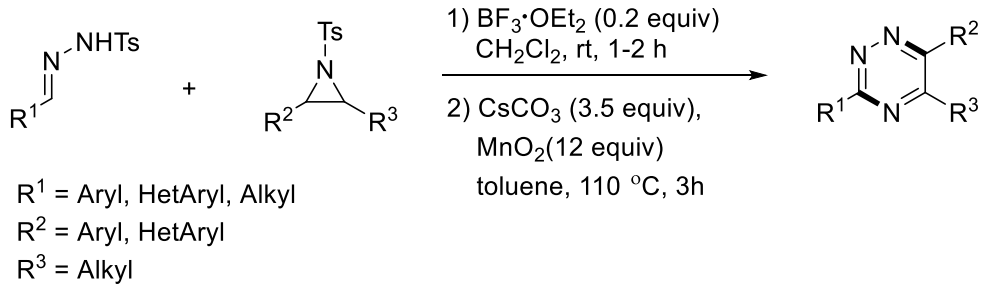
Scheme 1. Cu-Catalyzed Coupling of *N*-Sulfonylaziridines with Indoles

Our group reported a stereoselective Cu-catalyzed domino tring opening of aryl and alkyl aziridine with N-substituted anilines followed by sp^3 C-H functionalization (Scheme 2).[11] This reaction was extended for the reaction of enantioenriched aziridines to deliver chiral imidazolidines with high enantiomeric purity.



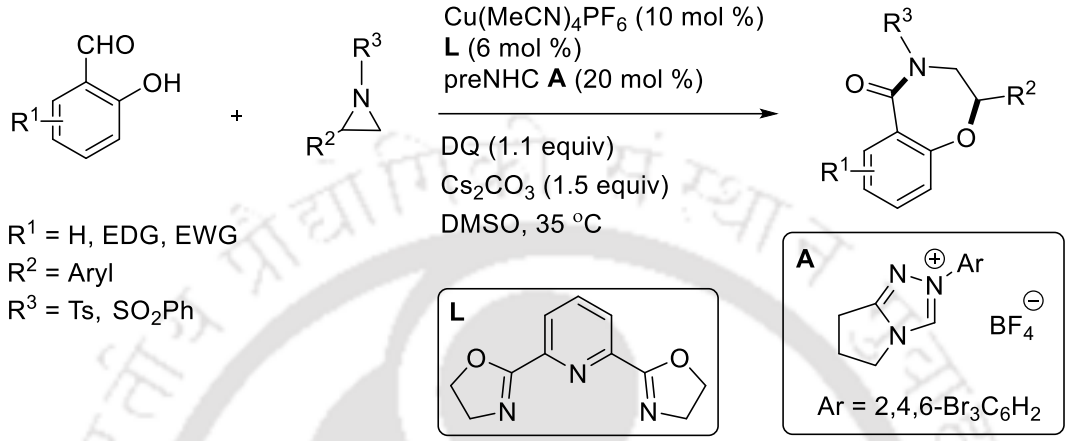
Scheme 2. Cu-Catalyzed annulation of Aziridines with *N*-Methyl Anilines

Ley and co-workers reported one-pot acid-catalyzed ring-opening/cyclization/oxidation of aziridines with N-tosylhydrazones (Scheme 1).[1] A wide range of tosylhydrazones reacted with phenylaziridine in the presence of BF_3•OEt_2 to give the amino hydrazones and further use of activated MnO_2 was chosen as the oxidant for its compatibility with the cyclization conditions step (Scheme 3).[12]



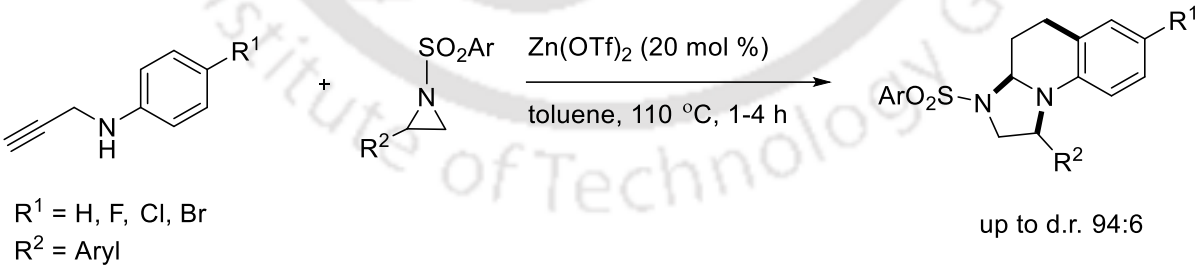
Scheme 3. Acid-Catalyzed Cyclization of Aziridines with *N*-Tosylhydrazones

N-Heterocyclic carbene/Cu-catalyzed (4+3)-annulation of salicylaldehydes with aziridines was accomplished using Pybox as a ligand, giving the corresponding 1,4-benzoxazepinones in good yields with exclusive regioselectivity. Cu acts as a Lewis acid to activate the small strained aziridines, and the formation of NHC-salicylaldehyde adduct plays an important role in improving the regioselectivity (Scheme 4).[13]



Scheme 4. NHC/Cu-Co-catalyzed (4+3)-Annulations of Salicylaldehydes with Aziridines

An efficient synthetic approach for the synthesis of 1,2,3,3a,4,5-hexahydroimidazo[1,2-a]quinolines with excellent stereoselectivity (d.r. up to 94:6, ee up to >99%) under one-pot domino ring-opening cyclization (DROC) conditions was reported. The DROC protocol involves a cascade of chemical reactions, initiated by the Lewis acid-catalyzed S_N2-type ring-opening of activated aziridines with *N*-propargylanilines. Subsequent intramolecular cyclization leads to the formation of hexahydroimidazo[1,2-a]quinolines (Scheme 5).[14]

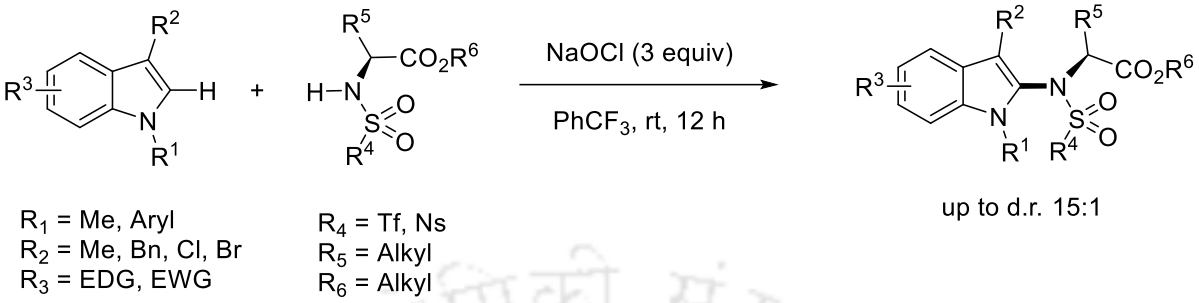


Scheme 5. Zn-catalyzed Cascade Annulation of Aziridines with *N*-Propargylanilines

1.1.2 C-N Coupling of Indoles

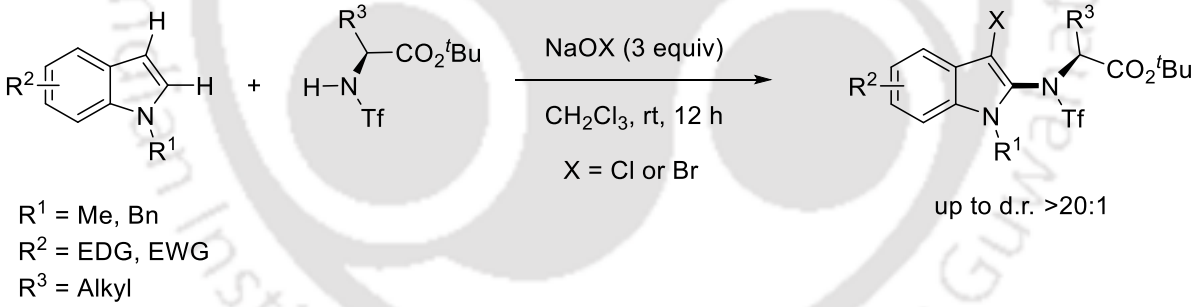
A distinct class of C-N axial chirality, centered around *N*-indole sulfonamides, was unveiled. These newly formed axially chiral *N*-indole sulfonamides were synthesized through NaOCl-promoted couplings between 3-substituted indoles and chiral amino acid-based sulfonamides.

Employing this established approach, a diverse *N*-indole sulfonamide-based atropisomers was successfully prepared. The stability of these atropisomers was significantly influenced by the C3-substituents of indoles and the side chains of amino acid derivatives (Scheme 6).[15]



Scheme 6. NaOCl-Promoted Coupling of Indoles with Amino Acids

An atroposelective coupling method was documented which enables the synthesis of 2-amido-3-haloindoles, possessing a C-N chiral axis, through the mediation of hypohalides. These strategically designed halogenated indoles allow for subsequent transformations. Additionally, diverse functionalities such as carbonyl, phosphine, aryl, and alkenyl groups can be selectively introduced at the C3 position. These structurally varied and axially chiral indole derivatives hold promise for further synthetic applications (Scheme 7).[16]



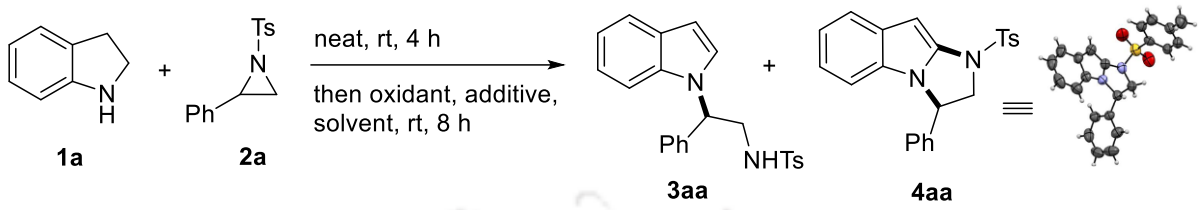
Scheme 7. Halo-Amidation of Indoles with Amino Acids

1.2 Present Study

Herein, a precise and selective oxidative annulative coupling between indoles and *N*-sulfonyl aziridines has been developed. By utilizing a combination of DDQ and NaOCl, the synthesis of imidazoindoles has been achieved under ambient conditions. This innovative approach enables the formation of C-N bonds in a tandem fashion. The optimization studies initiated employing indoline **1a** and 2-phenyl-1-tosylaziridine **2a** as the test substrates using a series of oxidants, additives and solvents (Table 1). The heterocycle **4aa** was formed in 10% along with

the ring opening **3aa** in 62%, when the neat substrates were stirred for 4 h at ambient conditions, and then 8 h with $PhI(OAc)_2$ as an oxidant and aqueous NaOCl as an additive in

Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3aa** **4aa**

Entry	Oxidant	Additive	Solvent	Yield (%)[b]	
				3aa	**4aa**
1	$PhI(OAc)_2$	NaOCl	1,4-dioxane	62	10
2	**DDQ**	**NaOCl**	**1,4-dioxane**	**trace**	**75**
3	BQ	NaOCl	1,4-dioxane	57	12
4	O_2	NaOCl	1,4-dioxane	n.d	n.d
5	TBHP	NaOCl	1,4-dioxane	n.d.	n.d.
6	DTBP	NaOCl	1,4-dioxane	n.d.	n.d.
7	DDQ	t-BuOCl	1,4-dioxane	71	n.d.
8	DDQ	Iodine	1,4-dioxane	67	n.d.
9	DDQ	NaOCl	THF	19	51
10	DDQ	NaOCl	DMF	45	21
11	DDQ	NaOCl	MeOH	42	34
12	DDQ	NaOCl	$(CH_2Cl)_2$	30	49
13	DDQ	NaOCl	toluene	14	57
14	DDQ	NaOCl	CH_3CN	16	55
15	-	NaOCl	1,4-dioxane	n.d.	n.d.
16	DDQ	-	1,4-dioxane	81	n.d.

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), neat, 4 h, room temperature; then, oxidant (0.2 mmol), additive (1.2 mmol), solvent (2 mL), 8 h, room temperature. [b]Isolated yield. n.d. = not detected.

1,4-dioxane. Subsequent screening of the oxidants led to an increase in the yield of **4aa** to 75% using DDQ, whereas *p*-benzoquinone produced inferior results. In contrast, O_2, TBHP and DTBP were not effective. In a set of additives studied, aqueous NaOCl, *t*-BuOCl and iodine,

the former produced the best results. 1,4-Dioxane was found to be the solvent of choice, whereas THF, DMF, MeOH, DCE, toluene and CH_3CN produced <57% yield. Control experiments confirmed that the combination of DDQ and NaOCl is essential to furnish the annulated **4aa**. Recrystallization of **4aa** gave single crystal, whose structure was determined using X-ray analysis (CCDC = 1978164).

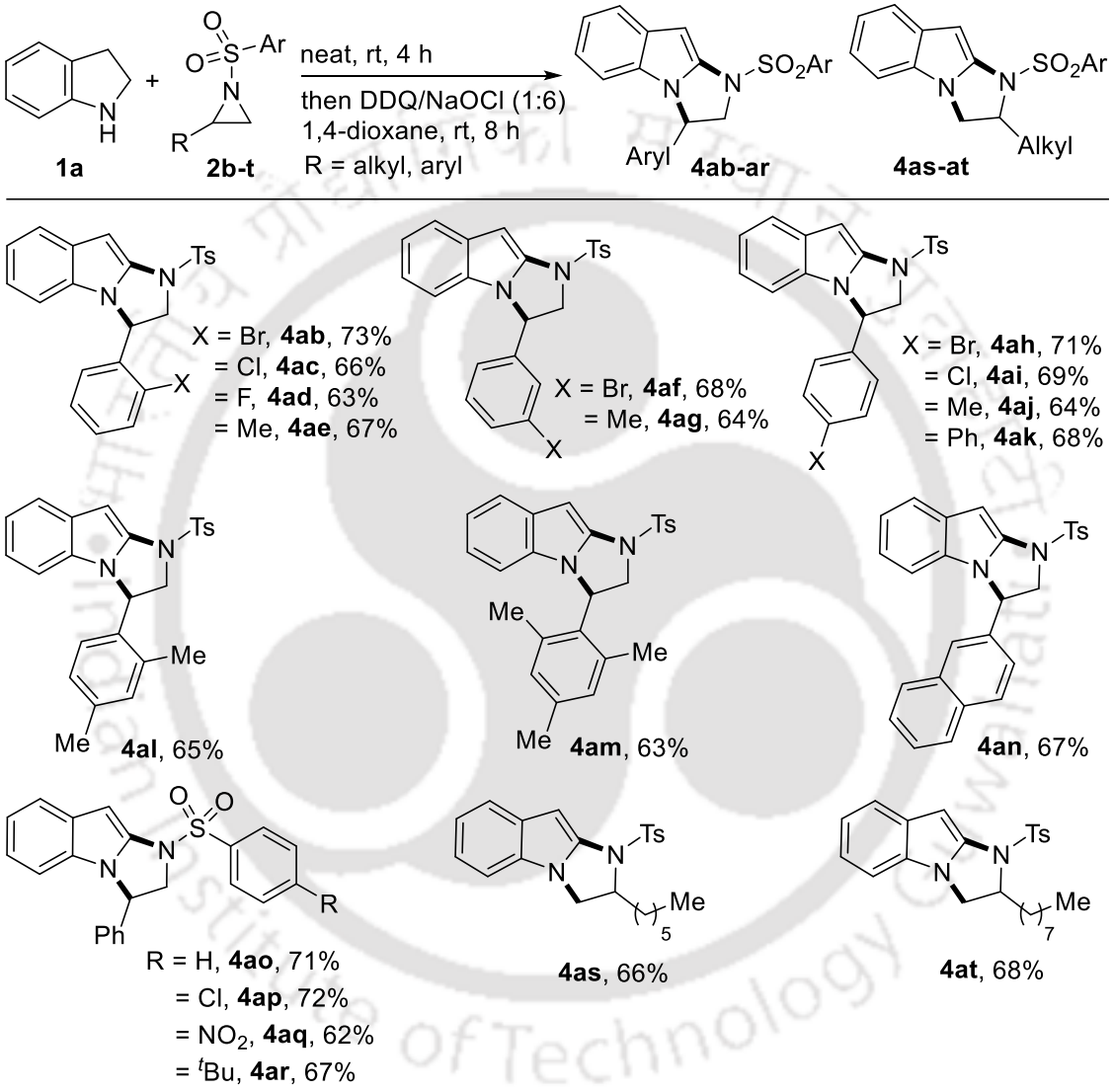
Having the optimized reaction conditions, the scope of the procedure was examined for a series of aziridines **2b-t** with indoline **1a** as a standard substrate (Table 2). Aziridines having substitution at the 2-position of the aryl ring with bromo **2b**, chloro **2c**, fluoro **2d** and methyl **2e** groups gave the target heterocycles **4ab-ae** in 63-73% yields. Similar results observed with aziridines bearing substitution at the 3-position of the aryl ring with bromo **2f** and methyl **2g** functionalities, giving **4af** and **4ag** in 68 and 64% yields, respectively. The reaction of aziridines containing substituents at the 4-position of the aryl ring with bromo **2h**, chloro **2i**, methyl **2j** and phenyl **2k** groups produced **4ah-ak** in 64-71% yields. Furthermore, di- and tri-methylphenyl substituted aziridines **2l-m** in the aryl ring participated to deliver **4al** and **4am** in 65 and 63% yields, respectively. In addition, 2-naphthyl aziridine **2n** was amenable to furnish **4an** in 67% yield. The reaction conditions were extended to the coupling of aziridines bearing a varied *N*-arylsulfonyl substituent. Aziridine having *N*-benzenesulfonyl **2o** produced **4ao** in 71% yield, whereas the reaction of aziridines having substitution at the 4-position of the *N*-sulfonyl aryl ring with chloro **2p**, nitro **2q** and *tert*-butyl **2r** functionalities, afforded **4ap-ar** in 62-72% yields. In addition, the reaction of 2-alkyl aziridines could be pursued and the ring opening occurred at the sterically less hindered C-3 position.[17] For examples, aziridines with hexyl **2s** and octyl **2t** substituents participated to produce **4as** and **4at** in 66 and 68% yields, respectively.

The scope of the procedure was further extended to the annulation of a series of substituted indolines **1b-i** with aziridine **2a** as a standard substrate (Table 3). The substrates bearing 3-methyl **1b**, 4-bromo **1c**, 5-benzyloxy **1d** and 5-bromo **1e** substituents delivered the target heterocycles **4ba-ea** in 58-71% yields, whereas the reaction of the substrates bearing 6-chloro **1f**, 6-fluoro **1g**, 7-chloro **1h** and 7-methyl **1i** functionalities afforded **4fa-ia** in 63-73% yields. These results suggest that the procedure can be employed for the annulative coupling of the broad range of indolines and aziridines.

To understand the stereochemical aspects, the reaction of **1a**, **1e** and **1g** studied using (*R*)-2-phenyl-1-tosylaziridine **2a′** as the representative substrates (Table 4). The reaction occurred with high enantiomeric purity (>99% *ee*). For examples, the reaction of **1a** furnished **4aa′** in 73% yield and 99% *ee*. Similar enantiomeric purity (>99% *ee*) observed with indolines having

5-bromo **1e** and 6-fluoro **1g** substituents, providing **4ea′** and **4ga′** in 70% and 68% yields, respectively. The absolute configuration of **4aa′** was determined using a single crystal X-ray analysis (CCDC=1987130). These results suggest that the ring opening of aziridine is stereospecific (S_N2) and the annulation can be realized in high enanatiomeric purity.

Table 2. Substrate Scope of Aziridines[a-c]

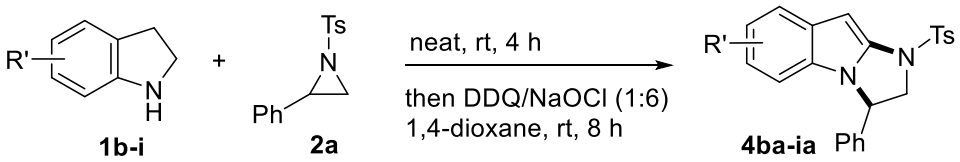


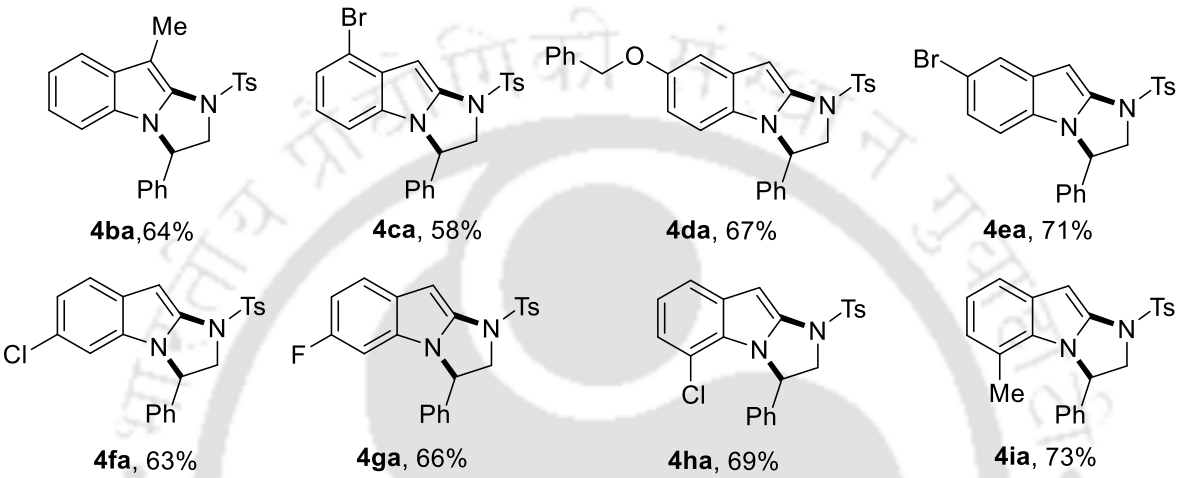
[a]Reaction conditions: **1a** (0.2 mmol), **2b-t** (0.24 mmol), neat, room temperature, 4 h; then DDQ (0.2 mmol), aq. NaOCl (4.2%, 2.1 mL), 1,4-dioxane (2 mL), room temperature, 8 h. [b]Isolated yield. [c]Accompanied a trace amount of **3**.

To get insight into the reaction pathway, the coupling of **1a** with **2a** was performed as the representative substrates in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as well as 2,6-di-*tert*-butyl-4-methylphenol (BHT) (Scheme 8a). As above, the reaction occurred,

which suggests that a radical pathway is not likely. In addition, **1a** with **2a** under neat conditions for 4 h, followed by treatment with DDQ for 2 h in 1,4-dioxane, produced **3aa** in 81% yield

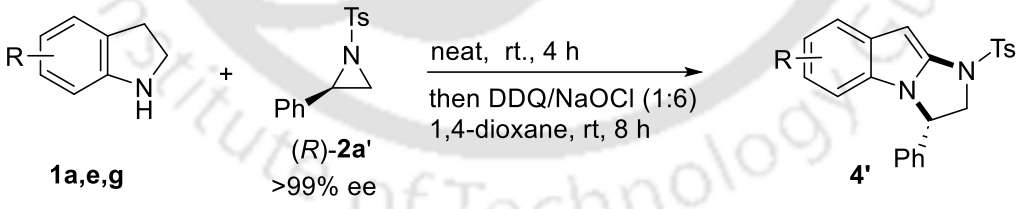
Table 3. Substrate Scope of Indolines[a-c]

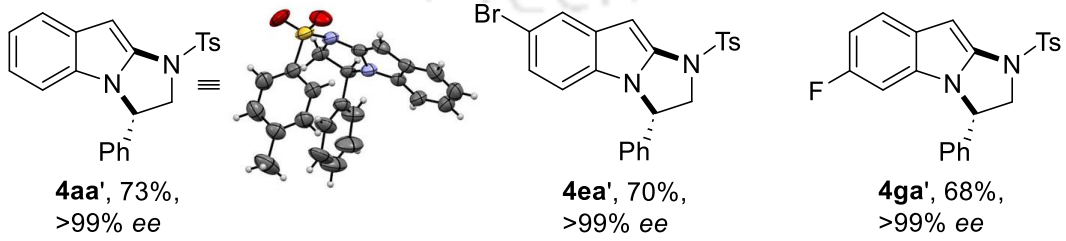




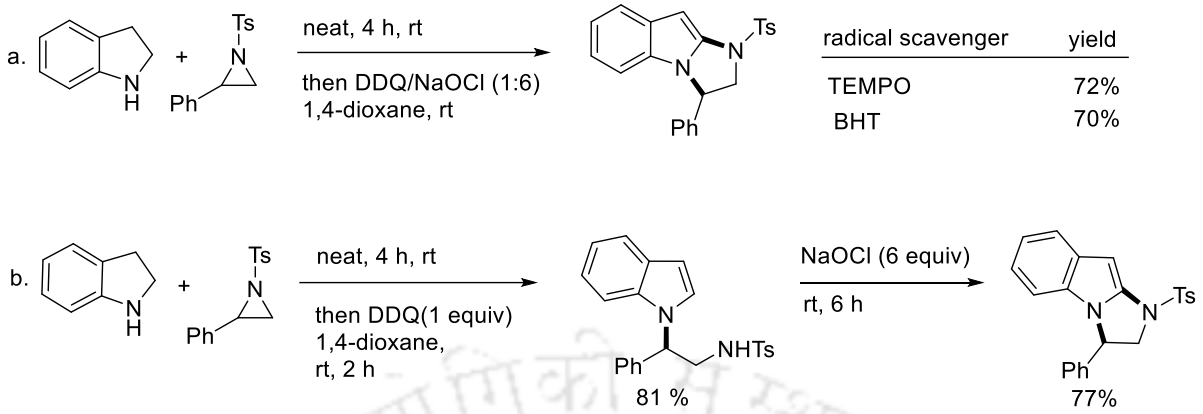
[a]Reaction conditions: **1b-i** (0.2 mmol), **2a** (0.24 mmol), neat, room temperature, 4 h; then DDQ (0.2 mmol), aq. NaOCl (4.2%, 2.1 mL), 1,4-dioxane (2 mL), room temperature, 8 h. [b]Isolated yield. [c]Accompanied a trace amount of **3**.

Table 4. Enantiospecific Synthesis[a-c]

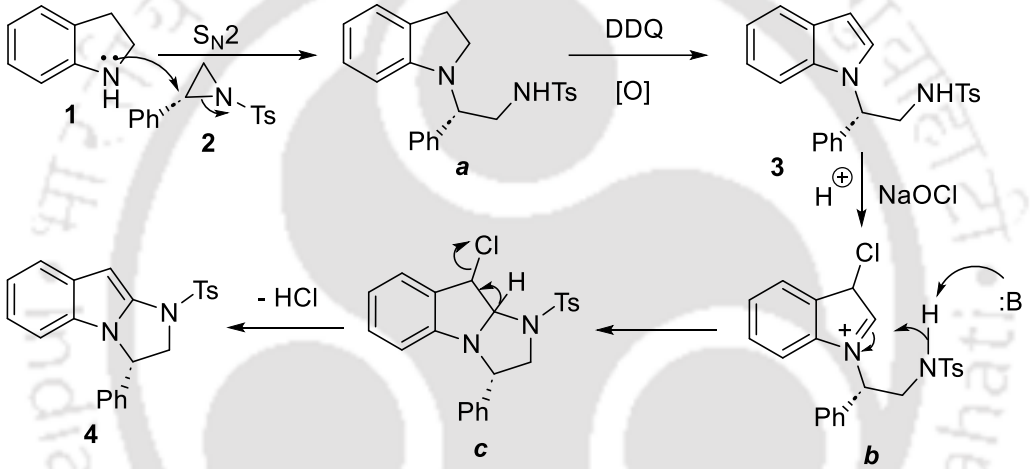




[a]Reaction conditions: **1a**,**e,g** (0.2 mmol), (*R*)-**2a′** (0.24 mmol), neat, room temperature, 4 h; then DDQ (0.2 mmol), aq. NaOCl (4.2%, 2.1 mL), 1,4-dioxane (2 mL), room temperature, 6 h. [b]Isolated yield. [c]Accompanied a trace amount of **3**.



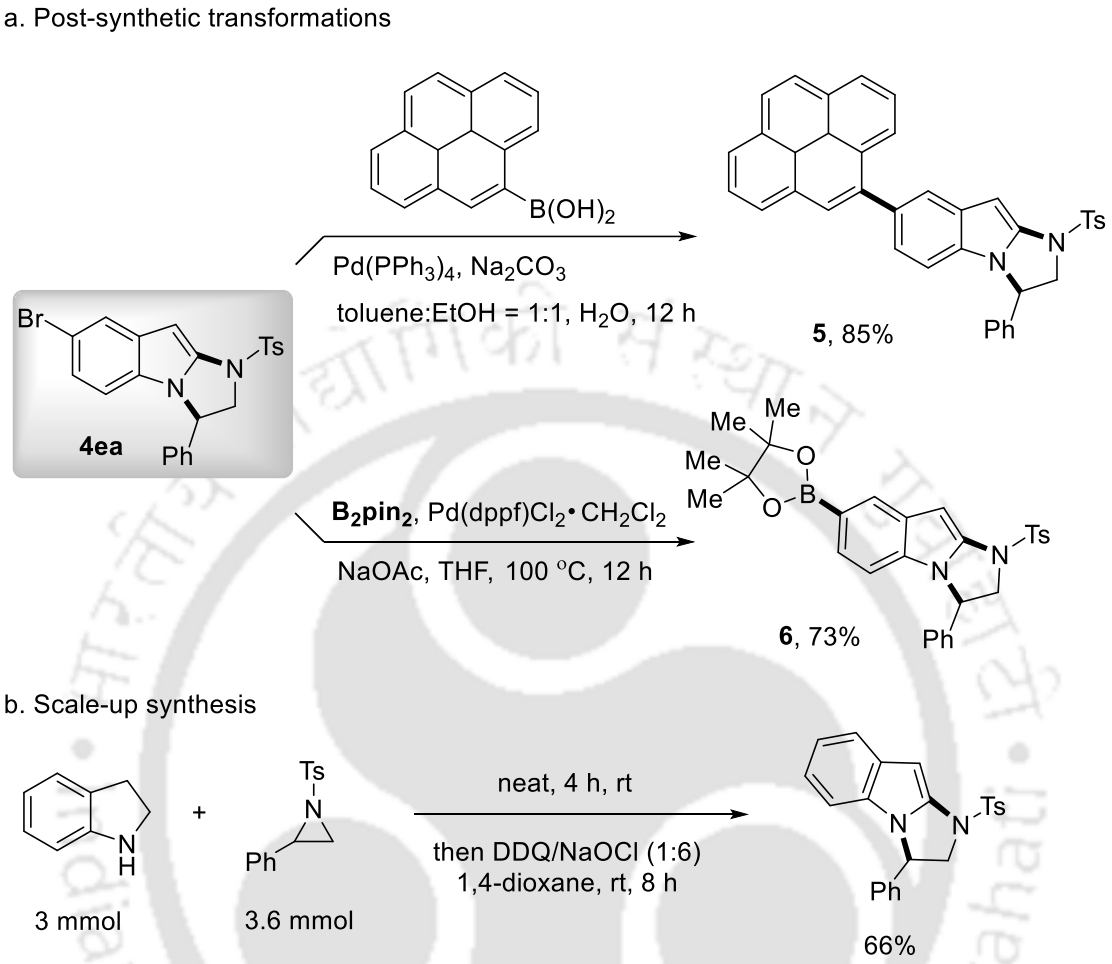
Scheme 8. Control Experiments



Scheme 9. Plausible Reaction Pathway

(Scheme 8b). The latter with NaOCl underwent annulation to produce **4aa** in 77% yield. These experimental results suggest that the stereospecific ring opening (S_N2) of aziridines with indolines can deliver ***a*** (Scheme 9).[18] The latter can oxidize using DDQ to furnish **3**, which can undergo an electrophilic chlorination using NaOCl to give the iminium ion ***b*** that can lead to an intramolecular cyclization to furnish ***c***. Base promoted dehydrochlorination ***c*** can furnish the target heterocycle **4**, which can be reduced using $NaBH_3CN$ to yield imidazoindolines that are privileged structural scaffold with broad bio-active spectrum. Scheme 10a presents some post synthetic applications for C-C coupling of **4** with organoboranes. The Pd-catalyzed Suzuki-coupling of **4ea** with 1-pyreneboronic acid produced **5** in 85% yield, while the borylation employing B_2pin_2 gave **6** in 73% yield. In addition, to reveal the scale up synthesis

(3 mmol), the coupling of **1a** and **2a** was examined as the representative substrates. The reaction was effective to furnish the annulated target product in 66% yield (Scheme 10b).



Scheme 10. Synthetic Utilities

In summary, an effective synthetic method has been accomplished for the stereospecific oxidative annulative coupling of indolines with aziridines. This process utilizes DDQ as the oxidant and NaOCl as the electrophilic chlorinating reagent, all under ambient conditions. Notably, this approach offers excellent enantiomeric purity, transition-metal-free tandem C-N bond formation, and a broad substrate scope.

1.3 Experimental Section

General Information. Alkenes, (*R*)-(-)-2-phenylglycinol (99%), DDQ (98%), $Pd(dppf)Cl_2•CH_2Cl_2$ (>99%) and $Pd(PPh_3)_4$ (99%) of Aldrich, and NaOCl (4.2% w/v available chlorine) and chloramine-T hydrate (95%) of Merck were used as received. Indolines[13] and aziridines[14] were prepared according to reported procedure. SRL silica gel G/GF 254 plates were used for analytical TLC and SRL silica gel (60-120 mesh) was used for column

chromatography. NMR spectra were recorded with Bruker Avance III 600 MHz and Ascend 400 MHz spectrometers using $CDCl_3$ as solvent and Me_4Si as an internal standard. Chemical shifts (δ) and spin-spin coupling constant (*J*) are reported in ppm and in Hz, respectively, and other data are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, dd = doublet of doublets. Melting points were determined using a Büchi B-540 apparatus and are uncorrected. FT-IR spectra were collected on Perkin Elmer IR spectrometer. Q-Tof ESI-MS instrument (model HAB 273) was used for recording mass spectra. Optical rotations were determined by using Rudolph autopol I automatic polarimeter. HPLC analysis was carried out using Waters-2489 with Daicel Chiralcel OD-H column using *iso*-propanol and hexane as an eluent. Single crystal X-ray data were collected on a Bruker SMART APEX equipped with a CCD area detector using Mo/Kα radiation and the structure was solved by direct method using *SHELXL-16* (Göttingen, Germany).

General Procedure for the Preparation of Indolines.[19] To a solution of indole (3.0 mmol) in AcOH (15 mL) at 0 °C was added $NaBH_3CN$ (756 mg, 12.0 mmol) in portion-wise. The reaction was allowed to stir at room temperature for 8 h. After completion, aqueous NaOH (250 μL) was added slowly to the mixture at 0 °C and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed successively with brine (10 mL) and water (10 mL). Drying (Na_2SO_4) and evaporation of the solvent produced a residue that was purified on silica gel column chromatography using ethyl acetate and hexane as an eluent.

Procedure for the Preparation of Chiral Aziridine.[20] To a stirred solution of (*R*)-(-)-2-phenylglycinol (1.0 mmol, 137 mg), TsCl (2.2 mmol, 420 mg) and DMAP (0.05 mmol, 6 mg) in dry CH_2Cl_2 (25 mL) at 0 °C was added Et_3N (3.0 mmol). The resultant mixture was allowed to warm to room temperature and the stirring was continued for 24 h. The mixture was then treated with a saturated NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 × 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on a silica gel column chromatography using hexane and ethyl acetate (9:1) as the eluent.

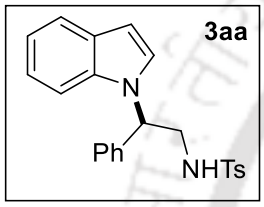
General Procedure for the Coupling of Indolines with Aziridines. A mixture of indoline **1** (0.2 mmol) and aziridine **2** (0.24 mmol) was stirred for 4 h at room temperature. The resultant mixture was treated with1,4-dioxane (2.0 mL), DDQ (45 mg, 0.2 mmol) and aq. NaOCl (4.2%, 2.1 mL, 1.2 mmol), and the stirring was continued for an additional 8 h. The reaction mixture was then diluted with ethyl acetate (10 mL) and organic layer was separated. The aqueous phase was extracted twice with ethyl acetate (2 ×10 mL). Drying (Na_2SO_4) and evaporation of

the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate and hexane as an eluent.

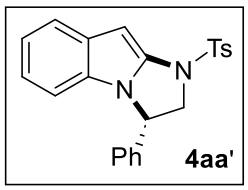
General Procedure for the Enantiospecific Annulative Coupling. Indoline **1** (0.2 mmol) and (*R*)-2-phenyl-1-tosylaziridine **2a′** (0.24 mmol) were subjected to the above described reaction conditions. The enantiomeric purity was determined using chiral HPLC analysis.

Scale-up Synthesis of 4aa: Indoline **1a** (357 mg, 3 mmol) and 2-phenyl-1-tosylaziridine **2a** (983 mg, 3.6 mmol) were subjected to the reaction condition described in the general procedure to produce **4aa** in 66% yield (768 mg).

1.4 Characterization Data

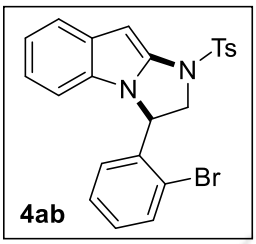


***N*-(2-(1H-Indol-1-yl)-2-phenylethyl)-4-methylbenzenesulfonamide 3aa**. Analytical TLC on silica gel, 1:6 ethyl acetate/hexane; R_f = 0.49; Purification on silica gel column chromatography using 1:9 ethyl acetate/hexane as eluent; colorless solid; mp 127-128 ^oC; yield 81% (63 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.4 Hz, 2H), 7.63-7.61 (m, 1H), 7.30-7.26 (m, 5H), 7.13-7.06 (m, 6H), 6.57 (d, *J* = 3.2 Hz, 1H), 5.59-5.56 (m, 1H), 4.49-4.45 (m, 1H), 3.89-3.83 (m, 1H), 3.76-3.69 (m, 1H), 2.44 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.9, 137.6, 136.7, 136.3, 130.0, 129.1, 128.8, 128.5, 127.1, 126.6, 124.5, 122.2, 121.2, 120.2, 109.9, 103.2, 59.0, 46.3, 21.7; FT-IR (KBr) 3283, 2922, 1598, 1493, 1458, 1326, 1308, 1158, 1092 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{23}N_2O_2S$: 391.1475, found: 391.1486.

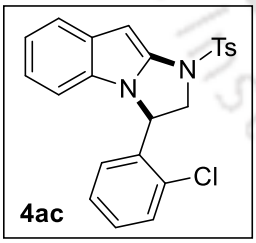


3-Phenyl-1-tosyl-2,3-dihydro-1H-imidazo[1,2-a]indole 4aa′. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.45; Purification on silica gel column chromatography using 1:14 ethyl acetate/hexane as eluent; colorless solid; mp 169-170 ^oC; yield 73% (56 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.22-7.18 (m, 1H), 7.15-7.11 (m, 4H), 6.98-6.94 (m, 1H), 6.82-6.78 (m, 3H), 6.50 (d, *J* = 8.0 Hz, 1H), 6.23 (s, 1H), 5.25-5.21 (m, 1H), 4.57-4.52 (m, 1H), 3.93-3.88 (m, 1H), 2.31

(s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 145.0, 141.8, 137.8, 133.3, 132.6, 130.5, 130.0, 129.2, 128.8, 127.8, 126.3, 120.56, 120.52, 109.5, 83.4, 61.2, 58.2, 21.7; FT-IR (KBr) 3053, 2918, 1616, 1597, 1566, 1493, 1454, 1422, 1361, 1306, 1168, 1106 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{21}N_2O_2S$: 389.1318, found: 389.1318; $[\alpha]_D^{27}$ = +54.00 (c= 0.01, $CHCl_3$); HPLC: >99% ee [CHIRALCEL OD-H, hexane/^{i}PrOH = 90:10, flow rate: 1 mL /min, λ = 254 nm, t_R = 23.67 min (minor), 31.97 min (major)].

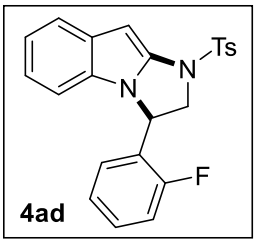


3-(2-Bromophenyl)-1-tosyl-2,3-dihydro-1H-imidazo[1,2-a]indole 4ab. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.42; Purification on silica gel column chromatography using 1:14 ethyl acetate/hexane as eluent; colorless solid; mp 175-176 ^{o}C; yield 73% (68 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.57-7.53 (m, 2H), 7.15-7.06 (m, 4H), 6.97-6.93 (m, 1H), 6.88 (t, *J* = 7.2 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.34 (s, 1H), 6.11-6.03 (m, 1H), 5.72-5.69 (m, 1H), 4.73-4.68 (m, 1H), 4.10-4.06 (m, 1H), 2.34 (s, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 144.9, 141.8, 137.2, 133.1, 132.6, 130.3, 129.9, 129.7, 128.1, 127.7, 126.8, 122.6, 121.6, 120.8, 120.72, 120.70, 109.7, 83.8, 60.2, 57.2, 21.7; FT-IR (KBr) 3054, 2918, 1617, 1567, 1477, 1455, 1421, 1362, 1306, 1167, 1106 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{20}BrN_2O_2S$: 467.0423, found: 467.0426.

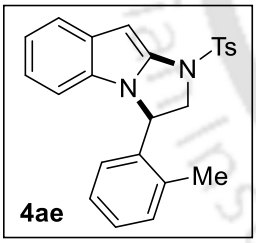


3-(2-Chlorophenyl)-1-tosyl-2,3-dihydro-1H-imidazo[1,2-a]indole 4ac. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane, R_f = 0.43; Purification on silica gel column chromatography using 1:14 ethyl acetate/hexane as eluent; colorless solid; mp 172-173 ^{o}C; yield 66% (55 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 9.2 Hz, 1H), 7.19-7.12 (m, 3H), 7.08(t, *J* = 7.6 Hz, 1H), 6.95 (t, *J* = 8.0 Hz, 1H), 6.84 (t, *J* = 7.6 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 6.34 (s, 1H), 6.13 (d, *J* = 6.8 Hz, 1H), 5.76-5.73 (m, 1H), 4.72-4.67 (m, 1H), 4.11-4.08 (m, 1H), 2.34 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 144.9, 141.8, 135.7, 133.1, 132.6, 131.8, 130.3, 129.9, 129.8, 129.4, 127.7, 127.4, 126.6, 120.8, 120.7, 120.6, 109.6, 83.8, 60.1, 54.9, 21.7; FT-IR (KBr) 3054,

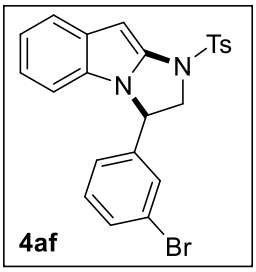
2917, 1617, 1595, 1566, 1476, 1455, 1421, 1361, 1305, 1166, 1106 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{20}ClN_2O_2S$: 423.0929, found: 423.0929.



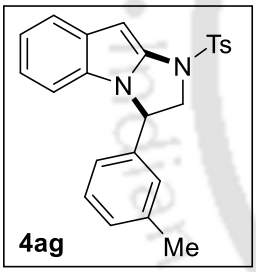
3-(2-Fluorophenyl)-1-tosyl-2,3-dihydro-1H-imidazo[1,2-a]indole 4ad. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.41; Purification on silica gel column chromatography using 1:11 ethyl acetate/hexane as eluent; colorless solid; mp 176-177 ^oC; yield 63% (51 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.24-7.20 (m, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.09-7.04 (m, 2H), 6.96-6.91 (m, 1H), 6.79 (t, *J* = 7.6 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 6.34-6.30 (m, 2H), 5.69-5.65 (m, 1H), 4.66-4.61(m, 1H), 4.13-4.09 (m, 1H), 2.36 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.0 (J_{C-F} = 245.3 Hz), 144.9, 141.7, 133.3, 132.7, 130.4, 130.1 (J_{C-F} = 8.2 Hz), 129.9, 127.8, 127.0 (J_{C-F} = 3.4 Hz), 125.4 (J_{C-F} = 12.8 Hz), 124.8 (J_{C-F} = 3.6 Hz), 120.76, 120.71, 120.6, 115.8 (J_{C-F} = 20.8 Hz), 109.4, 83.7, 60.2, 51.6 (J_{C-F} = 4.8 Hz), 21.7; FT-IR (KBr) 3052, 2924, 1616, 1567, 1490, 1455, 1422, 1362, 1306, 1168, 1108 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{20}FN_2O_2S$: 407.1224, found: 407.1226.



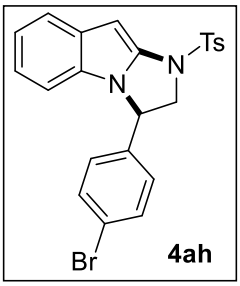
3-(*o*-Tolyl)-1-tosyl-2,3-dihydro-1H-imidazo[1,2-a]indole 4ae. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.45; Purification on silica gel column chromatography using 1:14 ethyl acetate/hexane as eluent; colorless solid; mp 176-177 ^oC; yield 67% (53 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.19-7.15 (m, 4H), 7.07-7.03 (m, 1H), 6.91-6.87 (m, 2H), 6.57 (d, *J* = 8.0 Hz, 1H), 6.329-6.327 (m, 2H), 5.54-5.51 (m, 1H), 4.68-4.63 (m, 1H), 3.93-3.89 (m, 1H), 2.37 (s, 3H), 2.28 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.9, 141.9, 135.5, 134.7, 133.3, 132.6, 131.0, 130.9, 130.6, 129.9, 128.3, 127.8, 126.8, 125.6, 120.58, 120.54, 120.50, 109.6, 83.5, 60.1, 55.1, 21.7, 19.2; FT-IR (KBr) 3052, 2921, 1616, 1597, 1566, 1477, 1455, 1425, 1361, 1306, 1168, 1089 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}N_2O_2S$: 403.1475, found: 403.1479.



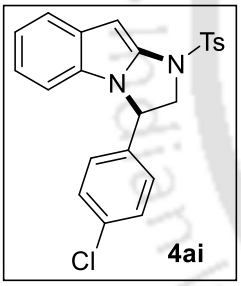
3-(3-Bromophenyl)-1-tosyl-2,3-dihydro-1H-imidazo[1,2-a]indole 4af. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.43; Purification on silica gel column chromatography using 1:14 ethyl acetate/hexane as eluent; colorless solid; mp 95-96 ^oC; yield 68% (63 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.09-7.00 (m, 3H), 6.91 (t, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 6.31 (s, 1H), 5.28-5.24 (m, 1H), 4.65-4.61 (m, 1H), 3.99-3.95 (m, 1H), 2.39 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 145.2, 141.8, 140.3, 133.4, 132.5, 132.0, 130.8, 130.4, 130.0, 129.3, 127.8, 124.9, 123.3, 120.78, 120.71, 109.4, 83.8, 61.0, 57.5, 21.8; FT-IR (KBr) 3052, 2918, 1616, 1596, 1568, 1476, 1455, 1420, 1362, 1306, 1185, 1167, 1107, 1089 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{20}BrN_2O_2S$: 467.0423, found: 467.0423.



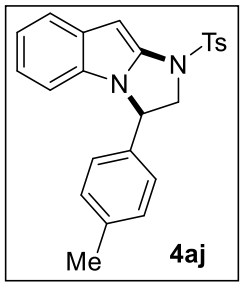
3-(*m*-Tolyl)-1-tosyl-2,3-dihydro-1H-imidazo[1,2-a]indole 4ag. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.44; Purification on silica gel column chromatography using 1:14 ethyl acetate/hexane as eluent; colorless solid; mp 143-144 ^oC; yield 64% (51 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 2H), 7.12-7.09 (m, 2H), 7.05-7.01 (m, 1H), 6.89-6.85 (m, 1H), 6.70-6.68 (m, 2H), 6.58 (d, *J* = 8.0 Hz, 1H), 6.30 (s, 1H), 5.27-5.23 (m, 1H), 4.63-4.59 (m, 1H), 3.99-3.94 (m, 1H), 2.39 (s, 3H), 2.22 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.9, 141.9, 139.0, 137.7, 133.3, 132.5, 130.6, 129.9, 129.6, 129.0, 127.94, 126.96, 123.5, 120.49, 120.45, 109.6, 83.3, 61.2, 58.2, 21.7, 21.4; FT-IR (KBr) 3051, 2921, 1615, 1596, 1566, 1477, 1456, 1421, 1362, 1306, 1185, 1168, 1107, 1089 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}N_2O_2S$: 403.1475, found: 403.1478.



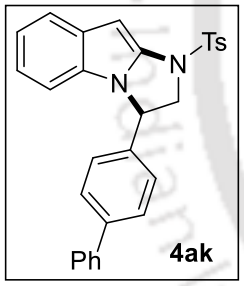
3-(4-Bromophenyl)-1-tosyl-2,3-dihydro-1H-imidazo[1,2-a]indole 4ah. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.42; Purification on silica gel column chromatography using 1:14 ethyl acetate/hexane as eluent; colorless solid; mp 171-172 ^oC; yield 71% (66 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.31-7.29 (m, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.08-7.04 (m, 1H), 6.93-6.89 (m, 1H), 6.68-6.66 (m, 2H), 6.60 (d, *J* = 8.0 Hz, 1H), 6.31 (s, 1H), 5.30-5.27 (m, 1H), 4.65-5.61 (m, 1H), 3.98-3.94 (m, 1H), 2.40 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 145.1, 141.6, 137.0, 133.3, 132.6, 132.3, 130.4, 129.9, 127.9, 127.8, 127.7, 122.7, 120.74, 120.71, 109.4, 83.7, 61.0, 57.5, 21.7; FT-IR (KBr) 3051, 2922, 1617, 1596, 1566, 1477, 1455, 1421, 1361, 1306, 1185, 1166, 1071 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{20}BrN_2O_2S$: 467.0423, found: 467.0423.



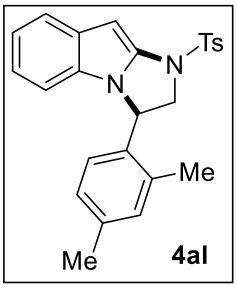
3-(4-Chlorophenyl)-1-tosyl-2,3-dihydro-1H-imidazo[1,2-a]indole 4ai. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.41; Purification on silica gel column chromatography using 1:14 ethyl acetate/hexane as eluent; colorless solid; mp 142-143 ^oC; yield 69% (58 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.17-7.14 (m, 2H), 7.07-7.03 (m, 1H), 6.92-6.88 (m, 1H), 6.75-6.73 (m, 2H), 6.59 (d, *J* = 8.0 Hz, 1H), 6.31 (s, 1H), 5.32-5.28 (m, 1H), 4.65-4.60 (m, 1H), 3.98-3.94 (m, 1H), 2.39 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 145.1, 141.7, 136.5, 134.6, 133.3, 132.7, 130.4, 129.9, 129.4, 128.6, 127.8, 127.5, 126.8, 120.75, 120.73, 109.4, 83.7, 61.1, 57.5, 21.7; FT-IR (KBr) 3063, 2922, 1708, 1567, 1492, 1456, 1362, 1306, 1168, 1090 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{20}ClN_2O_2S$: 423.0929, found: 423.0927.



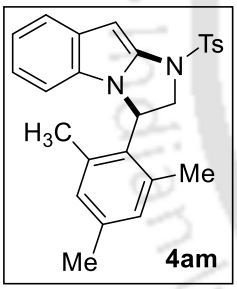
3-(*p*-Tolyl)-1-tosyl-2,3-dihydro-1H-imidazo[1,2-a]indole 4aj. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.44; Purification on silica gel column chromatography using 1:14 ethyl acetate/hexane as eluent; colorless solid; mp 135-136 °C; yield 64% (51 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.04-7.01 (m, 3H), 6.89-6.85 (m, 1H), 6.79 (d, *J* = 8.0 Hz, 2H), 6.57 (d, *J* = 8.0 Hz, 1H), 6.29 (s, 1H), 5.28-5.25 (m, 1H), 4.62-4.57 (m, 1H), 3.97-3.93 (m, 1H), 2.39 (s, 3H), 2.31 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 144.9, 141.8, 138.7, 134.7, 133.3, 132.7, 130.6, 129.9, 129.86, 129.81, 127.8, 126.3, 120.5, 120.4, 109.6, 83.3, 61.2, 58.1, 21.7, 21.2; FT-IR (KBr) 3051, 2922, 1693, 1597, 1566, 1477, 1455, 1360, 1306, 1185, 1168, 1105 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{24}H_{23}N_2O_2S$: 403.1475, found: 403.1480.



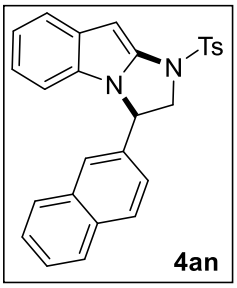
3-([1,1'-Biphenyl]-4-yl)-1-tosyl-2,3-dihydro-1H-imidazo[1,2-a]indole 4ak. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.46; Purification on silica gel column chromatography using 1:14 ethyl acetate/hexane as eluent; colorless solid; mp 198-199 °C; yield 68% (63 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.54-7.51 (m, 3H), 7.45-7.42 (m, 4H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 2H), 7.05 (t, *J* = 7.2 Hz, 1H), 6.94-6.88 (m, 3H), 6.65 (d, *J* = 8.0 Hz, 1H), 6.33(s, 1H), 5.38-5.34 (m, 1H), 4.68-4.63 (m, 1H), 4.05-4.00 (m, 1H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 145.0, 141.8, 141.7, 140.2, 136.7, 133.3, 132.6, 130.5, 129.9, 129.0, 127.9, 127.89, 127.81, 127.1, 126.7, 120.59, 120.56, 109.6, 83.4, 61.2, 58.0, 21.7; FT-IR (KBr) 3030, 2925, 1616, 1597, 1566, 1487, 1456, 1362, 1306, 1260, 1168, 1089 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{29}H_{25}N_2O_2S$: 465.1631, found: 465.1631.



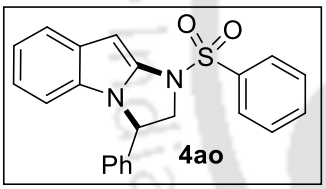
3-(2,4-Dimethylphenyl)-1-tosyl-2,3-dihydro-1H-imidazo[1,2-a]indole 4al. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.44; Purification on silica gel column chromatography using 1:14 ethyl acetate/hexane as eluent; colorless solid; mp 146-147 ^oC; yield 65% (54 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.06-7.02 (m, 1H), 6.98 (s, 1H), 6.91-6.86 (m, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 6.31(s, 1H), 6.27 (s, 1H), 5.51-5.47 (m, 1H), 4.65-4.60 (m, 1H), 3.89-3.85 (m, 1H), 2.37 (s, 3H), 2.26-2.22 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.9, 141.9, 138.1, 134.5, 133.2, 132.6, 132.4, 131.8, 130.6, 129.9, 127.8, 127.5, 120.5, 120.47, 120.44, 109.7, 83.4, 60.2, 55.3, 21.7, 21.1, 19.0; FT-IR (KBr) 3052, 2922, 1615, 1596, 1565, 1477, 1455, 1361, 1306, 1185, 1168, 1103, 1089 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{25}N_2O_2S$: 417.1631, found: 417.1632.



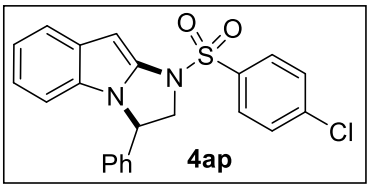
3-Mesityl-1-tosyl-2,3-dihydro-1H-imidazo[1,2-a]indole 4am. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.43; Purification on silica gel column chromatography using 1:14 ethyl acetate/hexane as eluent; colorless solid; mp 196-197 ^oC; yield 63% (54 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.27-7.25 (m, 2H), 7.02-6.98 (m, 1H), 6.90 (s, 1H), 6.84-6.80 (m, 1H), 6.67 (s, 1H), 6.39 (d, *J* = 8.0 Hz, 1H), 6.28 (s, 1H), 5.80 (t, *J* = 9.2 Hz, 1H), 4.58-4.53 (m, 1H), 4.01-3.96 (m, 1H), 2.39 (d, *J* = 2.4 Hz, 6H), 2.24 (s, 3H), 1.22 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 145.1, 141.4, 138.5, 137.3, 136.7, 132.9, 132.7, 131.9, 130.6, 129.9, 127.9, 120.4, 120.3, 108.6, 83.1, 57.3, 53.8, 21.7, 20.9, 20.8, 18.2; FT-IR (KBr) 2922, 1615, 1457, 1425, 1363, 1306, 1170, 1090 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{27}N_2O_2S$: 431.1788, found: 431.1790.



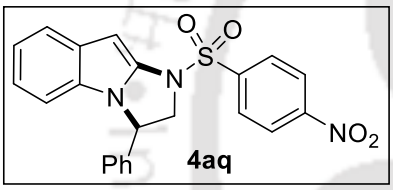
3-(Naphthalen-2-yl)-1-tosyl-2,3-dihydro-1H-imidazo[1,2-a]indole 4an. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.47; Purification on silica gel column chromatography using 1:14 ethyl acetate/hexane as eluent; colorless solid; mp 183-184 ^oC; yield 67% (58 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.80-7.76 (m, 3H), 7.68-7.64 (m, 2H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.49-7.47 (m, 2H), 7.39 (s, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.03 (t, *J* = 8.0 Hz, 1H), 6.89-6.81 (m, 2H), 6.57 (d, *J* = 8.0 Hz, 1H), 6.35 (s, 1H), 5.50-5.46 (m, 1H), 4.74-4.69 (m, 1H), 4.09-4.05 (m, 1H), 2.34 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 145.0, 141.9, 135.2, 133.3, 133.1, 132.6, 130.6, 129.9, 129.4, 128.1, 127.8, 126.8, 126.7, 125.8, 123.2, 120.6, 120.58, 120.56, 109.6, 83.6, 61.1, 58.4, 21.7; FT-IR (KBr) 3053, 2923, 1616, 1597, 1566, 1477, 1456, 1361, 1306, 1185, 1168, 1106, 1089 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{23}N_2O_2S$: 439.1475, found: 439.1478.



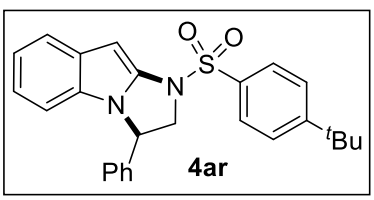
3-Phenyl-1-(phenylsulfonyl)-2,3-dihydro-1H-imidazo[1,2-a]indole 4ao. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.44; Purification on silica gel column chromatography using 1:14 ethyl acetate/hexane as eluent; colorless solid; mp 174-175 ^oC; yield 71% (53 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.2 Hz, 2H), 7.62-7.58 (m, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.47-7.43 (m, 2H), 7.29-7.19 (m, 3H), 7.06-7.02 (m, 1H), 6.90-6.85 (m, 3H), 6.57 (d, *J* = 8.0 Hz, 1H), 6.33 (s, 1H), 5.33-5.29 (m, 1H), 4.66-4.61 (m, 1H), 4.00-3.96 (m, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 141.7, 137.6, 135.5, 134.0, 133.3, 130.5, 129.4, 129.2, 128.9, 127.8, 126.3, 120.58, 120.56, 109.6, 83.4, 61.2, 58.2; FT-IR (KBr) 3060, 2924, 1616, 1566, 1477, 1454, 1362, 1307, 1220, 1171, 1090 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{18}N_2O_2S$: 375.1162, found: 375.1166.



1-((4-Chlorophenyl)sulfonyl)-3-phenyl-2,3-dihydro-1H-imidazo[1,2-a]indole 4ap. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.42; Purification on silica gel column chromatography using 1:11 ethyl acetate/hexane as eluent; colorless solid; mp 192-193 ^oC; yield 72% (58 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.38-7.36 (m, 2H), 7.31-7.27 (m, 1H), 7.23-7.19 (m, 2H), 7.08-7.04 (m, 1H), 6.93-6.89 (m, 1H), 6.81-6.79 (m, 2H), 6.61 (d, *J* = 8.0 Hz, 1H), 6.32 (s, 1H), 5.37-5.33 (m, 1H), 4.69-4.64 (m, 1H), 4.02-3.97 (m, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 141.2, 140.7, 137.7, 134.0, 133.1, 130.5, 129.6, 129.3, 129.1, 128.8, 126.0, 120.8, 120.6, 109.7, 83.6, 61.3, 58.1; FT-IR (KBr) 3060, 2925, 1616, 1573, 1475, 1454, 1366, 1307, 1281, 1171, 1092 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{17}ClN_2O_2S$: 409.0772, found: 409.0777.

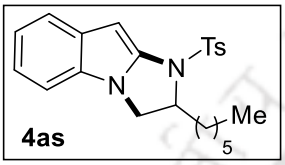


1-((4-Nitrophenyl)sulfonyl)-3-phenyl-2,3-dihydro-1H-imidazo[1,2-a]indole 4aq. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.40; Purification on silica gel column chromatography using 1:11 ethyl acetate/hexane as eluent; orange solid; mp 194-195 ^oC; yield 62% (51 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.8 Hz, 2H), 8.03 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.27-7.23 (m, 1H), 7.16 (t, *J* = 7.6 Hz, 2H), 7.08 (t, *J* = 8.0 Hz, 1H), 6.96-6.92 (m, 1H), 6.77 (d, *J* = 7.2 Hz, 2H), 6.64 (d, *J* = 8.0 Hz, 1H), 6.36 (s, 1H), 5.40-5.37 (m, 1H), 4.75-4.70 (m, 1H), 4.09-4.05 (m, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 150.8, 141.2, 140.4, 137.6, 132.8, 130.7, 129.2, 128.9, 128.8, 125.8, 124.4, 121.2, 120.9, 120.8, 109.8, 83.9, 61.5, 58.0; FT-IR (KBr) 3104, 2924, 1606, 1595, 1567, 1477, 1454, 1370, 1309, 1256, 1173, 1089 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{18}N_3O_4S$: 420.1013, found: 420.1012.

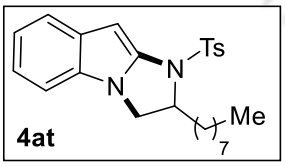


1-((4-(*tert*-Butyl)phenyl)sulfonyl)-3-phenyl-2,3-dihydro-1H-imidazo[1,2-a]indole 4ar. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.44;

Purification on silica gel column chromatography using 1:14 ethyl acetate/hexane as eluent; colorless solid; mp 193-194 °C; yield 67% (57 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.21 (t, *J* = 7.6 Hz, 2H), 7.04 (t, *J* = 8.0 Hz, 1H), 6.89-6.86 (m, 3H), 6.58 (d, *J* = 8.0 Hz, 1H), 6.32 (s, 1H), 5.35-5.31 (m, 1H), 4.65-4.60 (m, 1H), 3.99-3.95 (m, 1H), 1.30 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.9, 141.9, 137.8, 133.4, 132.4, 130.5, 129.2, 128.9, 127.8, 126.39, 126.38, 120.52, 120.52, 120.4, 109.5, 83.2, 61.1, 58.2, 35.4, 31.1; FT-IR (KBr) 3057, 2963, 1617, 1593, 1566, 1476, 1455, 1361, 1307, 1266, 1131, 1085 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{27}N_2O_2S$: 431.1788, found: 431.1791.

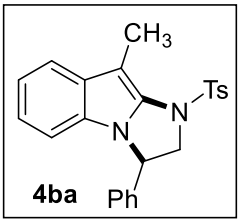


2-Hexyl-1-tosyl-2,3-dihydro-1H-imidazo[1,2-a]indole 4as. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.43; Purification on silica gel column chromatography using 1:14 ethyl acetate/hexane as eluent; colorless solid; mp 113-114 °C; yield 66% (52 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.53-7.50 (m, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.08-7.05 (m, 2H), 7.01-6.99 (m, 1H), 6.27 (s, 1H), 4.50-4.44 (m, 1H), 3.81-3.77 (m, 1H), 3.70-3.67 (m, 1H), 2.34 (s, 3H), 2.06-1.98 (m, 1H), 1.90-1.81 (m, 1H), 1.44-1.25 (m, 8H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 144.7, 141.3, 133.9, 132.8, 130.8, 129.9, 127.5, 120.6, 120.5, 120.1, 108.7, 84.8, 66.2, 46.5, 35.8, 31.80, 29.1, 24.8, 22.7, 21.7, 14.2; FT-IR (KBr) 2922, 2859, 1562, 1457, 1428, 1306, 1185, 1167, 1090, 1008 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{29}N_2O_2S$: 397.1944, found: 397.1951.

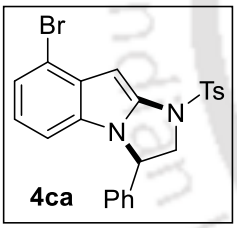


2-Octyl-1-tosyl-2,3-dihydro-1H-imidazo[1,2-a]indole 4at. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.42; Purification on silica gel column chromatography using 1:11 ethyl acetate/hexane as eluent; colorless solid; mp 90-91 °C; yield 68% (57 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.53-7.50 (m, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.09-7.04 (m, 2H), 7.02-6.99 (m, 1H), 6.27 (s, 1H), 4.50-4.44 (m, 1H), 3.81-3.77 (m, 1H), 3.70-3.67 (m, 1H), 2.34 (s, 3H), 2.06 – 1.98 (m, 1H), 1.90-1.81 (m, 1H), 1.45-1.27 (m, 12H), 0.88 (t, *J* = 6.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 144.7, 141.3, 134.0, 132.8, 130.8, 129.9, 127.5, 120.6, 120.5, 120.1, 108.7, 84.8, 66.2, 46.5, 35.8, 31.9,

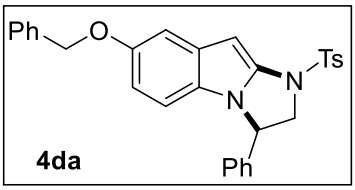
29.57, 29.51, 29.3, 24.9, 22.7, 21.7, 14.2; FT-IR (KBr) 3051, 2924, 1618, 1597, 1562, 1478, 1457, 1361, 1306, 1276, 1167, 1089 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{33}N_2O_2S$: 425.2257, found: 425.2260.



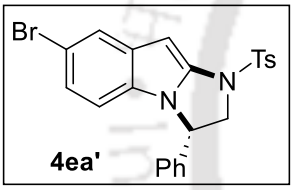
9-Methyl-3-phenyl-1-tosyl-2,3-dihydro-1H-imidazo[1,2-a]indole 4ba. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.51; Purification on silica gel column chromatography using 1:16 ethyl acetate/hexane as eluent; colorless solid; mp 130-131 ^oC; yield 64% (53 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.4 Hz, 3H), 7.279-7.277 (m, 1H), 7.18 (t, *J* = 7.6 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.09-7.05 (m, 1H), 6.93-6.89 (m, 1H), 6.80 (d, *J* = 7.2 Hz, 2H), 6.45 (d, *J* = 8.0 Hz, 1H), 4.87 (t, *J* = 7.6 Hz, 1H), 4.78-4.73 (m, 1H), 4.15-4.10 (m, 1H), 2.55 (s, 3H), 2.36 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.6, 137.8, 137.2, 133.8, 133.3, 130.4, 130.0, 129.0, 128.4, 127.8, 126.3, 121.2, 119.8, 119.1, 109.6, 96.2, 63.3, 57.2, 21.7, 8.9; FT-IR (KBr) 2922, 1596, 1457, 1361, 1275, 1168, 1090, 1006 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}N_2O_2S$: 403.1475, found: 403.1477.



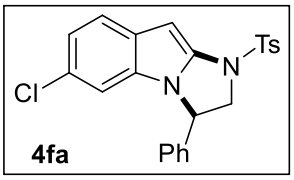
8-Bromo-3-phenyl-1-tosyl-2,3-dihydro-1H-imidazo[1,2-a]indole 4ca. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.46; Purification on silica gel column chromatography using 1:14 ethyl acetate/hexane as eluent; solid; colorless solid; mp 192-193 ^oC; yield 58% (54 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.24-7.16 (m, 4H), 7.15-7.11 (m, 2H), 6.77 (d, *J* = 7.2 Hz 2H), 6.66 (t, *J* = 8 Hz, 1H), 6.44 (d, *J* = 8.4 Hz, 1H), 6.31 (s, 1H), 5.28-5.25 (m, 1H), 4.58-4.53 (m, 1H), 3.94-3.90 (m, 1H), 2.33 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 145.2, 142.2, 137.4, 133.7, 132.5, 130.6, 130.1, 129.3, 129.0, 127.8, 126.2, 123.5, 121.4, 113.8, 108.5, 83.6, 61.0, 58.4, 21.7; FT-IR (KBr) 3066, 2923, 1611, 1597, 1566, 1493, 1456, 1428, 1363, 1167 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{20}BrN_2O_2S$: 467.0423, found: 467.0426.



7-(Benzyloxy)-3-phenyl-1-tosyl-2,3-dihydro-1H-imidazo[1,2-a]indole 4da. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.42; Purification on silica gel column chromatography using 1:11 ethyl acetate/hexane as eluent; colorless solid; mp 150-151 ^oC; yield 67% (66 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.38-7.36 (m, 2H), 7.32-7.28 (m, 2H), 7.26 – 7.20 (m, 2H), 7.17-7.12 (m, 4H), 7.02 (d, *J* = 2.4 Hz, 1H), 6.80-6.78 (m, 2H), 6.54 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.39 (d, *J* = 8.8 Hz, 1H), 6.17 (s, 1H), 5.20-5.17 (m, 1H), 4.98 (s, 2H), 4.55-4.50 (m, 1H), 3.89-3.85 (m, 1H), 2.32 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 154.0, 145.0, 142.5, 137.76, 137.72, 134.0, 132.5, 130.0, 129.2, 128.8, 128.6, 127.9, 127.8, 127.6, 126.3, 125.8, 110.4, 110.2, 104.8, 83.5, 70.8, 61.1, 58.4, 21.7; FT-IR (KBr) 3063, 2921, 1621, 1576, 1494, 1478, 1451, 1363, 1289, 1168 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{30}H_{27}N_2O_3S$: 495.1737, found: 495.1737.

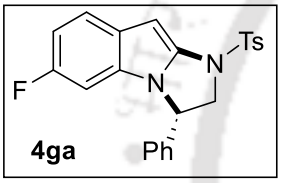


7-Bromo-3-phenyl-1-tosyl-2,3-dihydro-1H-imidazo[1,2-a]indole 4ea′. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.45; Purification on silica gel column chromatography using 1:14 ethyl acetate/hexane as eluent; colorless solid; mp 186-187 ^oC; 70% (65 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 1.6 Hz, 1H), 7.23-7.12 (m, 5H), 6.89 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.75-6.73 (m, 2H), 6.35 (d, *J* = 8.4 Hz, 1H), 6.17 (s, 1H), 5.24-5.21 (m, 1H), 4.58-4.53 (m, 1H), 3.93-3.88 (m, 1H), 2.32 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 145.2, 142.8, 137.3, 134.9, 132.5, 130.0, 129.2, 129.1, 128.9, 127.8, 126.2, 123.2, 122.9, 113.8, 110.8, 82.8, 61.1, 58.3, 21.7; FT-IR (KBr) 3063, 2923, 1612, 1595, 1565, 1459, 1364, 1275, 1168 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{20}BrN_2O_2S$: 467.0423, found: 467.0427; $[\alpha]_D^{26}$ = +24.00 (c= 0.01, $CHCl_3$); HPLC: >99% *ee* [CHIRALCEL OD-H, hexane/^{i}PrOH = 90:10, flow rate: 1 mL /min, λ = 254 nm, t_R = 18.56 min (minor), 25.91 min (major)].



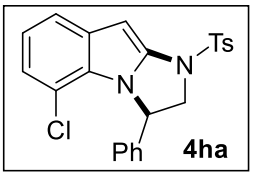
6-Chloro-3-phenyl-1-tosyl-2,3-dihydro-1H-imidazo[1,2-a]indole

4fa. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.44; Purification on silica gel column chromatography using 1:14 ethyl acetate/hexane as eluent; colorless solid; mp >200 ^oC; yield 63% (53 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.32-7.28 (m, 1H), 7.25-7.21 (m, 4H), 7.01 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.84-6.82 (m, 2H), 6.54 (d, *J* = 2.0 Hz, 1H), 6.27 (s, 1H), 5.29-5.25 (m, 1H), 4.64-4.59 (m, 1H), 3.99-3.95 (m, 1H), 2.40 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 145.2, 142.3, 137.3, 132.5, 131.8, 130.8, 130.0, 129.3, 129.0, 127.8, 126.1, 121.2, 121.1, 109.5, 83.3, 61.1, 58.3, 21.7; FT-IR (KBr) 3063, 2923, 1611, 1597, 1572, 1493, 1456, 1419, 1363, 1279, 1167 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{20}ClN_2O_2S$: 423.0929, found: 423.0928.

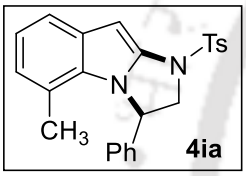


6-Fluoro-3-phenyl-1-tosyl-2,3-dihydro-1H-imidazo[1,2-a]indole

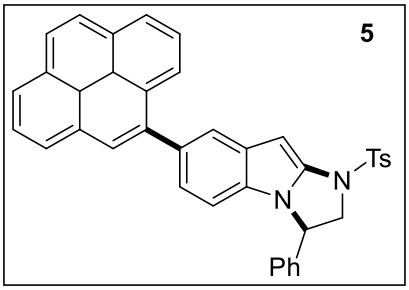
4ga′. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.42; Purification on silica gel column chromatography using 1:11 ethyl acetate/hexane as eluent; colorless solid; mp 188-189 ^oC; yield 68% (55 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.41-7.38 (m, 1H), 7.32-7.27 (m, 1H), 7.24-7.21 (m, 4H), 6.85- 6.83 (m, 2H), 6.81-6.76 (m, 1H), 6.27 (s, 1H), 6.26-6.23 (m, 1H), 5.27-5.23 (m, 1H), 4.64-4.59 (m, 1H), 3.99-3.95 (m, 1H), 2.40 (s, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 159.4 (J_{C-F} = 235.65 Hz), 145.1, 142.05 (J_{C-F} = 3.15 Hz), 137.2, 132.5, 130.3 (J_{C-F} = 12.45 Hz), 130.0, 129.5, 129.3, 129.0, 127.8, 126.2, 121.0 (J_{C-F} = 9.75 Hz), 108.7 (J_{C-F} = 24 Hz), 96.6 (J_{C-F} = 2.67 Hz), 83.2, 61.1, 58.2, 21.7; FT-IR (KBr) 3063, 2923, 1622, 1575, 1484, 1421, 1358, 1279 1167 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{20}FN_2O_2S$: 407.1224, found: 407.1228; $[\alpha]_D^{27}$ = +22.00 (c= 0.01, $CHCl_3$); HPLC: >99% *ee* [CHIRALCEL OD-H, hexane/^{i}PrOH = 90:10, flow rate: 1 mL /min, λ = 254 nm, t_R = 17.63 min (minor), 28.30 min (major)].



5-Chloro-3-phenyl-1-tosyl-2,3-dihydro-1H-imidazo[1,2-a]indole 4ha. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.43; Purification on silica gel column chromatography using 1:11 ethyl acetate/hexane as eluent; colorless solid; mp 164-165 ^oC; yield 69% (58 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.18-7.14 (m, 3H), 7.09-7.05 (m, 2H), 6.96 (t, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 7.2 Hz, 1H), 6.55 (d, *J* = 7.6 Hz, 2H), 6.33 (s, 1H), 5.87-5.85 (m, 1H), 4.50-4.46 (m, 1H), 4.18-4.15 (m, 1H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 145.0, 142.7, 141.0, 135.3, 132.5, 130.0, 128.9, 128.0, 127.7, 127.4, 124.6, 121.5, 121.1, 118.9, 116.1, 83.2, 60.8, 59.4, 21.7; FT-IR (KBr) 3063, 2924, 1616, 1597, 1575, 1485, 1455, 1429, 1362, 1276, 1167 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{20}ClN_2O_2S$: 423.0929, found: 423.0931.

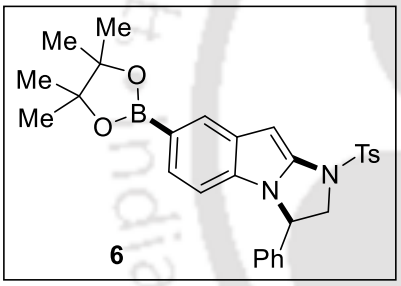


5-Methyl-3-phenyl-1-tosyl-2,3-dihydro-1H-imidazo[1,2-a]indole 4ia. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.46; Purification on silica gel column chromatography using 1:14 ethyl acetate/hexane as eluent; colorless solid; mp 174-175 ^oC; yield 73% (58 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.17-7.13 (m, 3H), 7.09-7.05 (m, 2H), 6.96 (t, *J* = 7.2 Hz, 1H), 6.70 (d, *J* = 7.2 Hz, 1H), 6.53-6.50 (m, 2H), 6.32 (s, 1H), 5.67-5.64 (m, 1H), 4.53-4.49 (m, 1H), 4.16-4.13 (m, 1H), 2.36 (s, 3H), 2.06 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 144.8, 141.8, 141.3, 133.4, 132.6, 129.9, 129.8, 129.1, 128.0, 127.7, 124.6, 122.4, 120.9, 120.3, 118.2, 83.1, 60.9, 59.5, 21.7, 17.7; FT-IR (KBr) 3049, 2925, 1607, 1597, 1572, 1492, 1455, 1416, 1358, 1263, 1165, 1090 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}N_2O_2S$: 403.1475, found: 403.1477.



3-Phenyl-7-(pyren-2-yl)-1-tosyl-2,3-dihydro-1H-imidazo[1,2-a]indole 5. Compound **4ea** (46 mg, 0.1 mmol), boronic acid (25 mg, 0.1 mmol), $Pd(PPh_3)_4$ (2.3 mg, 0.002 mmol), Na_2CO_3 (22 mg, 0.2 mmol) and H_2O (50 mL) were stirred in

toluene: EtOH (1:1, 2 mL) at 100 °C in an oil bath for 12 h under nitrogen atmosphere. After completion, the reaction mixture was cooled to room temperature 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 1:14 ethyl acetate/hexane as eluent to give **5.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.46; grey solid; mp 151-152 °C; yield 85% (50 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23-8.17 (m, 3H), 8.15 (d, *J* = 7.6 Hz, 1H), 8.10-8.05 (m, 2H), 8.01-7.97 (m, 3H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.76-7.75(m 1H), 7.36-7.29 (m, 5H), 7.16 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.01 (d, *J* = 6.8 Hz, 2H), 6.74 (d, *J* = 8.4 Hz, 1H), 6.40 (s, 1H), 5.43-5.39 (m, 1H), 4.71-4.67 (m, 1H), 4.07-4.03 (m, 1H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 145.1, 142.4, 138.9, 137.7, 133.6, 133.5, 132.6, 131.6, 131.1, 130.3, 130.1, 129.9, 129.3, 128.9, 128.8, 128.2, 127.9, 127.5, 127.25, 127.23, 126.4, 126.0, 125.9, 125.1, 125.0, 124.7, 124.6, 123.5, 122.5, 109.2, 83.5, 61.2, 58.4, 21.8; FT-IR (KBr) 2977, 2926, 1613, 1567, 1435, 1351, 1168, 1143, 1074 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{39}H_{29}N_2O_2S$: 589.1944, found: 589.1946.



6

3-Phenyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-2,3-dihydro-1H-imida-zo[1,2-a]indole 6. Compound **4ea** (46 mg, 0.1 mmol), diboron (25 mg, 0.1 mmol), KOAc (20 mg, 0.2 mmol) and $Pd(dppf)Cl_2$•CH_2Cl_2(4 mg, 0.005 mmol) were stirred in THF (2 mL) at 100 °C in an oil bath for 12 h under nitrogen atmosphere. The reaction mixture was cooled to room temperature and passed through a short pad of celite using CH_2Cl_2 (15 ml). Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using 1:14 ethyl acetate/hexane as eluent to give **6**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane, R_f = 0.48; colorless solid; mp 95-96 °C; yield 73% (37 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.35 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.24 (t, *J* = 1.6 Hz, 1H), 7.19-7.16 (m, 4H), 6.80 – 6.78 (m, 2H), 6.58 (d, *J* = 8.0 Hz, 1H), 6.31 (s, 1H), 5.35-5.31 (m, 1H), 4.65-4.61 (m, 1H), 4.02-3.98 (m, 1H), 2.37 (s, 3H), 1.32 (s, 12H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 145.0, 141.7, 137.8, 132.9, 132.4, 131.2, 129.9, 129.2, 128.7, 128.0, 127.8, 126.9, 126.1, 109.0, 83.7, 83.6, 61.3, 58.0, 25.0, 24.9, 21.7; FT-IR

(KBr) 3039, 2924, 1739, 1573, 1470, 1456, 1432, 1364, 1311, 1168, 1090 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{29}H_{32}BN_2O_4S$: 515.2170, found: 515.2184.

Crystal Data and Structure Refinement for 4aa

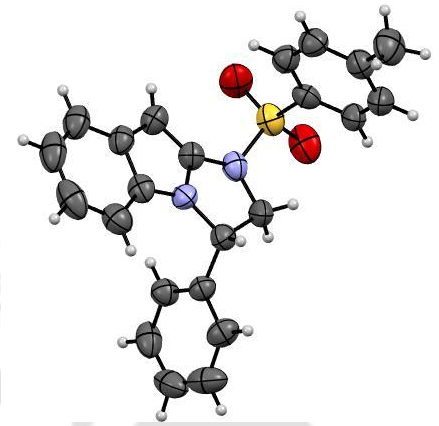


Figure S1. ORTEP diagram of 3-phenyl-1-tosyl-2,3-dihydro-1H-imidazo[1,2-a]indole **4aa** with 50% ellipsoid (CCDC 1978164).

Sample Preparation for Crystal Growth: The compound **4aa** was dissolved in CH_3CN and kept for slow evaporation at room temperature. Needle shaped crystals formed after 5 days. The single crystals were then subjected to X-ray diffraction analysis.

Identification code	**4aa**
Empirical formula	'C23 H20 N2 O2 S'
Formula weight	388.47
Crystal habit, colour	Needle /yellow
Crystal size, mm^3	0.32 x 0.27 x 0.21
Temperature, *T*/K	296 K
Wavelength, λ/Å	0.71073
Crystal system	'Monoclinic'
Space group	'P n'
Unit cell dimensions	a =9.1129(11)Å
	b = 11.1539(14)Å
	c = 10.0597(12) Å
	α = 90
	β = 107.223(4)
	γ = 90

Volume, V/Å^3	976.7(2)
Z	2
Calculated density, g cm^{-3}	1.321
Absorption coefficient, μ/mm^{-1}	0.187
F(000)	408.0
θ range for data collection	1.826 to 24.998°
Limiting indices	-10 ≤ h ≤ 10, –13 ≤ k ≤ 13, –11 ≤ l ≤ 11
Reflection collected / unique	3439/2724
Completeness to θ	100% (θ = 24.998°)
Absorption correction	None
Max. and min. transmission	0.961 and 0.942
Refinement method	'SHELXL-2014 (Sheldrick, 2014)'
Data / restraints / parameters	3439/2/ 254
Goodness–of–fit on F^2	0.933
Final R indices [I>2sigma(I)]	R1 = 0.0487, wR2 = 0.1284
R indices (all data)	R1 = 0.0657, wR2 = 0.1451

Crystal Data and Structure Refinement for 4aa′

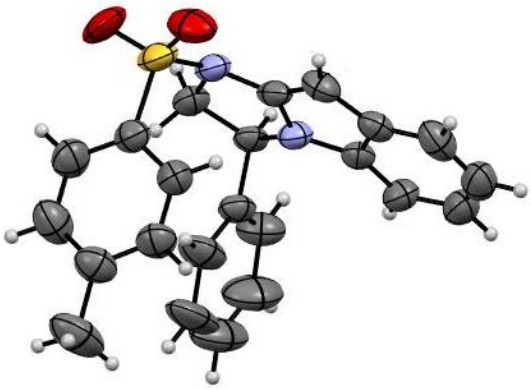


Figure S2. ORTEP diagram of (*S*)-3-phenyl-1-tosyl-2,3-dihydro-1H-imidazo[1,2-a]indole **4aa′** with 50% ellipsoid (CCDC 1987130).

Sample Preparation for Crystal Growth: The compound **4aa′** was dissolved in CH_3CN and kept for slow evaporation at room temperature. Block shaped crystals formed after 5 days. The single crystals were then subjected to X-ray diffraction analysis.

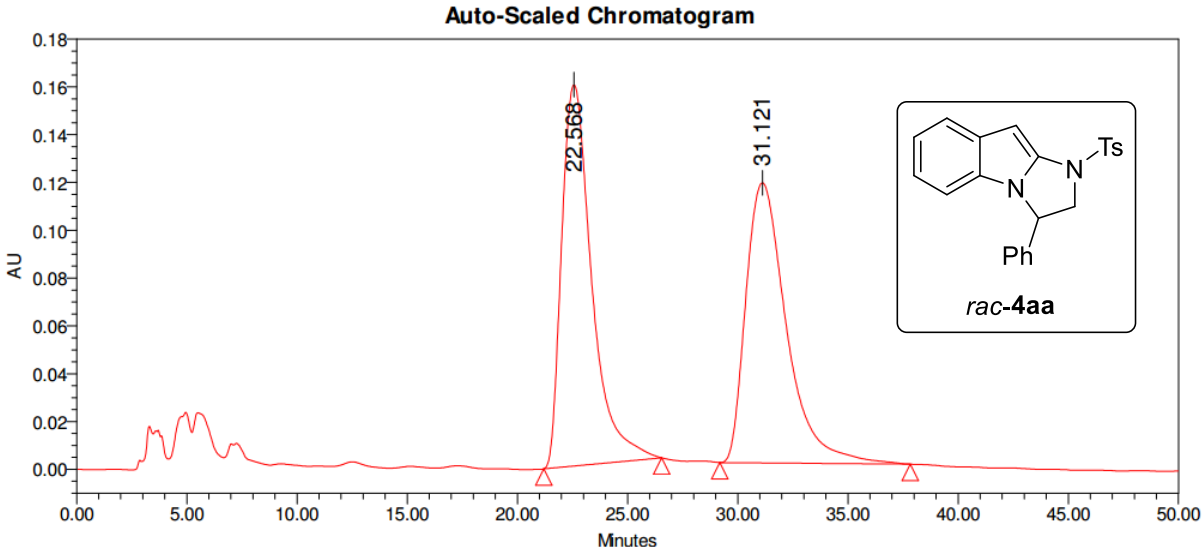
Identification code	**4aa′**
Empirical formula	'C23 H20 N2 O2 S'
Formula weight	388.47
Crystal habit, colour	Block / colourless
Crystal size, mm^3	0.32 x 0.26 x 0.19
Temperature, *T*/K	296 K
Wavelength, λ/Å	0.71073
Crystal system	'Monoclinic'
Space group	' P 21'
Unit cell dimensions	a = 9 11.3599(9)Å
	b = 8.5436(7)Å
	c = 21.1845(16)Å
	α = 90
	β = 102.804(2)
	γ = 90
Volume, *V*/$Å^3$	2004.9(3)
Z	4
Calculated density, g cm^{-3}	1.287
Absorption coefficient, μ/mm^{-1}	0.182
F(000)	816.0
θ range for data collection	1.838 to 25.045°
Limiting indices	-13 ≤ h ≤ 13, –10 ≤ k ≤ 10, –25 ≤ l ≤ 25
Reflection collected / unique	7104/5387
Completeness to θ	100% (θ = 25.045°)
Absorption correction	None
Max. and min. transmission	0.966 and 0.945
Refinement method	'SHELXL-2014 (Sheldrick, 2014)'
Data / restraints / parameters	7104/1/507
Goodness−of−fit on F^2	0.994
Final *R* indices [*I*>2sigma(*I*)]	R1 = 0.0586, wR2 = 0.1440
R indices (all data)	R1 = 0.0840, wR2 = 0.1701

1.5 References

1. (a) Thirunavukkarasu, V. S.; Kozhushkov, S. I.; Ackermann, L. *Chem. Commun.* **2014**, *50*, 29. (b) Park, Y.; Kim, Y.; Chang, S. *Chem. Rev*. **2017**, *117*, 9247. (c) Jarvis, C. L.; Hirschi, J. S.; Vetticatt, M. J.; Seidel, D. *Angew. Chem., Int. Ed*. **2017**, *56*, 2670. (d) Yu, J.-F.; Li, J.-J.; Wang, P.; Yu, J.-Q. *Angew. Chem. Int. Ed*. **2019**, *58*, 18141.
2. (a) Blunt, J. W.; Copp, B. R.; Keyzers, R. A.; Munroa, M. H. G.; Prinsep, M. R. *Nat. Prod. Rep*. **2012**, *29*, 144. (b) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem*. **2014**, *57*, 5845. (c) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem*. **2014**, *57*, 10257. (d) Moraski, G. C.; Oliver, A. G.; Markley, L. D.; Cho, S.; Franzblau, S. G.; Miller, M. J. *Bioorg. Med. Chem. Lett*. **2014**, *24*, 3493. (e) Zhang, M.-Z.; Chen, Q.; Yang, G.-F. *Eur. J. Med. Chem*. **2015**, *89*, 421.
3. (a) Kim, Y.; Park, J.; Chang, S. *Org. Lett*. **2016**, *18*, 1892. (b) Leitch, J. A.; Bhonoah, Y.; Frost, C. G. *ACS Catal*. **2017**, *7*, 5618. (c) Kalepu, J.; Gandeepan, P.; Ackermann, L.; Pilarski, L. T. *Chem. Sci*. **2018**, *9*, 4203. (d) Vargas, D. A.; Tinoco, A.; Tyagi, V.; Fasan, R. *Angew. Chem. Int. Ed.* **2018**, *57*, 9911.
4. Martynaitis, V.; Steponavičiūtė, R.; Krikštolaitytė, S.; Solovjova, J.; Mangelinckx, S.; Kimpe, N. D.; Holzer, W.; Šačkus, A. *Tetrahedron* **2011**, *67*, 3945.
5. (a) Sheldon, R. A. *Chem. Soc. Rev.* **2012**, *41*, 1437. (b) Newton, C. G.; Wang, S.-G.; Oliveira, C. C.; Cramer, N. *Chem. Rev*. **2017**, *117*, 8908.
6. (a) Huang, C.- Y.; Doyle, A. G. *Chem. Rev*. **2014**, *114*, 8153. (b) Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chem. Int. Ed*. **2014**, *53*, 5504. (c) Fumagalli, G.; Stanton, S.; Bower, J. F. *Chem. Rev*. **2017**, *117*, 9404. (d) Liang, Y.-F.; Mgller, V.; Liu, W.; Mgnch, A.; Stalke, D.; Ackermann, L. *Angew. Chem. Int. Ed*. **2017**, *56*, 9415. (e) Chagarovskiy, A. O.; Vasin, V. S.; Kuznetsov, V. V.; Ivanova, O. A.; Rybakov, V. B.; Shumsky, A. N.; Makhova, N. N.; Trushkov, I. V. *Angew. Chem. Int. Ed*. **2018**, *57*, 10338.
7. (a) Cardoso, A. L.; Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem*. **2012**, *33*, 6479. (b) He, Z.; Zajdlik, A.; Yudin, A. K. *Acc. Chem. Res*. **2014**, *47*, 1029. (c) Craig II, R. A.; O'Connor, N. R.; Goldberg, A. F. G.; Stoltz, B. M. *Chem. Eur. J*. **2014**, *20*, 4806. (d) Woods, B. P.; Orlandi, M.; Huang, C.-Y.; Sigman, M. H.; Doyle, A. G. *J. Am. Chem. Soc*. **2017**, *139*, 5688.
8. Tietze, L. F. Domino Reactions in Organic Synthesis. *Chem. Rev*. **1996**, *96*, 115.

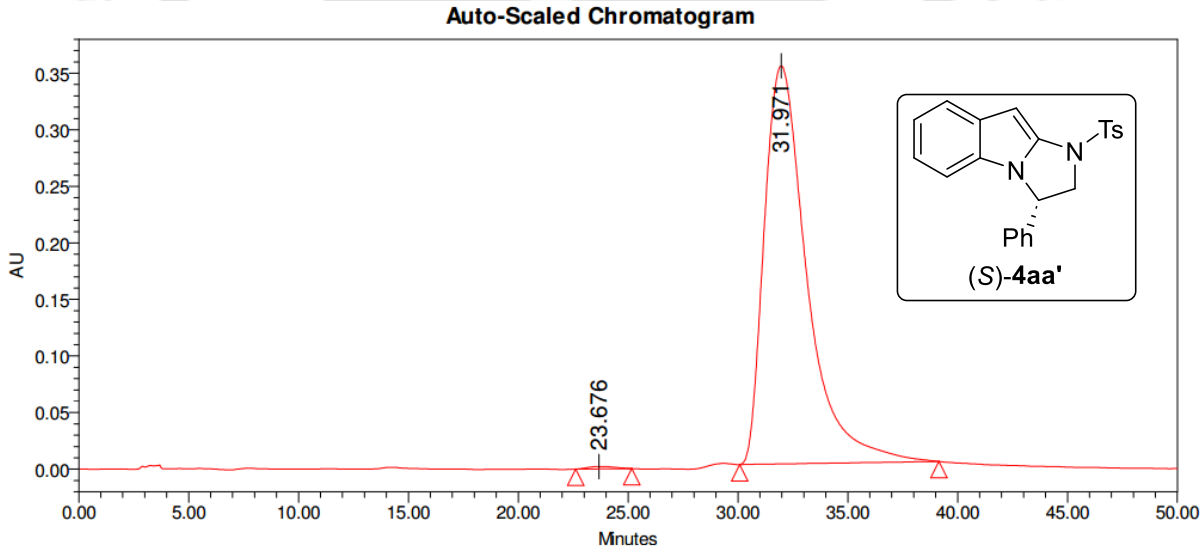
9. (a) Kirihara, M.; Okada, T.; Sugiyama, Y.; Akiyoshi, M.; Matsunaga, T.; Kimura, Y. *Org. Process Res. Dev*. **2017**, *21*, 1925. (b) de Souza, G. F. P.; von Zuben, T. W. Salles Jr., A. G. *ACS Sustainable Chem. Eng*. **2017**, *5*, 8439.
10. Chai, Z.; Zhu, Y.-M.; Yang, P.-J.; Wang, S.; Wang, S.; Liu, Z.; Yang, G. *J. Am. Chem. Soc.* **2015**, *137*, 10088.
11. Sengoden, M.; Bhowmick, A.; Punniyamurthy, T. *Org. Lett.* **2017**, *19*, 158.
12. Crespin, L.; Biancalana, L.; Morack, T.; Blakemore, D. C.; Ley, S. V. *Org. Lett*. **2017**, *19*, 1084.
13. Han, Y.-F.; Gao, Z.-H.; Zhang, C.-L.; Ye, S. *Org. Lett.* **2020**, *22*, 8396
14. Pradhan, S.; Chauhan, N.; Shahi, C. K.; Bhattacharyya, A.; Ghorai, M. K. *Org. Lett.* **2020**, *22*, 7903.
15. Li, Z.; Zhang, H.; Yu, S. *Org. Lett.* **2019**, *21*, 4754.
16. Li, Z.; Tang, M.; Hu, C.; Yu, S. *Org. Lett.* **2019**, *21*, 8819.
17. Stankovic, S.; D'hooghe, M.; Catak, S.; Eum, H.; Waroquier, M.; Speybroeck, V. V.; Kimpe, N. D.; Ha, H.-J. *Chem. Soc. Rev*. **2012**, *41*, 643.
18. (a) Tanner, D. *Angew. Chem. Int. Ed*. **1994**, *33*, 599. (b) Li, Z.; Fernández, M.; Jacobsen, E. N. *Org. Lett*. **1999**, *1*, 1611. (c) Xu, Y.; Lin, L.; Kanai, M.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc*. **2011**, *133*, 5791.
19. (a) Gandeepan, P.; Koeller, J.; Ackermann, L. *ACS Catal*. **2017**, *7*, 1030. (b) Luo, H.; Xie, Q.; Sun, K.; Deng, J.; Xu, L.; Wangand, K.; Luo, X. *RSC Adv*. **2019**, *9*, 18191. (c) Xie, W.; Li, B.; Wang, B. *J. Org. Chem*. **2016**, *81*, 396. (d) Zou, Y.; Melvin, J. E.; Gonzales, S. S.; Spafford, M. J.; Smith, A. B., III. *J. Am. Chem. Soc*. **2015**, *137*, 7095. (e) Han, C.; Fu, Z.; Guo, S.; Fang, X.; Lin A.; Yao, H. *ACS Catal*. **2019**, *9*, 4196.
20. (a) De, P. B.; Atta, S.; Pradhan, S.; Banerjee, S.; Shah, T. A.; Punniyamurthy, T. *J. Org. Chem*. **2020**, *85*, 4785.

1.6 HPLC Chromatograms



Peak Results

	RT	% Area
1	22.568	50.17
2	31.121	49.83



Peak Results

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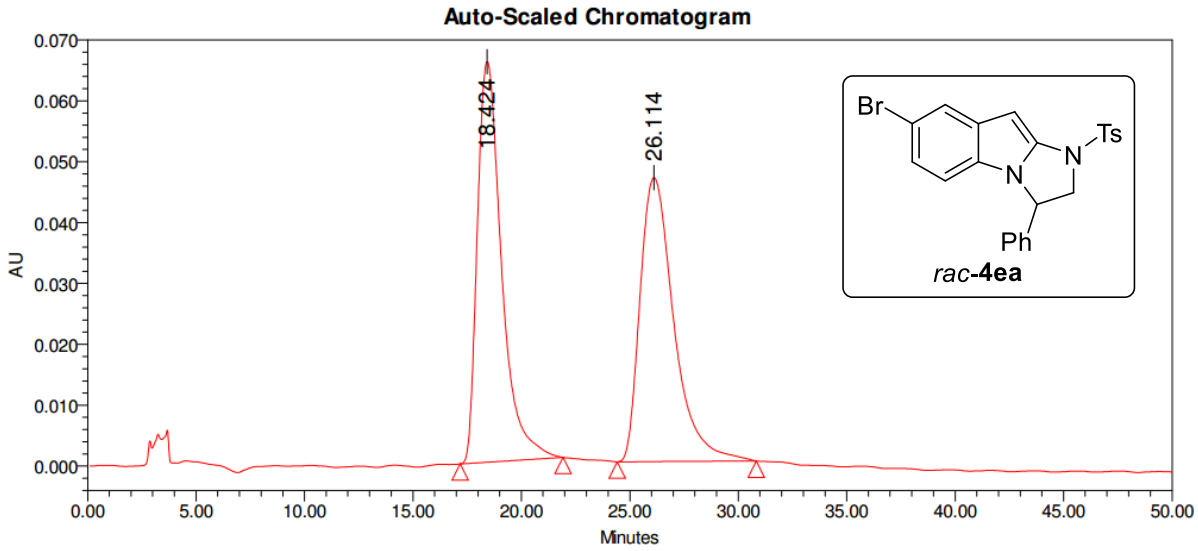

Peak Results

	RT	% Area
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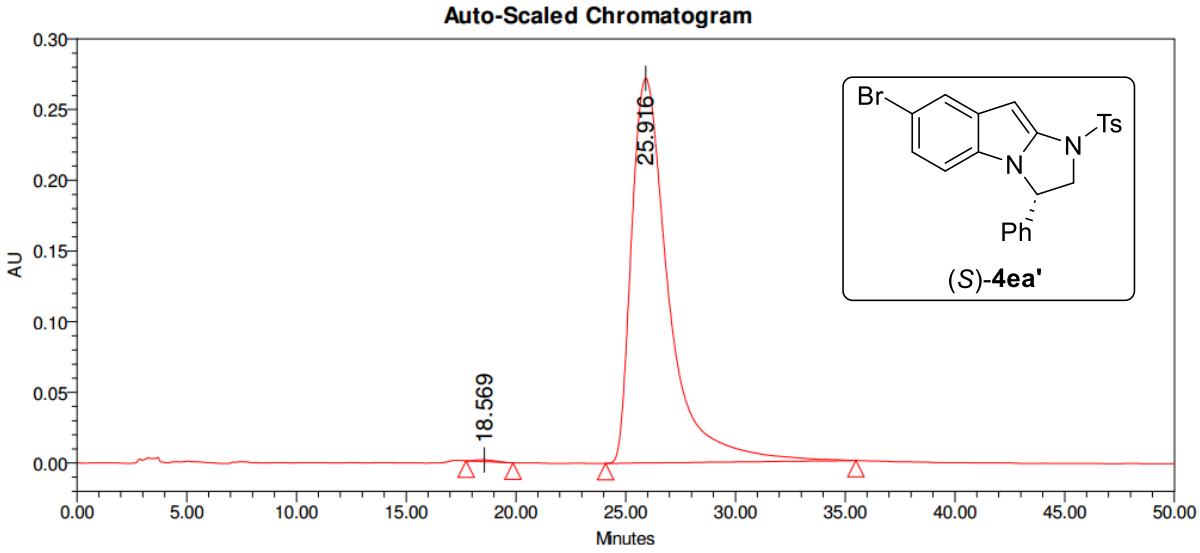

Peak Results

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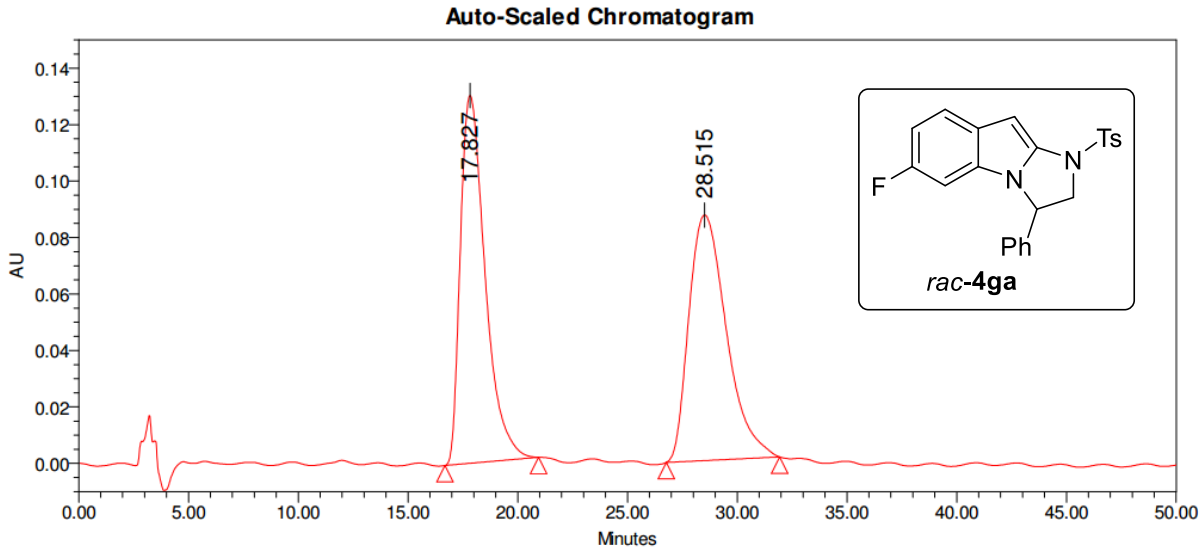

Peak Results

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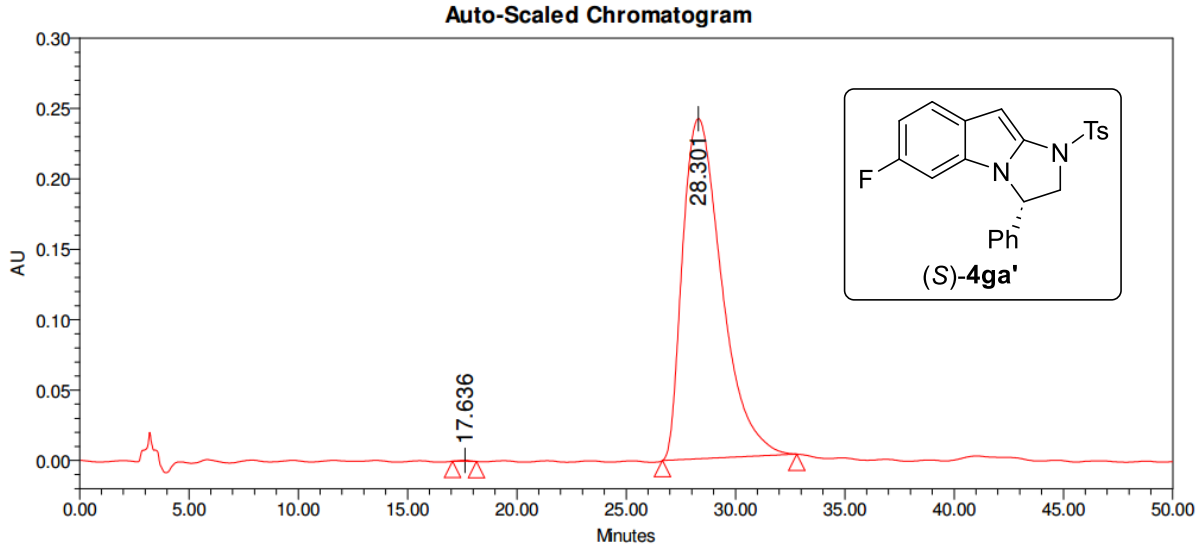

Peak Results

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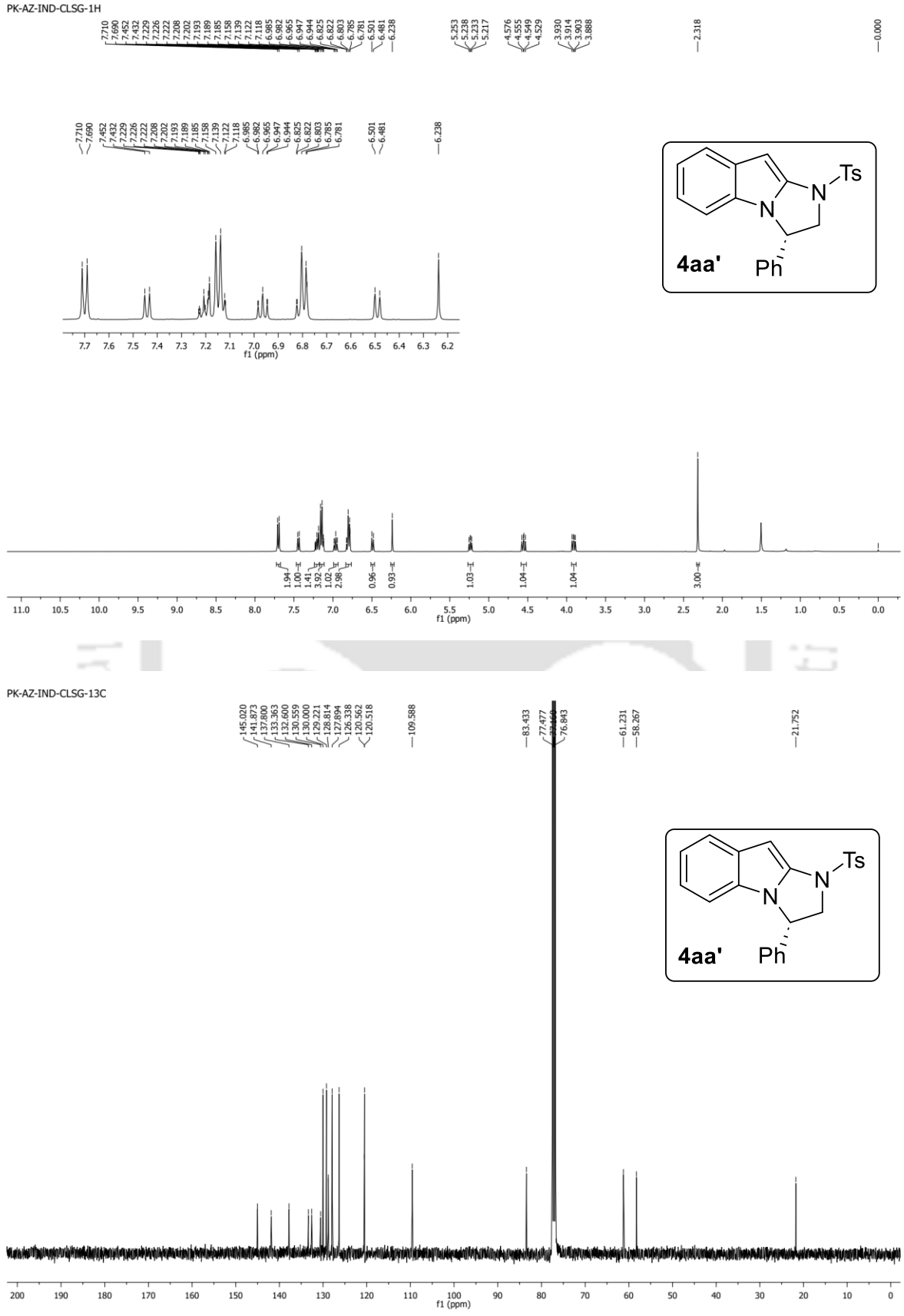
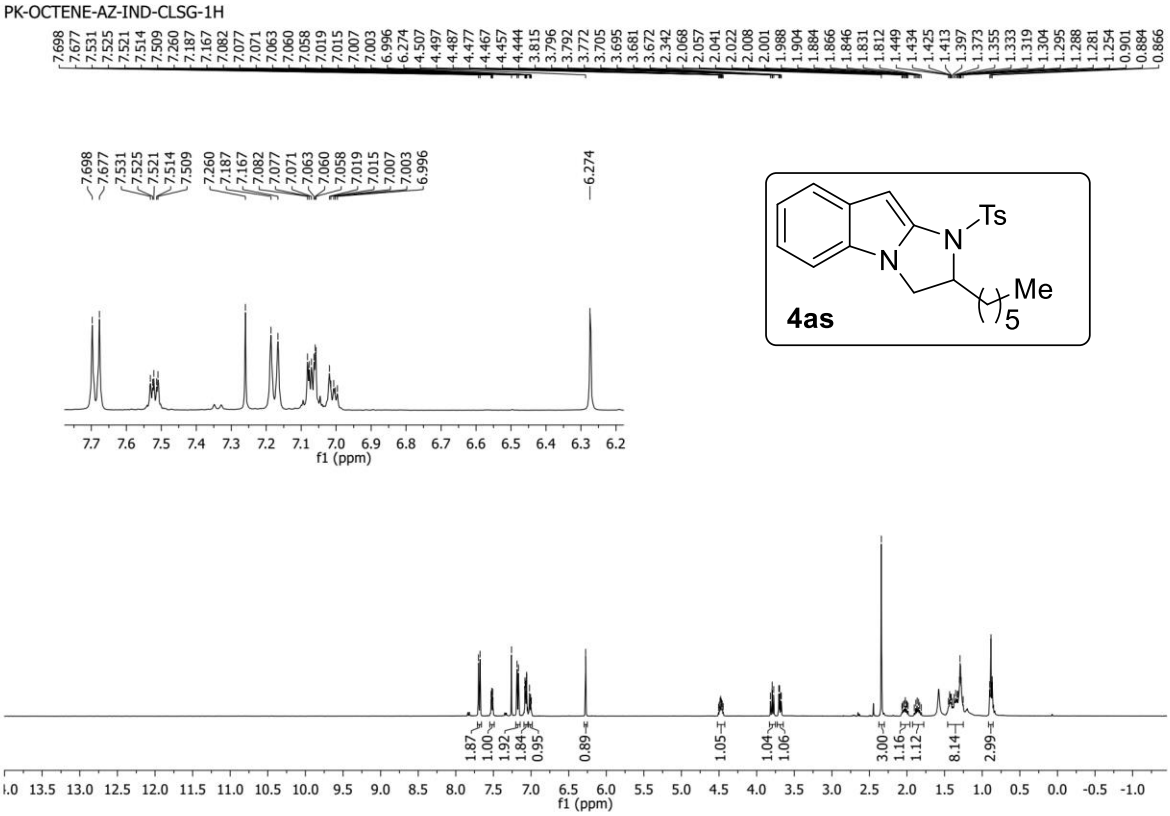
2	28.301	99.91

1.7 Selected NMR Spectra



PK-OCTENE-AZ-IND-CLSG-1H



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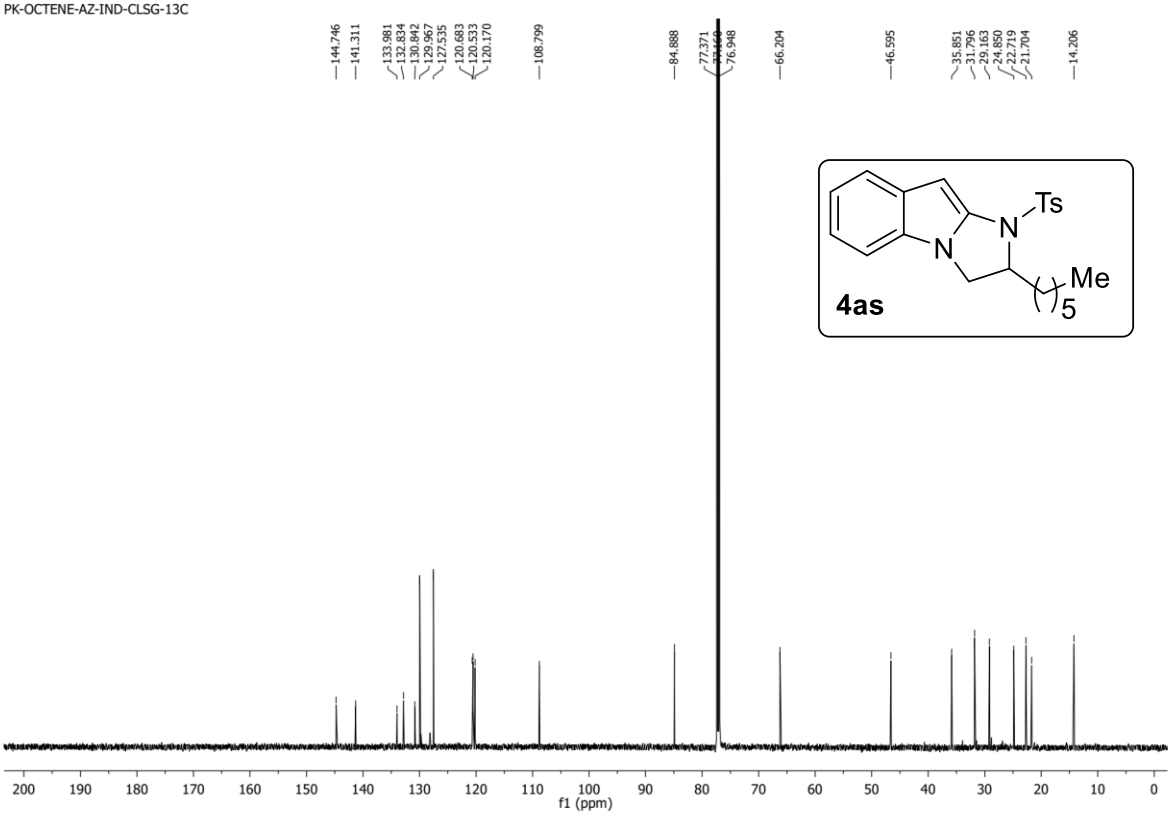

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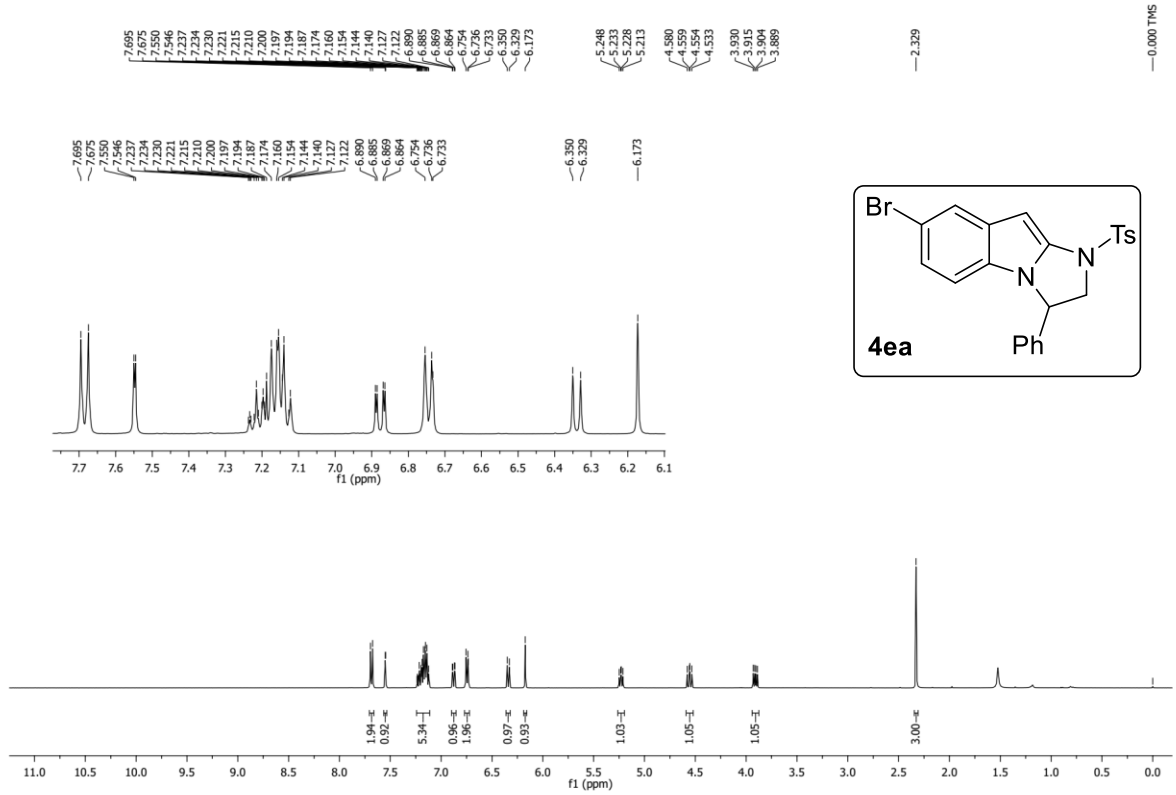

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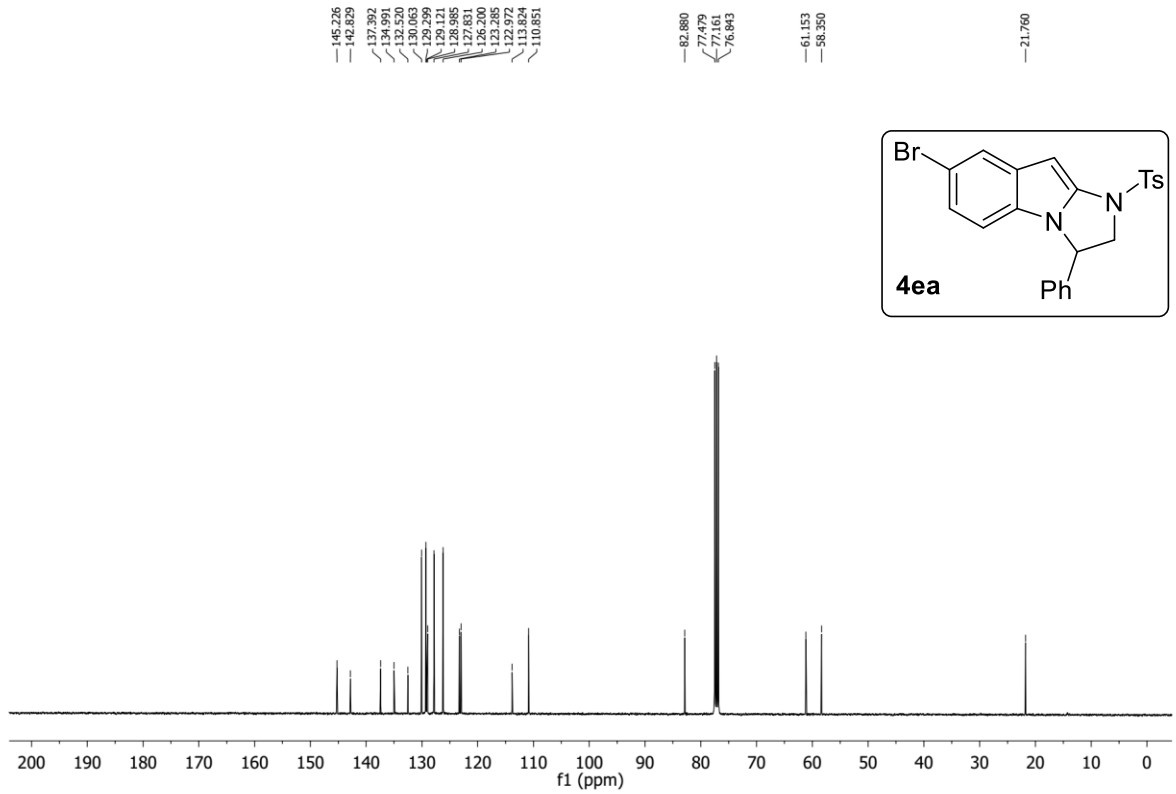
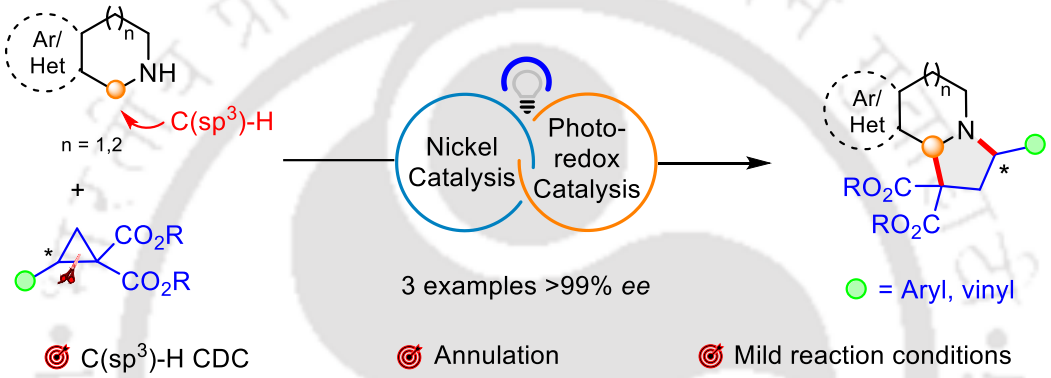


Chapter II

Stereospecific Coupling of Donor-Acceptor Cyclopropanes with Cyclic Secondary Amines



Chem. Commun. **2022**, *58*, 8670.

Chapter II

Stereospecific Coupling of Donor-Acceptor Cyclopropanes with Cyclic Secondary Amines

In recent years, there has been a notable surge of interest in donor-acceptor cyclopropanes (DACs) as versatile building blocks for the construction of three-carbon atom structural frameworks.[1] The inherent high ring strain (27.5 kcal/mol)[2] associated with DACs, coupled with vicinal donor-acceptor (DA) motifs, has paved the way for diverse synthetic transformations, facilitating the construction of both carbo- and heterocycles.[3-5] Concurrently, the cross-dehydrogenative coupling (CDC) of C-H bonds has emerged as a promising synthetic tool for C-C bond formation under oxidative conditions. Notable progress in these reactions has been achieved using transition-metals such as Pd and Rh to activate C-H bonds, along with stoichiometric amounts of peroxo-compounds as oxidants to complete the catalytic cycle.[6] Recently, visible-light photocatalysis has been explored as a complementary strategy to transition-metal-catalyzed CDC of C-H bonds, offering environmental and economic advantages.[7] This approach has gained attention for its potential to address limitations associated with certain substrates. Pyrrolidine alkaloids, characterized by privileged structural frameworks, have garnered significant interest due to their compelling biological and medicinal properties (Figure 1).[8] Alkaloids featuring the pyrrolidine tricyclic core structure, for instance, exhibit anti-viral, DPPH radical scavenging, anti-tumor, and antileishmanial properties.[8] Consequently, the development of effective synthetic methods for constructing pyrrolidine structural scaffolds holds considerable value. This chapter delineates an efficient annulative coupling of DACs with cyclic secondary amines, resulting in the formation of pyrrolotetrahydroisoquinoline structural frameworks under mild reaction conditions. The synthetic protocol involves a tandem C-N and C-C bond formation, combining the stereospecific ring opening of DACs by the abundant first-row $Ni(OTf)_2$ and the annulation employing visible light eosin Y for CDC of two distinct C(sp^3)-H bonds. Notably, these reactions proceed under neutral conditions, demonstrating potential for scale-up synthesis.

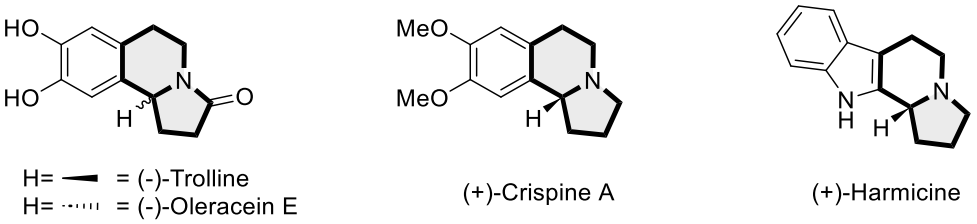
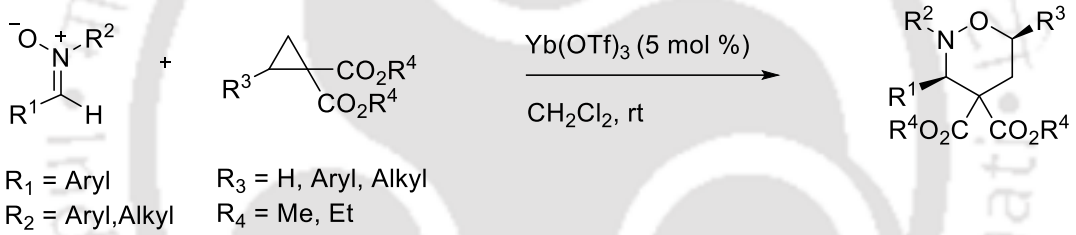


Figure 1. Examples of Biologically Important Fuzed Pyrrolidine Derivatives.

2.1 Literature Study

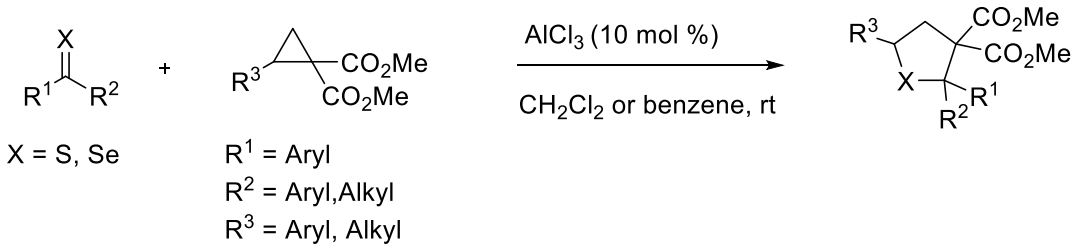
2.1.1 Metal-Catalyzed Annulation of DACs

Kerr and co-workers revealed the reaction between a nitrone and a cyclopropane, leading to the production of a tetrahydro-1,2-oxazine. Furthermore, they demonstrated the application in the synthesis of the [3.3.1]-bicyclic core (Scheme 1).[9] A variety of nitrone and cyclopropane engaged effectively in the reaction, resulting in high yields.



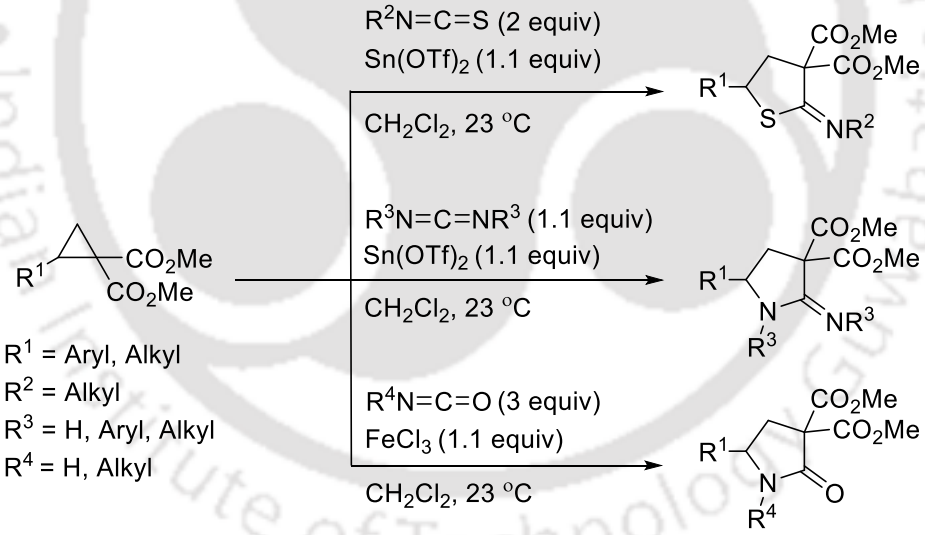
Scheme 1. Yb-Catalyzed (3 + 2)-Dipolar Cycloaddition

Werz Group achieved a Lewis acid-catalyzed reactions of 2-substituted cyclopropane 1,1-dicarboxylates with thioketones. These reactions result in highly substituted tetrahydrothiophenes with two adjacent quaternary carbon atoms. These compounds were obtained in a stereospecific manner under mild conditions and yielded high results when using $AlCl_3$ as the Lewis acid. Additionally, an intramolecular approach was successfully implemented to gain access to sulfur-bridged [n.2.1]-bicyclic ring systems. The conversion of selenoketones, which are the heavier analogues, under similar conditions resulted in the formation of various tetrahydroselenophenes. (Scheme 2).[10]



Scheme 2. Al-Catalyzed Annulation of DACs with Thio- and Selenoketones

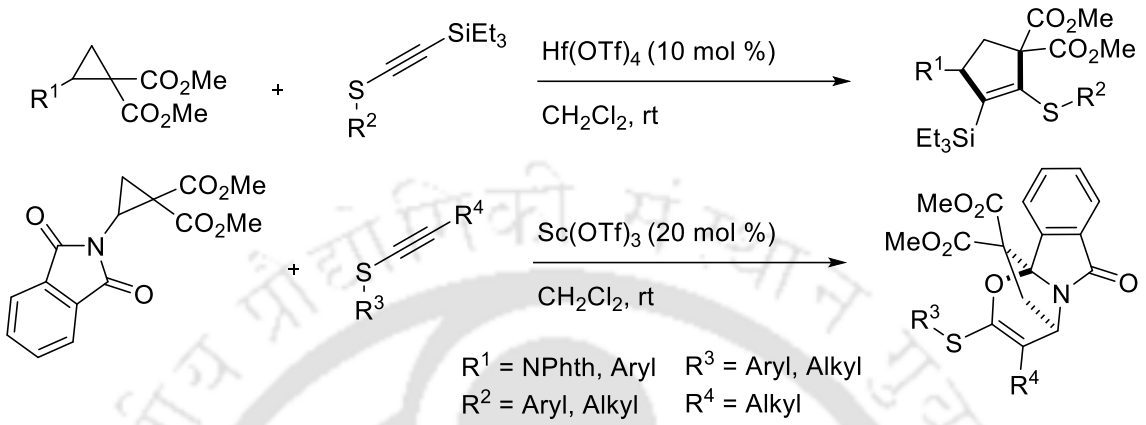
Stolz group introduced a sophisticated method to synthesize thioimidates through a (3 + 2)-annulation process. This process involved the reaction of aryl- or vinyl-substituted cyclopropane 1,1-dicarboxylates with isothiocyanates. The reaction necessitated stoichiometric quantities of $Sn(OTf)_2$ as the Lewis acid. It was found to be effective for allyl and aliphatic isothiocyanates, but aryl isothiocyanates did not exhibit reactivity (Scheme 3).[11] The authors demonstrated the insertion of isocyanates and carbodiimides under slightly altered conditions, resulting in the corresponding five-membered heterocycles.



Scheme 3. Metal-Catalyzed (3+2) Cycloadditions of DACs with Heterocumulenes

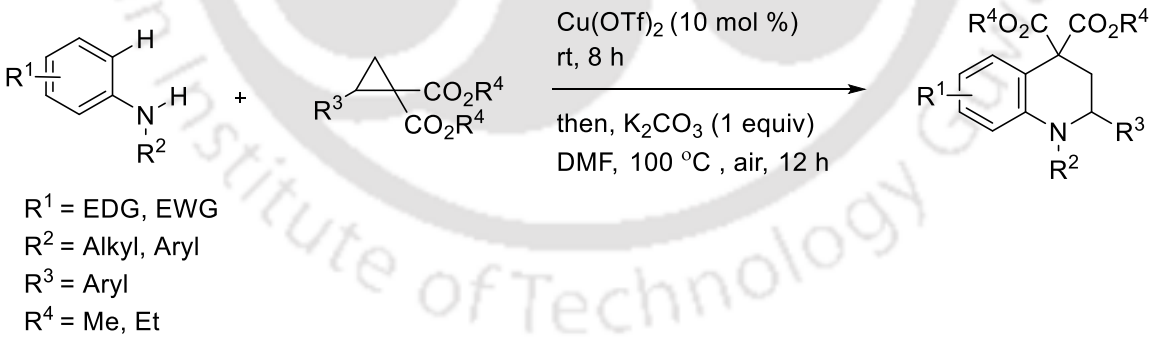
Waser and co-workers presented a new annulation reaction of thioalkynes with phthalimide-substituted donor-acceptor cyclopropanes (Scheme 4).[12] These reactions provide access to highly substituted cyclopentenes and polycyclic ring systems. When silyl-thioalkynes are used under $Hf(OTf)_4$ catalysis, (3 + 2)-annulation with donor-acceptor cyclopropanes occurs, yielding 1-thio-cyclopenten-3-amines. Conversely, an unprecedented polycyclic compound is formed with alkyl-

thioalkynes under $Sc(OTf)_3$ catalysis, through a reaction pathway that directly involves the phthalimide group. Both transformations proceed in good yields and tolerate a wide variety of functional groups.



Scheme 4. Lewis acid-Catalyzed (3+2) Cycloadditions of DACs with Thioalkynes

Our group reported an aerobic Cu-catalyzed tandem reaction involving *N*-alkyl anilines and donor-acceptor cyclopropanes (Scheme 5).[13] This reaction is utilized for the synthesis of tetrahydroquinolines through a sequential process involving stereospecific ring opening and oxidative cyclization. The catalyst serves a dual function, acting both as a Lewis acid and a redox catalyst.

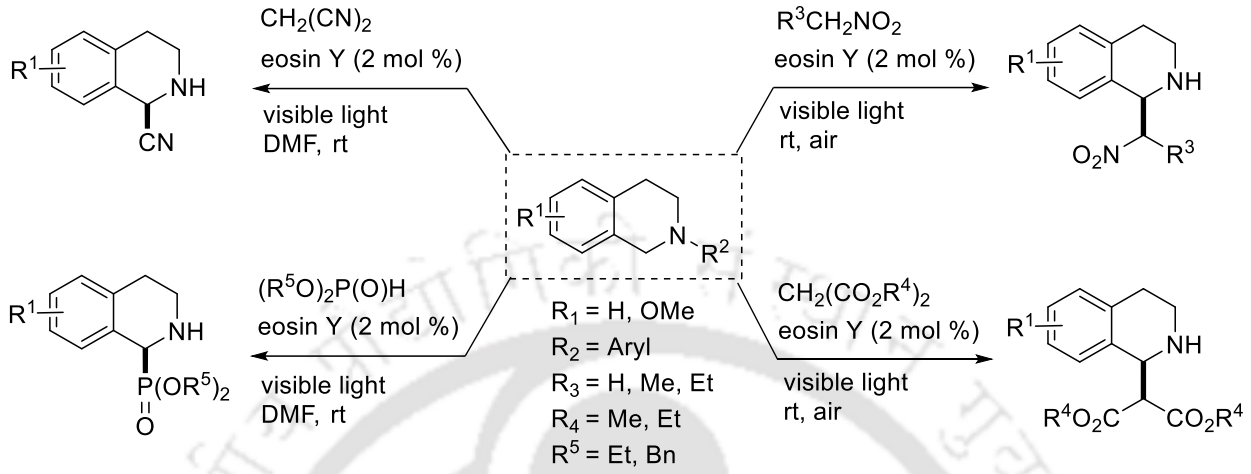


Scheme 5. Cu-Catalyzed Oxidative Cyclization of DACs with *N*-alkylanilines

2.1.2 Cross-Dehydrogenative Coupling of Cyclic Secondary Amines

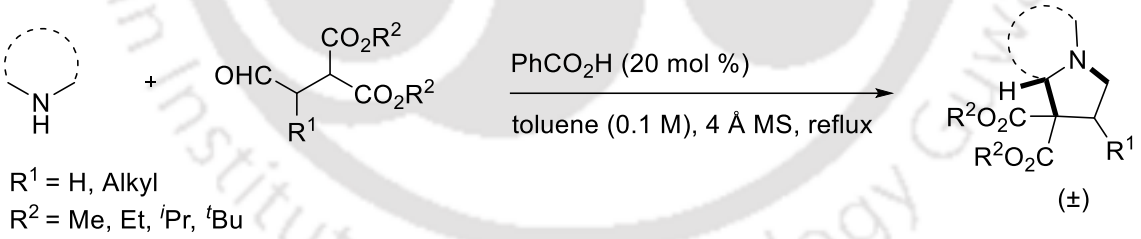
König and co-workers reported eosin Y catalyzed visible light-mediated coupling of C(sp^3)–H bonds that are adjacent to the nitrogen atom in tetrahydroisoquinoline derivatives, and this occurs without the need for an external oxidant. Various pronucleophiles, including nitroalkanes, dialkyl

malonates, malononitrile, and dialkyl phosphonates, were employed. This process demonstrates a practical and environmentally friendly approach (Scheme 6).[14]



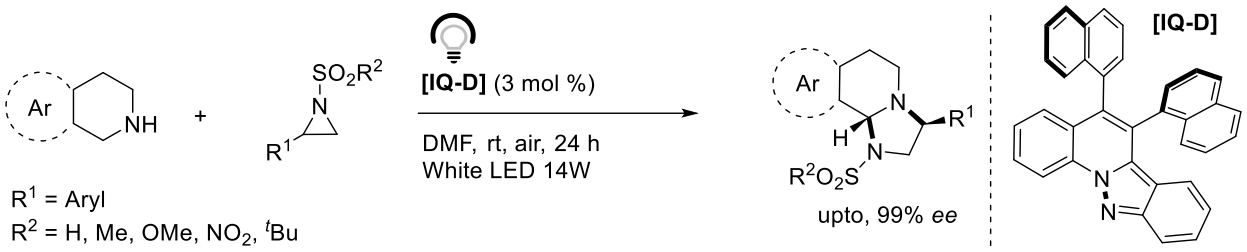
Scheme 6. Eosin Y-Catalyzed Visible Light Oxidative C–C and C–P bond Formation

Seidel and co-workers developed a redox-annulations of cyclic amines with 2-(2-oxoethyl)malonates in the presence of catalytic quantities of benzoic acid (Scheme 7).[15] This reaction sequence results in the formation of a fully saturated five-membered ring. Furthermore, it enables the synthesis of structures that bear a close resemblance to the natural products crispine A and harmicine.



Scheme 7. Redox-Annulations of Cyclic Amines with 2-(2-Oxoethyl)Malonates.

Our group reported a tandem ring opening and an oxidative amination of aziridines with cyclic secondary amines (Scheme 8).[16] This protocol delivered a stereospecific synthesis of imidazolidines. The reaction is facilitated by quinoline-based IQ-D photoredox catalysts under visible light conditions.



Scheme 8. Visible Light Photoredox (3+3) Cycloaddition of Aziridines with Cyclic Secondary Amines.

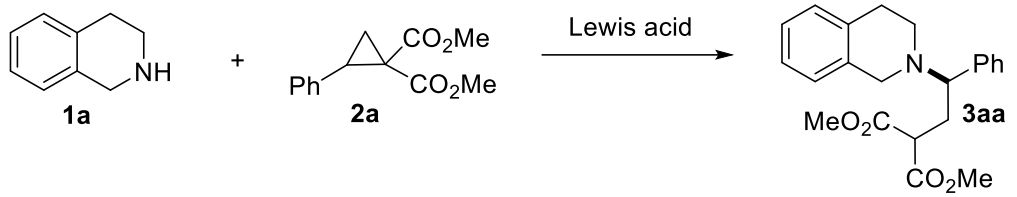
2.2 Present Study

Herein a robust $Ni(OTf)_2$ and visibile light assisted eosin Y catalysis annulative coupling of DACs with cyclic secondary amines has been accomplished. This methodology delivers a straightforward route for incorporating cyclic secondary amines into pyrrolidines backbone with broad scope and functional group diversity. First, the optimization of the ring-opening of DAC **2a** was performed using tetrahydroisoquinoline (THIQ)[17] **1a** as the test substrates in the presence of Lewis acids and solvents at varied temperature (Table 1). To our delight, the reaction occurred to give **3aa** in 91% yield when the substrates were stirred with 5 mol % $Ni(OTf)_2$ at 80 °C in toluene. In a set of Lewis acids screened, $Bi(OTf)_3$, $Sc(OTf)_3$, $Yb(OTf)_3$, $Cu(OTf)_2$ and $Ni(OTf)_2$, the latter gave the best result. Toluene was the solvent of choice, whereas 1,4-dioxane, DMF and 1,2- dichloroethane gave inferior results. Decreasing the reaction temperature (70 °C) led to drop in the yield. Control experiment confirmed that the reaction was unsuccessful in the absence of Lewis acid.

The CDC of **3aa** was then investigated using photocatalysis under visible light (Table 2). Gratifyingly, the reaction occurred to produce **4aa** in 90% yield as a 1.2:1 mixture of diastereomers when the substrate was reacted with 2 mol % eosin Y in DMF at room temperature. Reactions using rose Bengal, $Ru(bpy)_3Cl_2$ and $Ru(bpy)_3(PF_6)_2$, yielded inferior results (entries 1-4). Similar results observed using MeOH, CH_2Cl_2 and CH_3CN as the solvents (entries 5-7). In addition, decreasing the catalyst loading (1%) led to furnish **3aa** in 50% yield (entry 8). Control experiment revealed that no reaction was obtained in the absence of the visible light (entry 9).

Having the optimized conditions, the scope of the procedure was investigated for the reaction of a series of DACs **2a-o** with **1a** as the standard substrate (Table 3). In these reactions, the ring opening product **3** was (without isolation) subjected to the CDC to afford the heterocycles **4** in good yields. The substrate with substitution at the 2-position of the aryl ring with bromo group **2b**

Table 1. Optimization of Stereospecific Ring Opening of **2a** with **1a**[a]

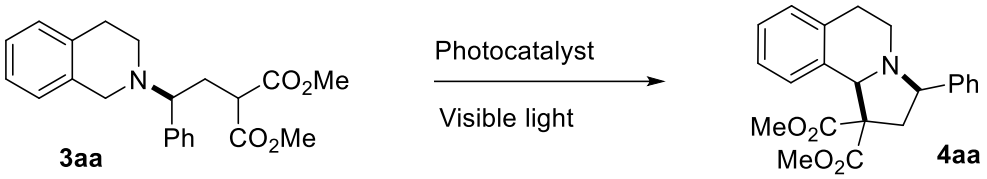


Entry	Lewis acid	Solvent	Yield (%)[b]
1	$Cu(OTf)_2$	$(CH_2Cl)_2$	23
2	$Sc(OTf)_3$	$(CH_2Cl)_2$	n.d.
3	$Bi(OTf)_3$	$(CH_2Cl)_2$	n.d.
4	$Ni(OTf)_2$	$(CH_2Cl)_2$	69
5	$Yb(OTf)_3$	$(CH_2Cl)_2$	35
6	$Ni(OTf)_2$	Toluene	91
7	$Ni(OTf)_2$	DMF	24
8	$Ni(OTf)_2$	1,4-Dioxane	32
9[c]	$Ni(OTf)_2$	Toluene	84
10	-	Toluene	n.d.

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), Lewis acid (5 mol %), solvent (2 mL), 6 h, 80 °C. [b]Isolated yield. [c]Reaction temperature 70 °C. n.d. = not detected.

delivered a trace amount of **4ab** may be due to the steric effect of bulky bromo group, while **2c** having methyl substituent afforded **4ac** in 58% yield. Further, the substrates with bromo **2d** and trifluoromethyl **2e** groups at the 3-position reacted to furnish **4ad** and **4ae** in 69% and 63% yield, respectively. Similar results obtained with the substrates containing bromo **2f**, fluoro **2g**, methoxy **2h**, nitro **2i**, phenyl **2j** and *tert*-butyl **2k** groups at the 4-position of aryl ring, delivering **4af-ak** in 62-75% yields. The substrates containing bulky 2-naphthyl **2l** and pyryl **2m** groups were amenable to produce **4al** and **4am** in 73% and 75% yields, respectively. The structure of **4al** was determined using a single crystal X-ray analysis (CCDC 2163965). Moreover, the substrate bearing 1,1-diester variant **2n** underwent reaction to afford **4an** in 78% yield, whereas vinyl cyclopropane **2o** reacted to give **4ao** in 45% yield.

Table 2. Optimization of the Reaction Conditions for Anuulation[a]

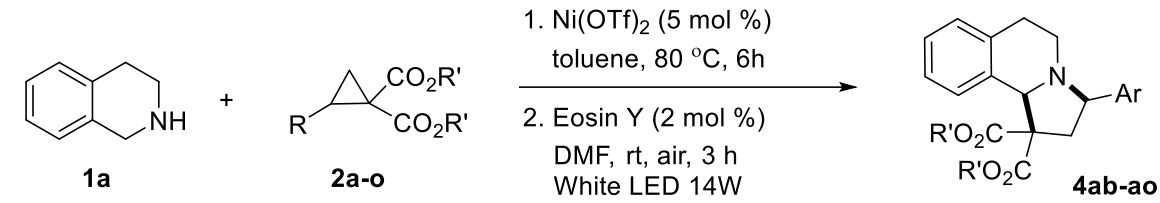


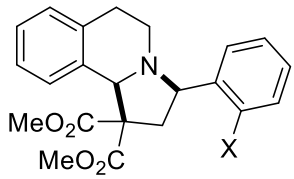
Entry	Photocatalyst	Solvent	Yield (%)[b]	d.r.
1	Rose Bengal	DMF	trace	-
2	Eosin Y	DMF	90	1.2:1
3	$Ru(bpy)_3Cl_2$	DMF	trace	-
4	$Ru(bpy)_3(PF_6)_2$	DMF	33	3:1
5	Eosin Y	MeOH	trace	-
6	Eosin Y	CH_2Cl_2	trace	-
7	Eosin Y	CH_3CN	23	4:1
8[c]	Eosin Y	DMF	50	1.1:1
9[d]	Eosin Y	DMF	n.d.	-

[a]Reaction conditions: **3aa** (0.2 mmol), photocatalyst (2 mol %), solvent (1 mL), white LED (14 W), air, rt, 3 h. [b]Isolated yield. [c]Eosin Y (1 mol %) used. [d]Dark condition. n.d. = not detected

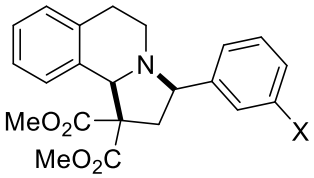
The reaction condition was further extended to the coupling of diverse amines **1b-h** with **2a** as the standard substrate (Table 4). The substrates bearing 5-bromo **1b**, 5-nitro **1c**, 6-bromo **1d** and 6,7-dimethoxy **1e** substituents underwent reaction to afford the target heterocycles **4ba-ea** in 56-72% yields. Further, the reaction of tetrahydro-1*H*-benzo[*b*]azepine **1f** and thiophene fused **1g** occurred to give **4fa** and **4ga** in 63% and 68% yields, respectively, whereas piperidine **1h** underwent reaction to produce the ring opening product, which showed no annulation to afford **4ha**. These results suggest that the reaction conditions can be utilized for the substrates with functional group diversities.

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

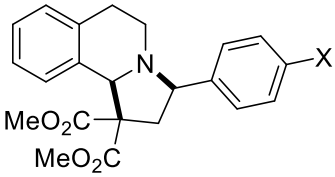




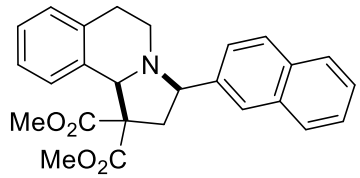
X= Br, **4ab**, trace
= Me, **4ac**, 58%, (d.r. 1:1)



X= Br, **4ad**, 69%, (d.r. 1:1)
= CF_3, **4ae**, 63%, (d.r. 1.1:1)

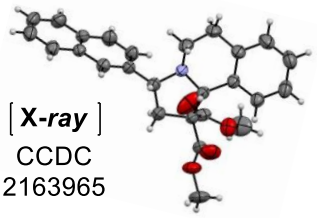


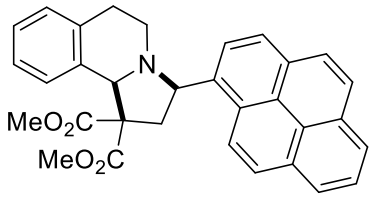
X = Br, **4af**,73% (d.r. 1.1:1)
= F, **4ag**, 74%, (d.r. 1:1)
= OCH_3, **4ah**, 69%, (d.r. 1:1)
= NO_2, **4ai**, 62%, (d.r. 1.1:1)
= Ph, **4aj**, 72% (d.r. 1.2:1)
= ^{t}Bu, **4ak**, 75% (d.r. 1:1)



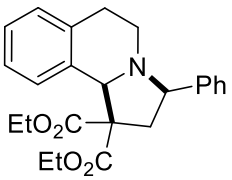
4al, 79%, (d.r. 1.2:1)

≡

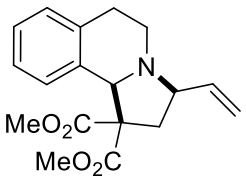




4am, 75%, (d.r. 1.2:1)



4an,78%, (d.r. 1.1:1)



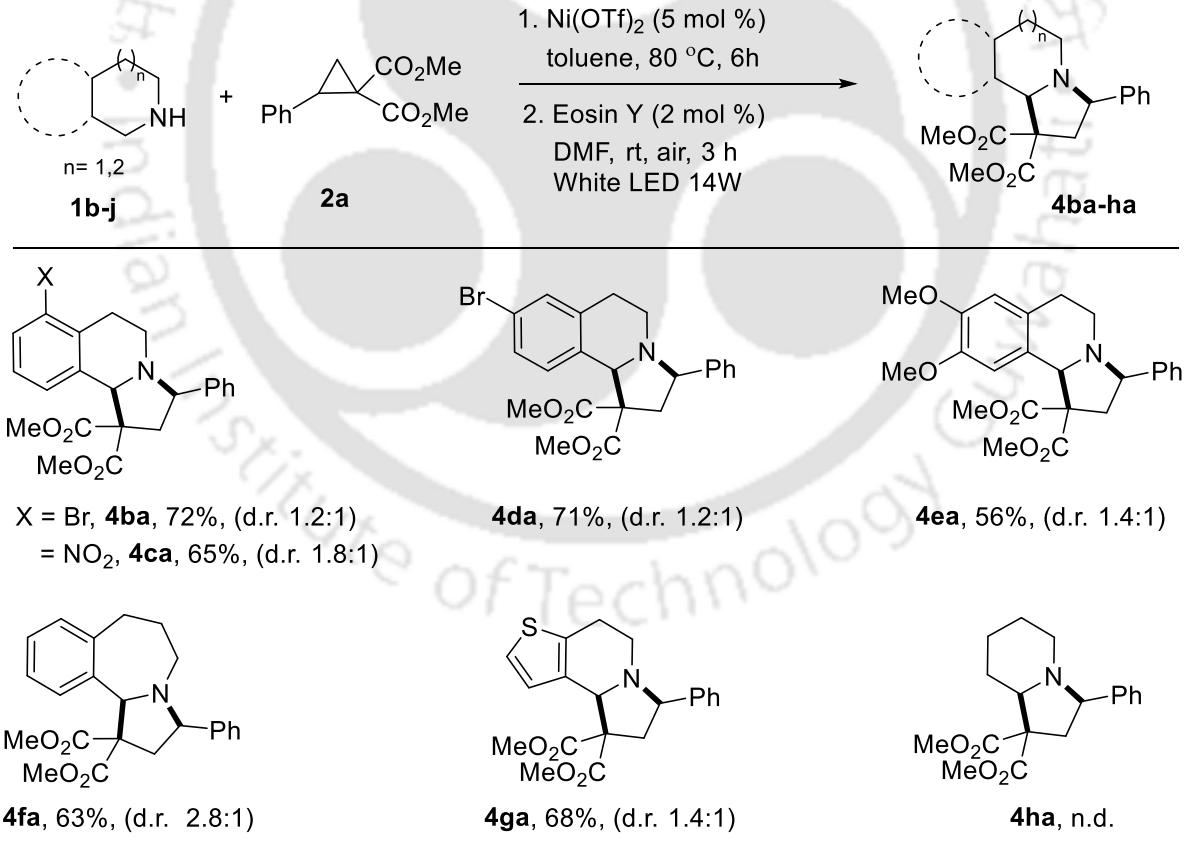
4ao, 45% d.r. 2.4:1

[a]Reaction conditions: **1a** (0.2 mmol), **2b-o** (0.24 mmol), $Ni(OTf)_2$ (5 mol %), toluene (2 mL), 80 ºC, 6 h; eosin Y (2 mol %), DMF (1 mL), white LED (14 W), air, rt, 3 h. [b]Isolated yield.

To descry the stereospecificity, the reaction of the amines was examined with DACs (*R*)-**2a'** and (*S*)-**2a''** as representative examples (Table 5). The reaction of (*R*)-**2a'** with **1c** and **1g** afforded **4ca'** and **4ga'**, respectively, in >99% ee. Likewise, the DAC (*S*)-**2a''** reacted with **1c** to furnish **4ca''** in >99% ee. These results suggest that the ring opening of DAC with amine occurs enantiospecifically.

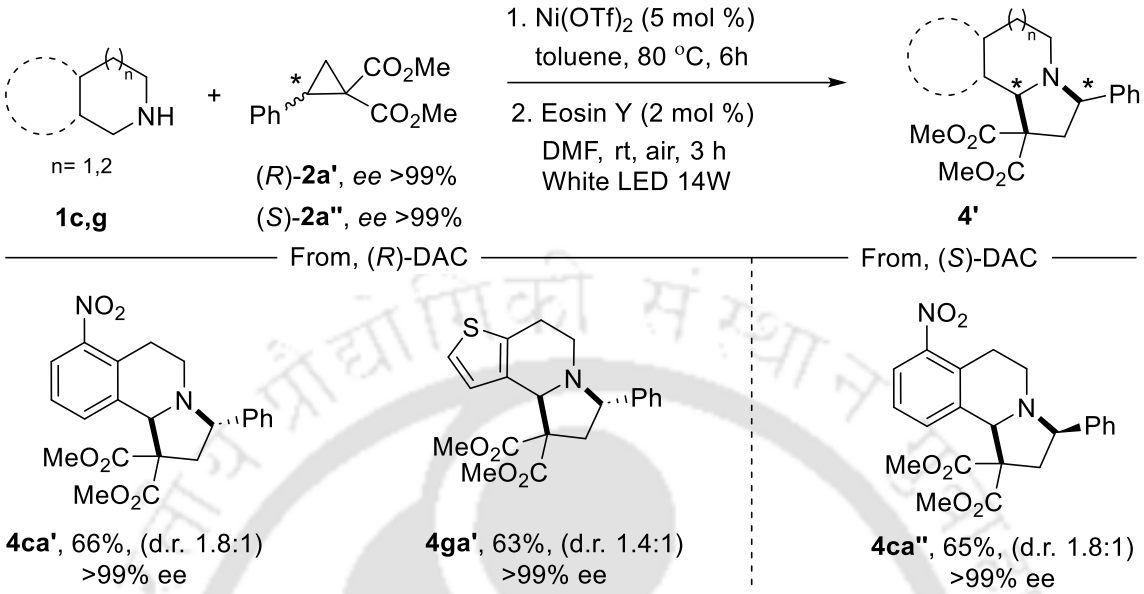
To gain insight into the reaction pathway, the reaction of **3aa** was pursued in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) as the radical scavengers (Scheme 9). The rate of reaction was slowed, affording **4aa** in 23% and15% yields, respectively. Further, the mass analysis of the reaction mixture revealed the formation a BHT-adduct **5**. These results suggest that the CDC involves a radical pathway. These experimental results suggest that $Ni(OTf)_2$ with DACs **2** can facilitate the stereospecific ring-opening to produce **3** (Scheme 10). The visible light with eosin Y can produce the excited eosin Y*, which can oxidize **3** by single electron transfer (SET) to give the radical cation **I**. Eosin Y radical ion with oxygen can generate O_2 radical ion that can react with radical cation **I** to afford intermediate **II**.[18] Further, electron transfer from **II** can provide the intermediate **III**. Deprotonation of **III** using HO_2^- can lead to the formation of H_2O_2 and carbanion, which can cyclize to the heterocyclic scaffolds **4**.

Table 4. Substrate Scope of Cyclic Secondary Amines[a,b]

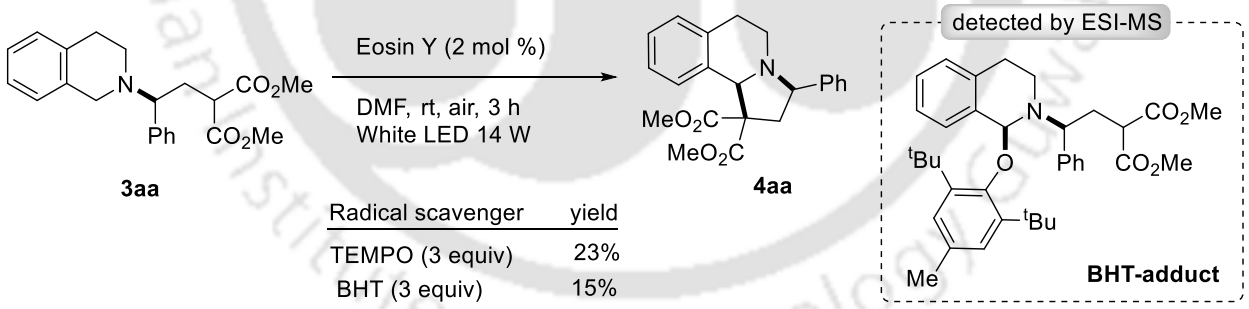


[a]Reaction conditions: **1b-j** (0.2 mmol), **2a** (0.24 mmol), $Ni(OTf)_2$ (5 mol %), toluene (2 mL), 80 °C, 6 h; eosin Y (2 mol %), DMF (1 mL), white LED (14 W), air, rt, 3 h. [b]Isolated yield.

Table 5. Enantiospecific synthesis.[a,b]

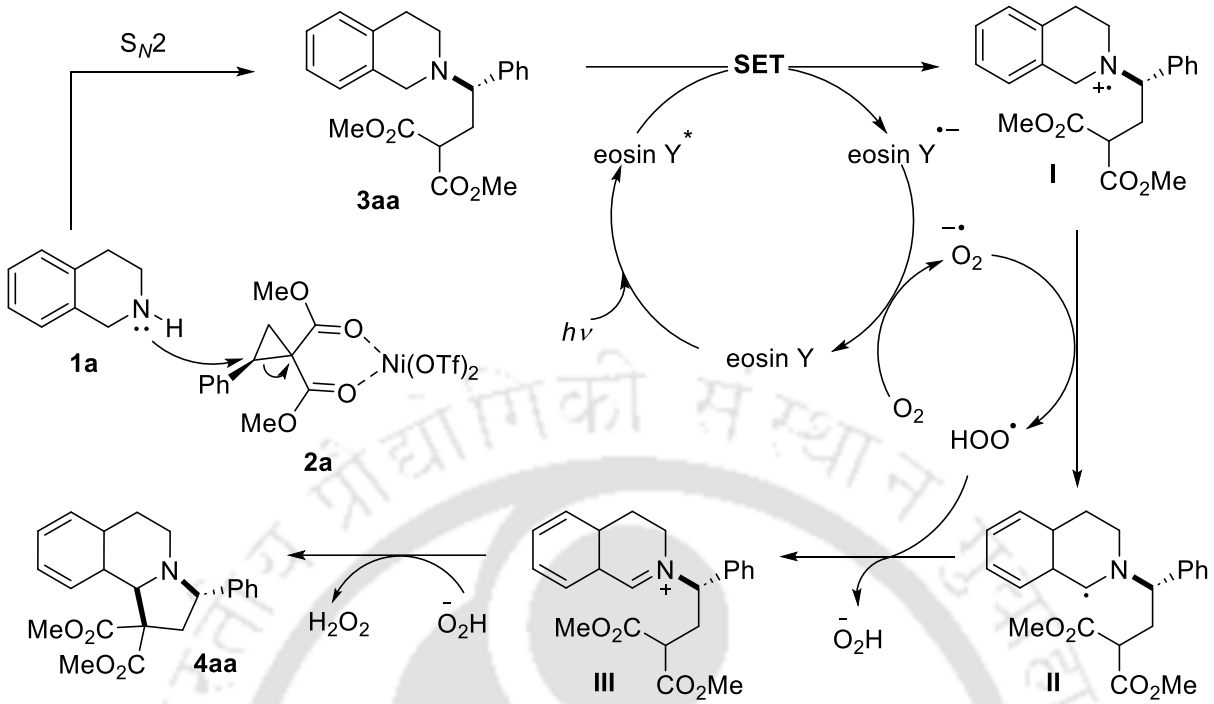


[a]Reaction conditions: **1c/1g** (0.2 mmol), **2a'/2a''** (0.24 mmol), $Ni(OTf)_2$ (5 mol %), toluene (2 mL), 80 °C, 6 h; eosin Y (2 mol %), DMF (1 mL), white LED (14 W), air, rt, 3 h. [b]Isolated yield.

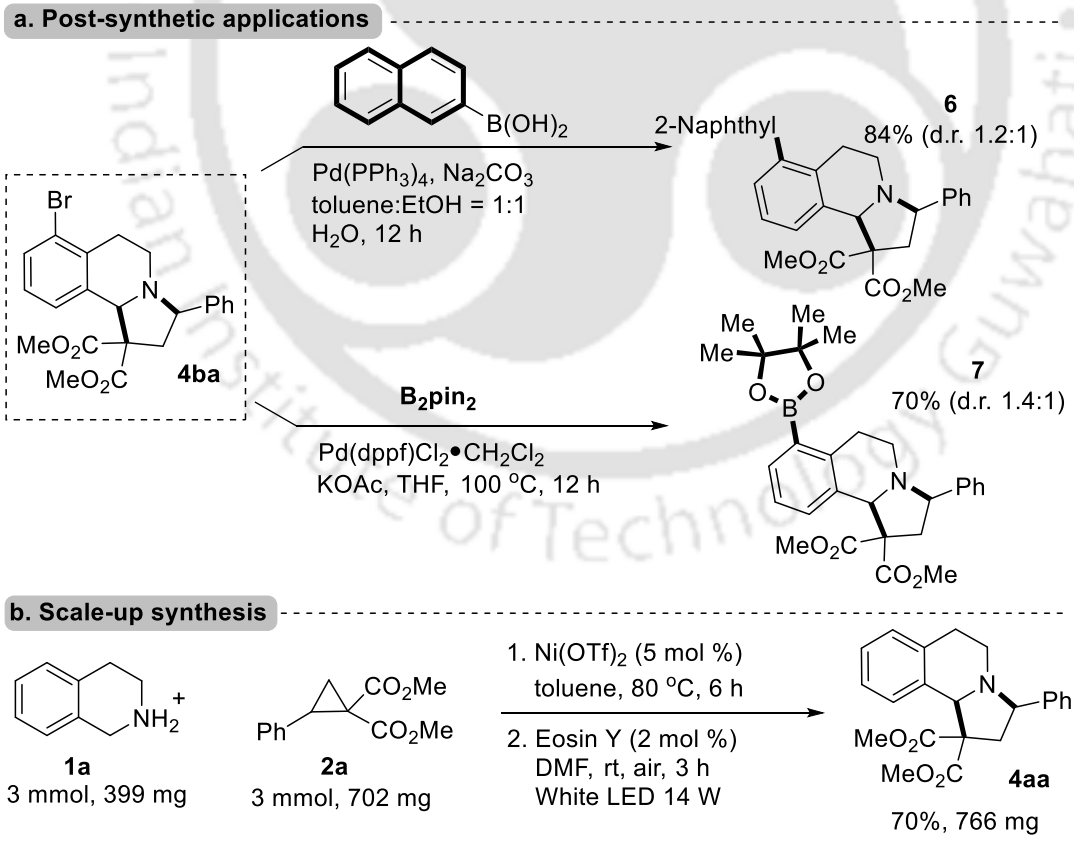


Scheme 9. Radical Scavenger Experiments

The products can be further converted to diverse scaffolds. For examples, the Pd-catalyzed C-C cross-coupling of **4ba** with boronic acid afforded **6** in 84% yield, while the Pd-catalyzed borylation using B_2pin_2 gave **7** in 70% yield (Scheme 11a). Further, the scale-up of the procedure was studied using **1a** and **2a** as the representative examples (Scheme 11b). The reaction occurred to produce **4aa** in 70% yield.



Scheme 10. Plausible Reaction Pathway



Scheme 11. Synthetic Applications and Scale-Up Synthesis

To summarize, a reaction sequence has been accomplished merging a Ni-catalyzed ring-opening of DACs with secondary cyclic amines and a visible light eosin Y catalyzed CDC of C(sp^3)-H bonds to yield pyrrolotetrahydroisoquinoline scaffolds. The merging of nickel/visible light organophotoredox catalysis for the annulation, substrate scope, scale-up and mild conditions are the important practical features.

2.3 Experimental Section

General Information. 1,2,3,4-Tetrahydroisoquinoline (95%), N-Benzylmethylamine (97%), $Cu(OTf)_2$ (98%), $Sc(OTf)_3$ (99%), $Bi(OTf)_3$, $Ni(OTf)_2$ (96%), $Yb(OTf)_3$ (99.99%), $Zn(OTf)_2$ (98%), Eosin Y (99%), rose bengal (95%), $[Ru(bby)_3]Cl_2•6H_2O$ (99.95%) and $Ru(bpy)_3(PF_6)_2$ (97%) were purchased from Aldrich and used as received. K_2CO_3, K_3PO_4, DABCO and NEt_3 were procured from Merck and used as received. Cyclopropanes, 2,3,4,5-tetrahydro-1*H*-benzo[c]azepine and N-Phenylbenzylamine were prepared according to the reported procedure. Merck silica gel G/GF254 plates used for analytical TLC. Rankem silica gel (60-120 mesh) utilized for column chromatography. NMR spectra were recorded with Bruker Avance III 600, 500 and 400 MHz spectrometers using $CDCl_3$ as solvent and Me_4Si as an internal standard. Chemical shifts (δ) and spin-spin coupling constant (*J*) are reported in ppm and in Hz, respectively, and other data are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, dd = doublet of doublets. Melting points were determined using a Büchi B-540 apparatus and are uncorrected. FT-IR spectra were collected on Perkin Elmer IR spectrometer. Q-Tof ESI-MS instrument (model HAB 273) was used for recording mass spectra. Optical rotations were determined using Rudolph autopol I polarimeter. HPLC analysis was carried out using Waters-2489 with Daicel Chiralcel AD-H column using *iso*-propanol and hexane as an eluent. 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 *SHELXL-16* (Göttingen, Germany).

Synthesis of 3aa. Amine **1a** (0.2 mmol, 26 mg), cyclopropane **2a** (0.24 mmol, 47 mg) and $Ni(OTf)_2$ (5 mol %, 3.5 mg) were stirred in toluene (2 mL) at 80 ºC for 6 h. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. The reaction mixture was cooled to room temperature and purified on silica gel column chromatography using ethyl acetate and hexane as an eluent.

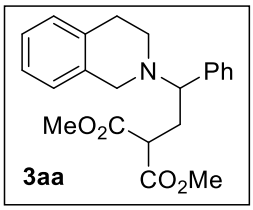
Synthesis of 4aa. Compound **3aa** (0.2 mmol, 74 mg) and eosin Y (2 mol %, 2.7 mg) were stirred in DMF (0.5 mL) for 3 h under 14 W white LED at ambient temperature. The progress of the reaction was monitored by TLC using ethyl acetate and hexane. The reaction was treated with CH_2Cl_2 (20 mL) and washed with water (5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave the residue that was purified over silica gel column chromatography using ethyl acetate and hexane as eluent to afford **4aa**.

General Procedure for the Synthesis of 4. Amine **1** (0.2 mmol), cyclopropane **2** (0.24 mmol) and $Ni(OTf)_2$ (5 mol %, 3.5 mg) were stirred in toluene (2 mL) at 80 ºC for 6 h. The reaction was cooled to room temperature and passed through a short pad of silica gel to remove the Ni-catalyst and toluene using hexane followed by 2% ethyl acetate in hexane. Evaporation of the solvent gave a residue that was reacted with eosin Y (2 mol %, 2.7 mg) in DMF (0.5 mL) for 3 h under 14 W white LED at ambient temperature. The progress of the reaction was monitored by TLC using ethyl acetate and hexane. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave the residue that was purified on silica gel column chromatography using ethyl acetate and hexane as eluent to afford **4**.

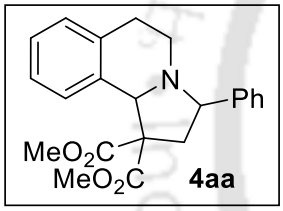
Enantiospecific Annulative Coupling. Amine **1c/1g** (0.2 mmol) and cyclopropane **2a′/2a″** (0.24 mmol) were subjected to the above-described reaction conditions. The *ee* was determined using chiral HPLC analysis.

Scale-up Synthesis of 4aa. Amine **1a** (3 mmol, 399 mg), cyclopropane **2a** (3.6 mmol, 842 mg) and $Ni(OTf)_2$ (5 mol %, 53 mg) were stirred in toluene (2 mL) at 80 ºC for 6 h. The reaction mixture was passed through a short pad of silica gel. Evaporation of the solvent gave a residue which was reacted with eosin Y (2 mol %, 41 mg) in DMF (5 mL) for 3 h under 14 W white LED at ambient temperature. The progress of the reaction was monitored by TLC using ethyl acetate and hexane. The reaction was then treated with CH_2Cl_2 (50 mL) and washed with water (3 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave the residue that was purified over silica gel column chromatography using ethyl acetate and hexane as eluent to afford **4aa**.

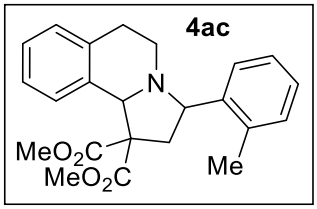
2.4 Characterization Data



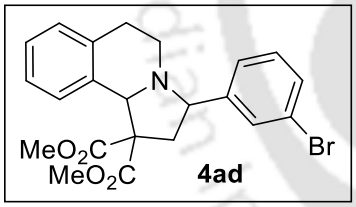
Dimethyl 2-(2-(3,4-dihydroisoquinolin-2(1H)-yl)-2-phenylethyl)malonate 3aa. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.47; thick liquid; yield 91% (66 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.0 Hz, 2H), 7.29-7.25 (m, 3H), 7.06-7.01 (m, 3H), 6.98-6.95 (m, 1H), 3.67-3.65 (m, 4H), 3.63-3.60 (m, 1H), 3.55 (s, 3H), 3.53-3.47 (m, 2H), 2.86-2.81 (m, 4H), 2.53-2.48 (m, 1H), 2.31-2.26 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.17, 170.11, 137.7, 135.3, 134.6, 128.7, 128.6, 128.3, 127.7, 126.7, 126.0, 125.5, 67.4, 52.6, 52.47, 52.45, 50.0, 47.6, 31.5, 29.4; FT-IR (Neat) 2951, 1749, 1731, 1495, 1434, 1346, 1196, 1150, 1099, 1029 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{26}NO_4$: 368.1856, found: 368.1868.



Dimethyl 3-phenyl-2,3,6,10b-tetrahydropyrrolo[2,1-a]isoquinoline-1,1(5H) dicarboxy-late 4aa. Analytical TLC on silica gel, 1:49 ethyl acetate/hexane; R_f = 0.37; thick liquid; yield 90% (66 mg); 1.2:1 mixture of diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.44 (m, 4.51H), 7.41 (d, *J* = 7.5Hz, 1H), 7.35 (q, *J* = 7.0 Hz, 3.80H), 7.30-7.25 (m, 1.81H), 7.14-7.04 (m, 5.66H), 5.60 (s, 0.80H), 4.67-4.64 (m, 0.82H), 4.31 (s, 1H), 3.86 (s, 3H), 3.78 (s, 2.41H), 3.53 (t, *J* = 8.5 Hz, 1H), 3.44 (s, 3H), 3.12 (s, 2.42H), 3.06-3.00 (m, 1H), 2.92-2.87 (m, 2.75H), 2.81-2.70 (m, 3.91H), 2.65 (d, *J* = 15.5 Hz, 1H), 2.39 (d, *J* = 15.5 Hz, 0.80H), 2.32-2.27 (m, 1H), 2.20 (dd, *J* = 12.5, 10.5 Hz, 0.83H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 172.0, 171.0, 170.9, 143.0, 141.4, 137.3, 135.8, 135.6, 134.4, 128.7, 128.67, 128.63, 128.5, 128.27, 128.24, 127.7, 127.5, 127.4, 127.0, 126.5, 126.2, 125.6, 125.0, 70.1, 66.9, 65.9, 65.6, 65.5, 61.8, 52.9, 52.8, 52.1, 51.9, 46.3, 44.5, 43.7, 43.4, 30.2, 24.7; FT-IR (Neat) 2952, 1731, 1650, 1603, 1495, 1434, 1266, 1215, 1155, 1063, 1031 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{24}NO_4$: 366.1700, found: 366.1703.

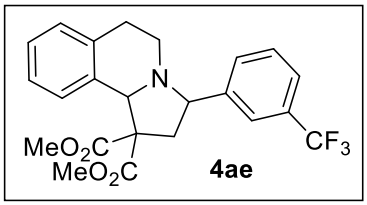


Dimethyl 3-(o-tolyl)-2,3,6,10b-tetrahydropyrrolo[2,1-a]isoquinoline-1,1(5H)-dicarboxy-late 4ac. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane; R_f = 0.45; thick liquid; yield 58% (43 mg); 1:1 mixture of diastereomers; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 16.2, 7.8 Hz, 2H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 7.2 Hz, 1H), 7.17-7.15 (m, 2.11H), 7.11-7.02 (m, 9.74H), 6.98 (d, *J* = 7.2 Hz, 1H), 5.58 (s, 1H), 4.90-4.87 (m, 1H), 4.27 (s, 1H), 3.80 (s, 3H), 3.75 (t, *J* = 8.4 Hz, 1H), 3.70 (s, 3H), 3.35 (s, 3H), 3.04 (s, 3H), 2.91-2.89 (m, 1H), 2.83-2.65 (m, 6H), 2.60-2.55 (m, 2H), 2.34 (s, 3H), 2.29 (s, 3H), 2.26-2.20 (m, 2H), 1.91 (t, *J* = 12.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.0, 171.9, 171.1, 170.7, 140.8, 139.3, 137.3, 136.3, 136.2, 135.7, 135.6, 134.4, 130.3, 130.2, 128.7, 128.4, 128.3, 127.1, 126.99, 126.90, 126.8, 126.6, 126.59, 126.51, 126.2, 125.9, 125.5, 125.0, 69.8, 65.5, 65.1, 62.3, 61.7, 61.2, 53.0, 52.9, 52.2, 51.9, 46.4, 44.5, 42.1, 41.6, 30.1, 24.4, 19.5, 19.3; FT-IR (Neat) 2952, 1731, 1646, 1603, 1458, 1434, 1266, 1211, 1151, 1152, 1083 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{26}NO_4$: 380.1856, found: 380.1856.

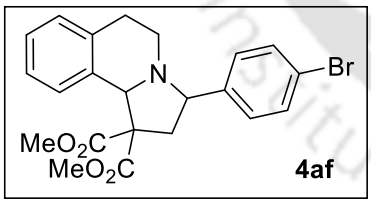


Dimethyl 3-(3-bromophenyl)-2,3,6,10b-tetrahydropyrrolo[2,1-a]isoquinoline-1,1(5H)-dicarboxylate 4ad. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane; R_f = 0.41; thick liquid; yield 69% (61 mg); 1:1 mixture of diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 12.0 Hz, 2H), 7.39 (d, *J* = 7.0 Hz, 1H), 7.35-7.30 (m, 5H), 7.14 (q, *J* = 8.0 Hz, 2H), 7.06-7.00 (m, 5H), 6.98 (d, *J* = 7.5 Hz, 1H), 5.50 (s, 1H), 4.57-4.54 (m, 1H), 4.23 (s, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 3.43 (t, *J* = 8.0 Hz, 1H), 3.37 (s, 3H), 3.03 (s, 3H), 2.99-2.95 (m, 1H), 2.84-2.77 (m, 3H), 2.71-2.68 (m, 2H), 2.64 (d, *J* = 8.0 Hz, 2H), 2.59 (d, *J* = 16 Hz, 1H), 2.33 (d, *J* = 15 Hz, 1H), 2.27-2.22 (m, 1H), 2.07 (dd, *J* = 12.5, 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 171.7, 170.9, 170.6, 145.8, 144.1, 137.2, 135.6, 135.3, 134.1, 131.2, 130.8, 130.6, 130.33, 130.32, 130.2, 128.7, 128.5, 128.3, 127.0, 126.8, 126.6, 126.3, 126.1, 125.6, 125.1, 122.8, 122.7, 69.9, 66.1, 65.8, 65.5, 65.2, 61.7, 53.0, 52.9, 52.2, 51.9, 46.4, 44.6, 43.5, 43.2, 30.2,

24.7; FT-IR (Neat) 2952, 1732, 1649, 1601, 1568, 1475, 1434, 1265, 1214, 1154, 1069 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{23}BrNO_4$: 444.0805, found: 444.0809.

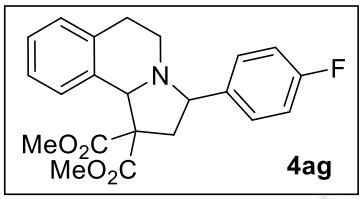


Dimethyl 3-(3-(trifluoromethyl)phenyl)-2,3,6,10b-tetrahydropyrrolo[2,1-a]isoquinoline-1,1(5H)-dicarboxylate 4ae. Analytical TLC on silica gel, 1:13 ethyl acetate/hexane; R_f = 0.48; thick liquid; yield 63% (54 mg); 1.1:1 mixture of diastereomers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.64 (m, 2.92H), 7.61 (d, *J* = 7.6 Hz, 0.90H), 7.47 (t, *J* = 8.0 Hz, 1.92H), 7.43-7.32 (m, 3.93H), 7.09-6.98 (m, 5.90H), 5.53 (s, 0.90H), 4.67-4.63 (m, 0.94H), 4.28 (s, 1H), 3.80 (s, 3H), 3.71 (s, 2.70H), 3.54 (t, *J* = 8.4 Hz, 1H), 3.38 (s, 3H), 3.04 (s, 2.69H), 3.01-2.94 (m, 1H), 2.84-2.70 (m, 5H), 2.66 (d, *J* = 8.4 Hz, 2H), 2.60-2.56 (m, 1.18H), 2.34-2.25 (m, 2.19H), 2.08 (dd, *J* = 12.8, 10.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 171.7, 170.9, 170.6, 144.4, 142.9, 137.2, 135.6, 135.2, 134.0, 131.5, 131.2 (J_{C-F} = 6.6 Hz), 130.8, 129.2, 129.1, 128.8, 128.5, 128.3, 127.0, 126.6, 126.4, 125.7, 125.2, 125.0 (J_{C-F} = 3.8 Hz), 124.6 (J_{C-F} = 3.4 Hz), 124.4, 124.1, 123.0 (J_{C-F} = 5.7 Hz), 69.9, 66.2, 65.8, 65.6, 65.3, 61.7, 53.0, 52.9, 52.2, 52.0, 46.4, 44.6, 43.5, 43.2, 30.2, 24.7; FT-IR (Neat) 2954, 1732, 1650, 1603, 1436, 1328, 1267, 1200, 1163, 1122, 1073 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{23}F_3NO_4$: 434.1574, found: 434.1576.

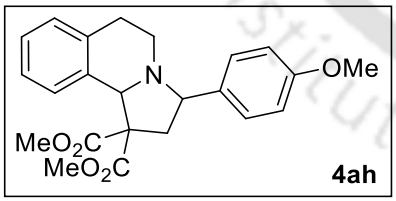


Dimethyl 3-(4-bromophenyl)-2,3,6,10b-tetrahydropyrrolo[2,1-a]isoquinoline-1,1(5H)-dicarboxylate 4af. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane; R_f = 0.42; thick liquid; yield 73% (64 mg); 1.1:1 mixture of diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.37 (m, 5H), 7.33-7.28 (m, 5H), 7.08-7.02 (m, 4H), 7.01-6.97 (m, 2H), 5.51 (s, 0.90H), 4.56-4.53 (m, 1H), 4.24 (s, 1H), 3.79 (s, 3H), 3.71 (s, 2.73H), 3.43 (t, *J* = 8.5 Hz, 1H), 3.36 (s, 3H), 3.03 (s, 2.74H), 2.99-2.92 (m, 1H), 2.82-2.66 (m, 5H), 2.63 (d, *J* = 8.5 Hz, 2H), 2.59-2.55 (m, 1H), 2.32 (d, *J* = 15.0 Hz, 1H), 2.26-2.21 (m, 1H), 2.08-2.03 (m, 1H).^{13}C NMR (150 MHz, $CDCl_3$) δ 172.8, 171.8, 170.9, 170.8, 142.1, 140.6, 137.2, 135.6, 135.2, 134.0,

131.79, 131.71, 129.9, 129.2, 128.7, 128.5, 128.2, 127.0, 126.6, 126.3, 125.6, 125.1, 121.5, 121.1, 69.8, 66.0, 65.7, 65.4, 64.9, 61.6, 53.09, 53.01, 52.3, 52.0, 46.3, 44.4, 43.5, 43.1, 30.1, 24.4; FT-IR (Neat) 2953, 1733, 1646, 1484, 1435, 1263, 1219, 1154, 1072, 1012 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{23}BrNO_4$: 444.0805, found: 444.0803.

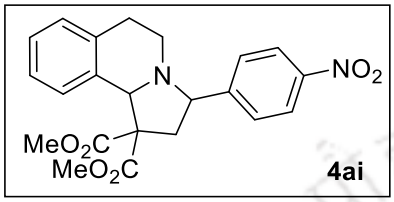


Dimethyl 3-(4-fluorophenyl)-2,3,6,10b-tetrahydropyrrolo[2,1-a]isoquinoline-1,1(5H)-dicarboxylate 4ag. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane; R_f = 0.41; thick liquid; yield 74% (56 mg); 1:1 mixture of diastereomers; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47-7.43 (m, 5H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.16-7.10 (m, 4H), 7.09 (d, *J* = 7.2 Hz, 1H), 7.06-7.02 (m, 5H), 5.59 (s, 1H), 4.65-6.63 (m, 1H), 4.31 (s, 1H), 3.87 (s, 3H), 3.79 (s, 3H), 3.51 (t, *J* = 8.4 Hz, 1H), 3.44 (s, 3H), 3.11 (s, 3H), 3.05-3.00 (m, 1H), 2.92-2.83 (m, 3H), 2.79-2.63 (m, 5H), 2.39 (d, *J* = 15.0 Hz, 1H), 2.32-2.27 (m, 1H), 2.15 (dd, *J* = 12.6, 10.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.9, 171.9, 171.0, 170.9, 163.2 (J_{C-F} = 27 Hz), 161.6 (J_{C-F} = 26.4 Hz), 138.5 (J_{C-F} = 2.25 Hz), 137.2, 137.1 (J_{C-F} = 3.15 Hz), 135.7, 135.4, 134.1, 129.7 (J_{C-F} = 7.8 Hz), 128.9 (J_{C-F} = 7.95 Hz), 128.7, 128.5, 128.2, 127.0, 126.5, 126.3, 125.6, 125.0, 115.5 (J_{C-F} = 13.05 Hz), 115.4 (J_{C-F} = 12.9 Hz), 69.8, 66.0, 65.7, 65.4, 64.7, 61.6, 53.0, 52.9, 52.3, 52.0, 46.2, 44.3, 43.6, 43.3, 30.2, 24.4; FT-IR (Neat) 2953, 1731, 1649, 1603, 1509, 1435, 1266, 1222, 1156, 1083 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{23}FNO_4$: 384.1606, found: 384.1611.

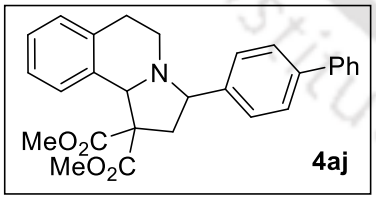


Dimethyl 3-(4-methoxyphenyl)-2,3,6,10b-tetrahydropyrrolo[2,1-a]isoquinoline-1,1(5H)-dicarboxylate 4ah. Analytical TLC on silica gel, 1:14 ethyl acetate/hexane; R_f = 0.38; thick liquid; yield 69% (54 mg); 1:1 mixture of diastereomers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.36 (m, 1H), 7.34-7.30 (m, 5H), 7.07-6.96 (m, 6H), 6.83-6.80(m, 4H), 5.51 (s, 1H), 4.54-4.50 (m, 1H), 4.22 (s, 1H), 3.79 (s, 3H), 3.73 (d, *J* = 2.0 Hz, 6H), 3.71 (s, 3H), 3.40 (t, *J* = 8.4 Hz, 1H), 3.36 (s, 3H), 3.03 (s, 3H), 2.98-2.91 (m, 1H), 2.85-2.77 (m, 3H), 2.72-2.54 (m, 5H), 2.31-2.27 (m, 1H), 2.23-2.16 (m, 1H), 2.12 (dd, *J* = 13.2, 10.4

Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.0, 172.1, 171.1, 171.0, 159.2, 159.0, 137.2, 135.8, 135.5, 134.6, 134.3, 133.2, 129.3, 128.9, 128.7, 128.59, 128.50, 128.1, 126.9, 126.5, 126.2, 125.5, 125.0, 113.9, 69.9, 66.2, 65.6, 65.3, 64.7, 61.7, 55.4, 55.3, 53.0, 52.9, 52.2, 51.9, 46.1, 44.1, 43.6, 43.2, 30.1, 24.3; FT-IR (Neat) 2953, 1730, 1646, 1609, 1215, 1434, 1246, 1215, 1116, 1083, 1032 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{26}NO_5$: 396.1805, found: 396.1810.

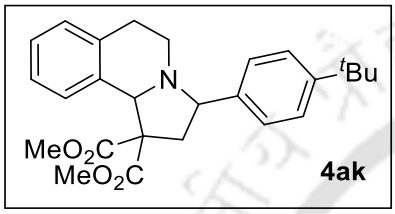


Dimethyl 3-(4-nitrophenyl)-2,3,6,10b-tetrahydropyrrolo[2,1-a]isoquinoline-1,1(5H)-dicarboxylate 4ai. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.36; thick liquid; yield 62% (50 mg); 1.1:1 mixture of diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 8.5, 5.5 Hz, 3.70H), 7.61 (d, *J* = 8.5 Hz, 3.71H), 7.41 (d, *J* = 7.0 Hz, 1H), 7.35 (d, *J* = 7.0 Hz, 1H), 7.10-6.99 (m, 6H), 5.54 (s, 0.90H), 4.74-4.71 (m, 0.90H), 4.32 (s, 1H), 3.80 (s, 3H), 3.71 (s, 2.70H), 3.62 (t, *J* = 8.0 Hz, 1H), 3.37 (s, 3H), 3.05 (s, 2.75H), 3.02-2.95 (m, 1H), 2.79-2.74 (m, 4H), 2.66-2.55 (m, 4H), 2.36-2.29 (m, 2H), 2.07(t, *J* = 11 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 171.4, 170.7, 170.5, 147.8, 147.6, 138.0, 136.9, 135.4, 133.7, 129.0, 128.8, 128.5, 128.3, 128.2, 127.16, 127.11, 126.8, 126.6, 125.8, 125.29, 125.25, 124.0, 123.9, 69.7, 65.83, 65.81, 65.6, 65.4, 61.7, 53.09, 53.01, 52.3, 52.0, 46.5, 44.9, 43.3, 43.0, 30.2, 24.8; FT-IR (Neat) 2951, 1728, 1604, 1519, 1434, 1344, 1267, 1156, 1065, 1034 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{23}N_2O_6$: 411.1551, found: 411.1555.

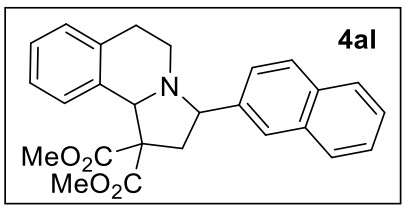


Dimethyl 3-([1,1'-biphenyl]-4-yl)-2,3,6,10b-tetrahydropyrrolo[2,1-a]isoquinoline-1,1(5H)-dicarboxylate 4aj. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane; R_f = 0.38; colorless solid; mp 151-152 °C; yield 72% (63 mg); 1.2:1 mixture of diastereomers; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54-7.47 (m, 12H), 7.40-7.34 (m, 6H), 7.28-7.26 (m, 2H), 7.09-6.98 (m, 6H), 5.56 (s, 0.80H), 4.65-4.63 (m, 0.80H), 4.26 (s, 1H), 3.80 (s, 3H), 3.72 (s, 2.44H), 3.51 (t, *J* = 8.4 Hz, 1H), 3.38 (s, 3H), 3.05 (s, 2.40H), 3.01-2.97 (m, 1H), 2.90-2.85 (m, 3H), 2.76-2.71 (m, 3H), 2.68-2.65 (m, 1H), 2.60 (d, *J* = 15.6 Hz, 1H), 2.33 (d, *J* =

15.6 Hz, 0.83H), 2.28-2.24 (m, 1H), 2.16 (dd, *J* = 12.6, 10.2 Hz, 0.84H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.9, 172.0, 171.0, 170.9, 142.0, 141.07, 141.04, 140.6, 140.5, 137.3, 135.7, 135.5, 134.2, 129.7, 128.87, 128.84, 128.7, 128.6, 128.5, 128.2, 127.8, 127.4, 127.38, 127.33, 127.2, 127.1, 126.9, 126.7, 126.5, 126.2, 125.5, 125.0, 70.0, 66.5, 65.7, 65.5, 65.1, 61.7, 53.0, 52.9, 52.3, 52.0, 46.3, 44.4, 43.6, 43.2, 30.2, 24.4; FT-IR (Neat) 2952, 1729, 1651, 1487, 1433, 1380, 1263, 1212, 1136, 1065, 1040 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{28}NO_4$: 442.2013, found: 442.2013.

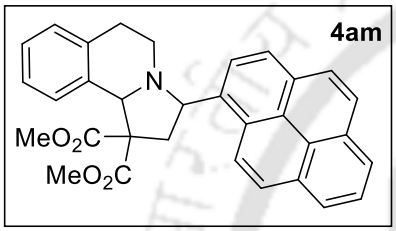


Dimethyl 3-(4-(tert-butyl)phenyl)-2,3,6,10b-tetrahydropyrrolo[2,1-a]isoquinoline-1,1(5H)-dicarboxylate 4ak. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane; R_f = 0.42; thick liquid; yield 75% (63 mg); 1:1 mixture of diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.5 Hz, 1H), 7.33-7.28 (m, 9H), 7.07-6.96 (m, 6H), 5.52 (s, 1H), 4.57-4.54 (m, 1H), 4.23 (s, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 3.44 (t, *J* = 8.5 Hz, 1H), 3.36 (s, 3H), 3.04 (s, 3H), 3.00-2.93 (m, 1H), 2.87-2.81 (m, 3H), 2.73-2.66 (m, 3H), 2.64-2.54 (m, 2H), 2.31-2.27 (m, 1H), 2.23-2.18 (m, 1H), 2.15 (dd, *J* = 13.0, 10.0 Hz, 1H), 1.26 (d, *J* = 3.0 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 172.1, 171.1, 170.9, 150.6, 150.4, 139.8, 138.1, 137.4, 135.8, 135.7, 134.5, 128.7, 128.4, 128.2, 127.8, 127.1, 126.9, 126.4, 126.2, 125.58, 125.53, 125.4, 125.0, 70.1, 66.6, 65.8, 65.6, 65.1, 61.9, 52.9, 52.8, 52.1, 51.9, 46.2, 44.5, 43.6, 43.4, 34.67, 34.64, 31.5, 30.3, 24.6; FT-IR (Neat) 2954, 1732, 1650, 1604, 1434, 1265, 1215, 1155, 1111, 1084, 1018 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{32}NO_4$: 422.2326, found: 422.2326.

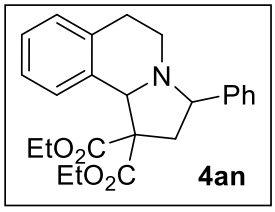


Dimethyl 3-(naphthalen-2-yl)-2,3,6,10b-tetrahydropyrrolo[2,1-a]isoquinoline-1,1(5H)-dicarboxylate 4al. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane; R_f = 0.37; colourless solid; mp 62-63 °C; yield 73% (60 mg); 1.2:1 mixture of diastereomers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 0.91H), 7.79-7.74 (m, 7H), 7.67

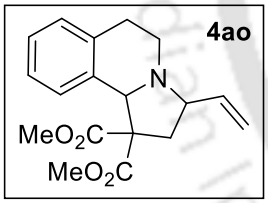
(d, *J* = 8.4 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 0.90H), 7.42-7.35 (m, 5.80H), 7.10-6.98 (m, 6H), 5.60 (s, 0.80H), 4.77-4.73 (m, 0.89H), 4.30 (s, 1H), 3.80 (s, 3H), 3.71 (s, 2.44H), 3.63 (t, *J* = 8.4 Hz, 1H), 3.40 (s, 3H), 3.06 (s, 2.46H), 2.99-2.94 (m, 1H), 2.89-2.82 (m, 3H), 2.78-2.67 (m, 4H), 2.58 (d, *J* = 15.6 Hz, 1H), 2.33-2.20 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 172.0, 171.0, 170.9, 138.9, 137.3, 135.8, 135.5, 134.4, 133.6, 133.48, 133.41, 133.3, 128.8, 128.6, 128.5, 128.4, 128.3, 127.93, 127.91, 127.85, 127.81, 127.3, 127.0, 126.5, 126.4, 126.3, 126.1, 126.0, 125.9, 125.7, 125.6, 125.4, 125.1, 70.1, 67.0, 65.9, 65.76, 65.74, 61.9, 52.9, 52.8, 52.2, 51.9, 46.3, 44.5, 43.5, 43.2, 30.2, 24.7; FT-IR (Neat) 2952, 1732, 1648, 1434, 1267, 1213, 1067 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{26}NO_4$: 416.1856, found: 416.1858.



Dimethyl 3-(pyren-1-yl)-2,3,6,10b-tetrahydropyrrolo[2,1-a]isoquinoline-1,1(5H)-dicarboxylate 4am. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane; R_f = 0.34; thick liquid; yield 75% (73 mg); 1.2:1 mixture of diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 0.73H), 8.47 (d, *J* = 9.5 Hz, 1H), 8.41 (d, *J* = 8.0 Hz, 0.94H), 8.29 (s, 1H), 8.15 (dd, *J* = 8.0, 2.5 Hz, 1.90H), 8.11-8.09 (m, 3.86H), 8.05 (dd, *J* = 9.0, 3.0 Hz, 2H), 8.00-7.96 (m, 4H), 7.94-7.90 (m, 2H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.42 (d, *J* = 6.5 Hz, 1H), 7.12-7.01 (m, 6H), 5.80-5.77 (m, 0.84H), 5.76 (s, 0.80H), 4.59 (s, 1H), 4.52 (s, 1H), 3.84 (s, 3H), 3.68 (s, 2.42H), 3.40 (s, 3H), 3.13 (s, 2.49H), 3.10-3.04 (m, 1.81H), 2.99-2.85 (m, 6H), 2.62 (d, *J* = 16.0 Hz, 1H), 2.37-2.29 (m, 2H), 2.17 (t, *J* = 12.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.0, 171.8, 171.3, 170.9, 137.5, 136.7, 135.8, 135.7, 134.4, 131.55, 131.52, 130.8, 130.7, 130.5, 129.3, 129.2, 128.8, 128.6, 128.5, 127.7, 127.68, 127.65, 127.63, 127.3, 127.0, 126.9, 126.6, 126.4, 126.0, 125.9, 125.68, 125.65, 125.5, 125.26, 125.24, 125.20, 125.09, 125.06, 125.02, 123.8, 123.1, 122.6, 70.2, 65.9, 62.2, 61.7, 53.1, 52.9, 52.3, 52.0, 46.5, 44.9, 43.2, 43.1, 30.2, 24.7; FT-IR (Neat) 2950, 1727, 1643, 1433, 1267, 1200, 1157, 1083, 1066 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{28}NO_4$: 490.2013, found: 490.2017.

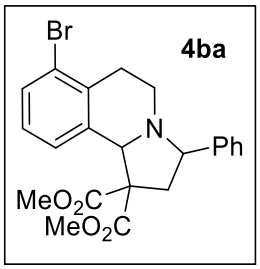


Diethyl 3-phenyl-2,3,6,10b-tetrahydropyrrolo[2,1-a]isoquinoline-1,1(5H)-dicarboxylate 4an. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane; R_f = 0.36; thick liquid; yield 78% (61 mg); 1.1:1 mixture of diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50-7.46 (m, 6H), 7.35-7.32 (m, 3.86H), 7.29-7.25 (m, 2.45H), 7.14-7.03 (m, 5.92H), 5.58 (s, 0.90H), 4.67-4.64 (m, 1H), 4.38-4.20 (m, 5H), 3.96-3.85 (m, 1.82H), 3.68-3.62 (m, 1H), 3.55-3.44 (m, 2H), 3.05-2.98 (m, 1H), 2.93-2.87 (m, 3H), 2.81-2.77 (m, 3H), 2.69-2.61 (m, 1.93H), 2.40 (d, *J* = 15.5 Hz, 1H), 2.32-2.27 (m, 1H), 2.20 (dd, *J* = 13.0, 10.0 Hz, 1H), 1.33 (t, *J* = 7.0 Hz, 2.71H), 1.26 (t, *J* = 7.0 Hz, 3H), 0.91 (t, *J* = 7.0 Hz, 2.71H), 0.85 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.5, 171.5, 170.7, 170.4, 143.1, 141.6, 137.3, 135.8, 135.7, 134.5, 128.63, 128.62, 128.61, 128.48, 128.44, 128.2, 127.7, 127.55, 127.50, 127.4, 126.4, 126.2, 125.6, 124.9, 69.8, 66.7, 65.7, 65.6, 65.3, 61.8, 61.7, 61.6, 61.24, 61.22, 46.1, 44.6, 43.5, 43.4, 30.3, 24.8, 14.2, 14.1, 13.7, 13.5; FT-IR (Neat) 2933, 1727, 1651, 1603, 1495, 1455, 1367, 1262, 1214, 1189, 1094, 1061, 1031 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{28}NO_4$: 394.2013, found: 394.2023.

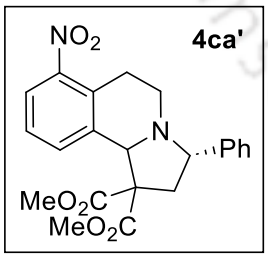


Dimethyl 3-vinyl-2,3,6,10b-tetrahydropyrrolo[2,1-a]isoquinoline-1,1(5H)-dicarboxylate 4ao. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane; R_f = 0.32; thick liquid; yield 45% (28 mg); 2.4:1 Mixture of diasteroisomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 6.5 Hz, 1H), δ 7.27 (d, *J* = 7.5 Hz, 0.43H), 7.06-7.00 (m, 3.51H), 6.98 (d, *J* = 6.0 Hz, 1H), 5.81-5.74 (m, 0.53H), 5.68-5.61 (m, 1H), 5.32 (s, 1H), 5.23 (d, *J* = 17 Hz, 1H), 5.17 (d, *J* = 10.5 Hz, 0.49H), 5.11 (d, *J* = 10.5 Hz, 1H), 4.12 (s, 0.42H), 3.94-3.90 (m, 1H), 3.78 (s, 1.30H), 3.74 (s, 3H), 3.33 (s, 1.34H), 3.14-3.11 (m, 0.45H), 3.05-3.03 (m, 1H), 3.02 (s, 3H), 3.01-2.97 (m, 0.50H), 2.95-2.92 (m, 0.48H), 2.80-2.65 (m, 3H), 2.61 (d, *J* = 5.5 Hz, 0.44H), 2.59 (d, *J* = 5.5 Hz, 0.47H), 2.53-2.47 (m, 1H), 2.41-2.38 (m, 1H), 2.30-2.35 (m, 0.53H), 2.07 (dd, *J* = 13.0, 9.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 172.1, 171.1, 170.9, 140.2, 138.4, 136.9, 135.5, 135.0, 134.4, 128.7, 128.4, 128.2, 126.8, 126.5, 126.3, 125.5, 125.1, 118.5, 117.4, 70.0, 65.9, 65.7, 65.5,

65.0, 62.1, 52.99, 52.93, 52.2, 51.9, 46.0, 44.3, 40.6, 40.1, 29.9, 25.2; FT-IR (Neat) 2951, 1728, 1642, 1493, 1453, 1433, 1352, 1253, 1206, 1146, 1112, 1087, 1008 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{18}H_{22}NO_4$: 316.1543, found: 316.1548.

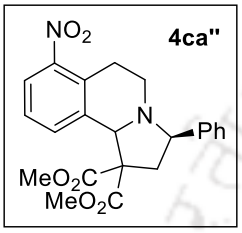


Dimethyl 7-bromo-3-phenyl-2,3,6,10b-tetrahydropyrrolo[2,1-a]isoquinoline-1,1(5H)-dicarboxylate 4ba. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane; R_f = 0.42; thick liquid; yield 72% (63 mg); 1.6:1 mixture of diastereomers; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40-7.38 (m, 3.80H), 7.35-7.32 (m, 3H), 7.29-7.25 (m, 4H), 7.23-7.20 (m, 2H), 6.95 (q, *J* = 8.0 Hz, 1.73H), 5.49(s, 0.60H), 4.55-4.52 (m, 0.62H), 4.21 (s, 1H), 3.79 (s, 3H), 3.70 (s, 1.84H), 3.44 (t, *J* = 8.5 Hz, 1H), 3.37 (s, 3H), 3.08 (s, 1.80H), 2.90-2.76 (m, 3H), 2.73-2.67 (m, 5.61H), 2.60 (d, *J* = 12.5 Hz, 0.65H), 2.22-2.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 171.9, 170.8, 170.7, 142.4, 141.0, 138.4, 137.0, 136.8, 135.6, 130.8, 130.3, 128.7, 128.6, 128.1, 127.8, 127.6, 127.4, 127.2, 126.7, 126.3, 126.1, 125.1, 124.7, 70.0, 66.7, 65.9, 65.7, 65.4, 61.8, 53.0, 52.9, 52.3, 52.0, 46.1, 44.0, 43.9, 43.3, 31.5, 24.7; FT-IR (Neat) 2952, 1729, 1651, 1561, 1435, 1261, 1204, 1178, 1150, 1061, 1025 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{23}BrNO_4$: 444.0805, found: 444.0808.

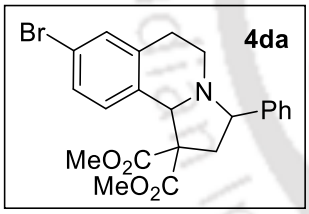


Dimethyl (3*S*,10b*R*)-7-nitro-3-phenyl-2,3,6,10b-tetrahydropyrrolo[2,1-a]isoquinoline-1,1(5H)-dicarboxylate 4ca′. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane; R_f = 0.37; thick liquid; yield 65% (53 mg); 1.8:1 mixture of diastereomers; ^1H NMR (500 MHz, $CDCl_3$) δ 7.79-7.73 (m, 3.14H), 7.47-7.45 (m, 3.19H), 7.36 (q, *J* = 7.0 Hz, 3.18H), 7.32-7.25 (m, 3.85H), 5.66 (s, 0.55H), 4.68-4.65 (m, 0.60H), 4.34 (s, 1H), 3.88 (s, 3H), 3.79 (s, 1.70H), 3.56 (t, *J* = 8.5 Hz, 1H), 3.45 (s, 3H), 3.30-3.25 (m, 1H), 3.18 (s, 1.70H), 3.10-3.04 (m, 0.65H), 2.99-2.95 (m, 1H), 2.93-2.86 (m, 1.73H), 2.82-2.78 (m, 1.66H), 2.75-2.69 (m,

2.34H), 2.28-2.22 (m, 1.69H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 171.7, 170.5, 170.2, 149.8, 149.4, 142.1, 140.7, 138.8, 137.5, 133.2, 132.8, 132.2, 131.4, 128.8, 128.7, 128.09, 128.05, 127.8, 127.4, 125.7, 125.6, 123.1, 122.5, 69.7, 66.6, 66.0, 65.5, 65.4, 62.1, 53.2, 53.1, 52.4, 52.2, 45.4, 43.5, 43.4, 43.2, 27.9, 21.5; FT-IR (Neat) 2953, 1730, 1656, 1525, 1434, 1349, 1265, 1209, 1127, 1064, 1027 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{23}N_2O_6$: 411.1551, found: 411.1562. $[\alpha]_D^{25}$ = +50.00 (c = 0.02, CH_2Cl_2); HPLC analysis: *ee* for major diastereomer = >99% [Daicel CHIRALCEL AD-H column, hexane/iPrOH = 92:8, flow rate: 1 mL/min, λ = 254 nm, t_R= 10.62 min (major), 12.64 min (minor)].

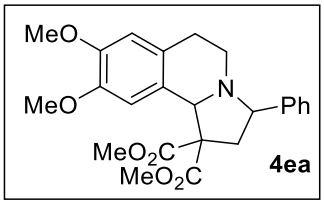


Dimethyl (3R,10bR)-7-nitro-3-phenyl-2,3,6,10b-tetrahydropyrrolo[2,1-a]isoquinoline-1,1(5H)-dicarboxylate 4ca′′. $[\alpha]_D^{25}$ = -95.00 (c = 0.02, CH_2Cl_2); HPLC analysis: *ee* for major diastereomer = >99% ee [Daicel CHIRALCEL AD-H column, hexane/iPrOH = 92:8, flow rate: 1 mL/min, λ = 254 nm, t_R= 11.53 min (major), 10.03 min (minor)].

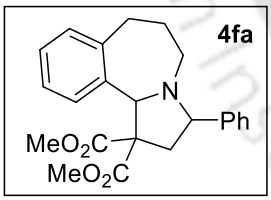


Dimethyl 8-bromo-3-phenyl-2,3,6,10b-tetrahydropyrrolo[2,1-a]isoquinoline-1,1(5H)-dicarboxylate 4da. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane; R_f = 0.39; thick liquid; yield 71% (62 mg); 1.2:1 mixture of diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.37 (m, 3.73H), 7.29-7.26 (m, 4H), 7.25-7.19 (m, 4H), 7.18-7.15 (m, 4H), 5.44 (s, 0.80H), 4.57-4.54 (m, 0.81H), 4.14 (s, 1H), 3.78 (s, 3H), 3.70 (s, 2.44H), 3.45 (t, *J* = 8.5 Hz, 1H), 3.39 (s, 3H), 3.12 (s, 2.41H), 2.97-2.90 (m, 1H), 2.83-2.78 (m, 2.90H), 2.72-2.60 (m, 4H), 2.55-2.51 (m, 1H), 2.30-2.26 (m, 0.87H), 2.22-2.10 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 171.9, 170.8, 170.6, 142.7, 141.2, 139.7, 138.3, 134.6, 133.5, 131.5, 131.2, 130.0, 128.9, 128.7, 128.6, 128.2, 128.1, 127.8, 127.6, 127.3, 120.4, 120.2, 69.6, 66.7, 65.7, 65.6, 65.2, 61.7, 53.0, 52.9, 52.3, 52.0, 45.9, 44.2, 43.5, 43.2, 30.1, 24.7; FT-IR (Neat) 2952, 1729, 1648,

1592, 1482, 1434, 1264, 1212, 1150, 1120, 1092, 1030 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{23}BrNO_4$: 444.0805, found: 444.0804.

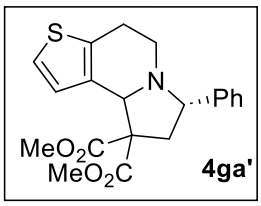


Dimethyl 8,9-dimethoxy-3-phenyl-2,3,6,10b-tetrahydropyrrolo[2,1-a]isoquinoline-1,1(5H)-dicarboxylate 4ea. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.32; thick liquid; yield 56% (47 mg); 1.4:1 mixture of diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50-7.46 (m, 3.51H), 7.36 (q, *J* = 7.0 Hz, 3.66H), 7.30-7.28 (m, 1.37H), 7.07 (d, *J* = 10.5 Hz, 1.75H), 6.57 (d, *J* = 8.5 Hz, 1.72H), 5.50 (s, 0.70H), 4.66-4.63 (m, 0.74H), 4.23 (s, 1H), 3.86 (s, 2.70H), 3.84 (d, *J* = 5.5 Hz, 10.22H), 3.78 (s, 2.10H), 3.53 (t, *J* = 8.5 Hz, 1H), 3.47 (s, 3H), 3.20 (s, 2.13H), 3.00-2.94 (m, 1H), 2.90-2.72 (m, 6.80H), 2.57 (d, *J* = 14.5 Hz, 1H), 2.31-2.19 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 181.0, 171.0, 170.1, 170.0, 148.5, 147.29, 147.26, 146.9, 142.7, 137.7, 132.4, 128.76, 128.73, 128.5, 128.3, 127.77, 127.76, 127.0, 126.3, 126.0, 117.2, 114.5, 111.1, 109.3, 67.4, 64.1, 59.8, 56.1, 56.0, 55.9, 52.9, 52.7, 52.5, 51.9, 50.0, 47.7, 46.8, 41.8, 35.6, 34.7, 31.7, 31.4, 28.9, 25.3; FT-IR (Neat) 2925, 1732, 1642, 1602, 1514, 1454, 1434, 1342, 1276, 1213, 1090, 1025 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{28}NO_6$: 426.1911, found: 426.1915.

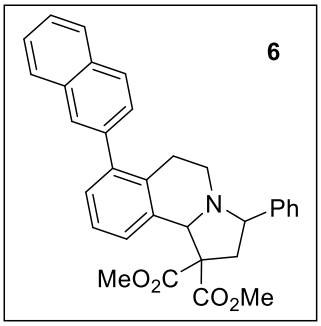


Dimethyl 3-phenyl-2,3,5,6,7,11b-hexahydro-1H-benzo[c]pyrrolo[1,2-a]azepine-1,1-dicarboxylate 4fa. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane; R_f = 0.34; thick liquid; yield 63% (47 mg); 2.8:1 mixture of diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49-7.46 (m, 3H), 7.43-7.39 (m, 1.14H), 7.36-7.31 (m, 2.81H), 7.28 (t, *J* = 7.5 Hz, 1.18H), 7.17-7.15 (m, 0.77H), 7.13-7.11 (m, 1.73H), 7.10-7.07 (m, 0.54H), 7.03-7.02 (m, 1H), 5.80 (s, 0.35H), 4.80 (s, 1H), 4.50-4.47 (m, 0.37H), 3.79 (s, 3H), 3.75-3.69 (m, 2.25H), 3.66-3.62 (m, 1H), 3.24 (s, 3H), 3.16 (s, 1.04H), 3.12-3.09 (m, 0.33H), 3.06-3.02 (m, 0.40H), 2.83 (dd, *J* = 13.0, 9.0 Hz, 1H), 2.72-2.68 (m, 1.35H), 2.66-2.60 (m, 0.46H), 2.48-2.37 (m, 3.66H), 2.15 (dd, *J* = 13.0, 9.0 Hz, 0.41H), 1.90-1.82 (m, 0.48H), 1.77-1.69 (m, 1.19H), 1.51-1.46 (m, 2H); ^{13}C NMR (150MHz,

$CDCl_3$) δ 172.5, 171.5, 171.4, 170.9, 143.0, 142.5, 140.8, 139.1, 138.5, 136.9, 130.37, 130.31, 129.6, 129.0, 128.6, 128.5, 128.0, 127.69, 127.68, 127.5, 127.1, 126.1, 125.8, 76.3, 71.6, 67.2, 64.47, 64.42, 63.3, 52.9, 52.8, 52.2, 52.1, 44.9, 43.5, 43.3, 41.6, 31.5, 30.6, 28.2, 23.6; FT-IR (Neat) 2950, 1731, 1637, 1493, 1449, 1434, 1356, 1265, 1228, 1199, 1095, 1060 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{26}NO_4$: 380.1856, found: 380.1860.

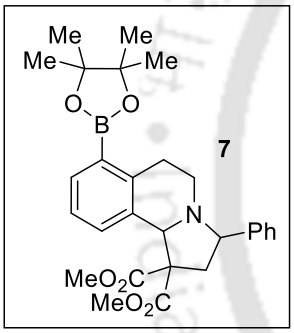


Dimethyl (7*S*,9a*S*)-7-phenyl-4,7,8,9a-tetrahydrothieno[2,3-g]indolizine-9,9(5H)-dicar-boxylate 4ga′. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane; R_f = 0.36; thick liquid; yield 68% (50 mg); 1.4:1 mixture of diastereomers; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.5 Hz, 2H), 7.38 (d, *J* = 7.5 Hz, 1.43H), 7.28 (q, *J* = 7.5 Hz, 3.68H), 7.23-7.19 (m, 1.73H), 6.95-6.94 (m, 2.58H), 6.85 (d, *J* = 5.5 Hz, 1H), 5.37 (s, 0.70H), 4.50-4.47 (m, 0.70H), 4.02 (s, 1H), 3.76 (s, 3H), 3.71 (s, 2.13H), 3.49 (t, *J* = 9.0 Hz, 1H), 3.42 (s, 3H), 3.29 (s, 2.12H), 2.92-2.83 (m, 3H), 2.81-2.47 (m, 6.90H), 2.26-2.21 (m, 1H), 2.16-2.12 (m, 0.74H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.3, 171.7, 170.9, 170.4, 142.7, 141.7, 136.1, 136.0, 133.2, 133.0, 128.68, 128.65, 128.2, 127.7, 127.5, 127.4, 126.5, 126.4, 121.2, 121.0, 68.5, 66.5, 64.6, 64.3, 64.2, 61.1, 52.9, 52.8, 52.3, 52.2, 46.5, 44.7, 43.0, 42.4, 26.2, 21.0; FT-IR (Neat) 2950, 1730, 1494, 1434, 1334, 1228, 1198, 1153, 1109, 1028 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{22}NO_4S$: 372.1264, found: 372.1271. $[\alpha]_D^{25}$ = -80.00 (c = 0.02, CH_2Cl_2); HPLC analysis: *ee* for major diasteromer = 99% [Daicel CHIRALCEL AD-H column, hexane/iPrOH = 95:5, flow rate: 1 mL/min, λ = 254 nm, t_R= 07.03 min (major), 08.37 min (minor)].



Dimethyl 7-(naphthalen-2-yl)-3-phenyl-2,3,6,10b-tetrahydropyrrolo[2,1-a]isoquinoline-1,1(5H)-dicarboxylate 6. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane; R_f = 0.43; thick liquid; yield 84% (82 mg); 1:1.2 mixture of

diastereomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80-7.75 (m, 6H), 7.70 (d, *J* = 16.5 Hz, 2H), 7.48 (dd, *J* = 7.0, 2.5 Hz, 1H), 7.44-7.40 (d, *J* = 6.9 Hz, 10H), 7.38 (d, *J* = 8.5 Hz, 1H), 7.27 (q, *J* = 7.5 Hz, 4H), 7.21 (d, *J* = 7.5 Hz, 2H), 7.17-7.14 (m, 2.93H), 7.11 (d, *J* = 7.5 Hz, 0.90H), 5.67 (s, 1H), 4.69-4.65 (m, 1H), 4.33 (s, 0.81H), 3.83 (s, 2.44H), 3.73 (s, 3H), 3.46 (s, 2.41H), 3.12 (s, 3H), 2.91-2.83 (m, 2H), 2.77-2.73 (m, 3H), 2.70-2.66 (m, 2H) 2.61-2.56 (m, 1H), 2.38 (d, *J* = 17.0 Hz, 1H), 2.23 (d, *J* = 16.0 Hz, 1H), 2.15-2.09 (m, 2H); ^{13}C NMR (150MHz, $CDCl_3$) δ 173.1, 171.9, 171.1, 171.0, 143.0, 141.8, 141.2, 139.5, 138.8, 136.2, 135.5, 134.8, 133.7, 133.4, 133.3, 132.46, 132.40, 128.67, 128.62, 128.3, 128.19, 128.15, 128.13, 128.08, 128.05, 127.966, 127.961, 127.93, 127.89, 127.81, 127.7, 127.6, 127.58, 127.56, 127.4, 126.4, 126.3, 126.2, 126.0, 125.9, 125.3, 125.0, 70.6, 66.8, 66.2, 66.1, 65.5, 62.0, 53.0, 52.9, 52.3, 52.1, 46.3, 44.6, 43.9, 43.4, 29.7, 23.3; FT-IR (Neat) 2951, 1731, 1650, 1587, 1334, 1271, 1204, 1060 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{30}NO_4$: 492.2169, found: 492.2169.



Dimethyl 3-phenyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3,6,10b-tetrahydro-pyrrolo[2,1-a]isoquinoline-1,1(5H)-dicarboxylate 7. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane; R_f = 0.44; colorless solid; mp 150-151°C; yield 70% (68 mg); 1.4:1 mixture of diastereomers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (t, *J* = 7.6 Hz, 1.72H), 7.46-7.39 (m, 5H), 7.29-7.25 (m, 3.70H), 7.22-7.18 (m, 1.71H), 7.05 (q, *J* = 7.6 Hz, 1.79H), 5.56 (s, 0.71H), 4.59 (dd, *J* = 10.0, 5.6 Hz, 0.71H), 4.26 (s, 1H), 3.79 (s, 3H), 3.70 (s, 2.12H), 3.43 (t, *J* = 8.4 Hz, 1H), 3.34 (s, 3H), 3.04-3.01 (m, 4H), 2.91-2.78 (m, 4H), 2.73-2.67 (m, 3H), 2.64-2.59 (m, 1H), 2.21-2.10 (m, 2H), 1.25 (d, *J* = 2.4 Hz, 9.27H), 1.23 (s, 11.09H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.1, 172.1, 171.1, 170.9, 143.7, 142.8, 142.3, 141.5, 135.0, 134.5, 134.2, 133.9, 131.1, 129.9, 128.69, 128.64, 128.60, 128.5, 128.29, 128.20, 127.7, 127.5, 124.6, 124.1, 83.57, 83.51, 70.5, 66.9, 66.1, 65.9, 65.3, 62.0, 52.98, 52.90, 52.2, 52.0, 46.4, 44.4, 43.7, 43.3, 30.5, 29.8, 29.7, 25.06, 25.02, 25.01, 24.9, 23.7; FT-IR (Neat) 2953, 2928, 1732, 1586, 1435, 1353, 1271, 1207, 1143, 1062 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{35}BNO_6$: 492.2552, found: 492.2543.

Crystal Data and Structure Refinement of 4al

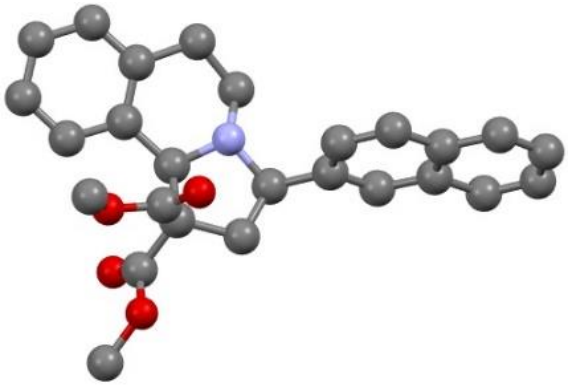


Figure 2. ORTEP diagram of dimethyl 3-(naphthalen-2-yl)-2,3,6,10b tetrahydropyrrolo[2,1-a]isoquinoline-1,1(5H)-dicarboxylate **4al** (CCDC 2163965). H-Atoms omitted for clarity.

Identification code	**4al**
Empirical formula	′C26 H25 N O4′
Formula weight	415.47
Crystal habit, colour	Block /colourless
Crystal size, mm^3	0.32 x 0.25 x 0.24
Temperature, *T*/K	296 K
Wavelength, λ/Å	0.71073
Crystal system	'Monoclinic'
Space group	'P 21/c'
Unit cell dimensions	a = 15.1009(6) Å
	b = 7.6217(3) Å
	c = 19.2497(7) Å
	α = 90
	β = 93.892(2)
	γ = 90
Volume, *V*/$Å^3$	2210.43(15)
Z	4
Calculated density, g cm^{-3}	1.248
Absorption coefficient, μ/mm^{-1}	0.084

F(000)	880.0
θ range for data collection	1.352 to 25.047°
Limiting indices	$-17 \leq h \leq 17, -9 \leq k \leq 9, -22 \leq l \leq 22$
Reflection collected / unique	3907/2799
Completeness to θ	100% (θ = 25.047°)
Absorption correction	None
Max. and min. transmission	0.975 and 0.980
Refinement method	'SHELXL-2014/7 (Sheldrick, 2014)'
Data / restraints / parameters	3907/0/282
Goodness–of–fit on F^2	1.060
Final R indices [I>2sigma(I)]	R1 = 0.0461, wR2 = 0.1055
R indices (all data)	R1 = 0.0695, wR2 = 0.1214

2.5 References

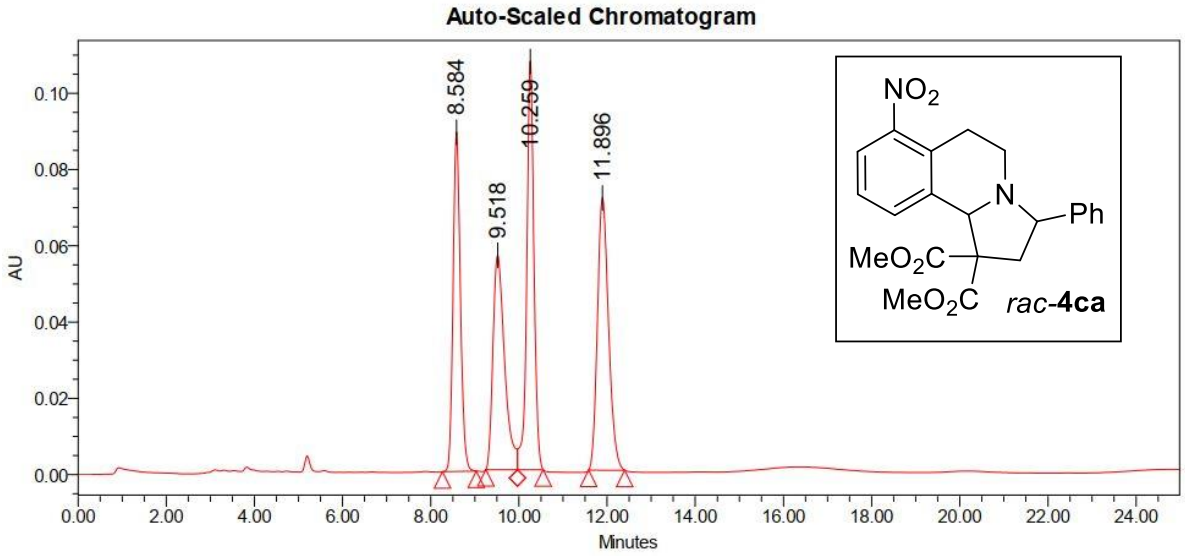
1. (a) Schneider, T. F.; Kaschel, J.; Werz, D. B. A *Angew. Chem. Int. Ed.* **2014**, *53*, 5504. (b) Ebner, C.; Carreira, E. M. *Chem. Rev.* **2017**, *117*, 11651. (c) Fumagalli, G.; Stanton, S.; Bower, J. F. *Chem. Rev.* **2017**, *117*, 9404. (d) Liang, Y.-F.; Müller, V.; Liu, W.; Münch, A.; Stalke, D.; Ackermann, L. *Angew. Chem. Int. Ed Engl.* **2017**, *56*, 9415.
2. (a) Gordon, M. S. *J. Am. Chem. Soc.* **1980**, *102*, 7419. (b) Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165.
3. (a) Ivanov, K. L.; Villemson, E. V.; Budynina, E. M.; Ivanova, O. A.; Trushkov, I. V.; Melnikov, M. Y. *Chem. -Eur. J.* **2015**, *21*, 4975. (b) Tejeda, J. E. C.; Landschoot, B. K.; Kerr, M. A. *Org. Lett.* **2016**, *18*, 2142. (c) Lücht, A.; Patalag, L. J.; Augustin, A. U.; Jones, P. G.; Werz, D. B. *Angew. Chem. Int. Ed.* **2017**, *56*, 10587. (d) Novikov, R. A.; Borisov, D. D.; Tarasova, A. V.; Tkachev, Y. V.; Tomilov, Y. V. *Angew. Chem. Int. Ed.* **2018**, *57*, 10293. (e) Zuo, Z.; Studer, A. *Org. Lett.* **2022**, *24*, 949.
4. (a) Ma, W.; Fang, J.; Ren, J.; Wang, Z. *Org. Lett.* **2015**, *17*, 4180. (b) Suleymanov, A. A.; Le Du, E.; Dong, Z.; Muriel, B.; Scopelliti, R.; Fadaei-Tirani, F.; Waser, J.; Severin, K. *Org. Lett.* **2020**, *22*, 4517. (c) Vartanova, A. E.; Plodukhin, A. Y.; Ratmanova, N. K.; Andreev, I. A.; Anisimov, M. N.; Gudimchuk, N. B.; Rybakov, V. B.; Levina, I. I.; Ivanova,

O. A.; Trushkov, I. V.; Alabugin, I. V. *J. Am. Chem. Soc.* **2021**, *143*, 13952. (d) Shao, J.; Luo, Q.; Bi, H.; Wang, S. R. *Org. Lett.* **2021**, *23*, 459.

5. (a) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642. (b) Goldberg, A. F. G.; O'Connor, N. R.; Craig, R. A., II; Stoltz, B. M. *Org. Lett.* **2012**, *14*, 5314. (c) Chakrabarty, S.; Chatterjee, I.; Wibbeling, B.; Daniliuc, C. G.; Studer, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 5964. (d) Xu, H.; Hu, J.-L.; Wang, L.; Liao, S.; Tang, Y. *J. Am. Chem. Soc.* **2015**, *137*, 8006. (e) Augustin, A. U.; Sensse, M.; Jones, P. G.; Werz, D. B. *Angew. Chem. Int. Ed.* **2017**, *56*, 14293. (f) Ortega, A.; Uria, U.; Tejero, T.; Prieto, L.; Reyes, E.; Merino, P.; Vicario, J. L. *Org. Lett.* **2021**, *23*, 2326.
6. (a) Ackermann, L. *Acc. Chem. Res*. **2014**, *47*, 281. (b) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900. (c) Fumagalli, G.; Stanton, S.; Bower, J. F. *Chem. Rev.* **2017**, *117*, 9404. (d) Dongbang, S.; Confair, D. N.; Ellman, J. A. *Acc. Chem. Res.* **2021**, *54*, 1766. (e) Prabagar, B.; Yang, Y.; Shi, Z. *Chem. Soc. Rev.* **2021**, *50*, 11249.
7. (a) Zeitler, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 9785. (b) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102. (c) Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617. (d) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (e) Marzo, L.; Pagire, S. K.; Reiser, O.; König, B. *Angew. Chem. Int. Ed.* **2018**, *57*, 10034. (f) Chan, A. Y.; Perry, I. B.; Bissonnette, N. B.; Buksh, B. F.; Edwards, G. A.; Frye, L. I.; Garry, O. L.; Lavagnino, M. N.; Li, B. X.; Liang, Y.; Mao, E.; Millet, A.; Oakley, J. V.; Reed, N. L.; Sakai, H. A.; Seath, C. P.; MacMillan, D. W. C. *Chem. Rev.* **2022**, *122*, 1485. (g) Holmberg-Douglas, N.; Nicewicz, D. A. *Chem. Rev.* **2022**, *122*, 1925.
8. (a) Allin, S. M.; Gaskell, S. N.; Towler, J. M. R.; Page, P. C. B.; Saha, B.; McKenzie, M. J.; Martin, W. P. *J. Org. Chem.* **2007**, *72*, 8972. (b) Guo, C.; Fleige, M.; Janssen-Müller, D.; Daniliuc, C. G.; Glorius, F. *Nat. Chem.* **2015**, *7*, 842. (c) Matveeva, M. D.; Purgatorio, R.; Voskressensky, L. G.; Altomare, C. D. *Future Med. Chem.* **2019**, *11*, 2735.
9. Young, I. S.; Kerr, M. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 3023.
10. Augustin, A. U.; Sensse, M.; Jones, P. G.; Werz, D. B. *Angew. Chem. Int. Ed.* **2017**, *56*, 14293.
11. Goldberg, A. F. G.; O'Connor, N. R.; Craig, R. A., II; Stoltz, B. M. *Org. Lett.* **2012**, *14*, 5314.

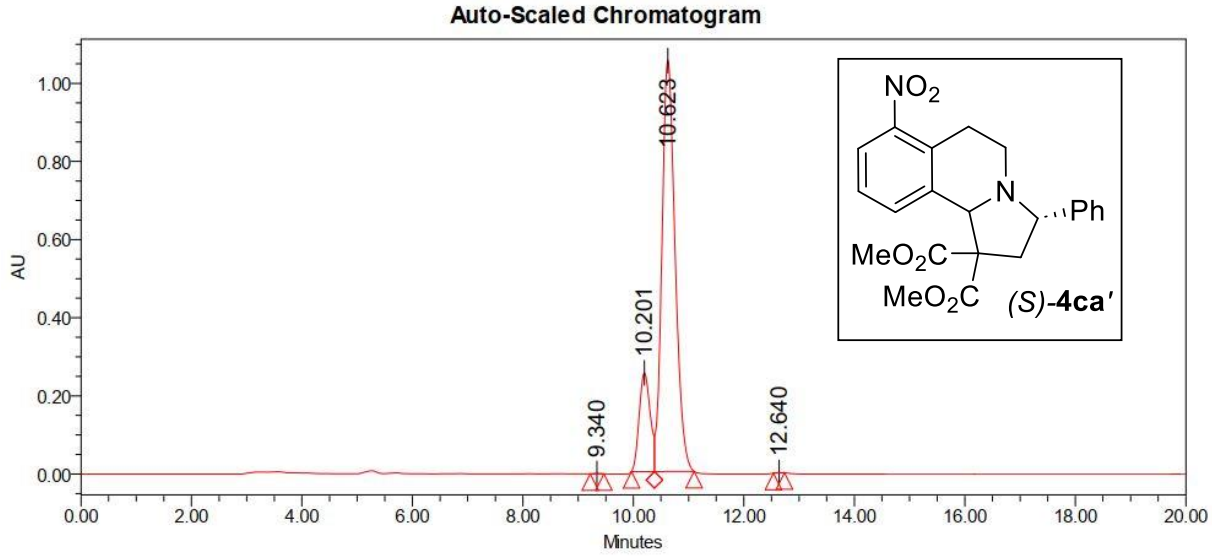
12. Racine, S.; Hegedüs, B.; Scopelliti, R.; Waser, J. *Chem.-Eur. J.* **2016**, *22*, 11997
13. Das, B. K.; Pradhan, S.; Punniyamurthy, T. *Chem. Commun.* **2019**, *55*, 8083.
14. Hari, D. P.; König, B. *Org. Lett.* **2011**, *13*, 3852.
15. Zhu, Z.; Chandak, H. S.; Seidel, D. *Org. Lett.* **2018**, *20*, 4090.
16. Vijay, M.; Kumar, S. V.; Satheesh, V.; Ananthappan, P.; Srivastava, H. K.; Ellairaja, S.; Vasantha, V. S.; Punniyamurthy, T. *Org. Lett.* **2019**, *21*, 7649.
17. Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669.
18. (a) Hari, D. P.; König, B. *Chem. Commun.* **2014**, *50*, 6688. (b) Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075. (c) Rostoll-Berenguer, J.; Blay, G.; Muñoz, M. C.; Pedro, J. R.; Vila, C. A. *Org. Lett.* **2019**, *21*, 6011.

2.6 HPLC Chromatograms



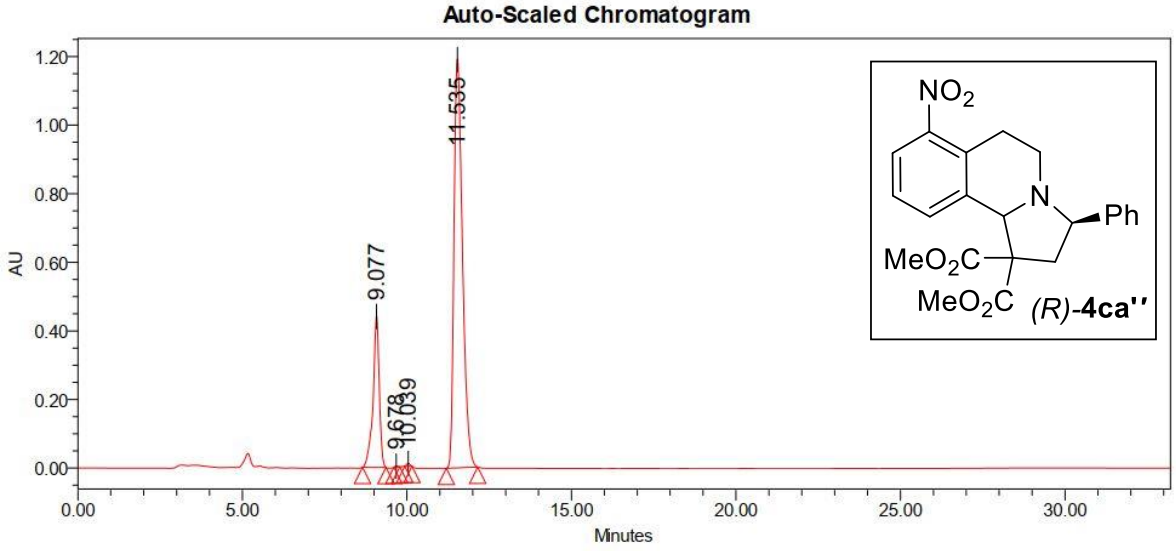
Peak Results

	Start Time (min)	End Time (min)	RT	Height (µV)	% Area
1	8.267	9.033	8.584	88978	22.67
2	9.250	9.967	9.518	56331	22.83
3	9.967	10.550	10.259	107659	26.87
4	11.583	12.400	11.896	71505	27.63



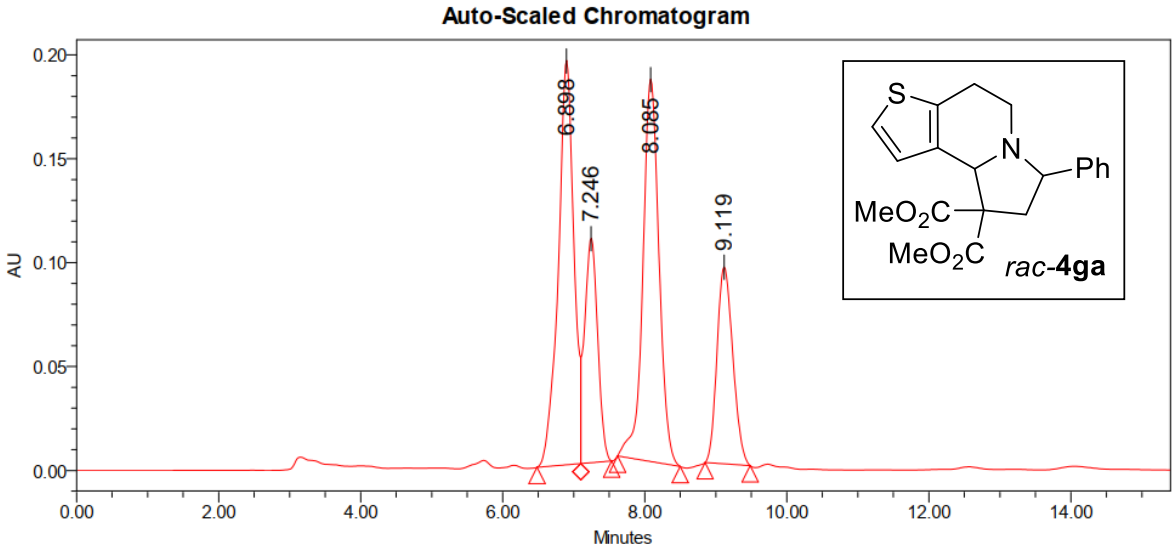
Peak Results

	Peak Codes	Start Time (min)	End Time (min)	RT	Height (µV)	% Area
1		9.217	9.467	9.340	1262	0.05
2		9.967	10.383	10.201	252783	16.70
3		10.383	11.100	10.623	1054997	83.21
4	I38	12.533	12.733	12.640	1079	0.04



Peak Results

	Start Time (min)	End Time (min)	RT	Height (µV)	% Area
1	8.650	9.367	9.077	442495	21.37
2	9.600	9.783	9.678	3442	0.08
3	9.933	10.150	10.039	8568	0.23
4	11.200	12.150	11.535	1192245	78.33



Peak Results

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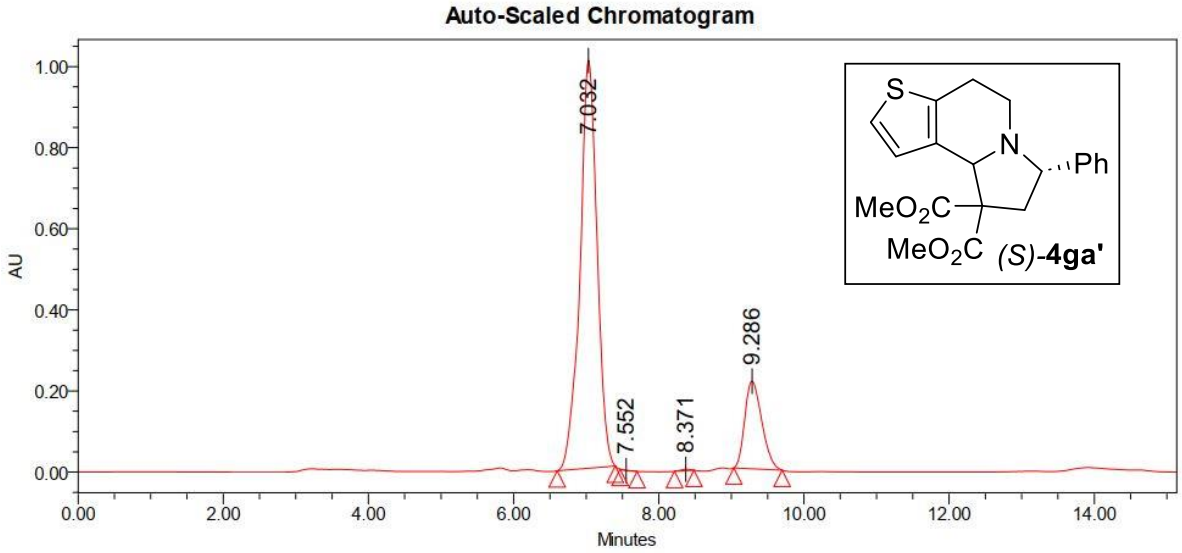
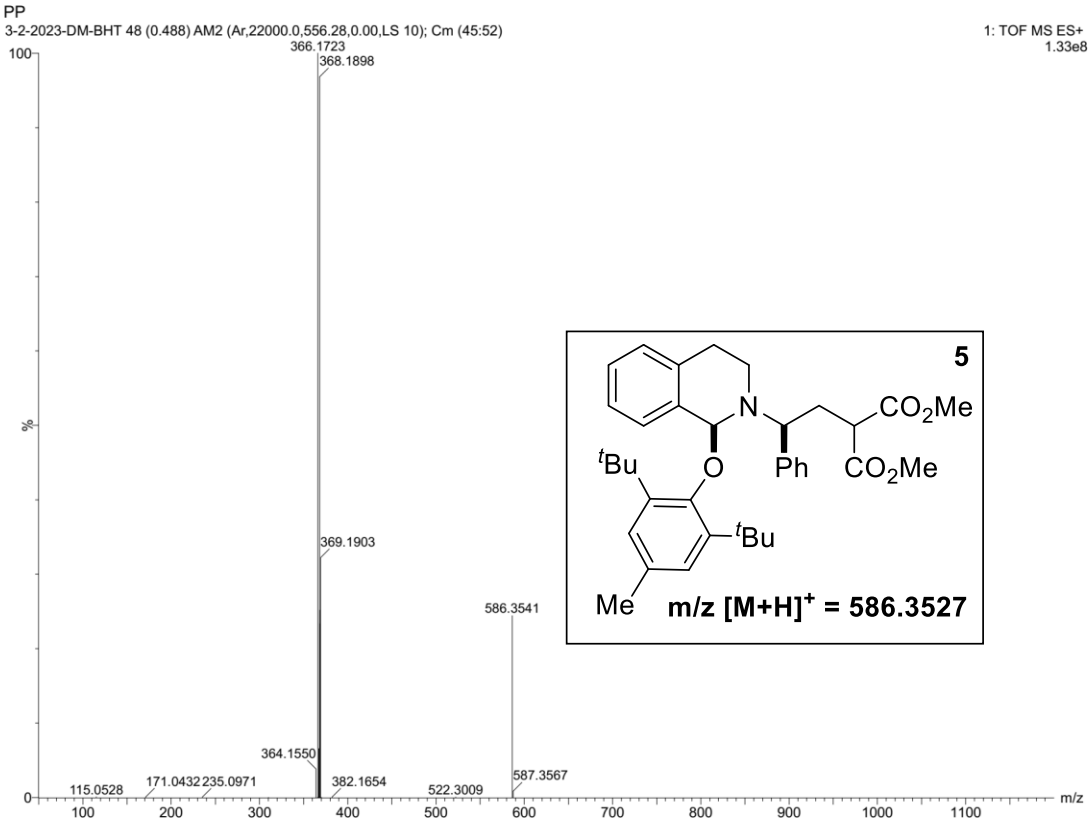
1	6.483	7.100	6.898	194598	33.85
2	7.100	7.533	7.246	108127	15.93
3	7.617	8.500	8.085	183949	33.36
4	8.850	9.483	9.119	94761	16.86



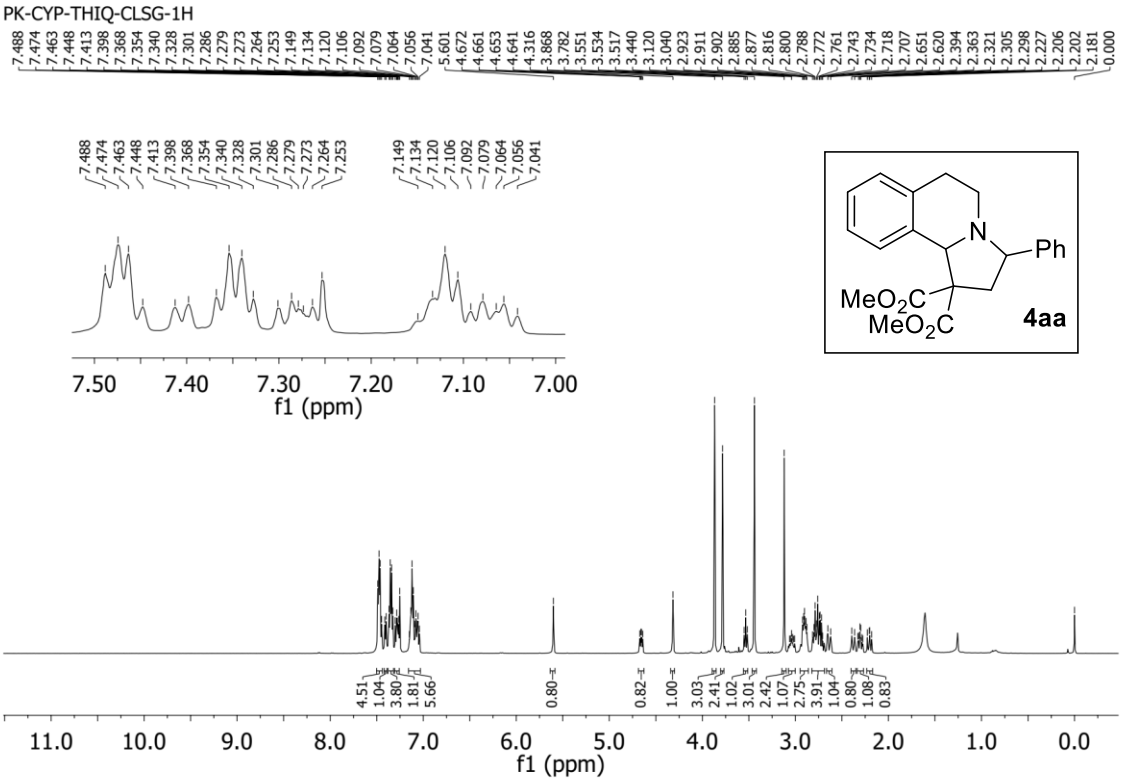
Peak Results

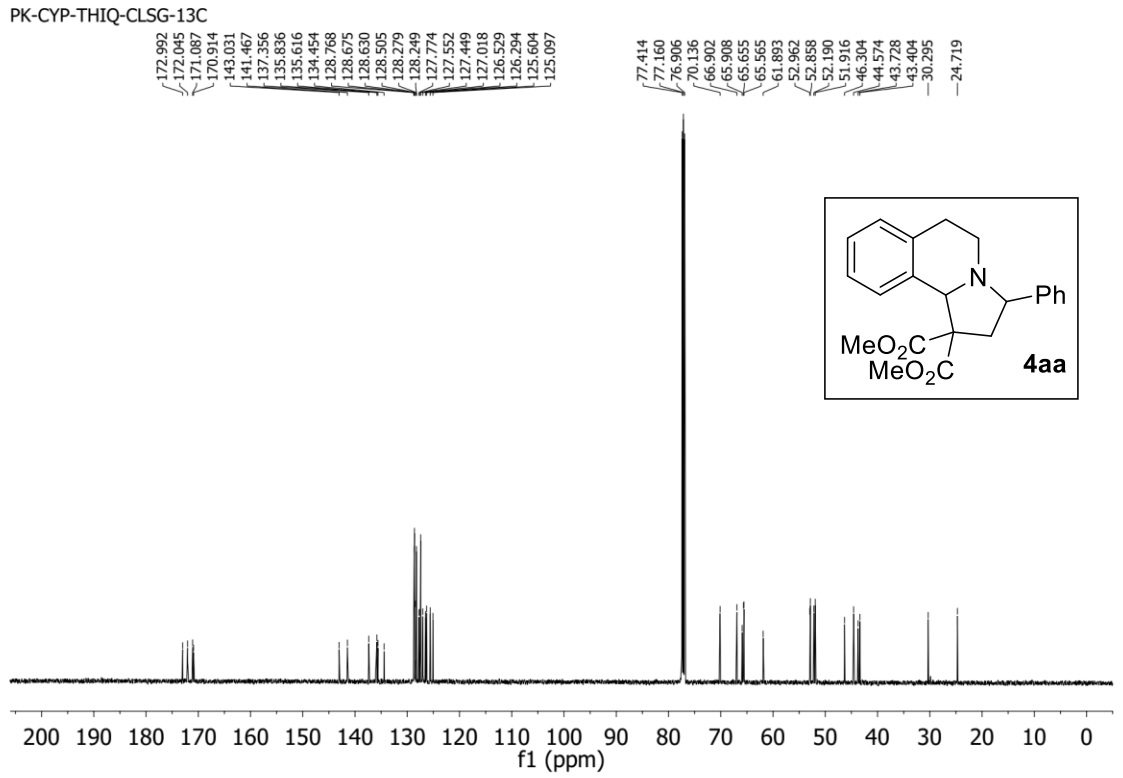
	Peak Codes	Start Time (min)	End Time (min)	RT	Height (µV)	% Area
1		6.600	7.400	7.032	1006043	82.20
2	I37	7.467	7.700	7.552	-1393	0.06
3	I37	8.217	8.483	8.371	3302	0.15
4		9.033	9.700	9.286	216581	17.59

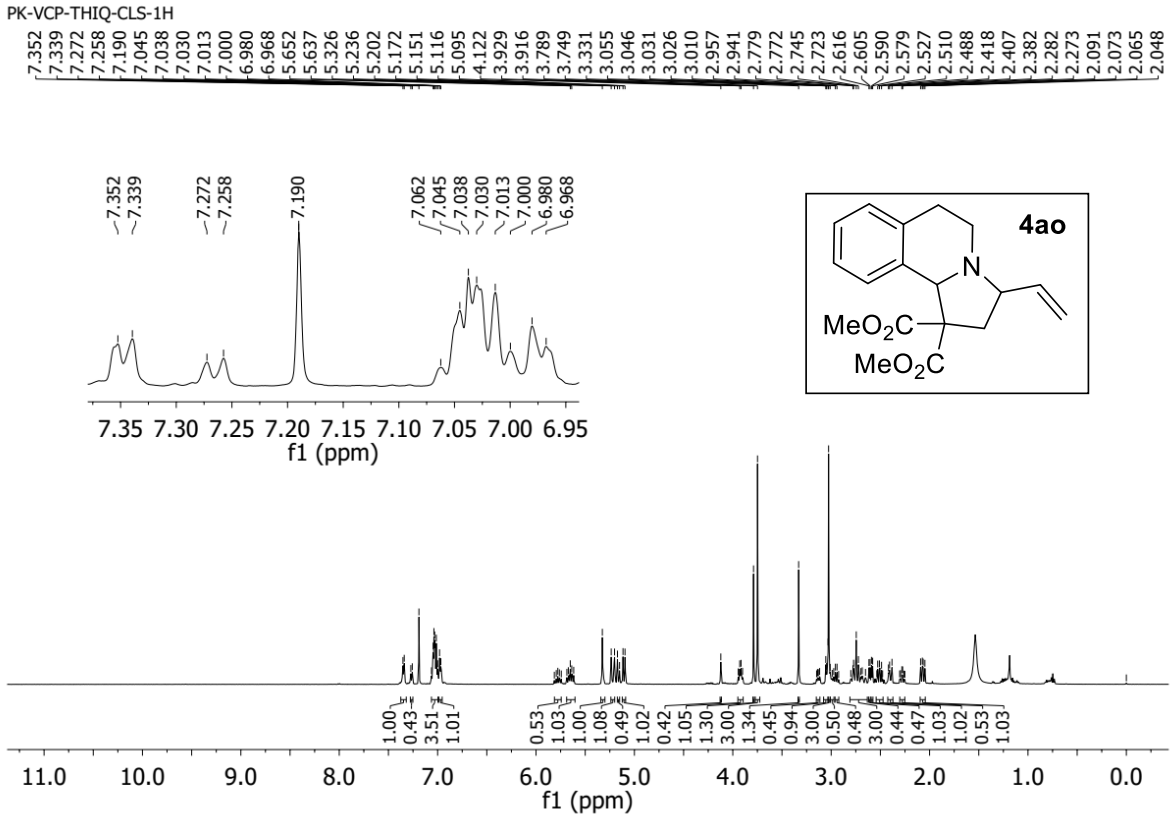
2.7 ESI-MS Spectrum of Radical Trapping Experiment

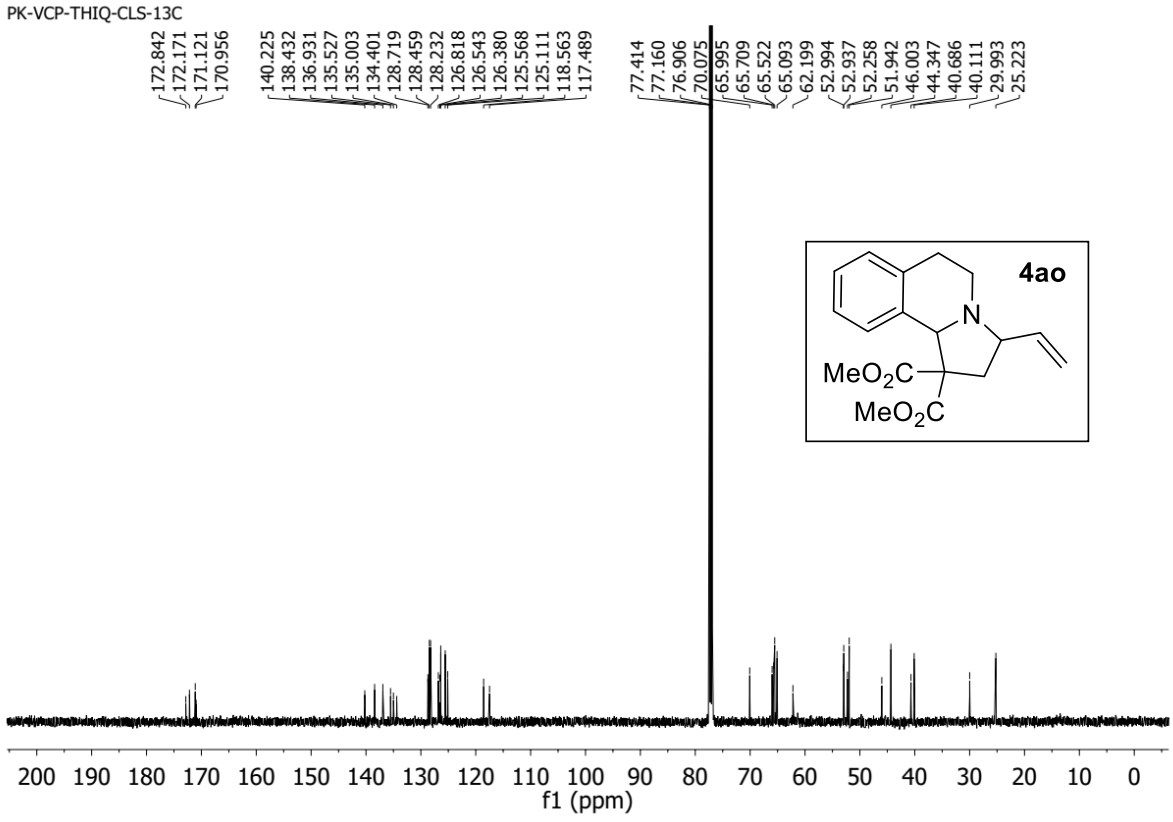


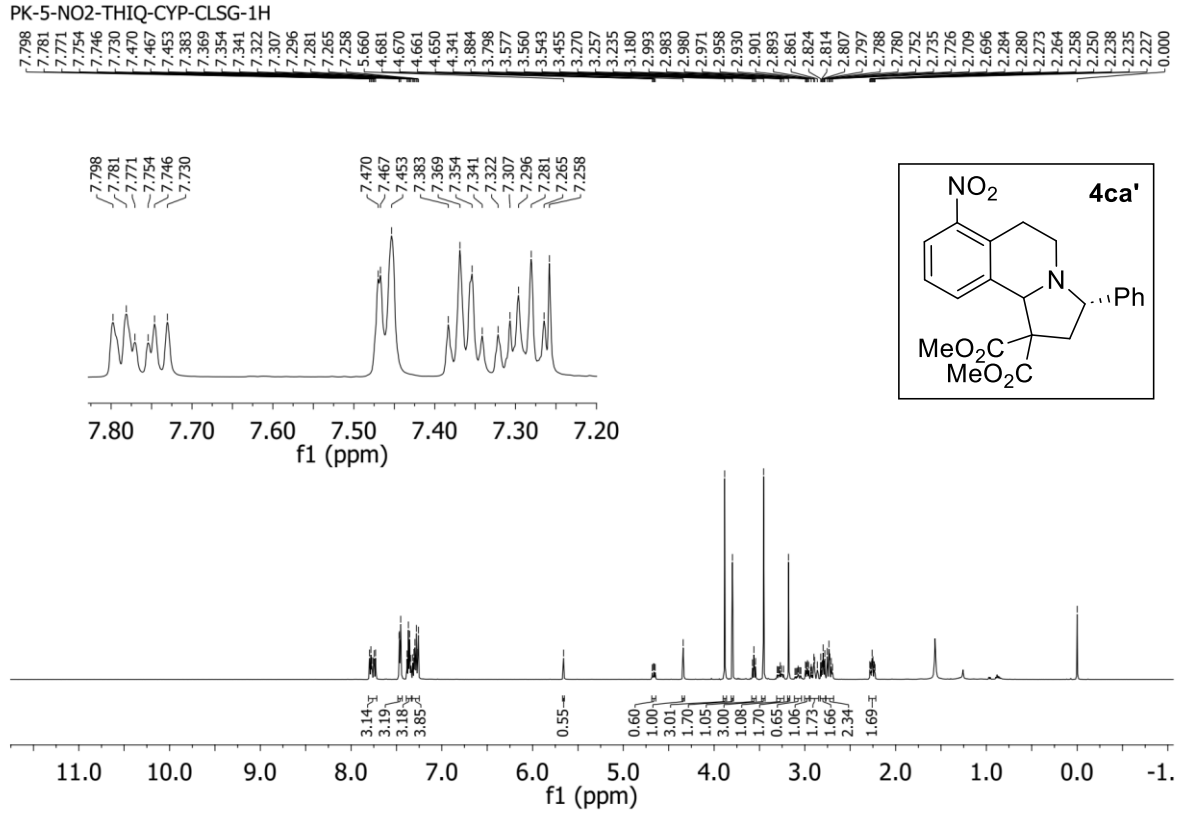
2.8 Selected NMR Spectra

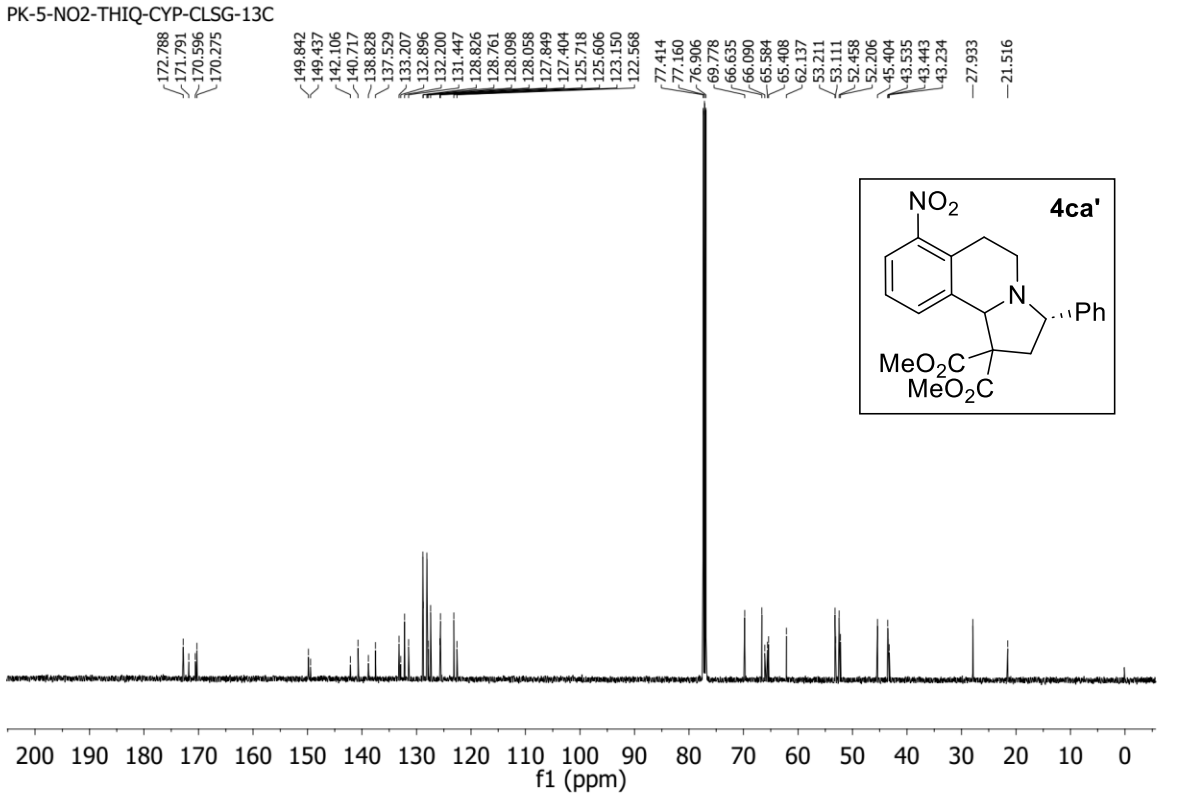






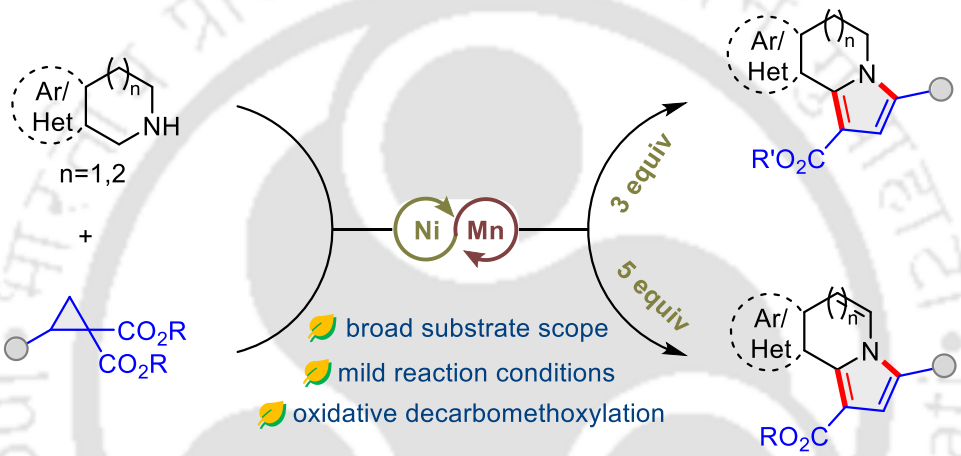






Chapter III

Oxidative Coupling of Donor-Acceptor Cyclopropanes with Cyclic Secondary Amines



Chem. Commun. **2024**, *60*, 4068.

Chapter III

Oxidative Coupling of Donor-Acceptor Cyclopropanes with Cyclic Secondary Amines

Aza heterocycles are prevalent constituents in a myriad of natural alkaloids and pharmaceutical compounds.[1] Within this domain, indolizine alkaloids represent privileged scaffolds that are omnipresent in a broad spectrum of potent natural products, bioactive compounds, and pharmacophores (Figure 1).[2] For example, compound bearing indolizine core exhibit anticancer activity, lamellarin I reverse multidrug resistance by directly inhibiting the P-glycoprotein-mediated drug efflux and lamellarin α-20-sulfate act as the HIV-1 integrase inhibitor. The construction of these significant frameworks using readily available elegant building blocks would thus be valuable. In recent years, donor-acceptor cyclopropanes (DACs) owing to their high ring strain (27.5 kcal/mol)[3] and vicinal DA motifs emerged as a valuable three carbon synthon (C–C–C) towards the construction of important carbo- and hetreo-cycles.[4] In addition, ready accessibility and versatile reactivity of DACs as (1,3)-dipolarophiles attracted for harnessing (3+n) (n=2-4) cycloadditions.[5] Along this line, rearrangement reactions involving DACs able to produce five-membered rings by inserting an acceptor moiety.[6] Also ring-opening reactions permit the substituents to react either in the 1-position or in the 1- and 3-positions.[7] Functionalized cyclic secondary amines were found as synthetic manifolds in several natural products and bio-active molecules.[8] The modification or derivatization to these cyclic amines are mainly involve C–H functionalization of α-C–H bonds.[9] Especially, the oxidative annulation *via* cross-dehydrogenative coupling (CDC) can deliver synthetically important alkaloids and pharmacophores. However, the growing interest to functionalize cyclic secondary amines is hardly surprising. The functionalization using first-row transition-metal becomes impeccable task in terms of sustainability.[10] More recently, Werz group has demonstrated an oxidative (3+2)-cyclopentannulation *via* synergistic action of tin and manganese catalyst using naphthoquinones and DACs as a coupling partner.[4d] Meanwhile, highly abundant, inexpensive and less toxic manganese-based catalysts were found to be effective and thus in focus due to its redox properties in a wide range of oxidation states (0 to +7).[11] In light of prior investigations conducted by the Carreira,[12a] Lautens,[12b] Johnson,[12c] Studer[13] and others our attention was drawn to the significance of Mg(II) in both activating and facilitating the ring opening of DAC. This underscores why Mg(II) stands out as the preferred Lewis acid for the proposed transformation. Inspired by these founding's, we envisioned that

it will be beneficial to observe the reactivity of cyclic secondary amines with donor-acceptor cyclopropanes under Mn-based systems. This chapter describes an oxidative (3+2)-cyclopentannulation of cyclic secondary amines with DACs utilizing dual action of Mg and Mn based systems to construct synthetically important fused indolizines. The reaction involves Mg(II)-catalyzed ring opening of DACs followed by Mn(III)-mediated oxidative CDC.

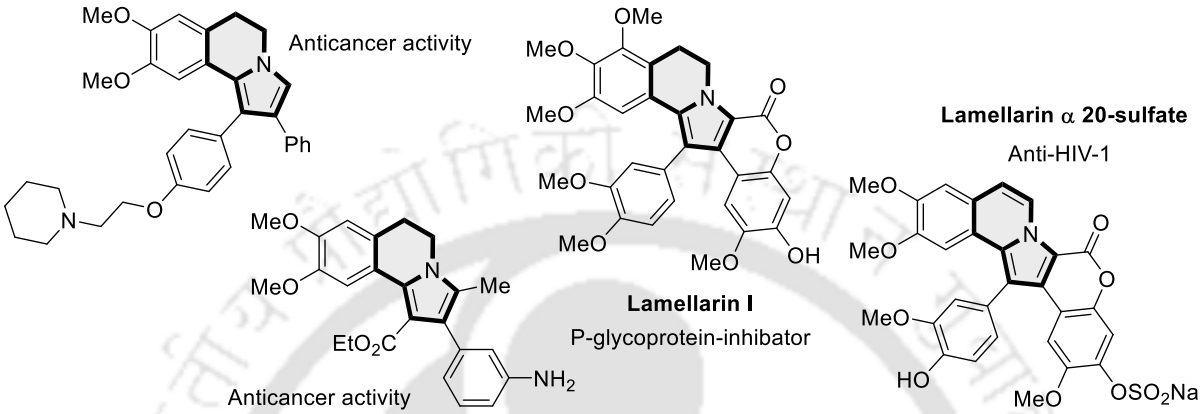
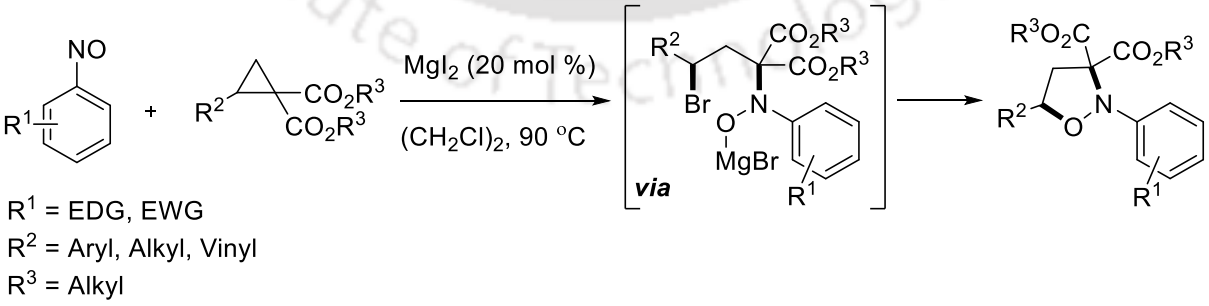


Figure 1. Selected examples of bioactive fused indolizine derivatives

3.1 Literature Study

3.1.1 Mg(II)-Catalyzed Ring-Opening/Cyclization of DACs

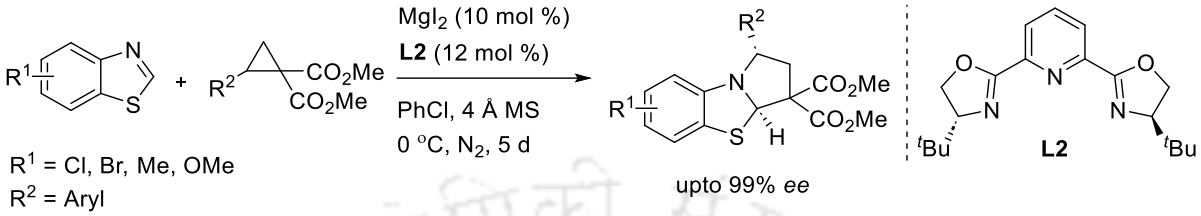
Studer and co-workers showed the formal cycloaddition of donor-acceptor cyclopropanes with nitrosoarenes, catalyzed by $MgBr_2$, provided a unique method for synthesizing structurally diverse isoxazolidines (Scheme 1).[13] These reactions are simple to perform experimentally and exhibit complete stereospecificity and absolute control over regioselectivity. The resulting isoxazolidines easily converted into α-amino lactones through reductive or decarboxylative N-O cleavage followed by lactonization.



Scheme 1. Mg-Catalyzed Ring-Opening/Oxidative-Cyclization of DACs with Indolines

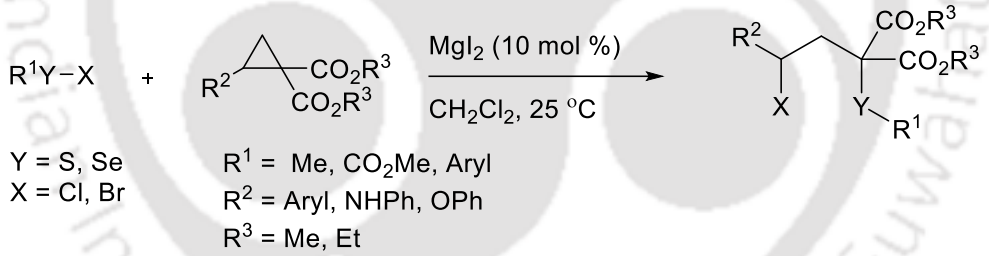
You and co-workers demonstrated an enantioselective dearomative (3+2)-cycloaddition of benzothiazole, which accommodates a broad spectrum of benzothiazoles and cyclopropane-

1,1-dicarboxylate substrates (Scheme 2).[14] The hydropyrrolo[2,1-*b*]thiazole compounds were procured with outstanding enantioselectivity and yields (up to 97% *ee*). Utilizing the identical catalytic system, a highly proficient kinetic resolution of 2-substituted cyclopropane-1,1-dicarboxylates has also been accomplished.



Scheme 2. Mg-Catalyzed Enantioselective (3+2)-Cycloaddition of Benzothiazoles with DACs

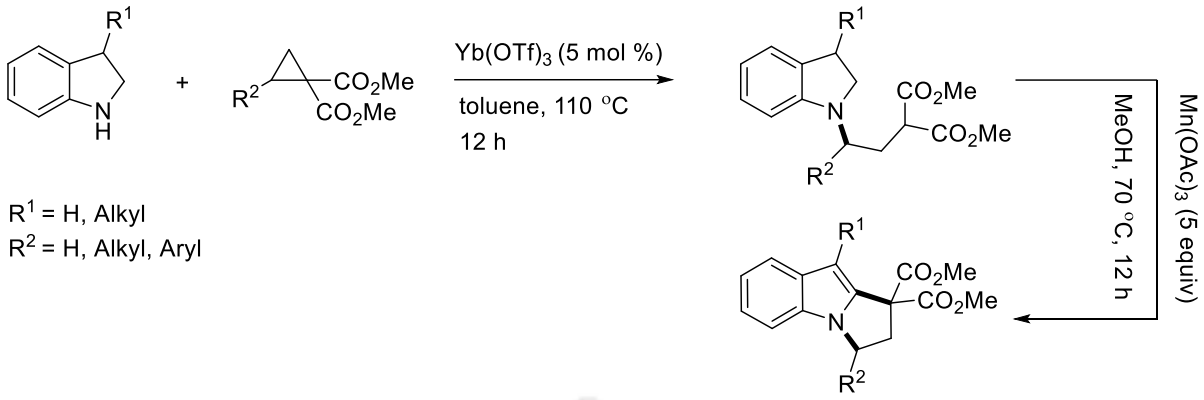
Donor-acceptor cyclopropanes, each possessing two geminal carboxylic esters, underwent reactions with chalcogenyl chlorides and bromides (Scheme 3).[15] This resulted in ring-opened products that carry halogen atoms in the 1-position, adjacent to the donor, and the chalcogenyl group in the 3-position, next to the two acceptor groups. The reaction accommodates a diverse range of donors, including aryl, N, and O. The stereospecific nature of this reaction is evidenced by the use of a chiral starting material.



Scheme 3. Mg-Catalyzed Ring-Opening 1,3-Halochalcogenation of DACs

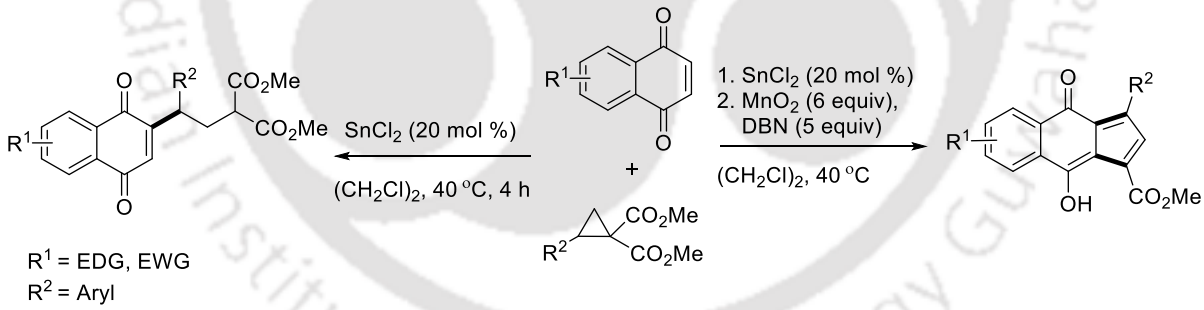
3.1.2 Metal-Catalyzed Ring-Opening/Oxidative-Cyclization of DACs

Kerr and co-workers described a Lewis acid catalyzed ring opening of donor/acceptor cyclopropanes with indolines (Scheme 4).[16] This results in the formation of *N*-alkyl indolines that carry a pendant malonyl group. These intermediates undergo oxidative cyclization to yield 1,2-pyrroloindoles. The efficacy of this method is demonstrated by the synthesis of the core structure of the flinderoles.



Scheme 4. Yb-Catalyzed Ring-Opening/Oxidative-Cyclization of DACs with Indolines

The reactions of 2-aryl cyclopropane dicarboxylates with naphthoquinones was documented by Werz and co-workers (Scheme 5).[4d] The pivotal aspect of this process is the employment of catalytic quantities of $SnCl_2$, which serves dual roles as an electron donor and a Lewis acid. This leads to an *in situ* umpolung of naphthoquinone, transforming the originally electrophilic species into a nucleophile. This nucleophile is then capable of initiating the ring-opening of the three-membered ring, resulting in the formation of a new C-C bond. Upon treating these products with a base, methyl formate is lost, yielding cyclopentannulated products. These products possess fully conjugated pi systems and exhibit strong absorption in the visible range.



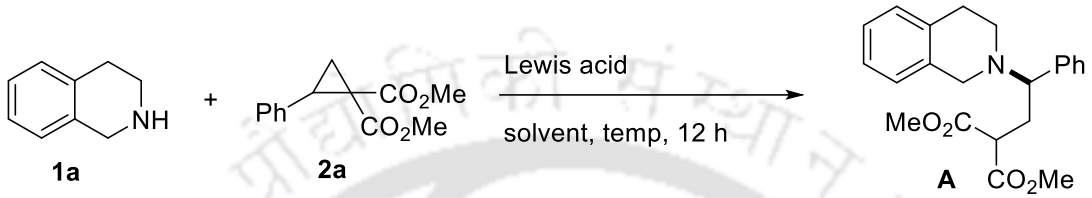
Scheme 5. Reactions of DACs with Naphthoquinones

3.2 Present Study

Herein, Mg(II)-catalyzed ring opening followed by Mn(III)-mediated oxidative (3+2)-cyclopentannulation of cyclic secondary amines with DACs has been developed to construct synthetically important fused indolizines. At the outset, the ring-opening optimization of DAC **2a** was conducted using tetrahydroisoquinoline (THIQ) **1a** as the test substrate, in the presence of various Lewis acids and solvents at varied temperature (Table 1). Among the Lewis acids tested, such as $InCl_3$, $FeCl_3$, $AlCl_3$, $SnCl_2$ and MgI_2 at room temperature (r.t.) in CH_2Cl_2, MgI_2

proved to be the most effective, delivering **A** in 15% yield (entries 1-5). When we changed the solvent to $(CH_2Cl)_2$ and increase the temperature to 80 ºC, an enhancement in the yield of **A** was observed (entry 6-7). Further solvent screening revealed that toluene was the choice, while CH_2Cl_2, $(CH_2Cl)_2$ and xylene yielded inferior results (entries 5-9). Increasing the temperature to 110 ºC led to a drop in the yield (entry 10).

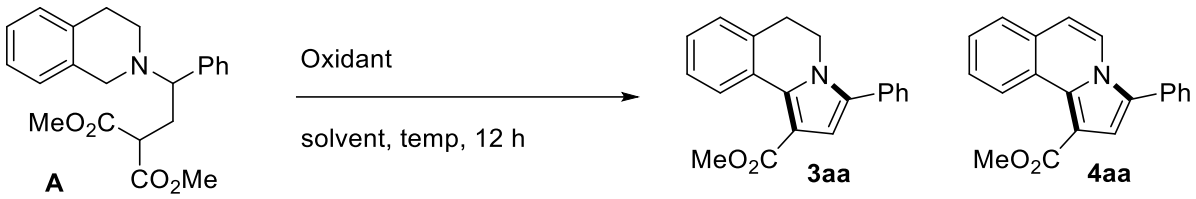
Table 1. Optimization of Reaction Conditions for Ring-Opening of DAC[a]



Entry	Lewis Acid	Solvent	Temp. (ºC)	Yield(%)[b]
1	$InCl_3$	CH_2Cl_2	r.t.	n.d.
2	$FeCl_3$	CH_2Cl_2	r.t.	n.d.
3	$AlCl_3$	CH_2Cl_2	r.t.	12
4	$SnCl_2$	CH_2Cl_2	r.t.	trace
5	MgI_2	CH_2Cl_2	r.t.	15
6	MgI_2	$(CH_2Cl)_2$	r.t.	22
7	MgI_2	$(CH_2Cl)_2$	80	61
8	MgI_2	toluene	80	88
9	MgI_2	xylene	80	75
10	MgI_2	toluene	110	79

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), Lewis acid (20 mol %), solvent (2 mL), 80 ºC, 12 h; [b]Isolated yield. r.t.= room temperature. n.d. = not detected.

Table 2. Optimization of Reaction Conditions for One-pot Annulation[a]

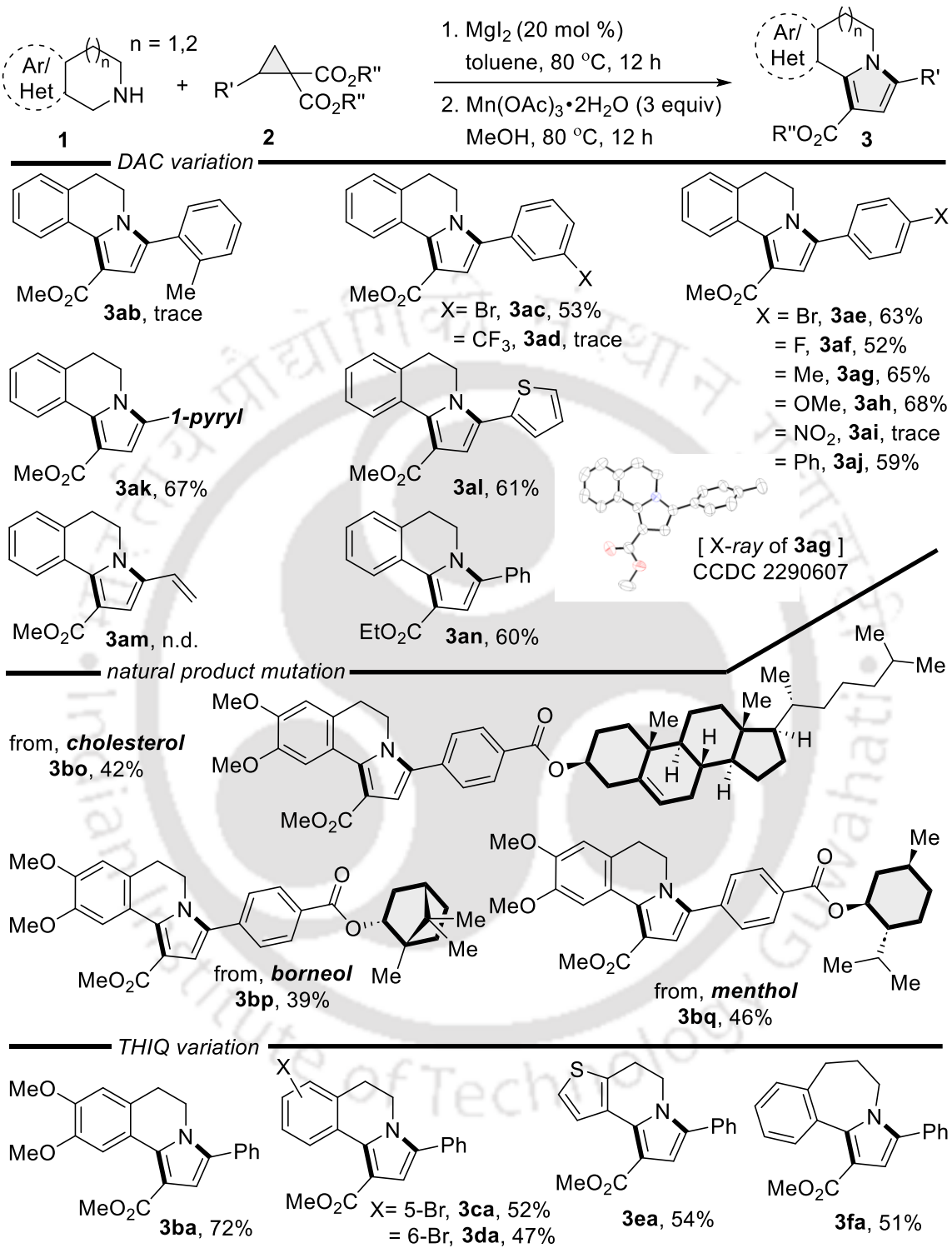


Entry	Oxidant	Solvent	Yield (%)[b]	
			3aa	**4aa**
1	$Mn(OAc)_3{\cdot}2H_2O$	MeOH	64	9
2[c]	$Mn(OAc)_3{\cdot}2H_2O$	MeOH	n.d.	n.d.
3[d]	$Mn(OAc)_3{\cdot}2H_2O$	MeOH	25	n.d.
4	$Mn(OAc)_3{\cdot}2H_2O$	EtOH	21	n.d.
5	$Mn(OAc)_3{\cdot}2H_2O$	$(CH_2Cl)_2$	n.d.	n.d.
6	$Mn(OAc)_3{\cdot}2H_2O$	toluene	n.d.	n.d.
7	$Mn(OAc)_3{\cdot}2H_2O$	THF	n.d.	n.d.
8	MnO_2	MeOH	10	n.d.
9[e]	$Mn(OAc)_3{\cdot}2H_2O$	MeOH	trace	48

[a]Reaction conditions: **A** (0.2 mmol), $Mn(OAc)_3{\cdot}2H_2O$ (3 equiv), MeOH (2 mL), air, 80 °C, 12 h. [b]Isolated yield. [c]$Mn(OAc)_3{\cdot}2H_2O$ (1 equiv). [d]$Mn(OAc)_3{\cdot}2H_2O$ (2 equiv). [e]$Mn(OAc)_3{\cdot}2H_2O$ (5 equiv). n.d. = not detected.

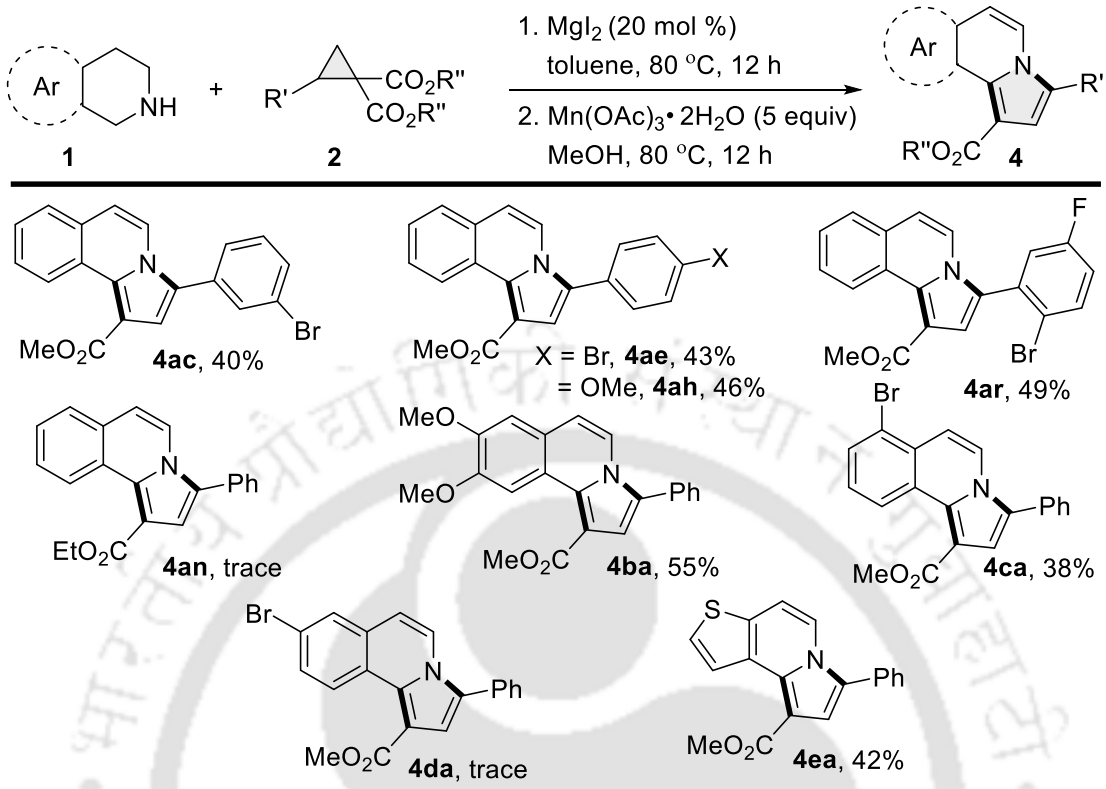
Subsequently, in pursuit of a proficient and broadly applicable method for the desired (3+2) annulation process, we examined the oxidative cyclization of **A** utilizing Mn-based reagents. Pleasingly, the reaction delivered **3aa** in 64% yield along with 9% of **4aa** when 3 equiv of $Mn(OAc)_3{\cdot}2H_2O$ used in MeOH at 80 °C for 12 h under open air (entry 1). Significant decrease in the conversion of **3aa** was observed when 1 and 2 equiv of $Mn(OAc)_3{\cdot}2H_2O$ was employed respectively (entries 2-3). Then, among a series of solvent screened, MeOH, EtOH, $(CH_2Cl)_2$, toluene and THF, the former gave the best result (entries 4-7). In addition, $Mn(OAc)_3{\cdot}2H_2O$ produced superior result compared to MnO_2 (entries 8). Interestingly, an increase of oxidant loading to 5 equiv, furnished **4aa** in 48% yield with a trace amount of **3aa** (entry 9).

Table 3. Synthesis of 3[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), MgI_2 (20 mol %), toluene (2 mL), 80 °C, 12 h; $Mn(OAc)_3 \cdot 2H_2O$ (3 equiv) MeOH (2 mL), air, 80 °C, 12 h. [b]Isolated yield. n.d. = not detected.

Table 4. Synthesis of 4[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), MgI_2 (20 mol %), toluene (2 mL), 80 °C, 12 h; $Mn(OAc)_3 \cdot 2H_2O$ (5 equiv) MeOH (2 mL), air, 80 °C, 12 h. [b]Isolated yield.

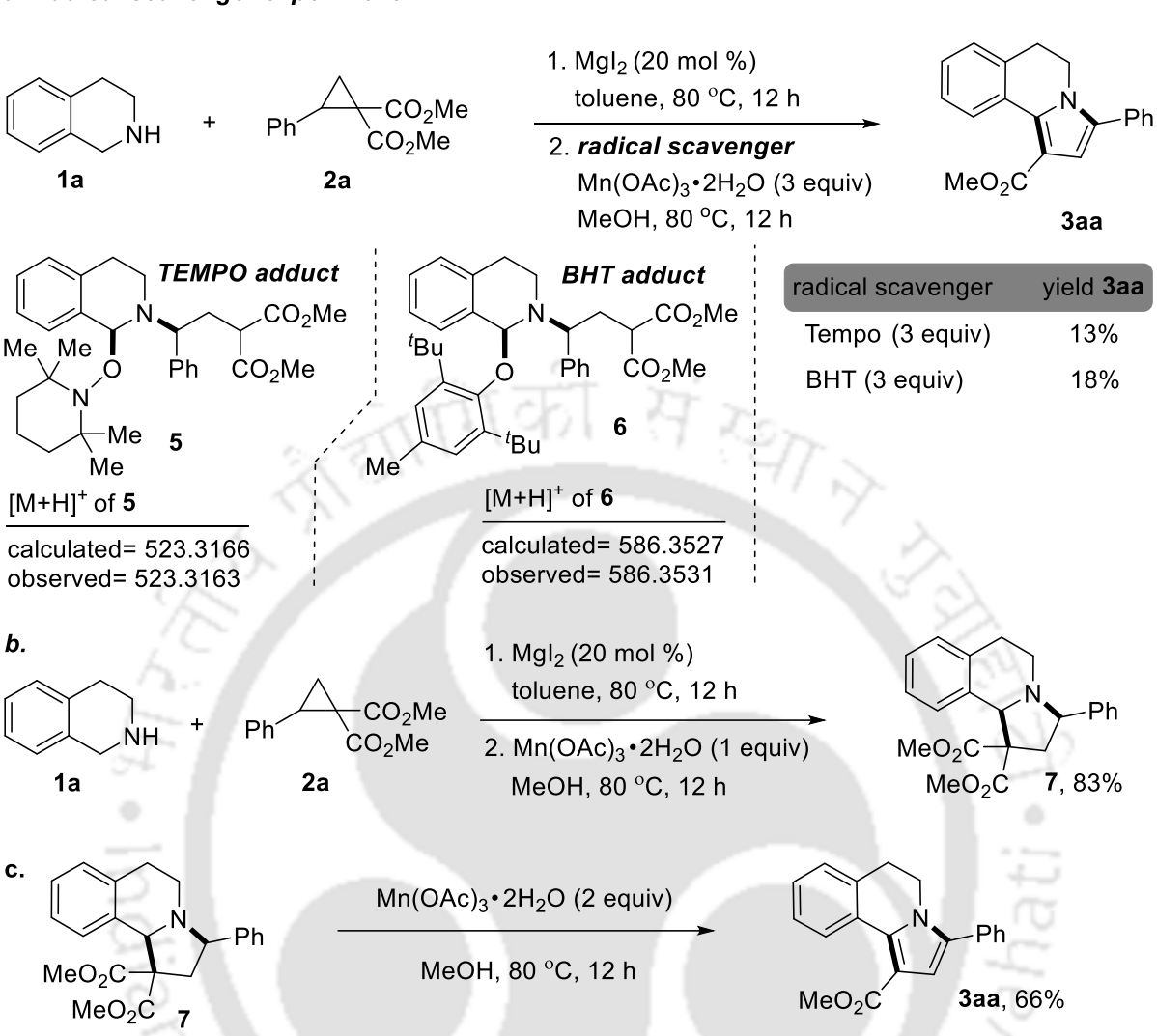
Under these optimized conditions the scope of the procedure was explored using a series of DACs **2a-q** and cyclic secondary amines **1a-f** for the synthesis of product **3ab-an, 3bo-bq** and **3ba-fa** in one-pot (Table 3). DAC with 2-methyl group in aryl ring **2b** delivered trace amount of **3ab** may be due to steric congestion. The substrate containing 3-bromo **2c** produced target product **3ac** in 53% yield while electron deficient 3-trifluoromethyl **2d** provided only a trace amount of **3ad**. Furthermore, a myriad of DACs with 4-bromo **2e**, 4-fluoro **2f**, 4-methyl **2g**, 4-methoxy **2h** and 4-phenyl **2j** substituents reacted to furnish **3ae-aj** in 52-68% yield. The structure of **3ag** was determined using a single-crystal X-ray analysis (CCDC 2290607, see SI). In contrast, electron withdrawing 4-nitro **2i** found to deliver only trace amount of product **3ai**. However, polyaromatic and heteroaryl DACs **2k** and **2l** were successfully reacted to afford **3ak** and **3al** in 67% and 61% yield, respectively, whereas, vinyl cyclopropane **2m** was an unsuccessful substrate. Furthermore, 1,1-carboxylate variants of DAC with diethyl group **2n** delivered **3an** in 60% yield. To showcase the synthetic versatility, DACs tethered with biologically active molecules were investigated. DACs derived from cholesterol **2o**, (–)-

borneol **2p** and *k*-opioid receptor agonist *L*-menthol **2q** successfully tolerated with amine **1b** to produce **3bo-bq** in 39-46% yields.

The scope of cyclic amines **1b-f** was then examined employing DAC **2a** as a standard substrate. Tetrahydroisoquinolines (THIQs) with various functionalities such as 6,7-dimethoxy **1b**, 5-bromo **1c** and 6-bromo **1d** reacted with DAC **2a** to furnish **3ba-da** in 47-72% yield. Furthermore, thiophene fused amine **1e** and tetrahydro-1*H*-benzo[*b*]azepine **1f** were well tolerated to afford **3ea** and **3fa** in 54% and 51% yields, respectively.

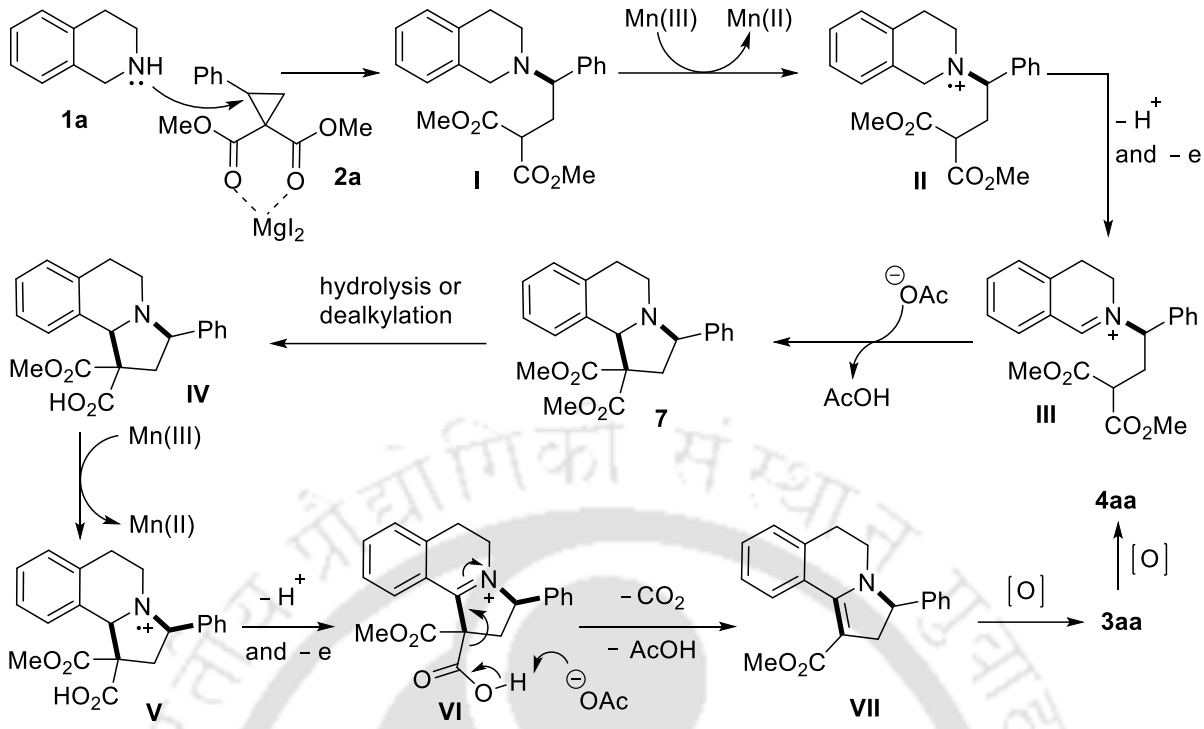
The scope of the procedure was further evaluated for the synthesis of **4** using a series of cyclic amines **1** and DACs **2** (Table 4). First, we varied the DACs **2** taking THIQ **1a** as a standard substrate. DACs bearing 3-bromo **2c**, 4-bromo **2e**, 4-methoxy **2h** and 2-bromo-5-fluoro **2r** substituents in the aryl ring were found to deliver **4ac**, **4ae**, **4ah** and **4ar**, in 40-49% yields, whereas diethyl-1,1-carboxylate DAC **2n** produced a trace amount of **4an**. Likewise, THIQs with 6,7-dimethoxy **1b** and 5-bromo **1c** favored the formation of **4ba** and **4ca** in 55% and 38% yields, respectively, whereas 6-bromo **1d** group was unsuccessful substrate. However, thiophene fused amine **1e** underwent to reaction to furnish **4ea** in 42% yield.

Next, we turned our attention to the mechanistic investigations. In the presence of radical scavengers such as, 2,2,6,6-tetramethyl-1-piperi-dinyloxy (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT), the reaction of **1a** with **2a** as the representative substrates under standard reaction conditions was investigated (Scheme 6a). The desired reaction was inhibited for the formation of **3aa** in both cases, which suggests that the reaction might involve a radical pathway. The observation further confirmed by the ESI-MS of the reaction mixture, clearly showcases the formation of TEMPO-adduct **5** and BHT-adduct **6**. Next, the reaction using 1 equiv of $Mn(OAc)_3 \cdot 2H_2O$ led to the formation of **7** in 83% yield (Scheme 6b). Further, reaction of **7** using an additional 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ resulted **3aa** in 66% yield, revealing the *in situ* generation of **7** (Scheme 4c). Based on these experimental results and literatures,[8d,12,13,17] a plausible reaction mechanism was proposed (Scheme 7). MgI_2 can catalyze the ring opening of DAC **2a** using THIQ **1a** to give **I,** which can convert to **II** by single electron transfer (SET) **II**. Subsequent deprotonation and intramolecular cyclization can result **7**. Further hydrolysis or dealkylation may furnish **IV**. SET process may lead to the formation **V**, which on deprotonation can give **VI**. Decarboxylation followed by oxidation can lead to the formation of **3aa** and further oxidation can furnish **4aa**.

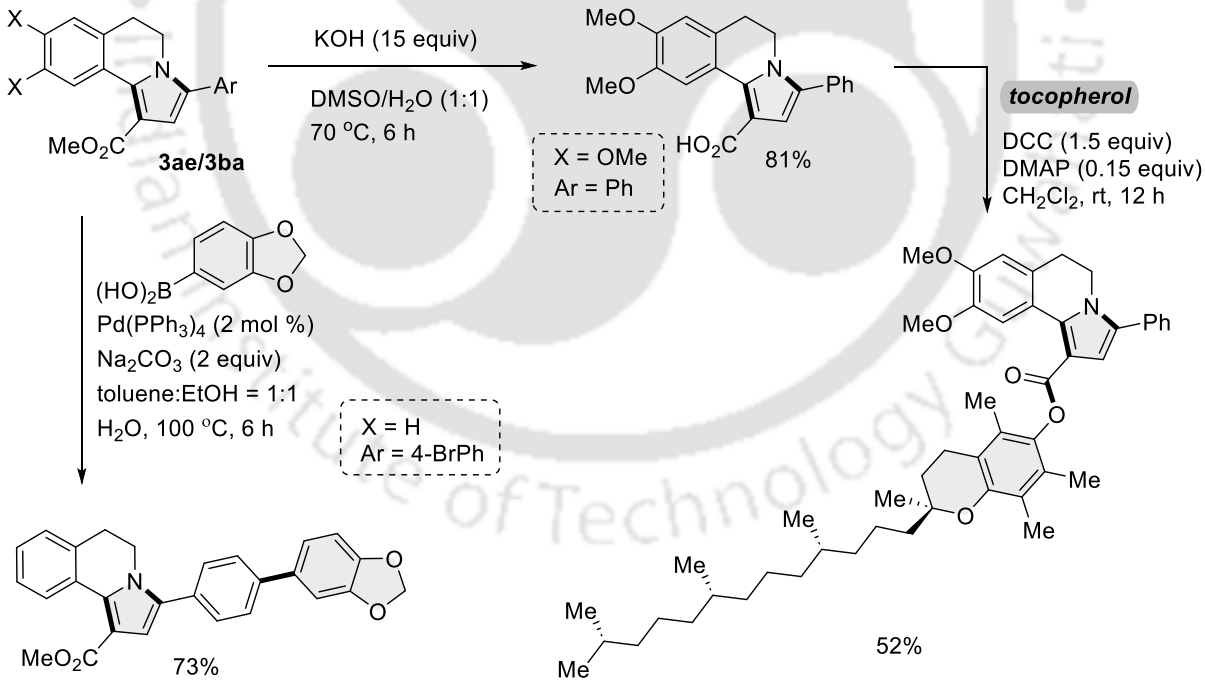


Scheme 6. Control Experiments

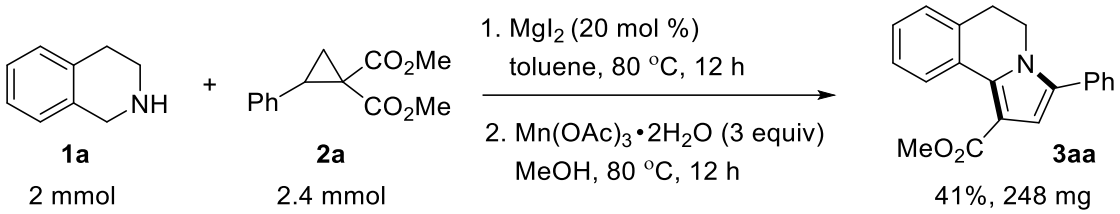
Finally, to explore the synthetic value we performed structural modifications to the products (Scheme 8). For example, a Suzuki C–C cross-coupling of **3ae** with boronic acid of naturally occurring sesamol delivered **8** in 73% yield. Furthermore, the hydrolysis of the ester group of **3ba** in presence of KOH, furnished carboxylic acid **9** in 81% yield, which on further esterification with naturally active tocopherol produced ester **10** in 52% yield. In addition, the scale-up synthesis (2 mmol) was performed employing **1a** and **2a** as representative substrates, and the target product **3aa** was achieved in 41% yield (Scheme 9).



Scheme 7. Plausible Mechanism



Scheme 8. Post-synthetic Utilities



Scheme 9. Scale-up Synthesis

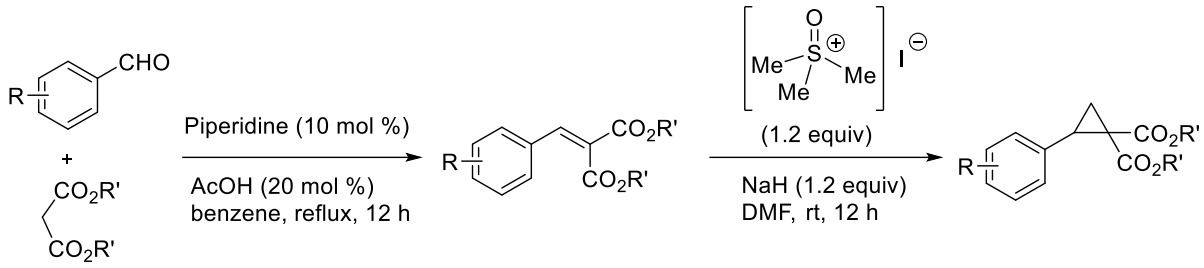
In summary, we described a synergistic action of MgI_2 and $Mn(OAc)_3$•$2H_2O$ salts utilizing cyclic secondary amines and DACs for the construction of synthetically important fused indolizine scaffolds. The CDC between two distinct C(sp^3)–H bonds occurs to give oxidative (3+2)-cyclopentannulation. The substrate scope, one-pot operation and natural product mutations are the practical advantages of the protocol.

3.3 Experimental Section

General Information. 1,2,3,4-Tetrahydroisoquinolines, MgI_2 (98%), $Mn(OAc)_3 \cdot 2H_2O$ (97%), MnO_2 (≥ 99%), 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (98%) of Aldrich, TCI chemicals and BLDpharm were used as received. Solvents were dried prior as per the standard procedure. Cyclopropanes[18] and 2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine[19] were prepared according to the reported procedure. Merck silica gel G/GF254 plates were used for analytical TLC and Rankem silica gel (60-120 mesh) was utilized for column chromatography. NMR spectra were recorded with Bruker Avance III 600, 500 and 400 MHz spectrometers using $CDCl_3$ as solvent and Me_4Si as an internal standard. Chemical shifts (δ) and spin-spin coupling constant (*J*) are reported in ppm and in Hz, respectively, and other data are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, dd = doublet of doublets. Melting points were determined using a Büchi B-540 apparatus and are uncorrected. FT-IR spectra were collected on Perkin Elmer IR spectrometer. UHPLC-QTOF-ESI-MS instrument was used for recording mass spectra. Single crystal X-ray data was collected on a Bruker SMART APEX equipped with a CCD area detector using Mo/K*α* radiation and the structure was solved by direct method using *SHELXL-2014/7* (Göttingen, Germany).

General Procedure for the Preparation of DA Cyclopropanes (GP-1).[18]

Starting cyclopropanes **2a-p** were synthesized from the corresponding aromatic aldehydes through a standard synthetic sequence of Knoevenagel/Corey-Chaykovsky reactions.

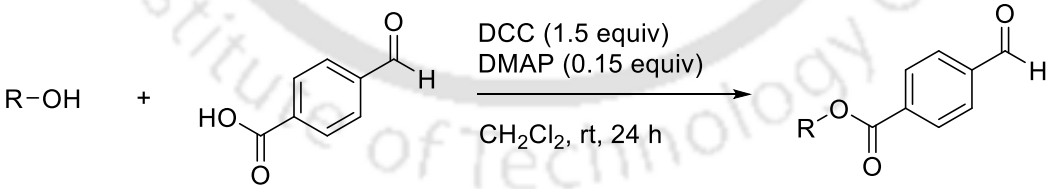


To a stirred solution of aldehyde (5 mmol) in benzene (10 mL), dimethyl malonate (5 mmol, 660 mg), piperidine (0.5 mmol, 50 μL), and acetic acid (0.5 mmol, 28 μL) were added. The flask was equipped with a Dean-Stark trap and condenser, and the solution was heated to reflux in an oil bath for 12 h. After completion, evaporation of the solvent gave a residue that was purified by silica gel column chromatography using ethyl acetate and hexane.

Sodium hydride (4 mmol, 60% dispersion in mineral oil, 96 mg) was suspended in anhydrous dimethylformamide (DMF) (10 mL) under nitrogen. Trimethylsulfoxonium iodide (3.85 mmol, 847 mg) was added, and the solution was stirred for 1 h at room temperature. A solution of the appropriate benzylidene malonate (3.5 mmol) in anhydrous DMF (1 mL) was added, and the reaction mixture was stirred for 12 h at room temperature. After completion, the solution was poured onto a mixture of ice and 2 M HCl (5 mL) and extracted with diethyl ether (25 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on a silica gel column chromatography using hexane and ethyl acetate as an eluent to give cyclopropanes.

General Procedure for the Synthesis of 2o-q.

Step 1: General Procedure for the Synthesis of Aldehydes.[8d]



First, carboxylic acid (1 mmol), dicyclohexylcarbodiimide (DCC) (1.5 mmol, 309 mg), 4-dimethylaminepyridine (DMAP) (0.15 mmol, 18 mg) and alcohol/phenol (1.2 mmol) were stirred in CH_2Cl_2 (10 mL) for 12 h at room temperature. The reaction mixture was then passed through as short pad of celite. The solvent was evaporated and the residue was purified on silica gel chromatography using ethyl acetate/hexane as an eluent.

Step 2: General Procedure for the Synthesis of DA Cyclopropanes. [18]

DA Cyclopropanes were made using GP-1.

General Procedure for the Synthesis of 3. Amine **1** (0.2 mmol), cyclopropane **2** (0.24 mmol) and $Ni(OTf)_2$ (5 mol %, 3.5 mg) were stirred in toluene (2 mL) at 80 ºC for 6 h. The reaction was cooled to room temperature and passed through a short pad of celite using ethyl acetate. Evaporation of the solvent gave a residue that was reacted with $Mn(OAc)_3 \cdot 2H_2O$ (0.6 mmol, 160 mg) in MeOH (2 mL) for 12 h at 80 ºC. The progress of the reaction was monitored by TLC using ethyl acetate and hexane. The reaction mixture was diluted with ethyl acetate (2 x 15 mL) and washed with water (2 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave the residue that was purified on silica gel column chromatography using ethyl acetate and hexane as eluent to afford **3**.

General Procedure for the Synthesis of 4. Amine **1** (0.2 mmol), cyclopropane **2** (0.24 mmol) and $Ni(OTf)_2$ (5 mol %, 3.5 mg) were stirred in toluene (2 mL) at 80 ºC for 6 h. The reaction was cooled to room temperature and passed through a short pad of celite using ethyl acetate. Evaporation of the solvent gave a residue that was reacted with $Mn(OAc)_3 \cdot 2H_2O$ (1.0 mmol, 268 mg) in MeOH (2 mL) for 12 h at 80 ºC. The progress of the reaction was monitored by TLC using ethyl acetate and hexane. The reaction mixture was diluted with ethyl acetate (2 x 15 mL) and washed with water (2 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave the residue that was purified on silica gel column chromatography using ethyl acetate and hexane as eluent to afford **4**.

Scale-up Synthesis of 3aa. 1,2,3,4-Tetrahydroisoquinoline **1a** (2 mmol, 266 mg), dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **2a** (2.4 mmol, 561 mg) and $Ni(OTf)_2$ (5 mol %, 35 mg) were stirred in toluene (10 mL) at 80 ºC for 6 h. The reaction was cooled to room temperature and passed through a short pad of celite using ethyl acetate. Evaporation of the solvent gave a residue that was reacted with $Mn(OAc)_3 \cdot 2H_2O$ (6 mmol, 1.6 g) in MeOH (10 mL) for 12 h at 80 ºC. The progress of the reaction was monitored by TLC using ethyl acetate and hexane. The reaction mixture was diluted with ethyl acetate (2 x 30 mL) and washed with water (2 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave the residue that was purified on silica gel column chromatography using ethyl acetate and hexane as eluent to afford **3aa** in 41% yield (248 mg).

Procedure for the Synthesis of 7. Amine **1a** (0.2 mmol), cyclopropane **2a** (0.24 mmol) and $Ni(OTf)_2$ (5 mol %, 3.5 mg) were stirred in toluene (2 mL) at 80 ºC for 6 h. The reaction was

cooled to room temperature and passed through a short pad of celite using ethyl acetate. Evaporation of the solvent gave a residue that was reacted with $Mn(OAc)_3 \cdot 2H_2O$ (0.2 mmol, 53 mg) in MeOH (2 mL) for 12 h at 80 ºC. The progress of the reaction was monitored by TLC using ethyl acetate and hexane. The reaction mixture was diluted with ethyl acetate (2 x 15 mL) and washed with water (2 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave the residue that was purified on silica gel column chromatography using ethyl acetate and hexane as eluent to afford **7**.

Procedures for the Post-Synthetic Modifications

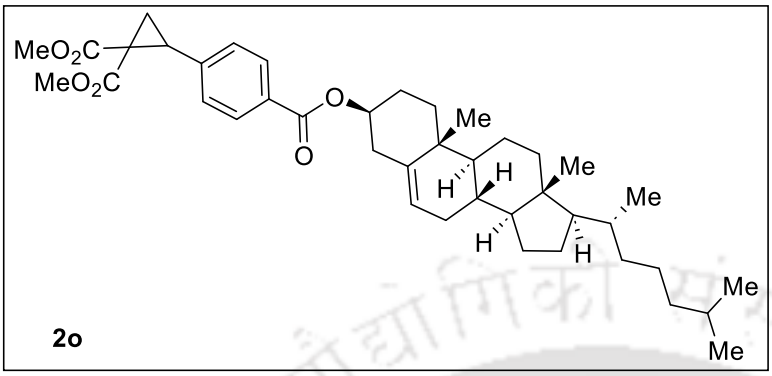
Synthesis of 8.[8d] Compound **3ae** (38 mg, 0.1 mmol), benzo[*d*][1,3]dioxol-5-ylboronic acid (0.1 mmol, 16 mg), $Pd(PPh_3)_4$ (0.002 mmol, 2.3 mg), Na_2CO_3 (0.2 mmol, 22 mg), H_2O (50 μL) and toluene:EtOH (1:1, 2 mL) were refluxed at 100 ºC for 6 h under nitrogen atmosphere. The reaction mixture was cooled to room temperature 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 to give **8**.

Synthesis of 9.[20] Compound **3ba** (0.2 mmol, 69 mg), KOH (3.00 mmol, 168 mg), DMSO (3 mL) and H_2O (3 mL) were subjected to stir at 70 °C in an oil bath for 6 h. The progress of the reaction was monitored by TLC using ethyl acetate and hexane. After completion of the reaction 3 M HCl was added until the pH = 1. The mixture was then extracted with Et_2O (3 x 15 mL). The combined organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue that was purified on silica gel column chromatography to give **9** in 81% yield.

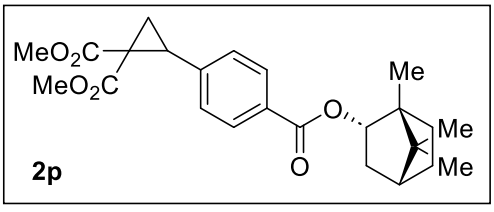
Synthesis of 10.[8d] Compound **9** (0.1 mmol, 34 mg), dicyclohexylcarbodiimide (DCC) (0.15 mmol, 30 mg), 4-dimethylaminepyridine (DMAP) (0.015 mmol, 1.8 mg) and tocopherol (0.12 mmol, 43 mg) were stirred in CH_2Cl_2 (1 mL) for 12 h at room temperature. The reaction mixture was then passed through as short pad of celite. The solvent was evaporated and the residue was purified on silica gel chromatography using ethyl acetate/hexane as an eluent to get **10** in 52% yield.

3.4 Characterization Data

3.4.1 Characterization Data of the Newly Synthesized Starting Materials

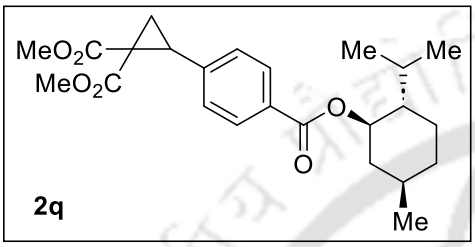


Dimethyl 2-(4-((((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl)oxy)carbonyl)phenyl)cyclopropane-1,1-dicarboxylate 2o. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane; R_f = 0.34; colorless solid; mp 97-98 ^oC; yield 63% (1.42 g); ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 5.41 (d, *J* = 4.0 Hz, 1H), 4.87-4.79 (m, 1H), 3.79 (s, 3H), 3.38 (s, 3H), 3.24 (t, *J* = 8.4 Hz, 1H), 2.46 (d, *J* = 7.6 Hz, 2H), 2.22 (dd, *J* = 8.0, 5.2 Hz, 1H), 2.03-1.96 (m, 3H), 1.93-1.88 (m, 1H), 1.86-1.81 (m, 1H), 1.79-1.76 (m, 1H), 1.74-1.68 (m, 1H), 1.62-1.45 (m, 7H), 1.40-1.31 (m, 3H), 1.27-1.23 (m, 2H), 1.21-1.20 (m, 1H), 1.18-1.17 (m, 1H), 1.13-1.11 (m, 2H), 1.10-1.09 (m, 1H), 1.06 (s, 3H), 1.03-0.96 (m, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.87 (dd, *J* = 6.8, 1.6 Hz, 6H), 0.69 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 166.9, 165.8, 139.9, 139.7, 130.0, 129.5, 128.4, 122.9, 74.8, 56.8, 56.2, 53.0, 52.5, 50.1, 42.4, 39.8, 39.6, 38.3, 37.6, 37.1, 36.7, 36.3, 35.9, 32.2, 32.07, 32.02, 28.3, 28.1, 28.0, 24.4, 23.9, 22.9, 22.7, 21.1, 19.5, 19.3, 18.8, 12.0; FT-IR (neat) 3420, 2934, 2867, 1714, 1612, 1438, 1333, 1274, 1115, 1020 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{41}H_{59}O_6$: 647.4306, found: 647.4308.

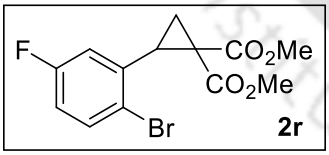


Dimethyl 2-(4-((((1*R*,2*S*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)oxy)carbonyl)phenyl)cyclopropane-1,1-dicarboxylate 2p. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane; R_f = 0.33; thick liquid; yield 68% (987 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.4 Hz, 2H), 7.27-7.25 (m, 2H), 5.10 (d, *J* = 9.6 Hz,

1H), 3.80 (s, 3H), 3.40 (s, 3H), 3.25 (t, *J* = 8.4 Hz, 1H), 2.50-2.42 (m, 1H), 2.22 (dd, *J* = 8.0, 5.6 Hz, 1H), 2.14-2.08 (m, 1H), 1.79 (dd, *J* = 9.2, 5.2 Hz, 2H), 1.73 (t, *J* = 4.4 Hz, 1H), 1.44-1.37 (m, 1H), 1.33-1.28 (m, 1H), 1.12 (d, *J* = 14.0 Hz, 1H), 0.96 (s, 3H), 0.91 (d, *J* = 4.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 166.9, 166.6, 139.9, 130.1, 129.5, 128.5, 80.7, 53.0, 52.5, 49.1, 47.9, 45.1, 37.6, 36.9, 32.2, 28.1, 27.5, 19.8, 19.3, 19.0, 13.7; FT-IR (neat) 2953, 2879, 1713, 1612, 1436, 1330, 1269, 1217, 1114, 1020 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{31}O_6$: 415.2115, found: 415.2115.

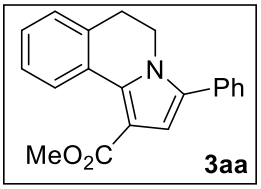


Dimethyl 2-(4-((((1*R*,2*S*,5*R*)-2-isopropyl-5-methyl cyclohexyl)oxy)carbonyl)phenyl)cyclo propane-1,1-dicarboxylate 2q. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane; R_f = 0.37; thick liquid; yield 65% (948 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.0 Hz, 2H), 7.27-7.24 (m, 2H), 4.94-4.88 (m, 1H), 3.80 (s, 3H), 3.40 (s, 3H), 3.25 (t, *J* = 8.4 Hz, 1H), 2.22 (dd, *J* = 7.6, 5.2 Hz, 1H), 2.12 (d, *J* = 11.6 Hz, 1H), 1.97-1.90 (m, 1H), 1.80-1.71 (m, 4H), 1.60-1.49 (m, 2H), 1.15-1.07 (m, 2H), 0.92 (dd, *J* = 6.4, 4.0 Hz, 6H), 0.79 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 166.8, 165.9, 139.8, 130.0, 129.5, 128.4, 75.0, 53.0, 52.5, 47.3, 41.0, 37.5, 34.4, 32.2, 31.5, 26.5, 23.7, 22.1, 20.8, 19.3, 16.6; FT-IR (neat) 2953, 2869, 1728, 1711, 1612, 1436, 1330, 1267, 1217, 1178, 1111, 1019 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{33}O_6$: 417.2272, found: 417.2275.

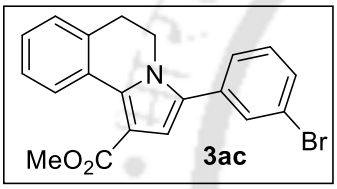


Dimethyl 2-(2-bromo-5-fluorophenyl)cyclopropane-1,1-dicarboxylate 2r. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane; R_f = 0.42; colorless solid; mp 53-54 °C; yield 72% (831 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 8.8, 5.6 Hz, 1H), 6.88-6.81 (m, 2H), 3.82 (s, 3H), 3.42 (s, 3H), 3.29 (t, *J* = 8.8 Hz, 1H), 2.18 (dd, *J* = 8.4, 5.6 Hz, 1H), 1.81 (dd, *J* = 9.2, 5.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 166.8, 162.7 (J_{C-F} = 245.37 Hz), 136.9 (J_{C-F} = 7.87 Hz), 133.7 (J_{C-F} = 7.87 Hz), 121.0 (J_{C-F} = 3.25 Hz), 116.7 (J_{C-F} = 23.75 Hz), 116.3 (J_{C-F} = 22 Hz), 53.1, 52.5, 36.6, 33.5, 19.5; FT-IR (neat) 2952, 1727, 1582, 1470, 1437, 1328, 1287, 1271, 1212, 1130, 1038 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{13}H_{13}BrFO_4$: 330.9976, found: 330.9981.

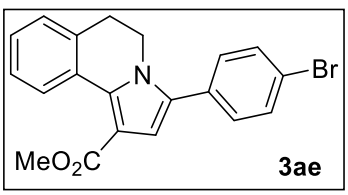
4.4.2 Characterization Data of the Products



Methyl 3-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-1-carboxylate 3aa. Analytical TLC on silica gel, 1:49 ethyl acetate/hexane; R_f = 0.42; thick liquid; yield 64% (38 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (d, *J* = 8.0 Hz, 1H), 7.45-7.33 (m, 6H), 7.25-7.21 (m, 2H), 6.79 (s, 1H), 4.06 (t, *J* = 6.0 Hz, 2H), 3.86 (s, 3H), 2.95 (t, *J* = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 133.8, 133.59, 133.55, 131.8, 129.1, 128.7, 128.6, 128.1, 127.75, 127.73, 127.3, 127.1, 112.2, 111.8, 51.3, 42.4, 30.3; FT-IR (neat) 2948, 1706, 1603, 1464, 1261, 1200, 1176, 1090, 1010 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{20}H_{18}NO_2$: 304.1332, found: 304.1335.

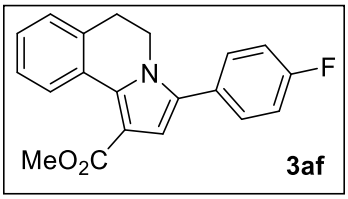


Methyl 3-(3-bromophenyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-1-carboxylate 3ac. Analytical TLC on silica gel, 1:49 ethyl acetate/hexane; R_f = 0.39; colorless solid; mp 94-95 °C; yield 53% (40 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 7.6 Hz, 1H), 7.49 (s, 1H), 7.43-7.39 (m, 1H), 7.30-7.23 (m, 3H), 7.21-7.14 (m, 2H), 6.74 (s, 1H), 3.98 (t, *J* = 6.4 Hz, 2H), 3.79 (s, 3H), 2.90 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 134.3, 133.9, 133.5, 131.9, 130.6, 130.1, 128.4, 128.2, 127.9, 127.5, 127.3, 127.2, 122.7, 112.9, 112.1, 51.3, 42.5, 30.2; FT-IR (neat) 2947, 1708, 1596, 1470, 1263, 1200, 1178, 1088, 1014 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{20}H_{17}BrNO_2$: 382.0437, found: 382.0437.

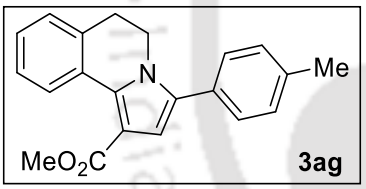


Methyl 3-(4-bromophenyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-1-carboxylate 3ae. Analytical TLC on silica gel, 1:49 ethyl acetate/hexane; R_f = 0.40; colorless solid; mp 93-94 °C; yield 63% (48 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.37-7.33 (m, 1H), 7.27-7.21 (m, 4H), 6.79 (s, 1H), 4.02 (t, *J* = 6.4 Hz, 2H), 3.85 (s, 3H), 2.96 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6,

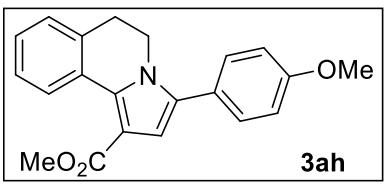
134.1, 133.4, 132.2, 131.9, 130.7, 130.5, 128.4, 128.1, 127.9, 127.3, 127.2, 121.9, 112.5, 112.0, 51.4, 42.4, 30.2; FT-IR (neat) 2924, 1708, 1551, 1483, 1462, 1201, 1177, 1089, 1007 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{20}H_{17}BrNO_2$: 382.0437, found: 382.0438.



Methyl 3-(4-fluorophenyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-1-carboxylate 3af. Analytical TLC on silica gel, 1:49 ethyl acetate/hexane; R_f = 0.37; orange solid; mp 122-123 °C; yield 52% (33 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 8.0 Hz, 1H), 7.30-7.26 (m, 3H), 7.18-7.14 (m, 2H), 7.06 (t, *J* = 8.4 Hz, 2H), 6.68 (s, 1H), 3.94 (t, *J* = 6.4 Hz, 2H), 3.78 (s, 3H), 2.89 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 163.5 (J_{C-F} = 246.3 Hz), 133.8, 133.4, 132.4, 130.9 (J_{C-F} = 8.1 Hz), 128.6, 128.19, 128.11 (J_{C-F} = 3.2 Hz), 127.8, 127.3, 127.2, 115.8 (J_{C-F} = 21.3 Hz), 112.3, 111.9, 51.3, 42.4, 30.3; FT-IR (neat) 2949, 1707, 1560, 1492, 1464, 1262, 1201, 1178, 1088, 1011 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{20}H_{17}FNO_2$: 322.1238, found: 322.1238.

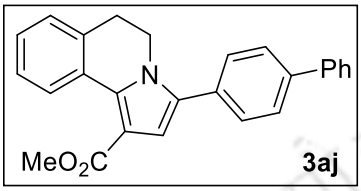


Methyl 3-(*p*-tolyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-1-carboxylate 3ag. Analytical TLC on silica gel, 1:49 ethyl acetate/hexane; R_f = 0.43; colorless solid; mp 97-98 °C; yield 65% (41 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, *J* = 8.0 Hz, 1H), 7.27 (t, *J* = 7.0 Hz, 1H), 7.22-7.13 (m, 6H), 6.68 (s, 1H), 3.97 (t, *J* = 6.5 Hz, 2H), 3.78 (s, 3H), 2.87 (t, *J* = 6.5 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 137.6, 133.6, 133.5, 129.4, 129.08, 129.02, 128.7, 128.1, 127.6, 127.2, 127.1, 111.9, 111.8, 51.3, 42.4, 30.3, 21.3; FT-IR (neat) 2923, 1708, 1493, 1464, 1261, 1200, 1176, 1089, 1018 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{20}NO_2$: 318.1489, found: 318.1491.

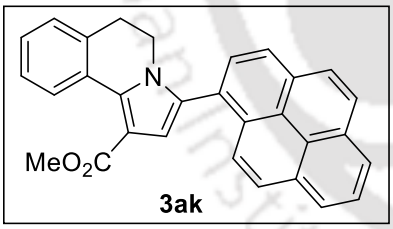


Methyl 3-(4-methoxyphenyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-1-carboxylate 3ah. Analytical TLC on silica gel, 1:49 ethyl acetate/hexane; R_f = 0.38; colorless solid; mp 115-116 °C; yield 68% (45 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44

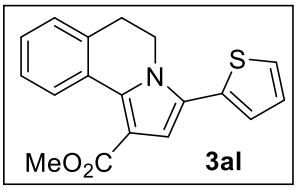
(d, *J* = 7.6 Hz, 1H), 7.29-7.23 (m, 3H), 7.18-7.13 (m, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.65 (s, 1H), 3.94 (t, *J* = 6.4 Hz, 2H), 3.78 (s, 6H), 2.87 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 159.4, 133.5, 133.38, 133.34, 130.4, 128.7, 128.0, 127.6, 127.3, 127.1, 124.3, 114.1, 111.7, 111.6, 55.5, 51.3, 42.2, 30.3; FT-IR (neat) 2947, 1704, 1558, 1493, 1463, 1249, 1200, 1175, 1088, 1036 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{20}NO_3$: 334.1438, found: 334.1438.



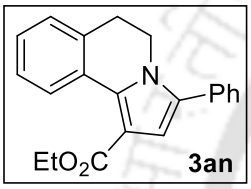
Methyl 3-([1,1'-biphenyl]-4-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-1-carboxylate 3aj. Analytical TLC on silica gel, 1:49 ethyl acetate/hexane; R_f = 0.39; colorless solid; mp 109-110 ^{o}C; yield 59% (44 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 8.0 Hz, 1H), 7.59 (dd, *J* = 15.2, 8.0 Hz, 4H), 7.41-7.37 (m, 4H), 7.32-7.26 (m, 2H), 7.19-7.14 (m, 2H), 6.77 (s, 1H), 4.04 (t, *J* = 6.4 Hz, 2H), 3.79 (s, 3H), 2.90 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 163.5, 161.5, 133.8, 133.4, 132.4, 130.9, 130.8, 128.5, 128.1, 128.03, 128.00, 127.8, 127.3, 127.1, 115.8, 115.6, 112.2, 111.8, 51.3, 42.3, 30.2; FT-IR (neat) 2947, 1706, 1549, 1483, 1463, 1263, 1200, 1176, 1089, 1007 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{26}H_{22}NO_2$: 380.1645, found: 380.1649.



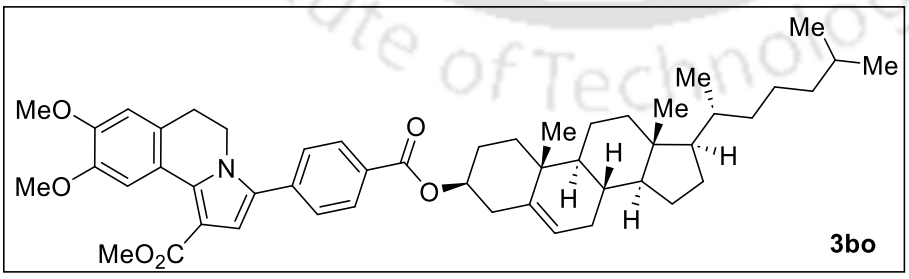
Methyl 3-(pyren-1-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-1-carboxylate 3ak. Analytical TLC on silica gel, 1:49 ethyl acetate/hexane; R_f = 0.41; yellow solid; mp 193-194 ^{o}C; yield 67% (57 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 8.0 Hz, 1H), 8.17-8.12 (m, 3H), 8.08-8.03 (m, 2H), 8.01-7.95 (m, 2H), 7.91 (dd, *J* = 16.0, 8.0 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.20-7.16 (m, 1H), 7.14-7.12 (m, 1H), 6.90 (s, 1H), 3.84 (s, 3H), 3.74-3.69 (m, 1H), 3.66-3.59 (m, 1H), 2.86 (q, *J* = 6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 133.5, 133.4, 131.7, 131.6, 131.4, 131.0, 130.7, 128.9, 128.6, 128.4, 128.2, 128.0, 127.8, 127.5, 127.4, 127.2, 126.6, 126.4, 125.7, 125.5, 124.99, 124.90, 124.7, 124.6, 114.1, 111.9, 51.4, 42.6, 30.1; FT-IR (neat) 2926, 1706, 1524, 1466, 1261, 1202, 1177, 1088, 1020 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{30}H_{22}NO_2$: 428.1645, found: 428.1646.



Methyl 3-(thiophen-2-yl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-1-carboxylate 3al. Analytical TLC on silica gel, 1:49 ethyl acetate/hexane; R_f = 0.37; colorless solid; mp 109-110 °C; yield 61% (37 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, *J* = 8.0 Hz, 1H), 7.28-7.25 (m, 2H), 7.18-7.14 (m, 2H), 7.04-7.03 (m, 1H), 6.97-6.95 (m, 1H), 6.79 (s, 1H), 4.05 (t, *J* = 6.0 Hz, 2H), 3.78 (s, 3H), 2.92 (t, *J* = 6.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.6, 134.2, 133.4, 133.2, 128.3, 128.1, 127.9, 127.6, 127.3, 127.1, 126.8, 126.1, 126.0, 113.6, 111.9, 51.4, 41.9, 30.1; FT-IR (neat) 2924, 1708, 1465, 1333, 1262, 1201, 1176, 1088, 1018 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{18}H_{16}NO_2S$: 310.0896, found: 310.0897.

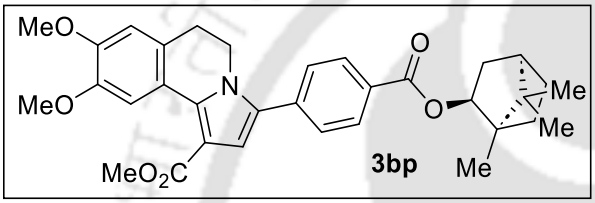


Ethyl 3-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-1-carboxylate 3an. Analytical TLC on silica gel, 1:49 ethyl acetate/hexane; R_f = 0.42; colorless solid; mp 68-69 °C; yield 60% (38 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 8.0 Hz, 1H), 7.46-7.41 (m, 3H), 7.39-7.32 (m, 3H), 7.23-7.20 (m, 2H), 6.81 (s, 1H), 4.34 (q, *J* = 7.2 Hz, 2H), 4.06 (t, *J* = 6.4 Hz, 2H), 2.95 (t, *J* = 6.4 Hz, 2H), 1.38 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.4, 133.6, 133.5, 133.4, 131.9, 129.1, 128.7, 128.6, 128.2, 127.7, 127.6, 127.2, 127.0, 112.32, 112.30, 60.0, 42.4, 30.3, 14.6; FT-IR (neat) 2927, 1701, 1603, 1521, 1484, 1462, 1261, 1198, 1175, 1089, 1036 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{20}NO_2$: 318.1489, found: 318.1492.



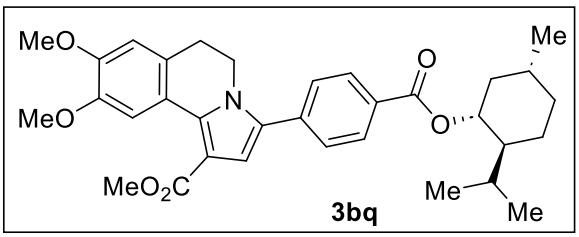
Methyl 3-(4-((((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl)oxy)carbonyl)phenyl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-1-carboxylate 3bo. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.47; colorless solid; mp 144-145 °C; yield

42% (65 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.11 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 6.86 (s, 1H), 6.74 (s, 1H), 5.44 (d, *J* = 4.0 Hz, 1H), 4.92-4.84 (m, 1H), 4.08 (t, *J* = 6.0 Hz, 2H), 3.99 (s, 3H), 3.92 (s, 3H), 3.86 (s, 3H), 2.92 (t, *J* = 6.4 Hz, 2H), 2.49 (d, *J* = 7.6 Hz, 2H), 2.04-1.91 (m, 5H), 1.86-1.73 (m, 3H), 1.56-1.46 (m, 7H), 1.41-1.32 (m, 4H), 1.28-1.22 (m, 5H), 1.16-1.12 (m, 3H), 1.08 (s, 3H), 1.03-0.98 (m, 3H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.88-0.86 (m, 6H), 0.69 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.8, 165.7, 148.7, 147.7, 139.7, 136.1, 135.1, 132.1, 129.9, 129.6, 128.5, 126.4, 123.0, 121.2, 113.3, 112.0, 111.2, 110.4, 74.9, 60.5, 56.8, 56.2, 56.1, 51.4, 50.2, 42.8, 42.4, 39.8, 39.6, 38.3, 37.1, 36.8, 36.3, 35.9, 32.09, 32.04, 29.7, 28.3, 28.1, 28.0, 24.4, 23.9, 22.9, 22.7, 21.2, 19.5, 18.8, 12.0; FT-IR (neat) 2933, 2867, 1707, 1607, 1501, 1468, 1271, 1251, 1200, 1171, 1145, 1088, 1028 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{50}H_{66}NO_6$: 776.4885, found: 776.4877.



3bp

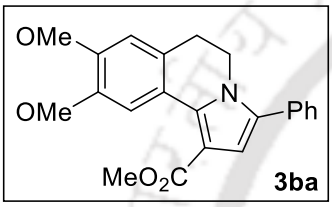
Methyl 8,9-dimethoxy-3-(4-((((1*R*,2*S*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)oxy)carbonyl)phenyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-1-carboxylate 3bp. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.42; colorless solid; mp 84-85 °C; yield 39% (42 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.13 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 6.87 (s, 1H), 6.74 (s, 1H), 5.16 (d, *J* = 10.0 Hz, 1H), 4.08 (t, *J* = 6.4 Hz, 2H), 3.99 (s, 3H), 3.92 (s, 3H), 3.86 (s, 3H), 2.92 (t, *J* = 6.4 Hz, 2H), 2.53-2.46 (m, 1H), 2.18-2.12 (m, 1H), 1.87-1.79 (m, 1H), 1.75 (t, *J* = 4.4 Hz, 1H), 1.36-1.29 (m, 2H), 1.15 (dd, *J* = 14.0, 3.6 Hz, 1H), 0.98 (s, 3H), 0.93 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.6, 165.7, 148.7, 147.8, 136.2, 135.1, 132.1, 129.9, 129.6, 128.5, 126.4, 121.2, 113.3, 112.0, 111.2, 110.4, 80.8, 56.3, 56.1, 51.4, 49.2, 48.0, 45.1, 42.8, 37.1, 28.2, 27.5, 19.8, 19.0, 13.7; FT-IR (neat) 2952, 1706, 1608, 1530, 1501, 1470, 1455, 1272, 1250, 1200, 1171, 1117, 1088, 1017 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{33}H_{38}NO_6$: 544.2694, found: 544.2693.



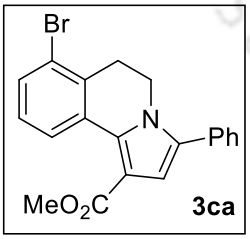
3bq

Methyl 3-(4-((((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl)oxy)carbonyl)phenyl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoqui-

noline-1-carboxylate 3bq. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.44; thick liquid; yield 46% (50 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.11 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 6.86 (s, 1H), 6.74 (s, 1H), 4.99-4.92 (m, 1H), 4.08 (t, *J* = 6.4 Hz, 2H), 3.99 (s, 3H), 3.92 (s, 3H), 3.86 (s, 3H), 2.92 (t, *J* = 6.4 Hz, 2H), 2.16 (d, *J* = 12.0 Hz, 1H), 2.01-1.94 (m, 1H), 1.77-1.71 (m, 2H), 1.62-1.53 (m, 3H), 1.13 (q, *J* = 11.6 Hz, 2H), 0.94 (dd, *J* = 6.4, 3.2 Hz, 6H), 0.82 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 165.7, 148.7, 147.7, 136.1, 135.0, 132.1, 129.9, 129.6, 128.5, 126.4, 121.2, 113.3, 112.0, 111.2, 110.4, 75.1, 56.2, 56.0, 51.4, 47.4, 42.8, 41.1, 34.4, 31.6, 29.7, 26.7, 23.7, 22.1, 20.9, 16.6; FT-IR (neat) 2952, 2869, 1704, 1608, 1501, 1469, 1455, 1336, 1272, 1250, 1200, 1172, 1089, 1029 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{33}H_{40}NO_6$: 546.2850, found: 546.2851.

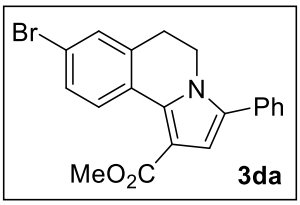


Methyl 8,9-dimethoxy-3-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-1-carboxylate 3ba. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.45; orange solid; mp 125-126 °C; yield 72% (52 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.45-7.33 (m, 5H), 6.77 (s, 1H), 6.72 (s, 1H), 4.04 (t, *J* = 6.4 Hz, 2H), 3.99 (s, 3H), 3.91 (s, 3H), 3.85 (s, 3H), 2.89 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.9, 148.5, 147.7, 134.1, 133.0, 131.9, 129.0, 128.6, 127.6, 126.3, 121.5, 112.1, 111.9, 110.8, 110.4, 56.2, 56.0, 51.3, 42.5, 29.7; FT-IR (neat) 2947, 1701, 1528, 1496, 1472, 1288, 1248, 1202, 1171, 1090 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{22}NO_4$: 364.1543, found: 364.1546.

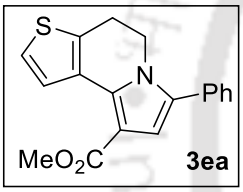


Methyl 7-bromo-3-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-1-carboxylate 3ca. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane; R_f = 0.44; colorless solid; mp 86-87 °C; yield 52% (39 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 8.0 Hz, 1H), 7.47 (dd, *J* = 14.0, 8.0 Hz, 3H), 7.40-7.36 (m, 3H), 7.21 (t, *J* = 8.0 Hz, 1H), 6.82 (s, 1H), 4.06 (t, *J* = 6.8 Hz, 2H), 3.85 (s, 3H), 3.13 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.7, 133.6, 133.1, 132.7, 131.6, 131.5, 130.6, 129.0, 128.7, 128.2, 127.9, 127.3, 123.1, 112.6,

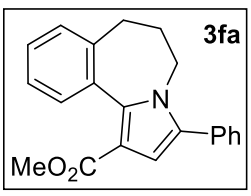
112.5, 51.4, 42.0, 29.8; FT-IR (neat) 2925, 1709, 1552, 1456, 1284, 1222, 1198, 1173, 1146, 1097 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{20}H_{17}BrNO_2$: 382.0437, found: 382.0454.



Methyl 8-bromo-3-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline -1-carboxylate 3da. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane; R_f = 0.43; thick liquid; yield 47% (35 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 8.4 Hz, 1H), 7.47-7.42 (m, 3H), 7.39-7.35 (m, 4H), 6.79 (s, 1H), 4.04 (t, *J* = 6.8 Hz, 2H), 3.85 (s, 3H), 2.93 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 135.5, 133.8, 132.8, 131.6, 130.25, 130.23, 129.7, 129.1, 128.7, 127.9, 127.6, 121.3, 112.4, 112.2, 51.4, 42.1, 30.0; FT-IR (neat) 2925, 1705, 1568, 1461, 1260, 1201, 1176, 1096, 1081, 1009 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{20}H_{17}BrNO_2$: 382.0437, found: 382.0437.

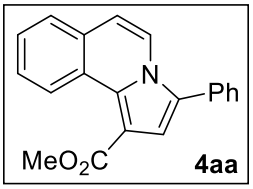


Methyl 7-phenyl-4,5-dihydrothieno[2,3-*g*]indolizine-9-carboxylate 3ea. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane; R_f = 0.41; thick liquid; yield 54% (33 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 5.2 Hz, 1H), 7.46-7.34 (m, 5H), 7.17 (d, *J* = 5.6 Hz, 1H), 6.69 (s, 1H), 4.15 (t, *J* = 6.4 Hz, 2H), 3.85 (s, 3H), 3.09 (t, J = 7.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 133.67, 133.60, 132.2, 132.1, 130.0, 129.1, 128.7, 127.88, 127.80, 122.1, 111.0, 110.1, 51.2, 43.0, 24.8; FT-IR (neat) 2948, 2925, 1704, 1571, 1469, 1436, 1265, 1196, 1090, 1061, 1042 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{18}H_{16}NO_2S$: 310.0896, found: 310.0895.

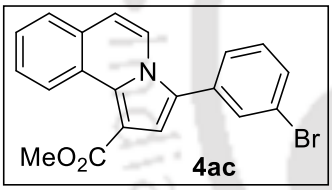


Methyl 3-phenyl-6,7-dihydro-5*H*-benzo[c]pyrrolo[1,2-*a*]azepine-1-carboxylate 3fa. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane; R_f = 0.42; thick liquid; yield 51% (32 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71-7.69 (m, 1H), 7.44-7.42 (m, 4H), 7.37-7.35 (m, 1H), 7.34-7.29 (m, 2H), 7.26-7.25 (m, 1H), 6.77 (s, 1H), 4.12-4.00 (m, 1H), 3.75 (s, 3H), 3.55-3.34 (m, 1H), 2.79-2.74 (m, 2H), 2.63-2.28 (m, 1H), 2.23-1.89 (m, 1H); ^{13}C

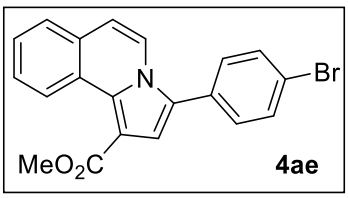
NMR (125 MHz, $CDCl_3$) δ 165.3, 139.1, 138.4, 134.1, 132.6, 131.9, 131.5, 128.8, 128.7, 128.5, 127.8, 126.2, 111.9, 110.9, 51.0, 42.6, 33.1, 30.7; FT-IR (neat) 2947, 2927, 1710, 1603, 1524, 1466, 1408, 1257, 1185, 1095, 1034 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{20}NO_2$: 318.1489, found: 318.1492.



Methyl 3-phenylpyrrolo[2,1-*a*]isoquinoline-1-carboxylate 4aa. Analytical TLC on silica gel, 1:49 ethyl acetate/hexane; R_f = 0.43; colorless solid; mp 90-92 °C; yield 48% (28 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 9.79 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 7.56-7.52 (m, 2H), 7.49-7.42 (m, 5H), 7.38-7.34 (m, 1H), 7.22 (s, 1H), 6.87 (d, *J* = 7.2 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.0, 132.8, 131.3, 129.4, 129.1, 129.0, 128.4, 128.2, 127.8, 127.7, 127.3, 126.7, 126.1, 122.0, 116.5, 113.6, 108.7, 51.6; FT-IR (neat) 2948, 2922, 1702, 1604, 1505, 1458, 1259, 1198, 1151, 1089, 1035 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{20}H_{16}NO_2$: 302.1176, found: 302.1176.

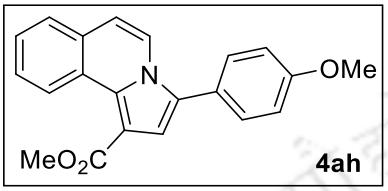


Methyl 3-(3-bromophenyl)pyrrolo[2,1-*a*]isoquinoline-1-carboxylate 4ac. Analytical TLC on silica gel, 1:49 ethyl acetate/hexane; R_f = 0.40; colorless solid; mp 105-106 °C; yield 40% (30 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.64 (t, *J* = 2.0 Hz, 1H), 7.58-7.53 (m, 2H), 7.50-7.40 (m, 3H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.24 (s, 1H), 6.91 (d, *J* = 7.2 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 133.4, 133.1, 132.1, 131.3, 130.6, 129.0, 127.98, 127.94, 127.7, 127.4, 126.8, 126.5, 126.0, 123.2, 121.6, 117.2, 114.1, 108.9, 51.6; FT-IR (neat) 2947, 2924, 1702, 1596, 1504, 1458, 1336, 1259, 1199, 1152, 1088, 1030 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{20}H_{15}BrNO_2$: 380.0281, found: 380.0282.

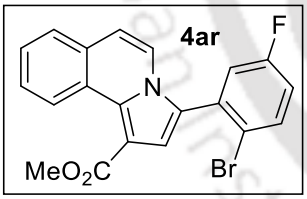


Methyl 3-(4-bromophenyl)pyrrolo[2,1-*a*]isoquinoline-1-carboxylate 4ae. Analytical TLC on silica gel, 1:49 ethyl acetate/hexane; R_f = 0.42; colorless

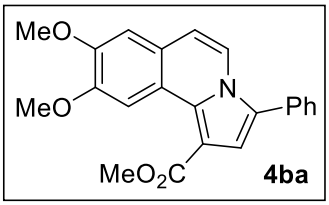
solid; mp 132-133 °C; yield 43% (32 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 1H), 7.66-7.59 (m, 4H), 7.54-7.50 (m, 1H), 7.43-7.40 (m, 2H), 7.29 (s, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 133.0, 132.4, 130.8, 130.2, 128.9, 127.9, 127.8, 127.4, 126.9, 126.8, 126.1, 122.5, 121.6, 116.8, 114.0, 108.9, 51.6; FT-IR (neat) 2948, 2924, 1701, 1547, 1504, 1471, 1458, 1337, 1259, 1199, 1088, 1028 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{20}H_{15}BrNO_2$: 380.0281, found: 380.0279.



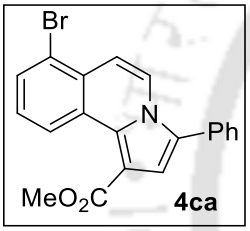
Methyl 3-(4-methoxyphenyl)pyrrolo[2,1-*a*]isoquinoline-1-carboxylate 4ah. Analytical TLC on silica gel, 1:49 ethyl acetate/hexane; R_f = 0.39; colorless solid; mp 99-100 °C; yield 46% (30 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 7.2 Hz, 1H), 7.63-7.58 (m, 2H), 7.52-7.48 (m, 1H), 7.47-7.43 (m, 2H), 7.23 (s, 1H), 7.06-7.02 (m, 2H), 6.93 (d, *J* = 7.2 Hz, 1H), 3.94 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.0, 159.8, 132.4, 130.8, 128.9, 128.0, 127.7, 127.6, 127.3, 126.7, 126.2, 123.6, 122.0, 116.1, 114.6, 113.5, 108.4, 55.5, 51.6; FT-IR (neat) 2949, 2924, 1700, 1564, 1511, 1496, 1458, 1336, 1250, 1200, 1088, 1035 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{18}NO_3$: 332.1281, found: 332.1278.



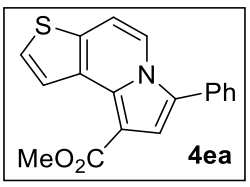
Methyl 3-(2-bromo-5-fluorophenyl)pyrrolo[2,1-*a*]isoquinoline-1-carboxylate 4ar. Analytical TLC on silica gel, 1:49 ethyl acetate/hexane; R_f = 0.43; colorless solid; mp 106-107 °C; yield 49% (39 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (d, *J* = 8.4 Hz, 1H), 7.64 (dd, *J* = 8.8, 5.2 Hz, 1H), 7.59-7.54 (m, 2H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.24 (s, 1H), 7.14 (dd, *J* = 8.4, 3.2 Hz, 1H), 7.05-7.00 (m, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 163.2 ($J_{C\text{-}F}$ = 247.7 Hz), 134.7 ($J_{C\text{-}F}$ = 8.2 Hz), 134.2 ($J_{C\text{-}F}$ = 8.6 Hz), 132.6, 129.0, 127.98, 127.91, 127.5, 126.8, 125.9, 125.3, 122.3, 120.7 ($J_{C\text{-}F}$ = 22.4 Hz), 120.1 ($J_{C\text{-}F}$ = 3.5 Hz), 118.1 ($J_{C\text{-}F}$ = 22 Hz), 117.5, 113.8, 108.5, 51.6; FT-IR (neat) 2949, 2924, 1701, 1575, 1504, 1479, 1458, 1335, 1260, 1198, 1089, 1060, 1024 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{20}H_{14}BrFNO_2$: 398.0186, found: 398.0198.



Methyl 8,9-dimethoxy-3-phenylpyrrolo[2,1-*a*]isoquinoline-1-carboxylate 4ba. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.46; orange solid; mp 111-112 °C; yield 55% (39mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.99 (d, *J* = 7.6 Hz, 1H), 7.56-7.48 (m, 4H), 7.44-7.40 (m, 1H), 7.28 (s, 1H), 7.02 (s, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 4.15 (s, 3H), 4.00 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.1, 149.6, 149.4, 133.3, 131.5, 129.3, 129.1, 128.2, 127.4, 124.0, 120.9, 120.5, 116.7, 113.0, 109.2, 107.0, 106.7, 56.5, 56.0, 51.5; FT-IR (neat) 2950, 2927, 1693, 1604, 1519, 1494, 1479, 1434, 1331, 1251, 1196, 1143, 1090, 1046 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{20}NO_4$: 362.1387, found: 362.1387.

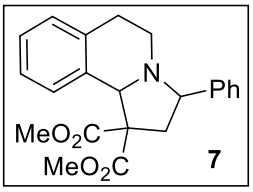


Methyl 7-bromo-3-phenylpyrrolo[2,1-*a*]isoquinoline-1-carboxylate 4ca. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane; R_f = 0.45; colorless solid; mp 120-121 °C; yield 38% (28 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (d, *J* = 8.4 Hz, 1H), 8.10 (d, *J* = 7.6 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.55-7.50 (m, 4H), 7.47-7.41 (m, 3H), 7.34 (s, 1H), 3.95 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.9, 131.7, 131.6, 130.9, 129.3, 129.2, 128.6, 128.4, 128.3, 127.9, 127.8, 126.8, 123.2, 121.5, 117.2, 112.1, 109.4, 51.7; FT-IR (neat) 2955, 2923, 1701, 1544, 1502, 1445, 1338, 1206, 1197, 1152, 1095, 1038 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{20}H_{15}BrNO_2$: 380.0281, found: 380.0296.

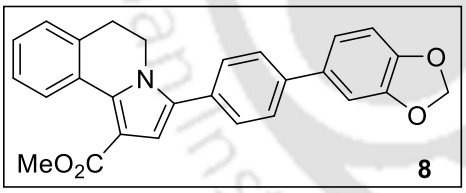


Methyl 7-phenylthieno[2,3-*g*]indolizine-9-carboxylate 4ea. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane; R_f = 0.42; thick liquid; yield 42% (25 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (d, *J* = 5.6 Hz, 1H), 8.12 (d, *J* = 7.2 Hz, 1H), 7.55-7.48 (m, 5H), 7.44-7.39 (m, 1H), 7.26-7.25 (m, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.4, 134.9, 132.7, 131.5, 129.9, 129.22, 129.21, 128.3, 127.34, 127.32, 125.1, 120.4, 115.6, 108.0, 104.7, 51.2; FT-IR (neat) 2948, 2927, 1695, 1622, 1510, 1474,

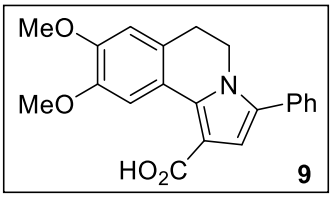
1437, 1413, 1320, 1279, 1208, 1196, 1089, 1057, 1018 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{18}H_{14}NO_2S$: 308.0740, found: 308.0737.



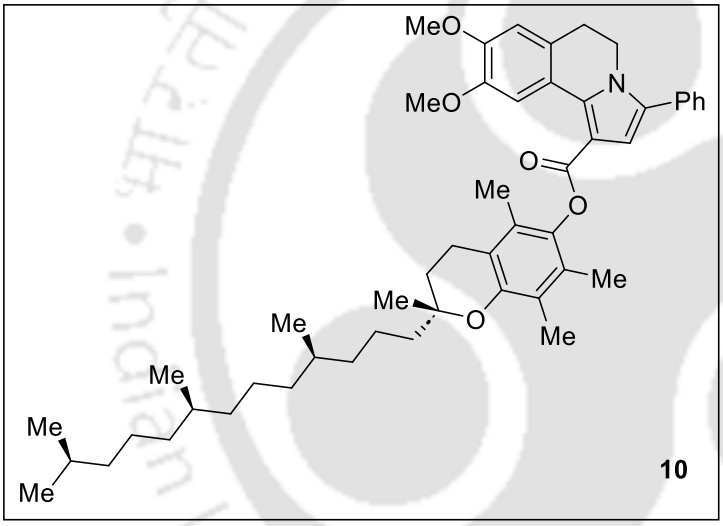
Dimethyl 3-phenyl-2,3,6,10b-tetrahydropyrrolo[2,1-a]isoquinoline-1,1(5*H*) dicarboxy-late 7. Analytical TLC on silica gel, 1:49 ethyl acetate/hexane; R_f = 0.36; thick liquid; yield 83% (60 mg); 1.05:1 mixture of diastereomers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.44 (m, 5H), 7.42-7.39 (m, 1H), 7.37-7.32 (m, 4H), 7.31 -7.26 (m, 2H), 7.14-7.04 (m, 6H), 5.60 (s, 1H), 4.66 (dd, *J* = 10.0, 6.0 Hz, 0.95H), 4.31 (s, 0.95H), 3.87 (s, 2.86H), 3.78 (s, 3H), 3.53 (t, *J* = 8.4 Hz, 1H), 3.44 (s, 2.85H), 3.11 (s, 3H), 3.07-3.00 (m, 1H), 2.93-2.86 (m, 3H), 2.82-2.71 (m, 4H), 2.65 (dd, *J* = 12.0, 3.2 Hz, 1H), 2.39-2.35 (m, 1H), 2.33-3.27 (m, 1H), 2.20 (dd, *J* = 13.2, 9.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 172.0, 171.0, 170.9, 142.9, 141.4, 137.3, 135.8, 135.5, 134.4, 128.7, 128.66, 128.62, 128.5, 128.25, 128.24, 127.7, 127.5, 127.4, 126.9, 126.5, 126.2, 125.5, 125.0, 70.1, 66.8, 65.8, 65.6, 65.5, 61.8, 52.9, 52.8, 52.2, 51.9, 46.2, 44.5, 43.7, 43.3, 30.2, 24.6; FT-IR (neat) 2953, 1730, 1652, 1604, 1493, 1437, 1266, 1214, 1156, 1065, 1030 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{24}NO_4$: 366.1700, found: 366.1708.



Methyl 3-(4-(benzo[*d*][1,3]dioxol-5-yl)phenyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-1-carboxylate 8. Analytical TLC on silica gel, 1:49 ethyl acetate/hexane; R_f = 0.40; colorless solid; mp 64-65 ^{o}C; yield 73% (30 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.37-7.33 (m, 1H), 7.25-7.22 (m, 2H), 7.11-7.09 (m, 2H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.83 (s, 1H), 6.02 (s, 2H), 4.10 (t, *J* = 6.4 Hz, 2H), 3.86 (s, 3H), 2.97 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 148.4, 147.4, 140.2, 134.9, 133.9, 133.6, 133.2, 130.4, 129.4, 128.6, 128.1, 127.7, 127.3, 127.1, 127.0, 120.7, 112.3, 111.9, 108.8, 107.6, 101.3, 51.3, 42.5, 30.3; FT-IR (neat) 2950, 2924, 1705, 1504, 1479, 1463, 1337, 1263, 1225, 1201, 1177, 1089, 1038 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{27}H_{22}NO_4$: 424.1543, found: 424.1546.



8,9-Dimethoxy-3-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline -1-carboxylic acid 9. Analytical TLC on silica gel, 1:1 ethyl acetate/hexane; R_f = 0.39; colorless solid; mp 203-204 ºC; yield 81% (56 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.46-7.35 (m, 5H), 6.86 (s, 1H), 6.74 (s, 1H), 4.06 (t, *J* = 6.4 Hz, 2H), 3.97 (s, 3H), 3.92 (s, 3H), 2.92 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 148.7, 147.7, 135.3, 133.3, 131.8, 129.1, 128.7, 127.7, 126.5, 121.2, 112.9, 112.1, 110.4, 109.8, 56.19, 56.13, 42.6, 29.7; FT-IR (neat) 2931, 1675, 1555, 1528, 1494, 1474, 1336, 1292, 1267, 1240, 1212, 1146, 1094, 1055 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{20}NO_4$: 350.1387, found: 350.1387.



(R)-2,5,7,8-tetramethyl-2((4R,8R)-4,8,12-trimethyltridecyl)chroman-6-yl 8,9-dimethoxy-3-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-1-carboxylate 10. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.40; thick liquid; yield 52% (39 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.48-7.44 (m, 3H), 7.41-7.36 (m, 1H), 7.03 (s, 1H), 6.73 (s, 1H), 4.10 (t, *J* = 6.4 Hz, 2H), 3.91 (d, *J* = 8.0 Hz, 6H), 2.95 (t, *J* = 6.8 Hz, 2H), 2.62 (t, *J* = 6.8 Hz, 2H), 2.12 (d, *J* = 3.6 Hz, 6H), 2.08 (s, 3H), 1.86-1.81 (m, 1H), 1.54-1.49 (m, 3H), 1.43-1.35 (m, 3H), 1.31-1.23 (m, 12H), 1.16-1.07 (m, 7H), 0.87-0.83 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.9, 149.3, 148.6, 147.8, 140.8, 135.0, 133.1, 132.0, 129.2, 128.7, 127.7, 127.5, 126.3, 125.7, 123.0, 121.4, 117.4, 112.7, 112.0, 110.4, 110.3, 75.1, 56.4, 56.0, 42.7, 39.5, 37.7, 37.5, 37.4, 32.95, 32.93, 29.7, 28.1, 24.9, 24.6, 23.6, 22.8, 22.7, 21.2, 20.8, 19.9, 19.86, 19.84, 19.79, 19.75, 13.3, 12.4, 12.0; FT-IR (neat) 2947, 2926, 1714, 1527, 1496, 1464, 1377, 1288, 1239, 1193, 1157, 1083, 1050 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{50}H_{68}NO_5$: 762.5092, found: 762.5096.

Crystal Data and Structure Refinement of 3ag

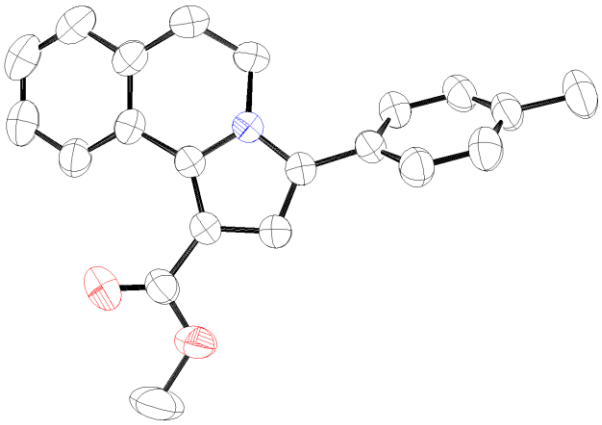


Figure 2. ORTEP diagram of Methyl 3-(*p*-tolyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-1-carboxylate **3ag** with 50% ellipsoid (CCDC 2290607). H-Atoms omitted for clarity.

Identification code	**3ag**
Empirical formula	'C21 H19 N1 O2'
Formula weight	317.37
Crystal habit, colour	Neddle /colourless
Crystal size, mm^3	0.32 x 0.29 x 0.27
Temperature, *T*/K	296 K
Wavelength, λ/Å	0.71073
Crystal system	' monoclinic '
Space group	' P 21/c '
Unit cell dimensions	a = 10.0187(6) Å
	b = 15.8815(10) Å
	c = 10.6953(7) Å
	α = 90
	β = 99.728
	γ = 90
Volume, *V*/$Å^3$	1677.28(18)
Z	4
Calculated density, g cm^{-3}	1.257
Absorption coefficient, μ/mm^{-1}	0.081
F(000)	672
θ range for data collection	2.062 to 28.345°

Limiting indices	$-13 \leq h \leq 12$, $-21 \leq k \leq 21$, $-14 \leq l \leq 14$
Reflection collected / unique	4177/2685
Completeness to θ	99.6% (θ = 28.345°)
Absorption correction	None
Max. and min. transmission	0.974 and 0.978
Refinement method	'SHELXL-2014/7 (Sheldrick, 2014)'
Data / restraints / parameters	4177/0/219
Goodness−of−fit on F^2	0.853
Final *R* indices [*I*>2sigma(*I*)]	R1 = 0.0640, wR2 = 0.1850
R indices (all data)	R1 = 0.1009, wR2 = 0.2209

3.5 References

1. (a) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (b) Blunt, J. W.; Copp, B. R.; Keyzers, R. A.; Munro, M. H. G.; Prinsep, M. R. *Nat. Prod. Rep.* **2012**, *29*, 144. (c) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257. (d) Kacprzak, K.; Skiera, I.; Piasecka, M.; Paryzek, Z. *Chem. Rev.* **2016**, *116*, 5689.
2. (a) Ploypradith, P.; Mahidol, C.; Sahakitpichan, P.; Wongbundit, S.; Ruchirawat, S. A *Angew. Chem., Int. Ed*. **2004**, *43*, 866. (b) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev*. **2008**, *108*, 264. (c) Kakhki, S.; Shahosseini, S.; Zarghi, A. *Iran. J. Pharm. Res.* **2016**, *15*, 743. (d) Toumi, A.; Boudriga, S.; Hamden, K.; Daoud, I.; Askri, M.; Soldera, A.; Lohier, J.-F.; Strohmann, C.; Brieger, L.; Knorr, M. *J. Org. Chem.* **2021**, *86*, 13420.
3. (a) Gordon, M. S. *J. Am. Chem. Soc.* **1980**, *102*, 7419. (b) Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165.
4. (a) Ebner, C.; Carreira, E. M. *Chem. Rev.* **2017**, *117*, 11651. (b) Fumagalli, G.; Stanton, S.; Bower, J. F. *Chem. Rev.* **2017**, *117*, 9404. (c) Liang, Y.-F.; Müller, V.; Liu, W.; Münch, A.; Stalke, D.; Ackermann, L. *Angew. Chem., Int. Ed.* **2017**, *56*, 9415. (d) Lücht, A.; Patalag, L. J.; Augustin, A. U.; Jones, P. G.; Werz, D. B. *Angew. Chem., Int. Ed.* **2017**, *56*, 10587. (e) Mishra, M.; De, P. B.; Pradhan, S.; Punniyamurthy, T. *J. Org. Chem.* **2019**, *84*, 10901. (f) Zhuang, Z.; Yu, J.-Q. *J. Am. Chem. Soc.* **2020**, *142*, 12015. (g) Bellotti, P.; Glorius, F. *J. Am. Chem. Soc.* **2023**, *145*, 20716.
5. (a) Cavitt, M. A.; Phun, L. H.; France, S. *Chem. Soc. Rev.* **2014**, *43*, 804. (b) Xiao, J.-A.; Li, J.; Xia, P.-J.; Zhou, Z.-F.; Deng, Z.-X.; Xiang, H.-Y.; Chen, X.-Q.; Yang, H. *J.*

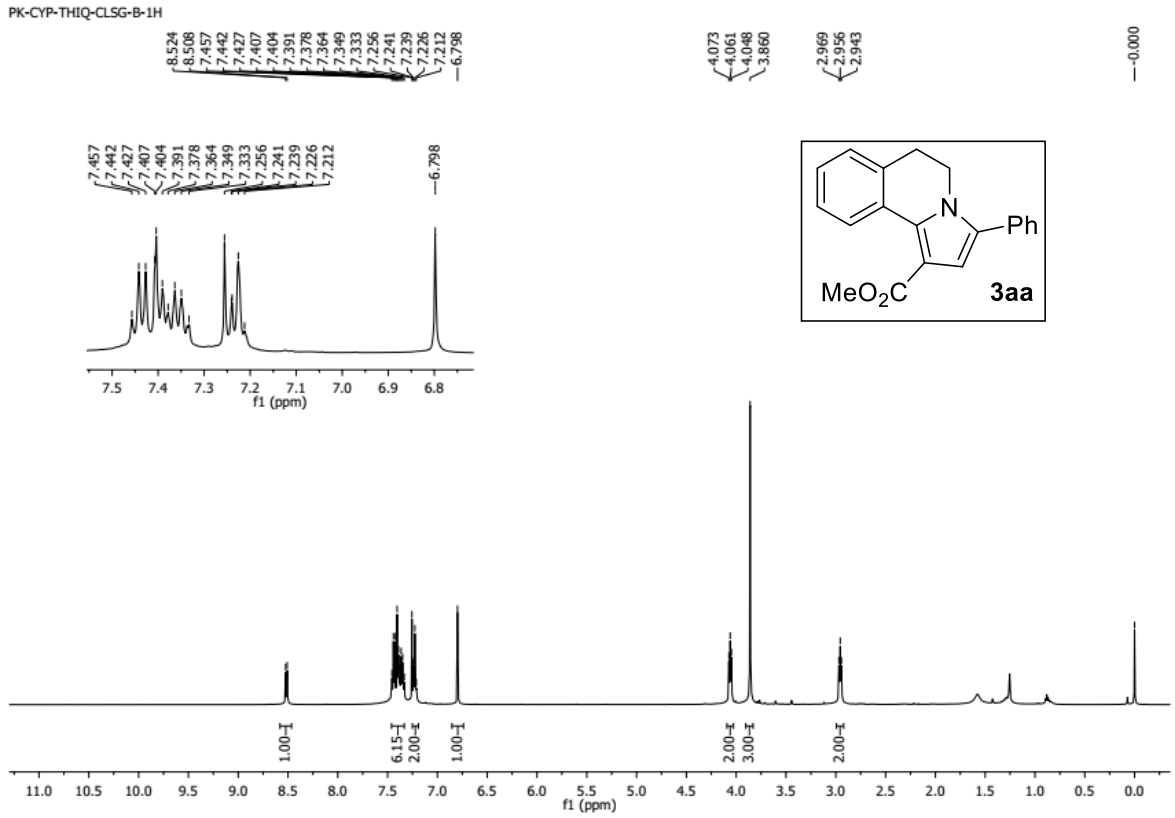
Org. Chem. **2016**, *81*, 11185. (c) Ivanova, O. A.; Andronov, V. A.; Vasin, V. S.; Shumsky, A. N.; Rybakov, V. B.; Voskressensky, L. G.; Trushkov, I. V. *Org. Lett.* **2018**, *20*, 7947. (d) Liu, J.; Liu, R.; Wei, Y.; Shi, M. *Trends Chem.* **2019**, *1*, 779. (h) Ketan Das, B.; Pradhan, S.; Punniyamurthy, T. *Chem. Commun.* **2019**, *55*, 8083.

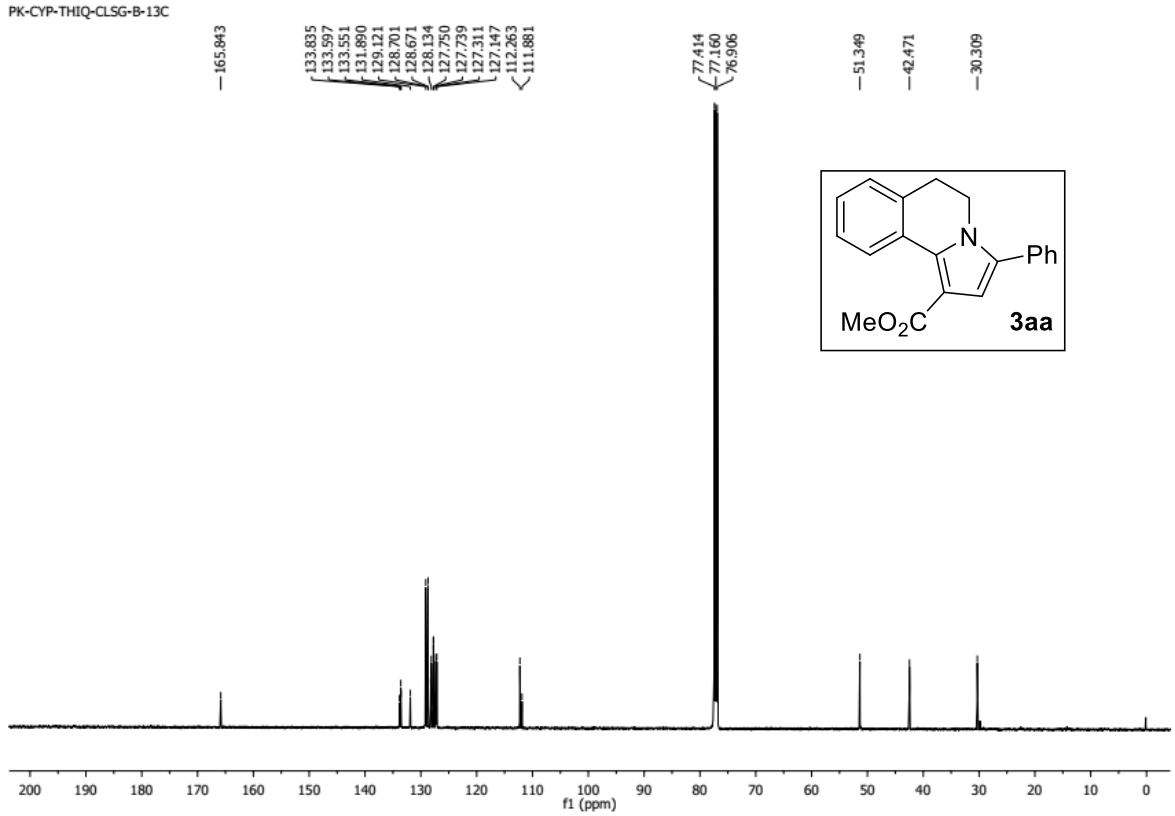
6. (a) Reissig, H.-U.; Hirsch, E. *Angew. Chem., Int. Ed.* **1980**, *19*, 813. (b) Brückner, C.; Reissig, H.-U. *Angew. Chem., Int. Ed.* **1985**, *24*, 588. (c) Schneider, T. F.; Werz, D. B. *Org. Lett.* **2011**, *13*, 1848. (d) Kaschel, J.; Schneider, T. F.; Kratzert, D.; Stalke, D.; Werz, D. B. *Angew. Chem., Int. Ed.* **2012**, *51*, 11153. (e) Kaschel, J.; Schmidt, C. D.; Mumby, M.; Kratzert, D.; Stalke, D.; Werz, D. B. *Chem. Commun.* **2013**, *49*, 4403.
7. (a) Kang, Q.-K.; Wang, L.; Liu, Q.-J.; Li, J.-F.; Tang, Y. *J. Am. Chem. Soc.* **2015**, *137*, 14594. (b) Xia, Y.; Lin, L.; Chang, F.; Fu, X.; Liu, X.; Feng, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 13748. (c) Nguyen, T. N.; Nguyen, T. S.; May, J. A. *Org. Lett.* **2016**, *18*, 3786. (d) Pitts, C. R.; Ling, B.; Snyder, J. A.; Bragg, A. E.; Lectka, T. *J. Am. Chem. Soc.* **2016**, *138*, 6598. (e) Ilchenko, N. O.; Hedberg, M.; Szabó, K. J. *Chem. Sci.* **2017**, *8*, 1056.
8. (a) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem.* **2014**, *57*, 5845; (b) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257. (c) Urquhart, L. *Nat. Rev. Drug Discov.* **2022**, *21*, 11. (d) Karjee, P.; Mishra, M.; Debnath, B.; Punniyamurthy, T. *Chem. Commun.* **2022**, *58*, 8670.
9. (a) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069. (b) Mitchell, E. A.; Peschiulli, A.; Lefevre, N.; Meerpoel, L.; Maes, B. U. W. *Chem. -Eur. J.* **2012**, *18*, 10092. (c) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74.
10. (a) van der Vlugt, J. I. *Eur. J. Inorg. Chem.* **2012**, *2012*, 363. (b) Miao, J.; Ge, H. *Eur. J. Org. Chem.* **2015**, *2015*, 7859. (c) Alig, L.; Fritz, M.; Schneider, S. *Chem. Rev.* **2019**, *119*, 2681. (d) Taylor, L. J.; Kays, D. L. *Dalton Trans.* **2019**, *48*, 12365. (e) Peng, J.-B.; Wu, F.-P.; Wu, X.-F. *Chem. Rev.* **2019**, *119*, 2090.
11. (a) Magolan, J.; Kerr, M. A. *Org. Lett.* **2006**, *8*, 4561. (b) Huang, X.; Bergsten, T. M.; Groves, J. T. *J. Am. Chem. Soc.* **2015**, *137*, 5300. (c) Trovitch, R. J. *Acc. Chem. Res.* **2017**, *50*, 2842. (d) Kallmeier, F.; Kempe, R. *Angew. Chem., Int. Ed.* **2018**, *57*, 46. (e) Hu, Y.; Zhou, B.; Wang, C. *Acc. Chem. Res.* **2018**, *51*, 816. (f) Borghs, J. C.; Tran, M. A.; Sklyaruk, J.; Rueping, M.; El-Sepelgy, O. *J. Org Chem.* **2019**, *84*, 7927.
12. (a) Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. Facile, *Angew. Chem., Int. Ed.* **1999**, *38*, 3186. (b) Lautens, M.; Han, W. *J. Am. Chem. Soc.* **2002**, *124*,

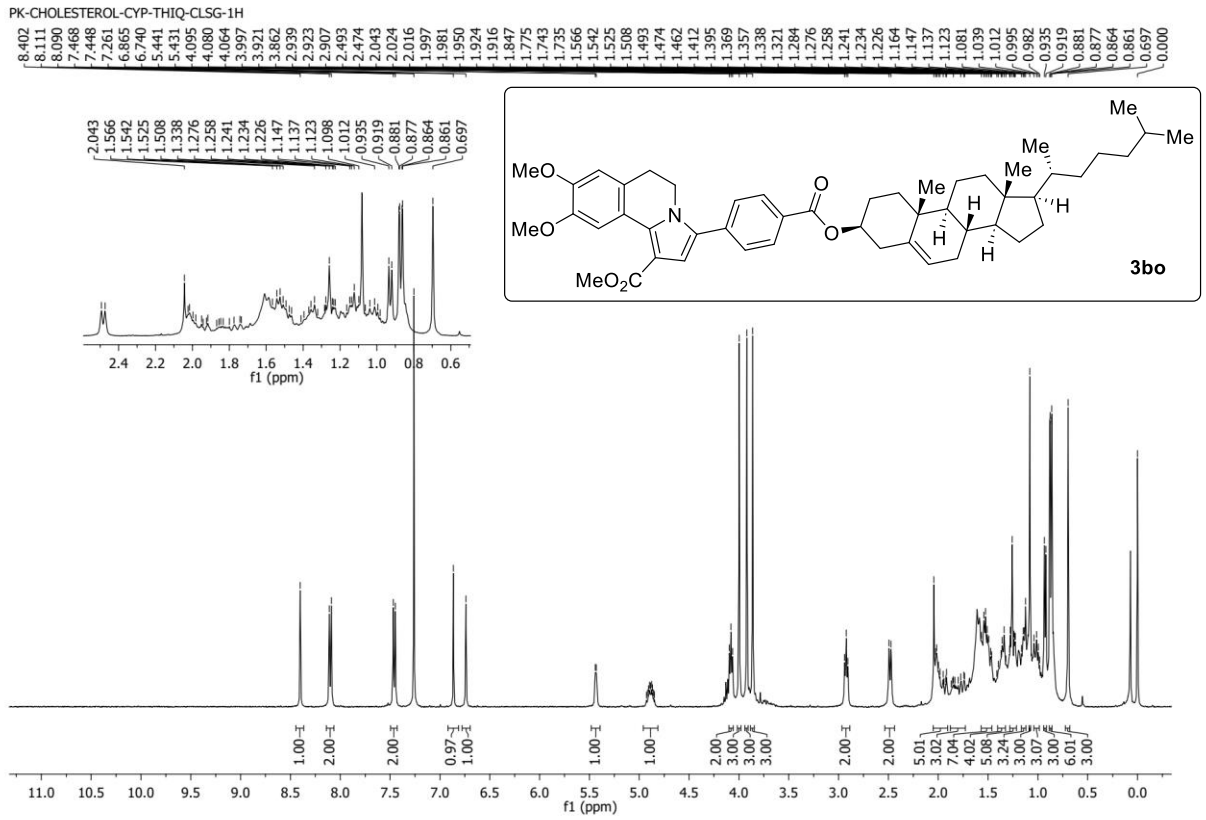
6312. (c) Parsons, A. T.; Smith, A. G.; Neel, A. J.; Johnson, J. S. *J. Am. Chem. Soc.* **2010**, *132*, 9688.

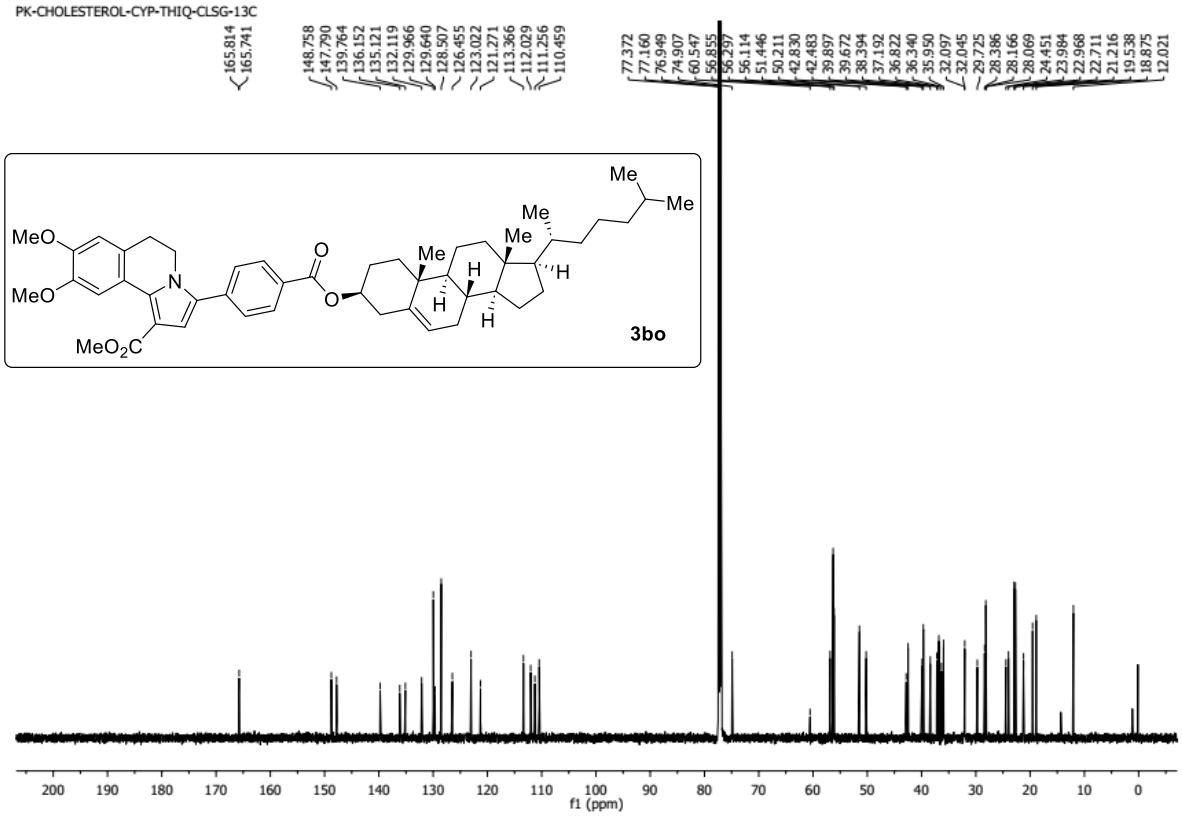
13. Chakrabarty, S.; Chatterjee, I.; Wibbeling, B.; Daniliuc, C. G.; Studer, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 5964.
14. Wang, D.-C.; Xie, M.-S.; Guo, H.-M.; Qu, G.-R.; Zhang, M.-C.; You, S.-L. *Angew. Chem. Int. Ed.* **2016**, *55*, 14111.
15. Wallbaum, J.; Garve, L. K. B.; Jones, P. G.; Werz, D. B. *Org. Lett.* **2017**, *19*, 98.
16. Tejeda, J. E. C.; Landschoot, B. K.; Kerr, M. A. *Org. Lett.* **2016**, *18*, 2142.
17. (a) Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E., Jr; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138. (b) Curran, D. P.; Zhang, Q. *Adv. Synth. Catal.* **2003**, *345*, 329. (c) Kurpil, B.; Otte, K.; Mishchenko, A.; Lamagni, P.; Lipiński, W.; Lock, N.; Antonietti, M.; Savateev, A. *Nat. Commun.* **2019**, *10*, 1. (d) Niu, X.; Yang, L. *Adv. Synth. Catal.* **2021**, *363*, 4209. (e) Liu, L.; Zhang, Y.; Zhao, W.; Li, J. *Org. Lett.* **2023**, *25*, 6251.
18. (a) Goldberg, A. F. G.; O'Connor, N. R.; Craig, R. A.; Stolz, B. M. *Org. Lett*. **2012**, *14*, 5314. (b) Mishra, M.; De, P. B.; Pradhan, S.; Punniyamurthy, T. *J. Org. Chem*. **2019**, *84*, 10901. (c) Jacob, A.; Barkawitz, P.; Jones, P. G.; Werz, D. B. *Org. Lett*. **2022**, *24*, 3028.
19. Darras, F. H.; Kling, B.; Heilmann, J.; Decker, M. *ACS Med. Chem. Lett*. **2012**, *3*, 914.
20. Xi, W.; Zhang, Y.; Wu, H.; Li, J.; Wang, Y.; Yang, J.; Wang, Z.; Yao, W. *Org. Lett*. **2023**, *25*, 4908.

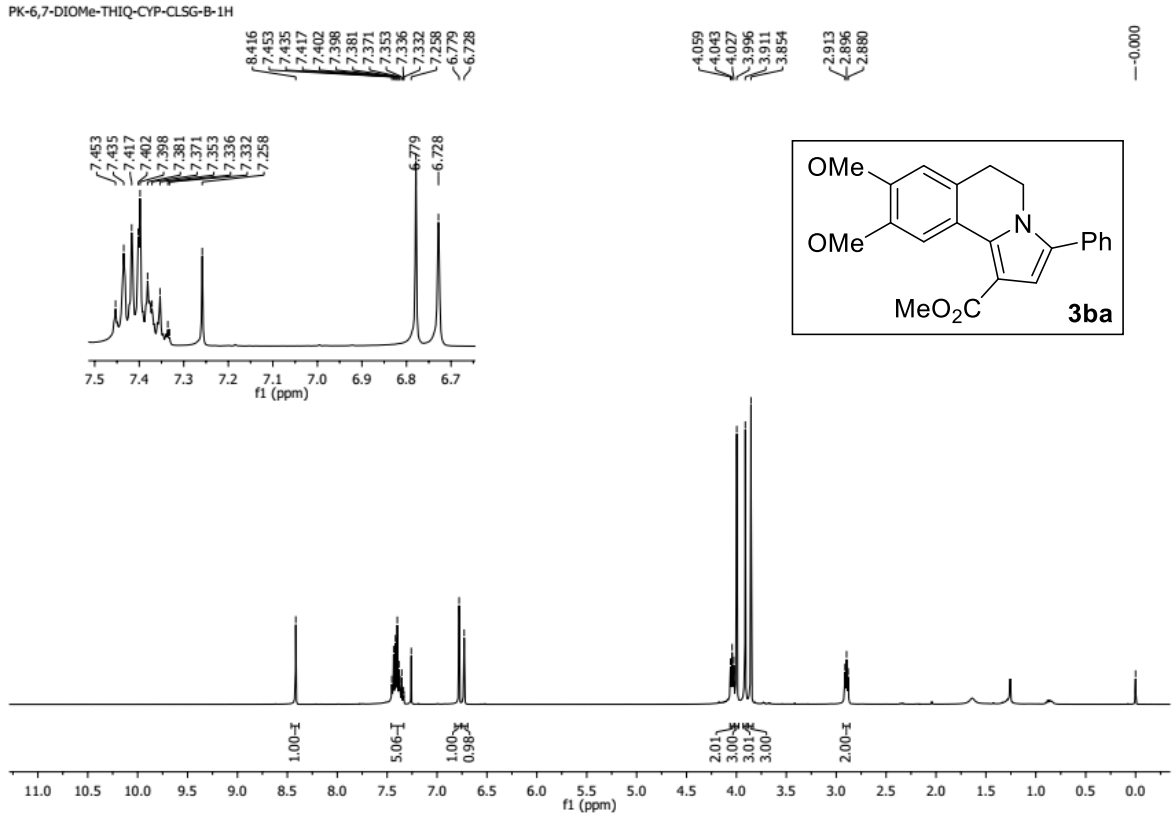
3.6 Selected NMR Spectra

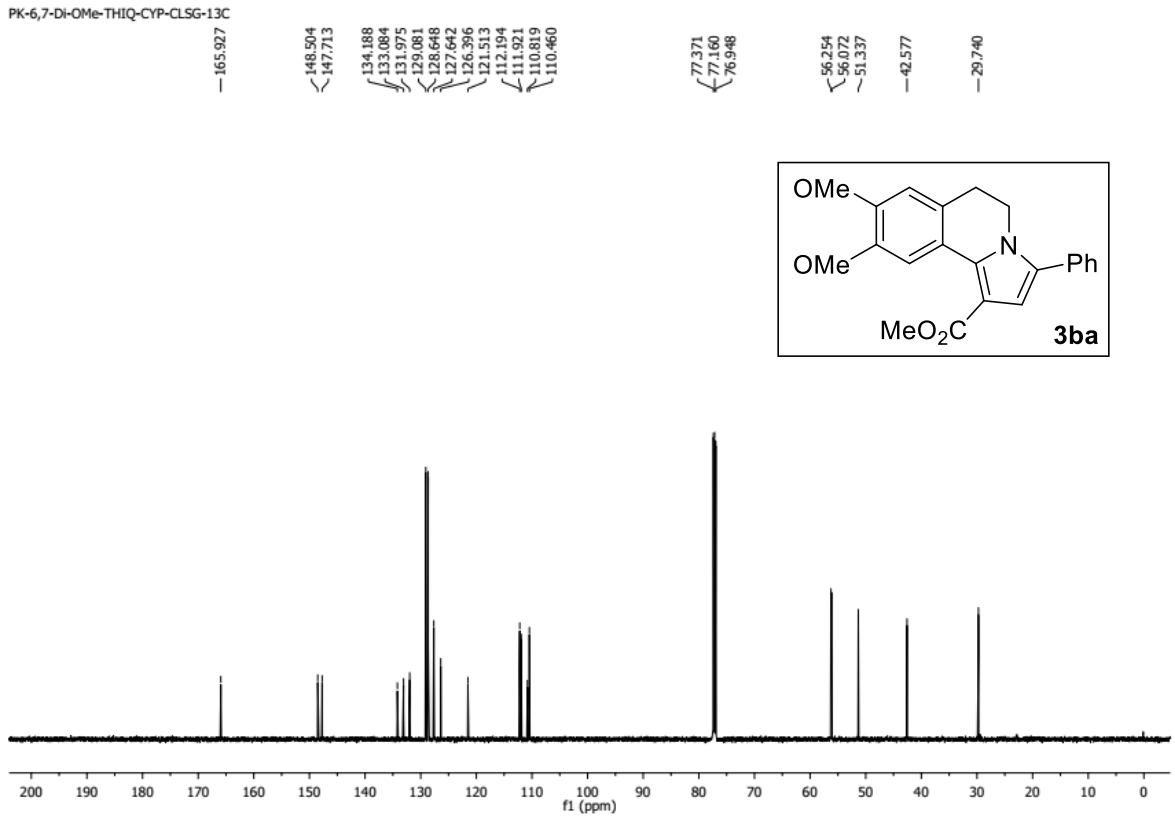


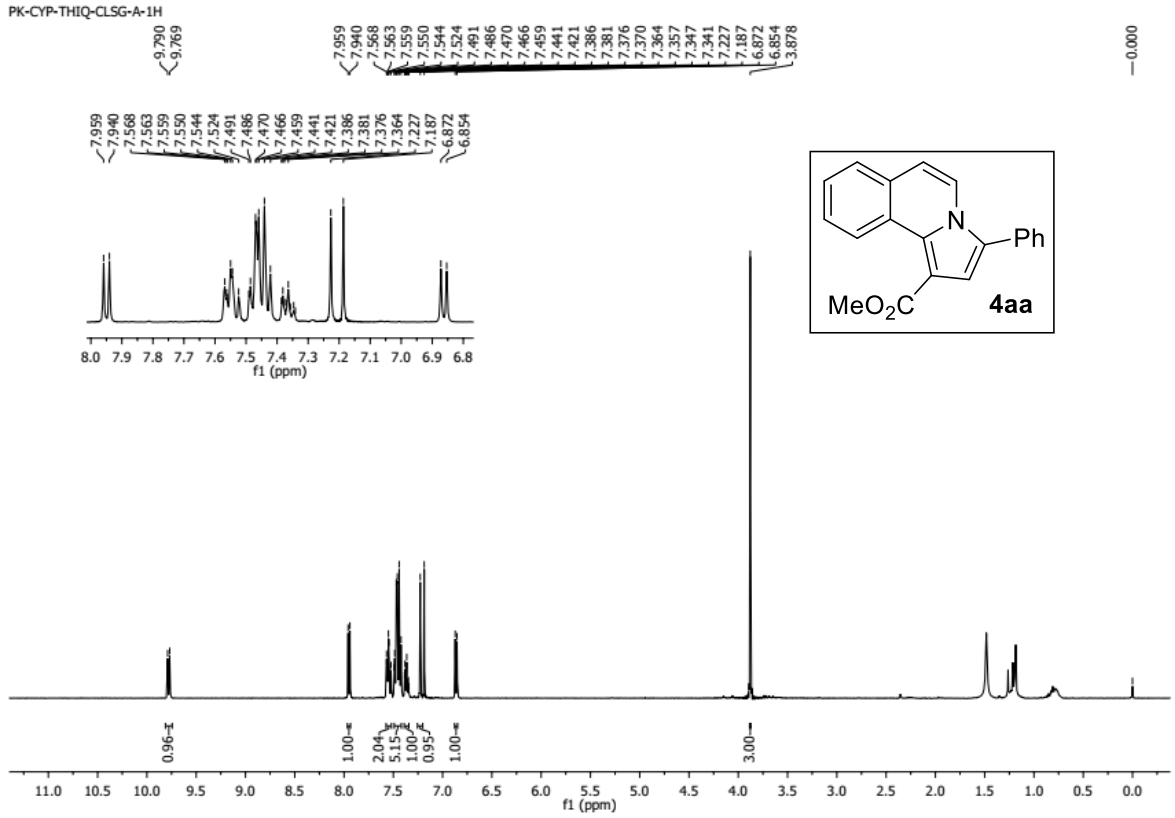


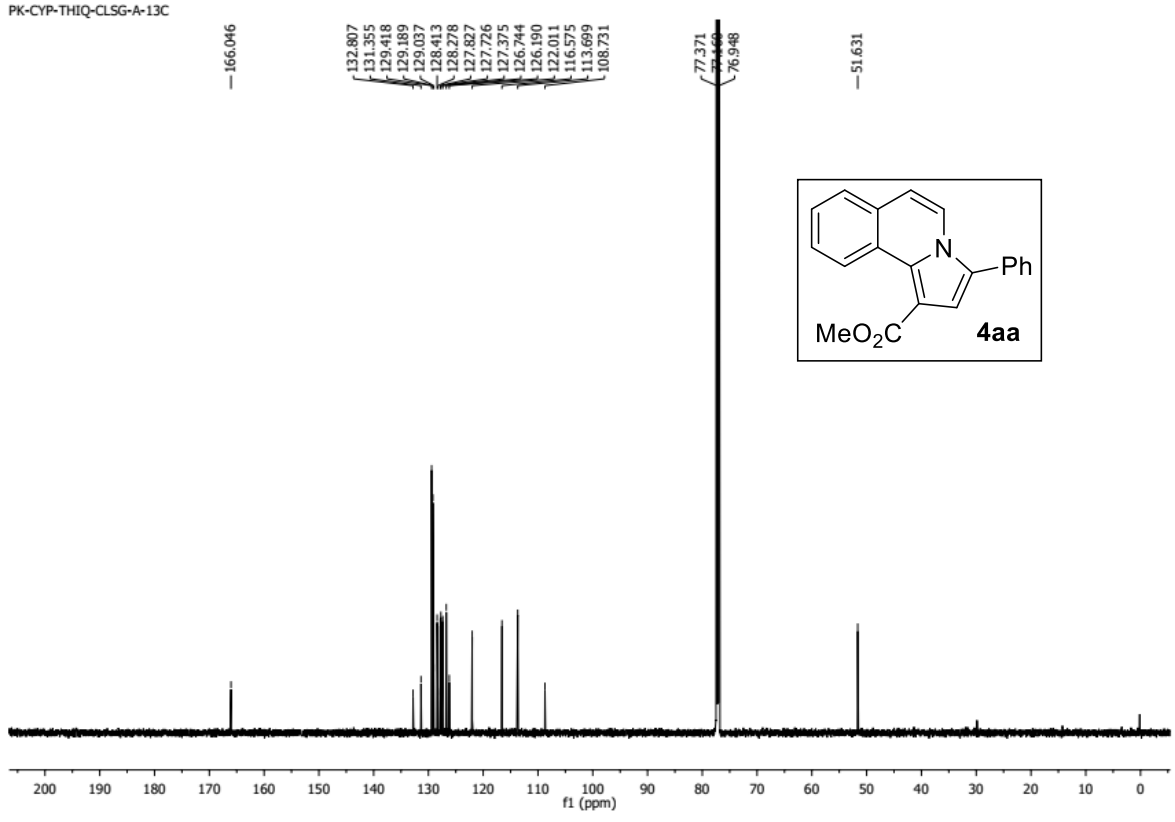






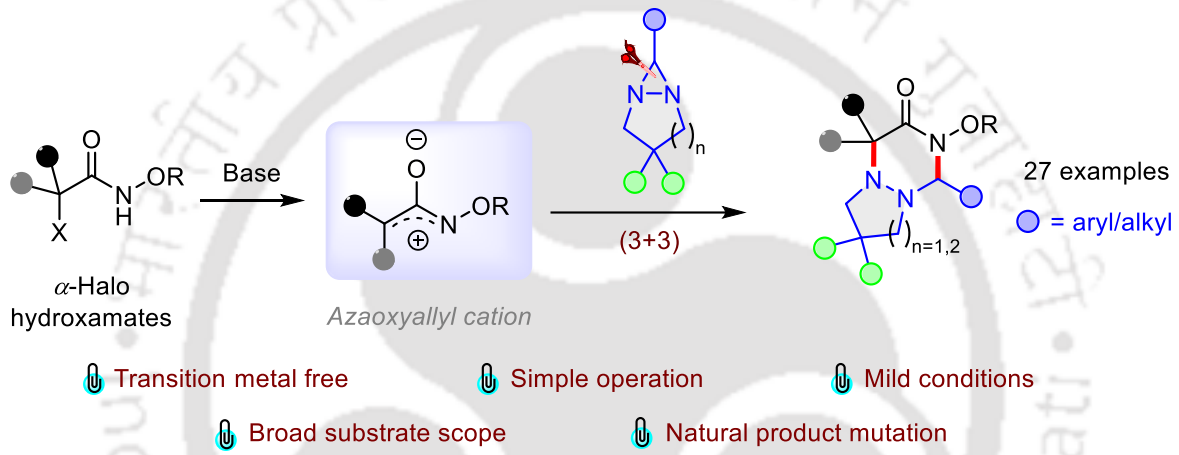






Chapter IV

Annulation of in situ Generated Azaoxyallyl Cations with Diaziridines



Chem. Commun. **2023**, *59*, 8270.

Chapter IV

Annulation of *in situ* Generated Azaoxyallyl Cations with Diaziridines

1,2,4-Triazines are often encountered as focal structural motifs in a wide range of natural products, bioactive molecules and agrochemicals (Figure 1).[1] For examples, riamilovir (TZV) is utilized to treat influenza,[1e] while metribuzin[1j] and metamitron[1h] are the herbicides. Azaribine is used to treat psoriasis and has anti-cancer and anti-viral properties,[1a,c] whereas ceftriaxone exhibits antibiotic properties.[1b] Thus, it would be valuable to develop effective synthetic methods for their construction, employing readily accessible simple building blocks.[2] Over the past few years, considerable progress has been made on the synthesis of heterocycles using (3+n)-annulations *via* 1,3-dipoles.[3] In this realm, (3+3)-cycloaddition has gained a significant attention as an alternate synthetic strategy of (4+2)-cycloaddition to provide six-membered heterocycles.[4] Contextually, three-membered ring systems due to innate ring strain and staple architecture have found to architect a variety of synthetic transformations.[5] Recently, diaziridines have emerged as two-nitrogen containing three-membered ring 1,3-dipolar systems.[6] They can be readily cleaved heterolytically using Lewis acid at the C-N bond to serve as synthetic precursor of azomethine imine, paving the way to construct N-heterocyclic structural frameworks.[6] While, α-halohydroxamates due to their ease of availability and high reactivity have witnessed an impeccable growth as the optimal three-atom synthon (C-C-N) for constructing N-heterocycles.[7] It can readily undergo dehydrohalogenation with base to give *in situ* azaoxyallyl cation, an active 1,3-dipolar intermediate, which can enable potential synthetic tool to construct biologically important scaffold in (3+n)-cycloadditon fashion. Jeffrey group has demonstrated the (3+4)-cycloaddition of azaoxyallyl cation with cyclic diene to afford seven-membered N-heterocycles.[8] Since then, considerable efforts have been made to develop (3+1),[9] (3+2),[10] (3+3)[11] and (3+4)-cycloaddition[8,12] of azaoxyallyl cation to afford four to seven-membered heterocycles. Inspired by these effective approaches, we envisioned that it will be valuable to observe the reactivity of azaoxyallyl cations with a stable three-membered ring system i.e., diaziridine. This chapter describes an efficient annulation of *in situ* formed azaoxyallyl cations using base with diaziridines to provide 1,2,4-triazines at room temperature.

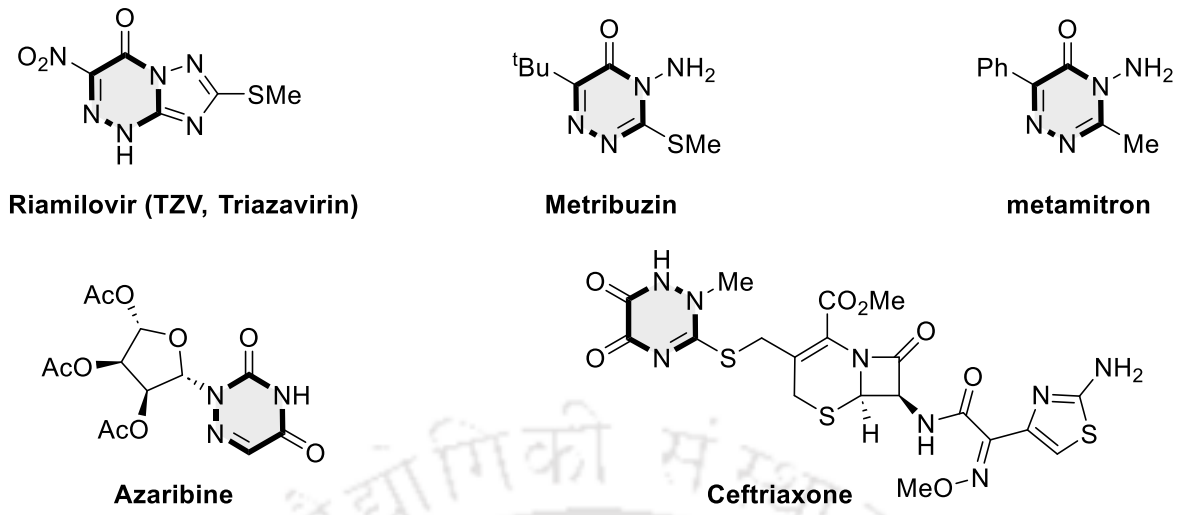
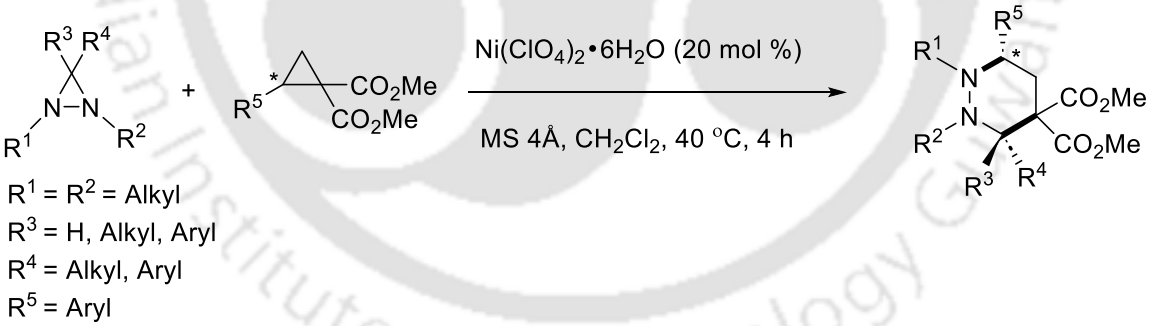


Figure 1. Examples of biologically important triazine derivatives.

4.1 Literature Study

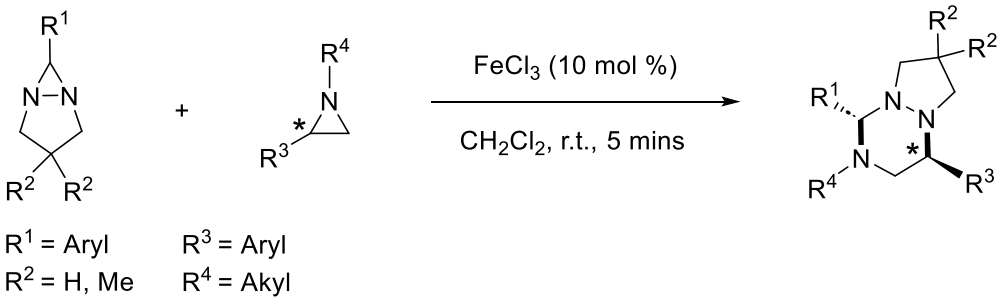
4.1.1 Metal-Catalyzed Annulationn of Diaziridines

Trushkov and co-workers reported the first successful example of a (3+3)-annulation involving two distinct saturated three-membered rings. This was achieved through the Lewis acid-induced coupling of donor-acceptor cyclopropanes with diaziridines. (Scheme 1).[13] A variety of DACs and diaziridines well tolerated.



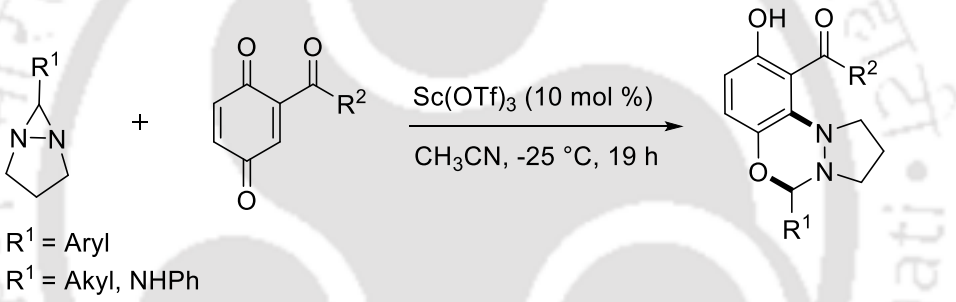
Scheme 1. (3+3)-Annulation of DACs with Diaziridines

Our group reported $FeCl_3$-catalyzed stereospecific (3+3)-annulation of aziridines with diaziridines to furnish [1,2,4]-triazines as a single diastereoisomer in high yield (Scheme 2).[14] This method offers a promising approach for the annulation of two distinct three-membered rings, leading to the synthesis of a new class of fused heterocycles.



Scheme 2. Fe-catalyzed (3+3)-Annulation of Aziridines with Diaziridines

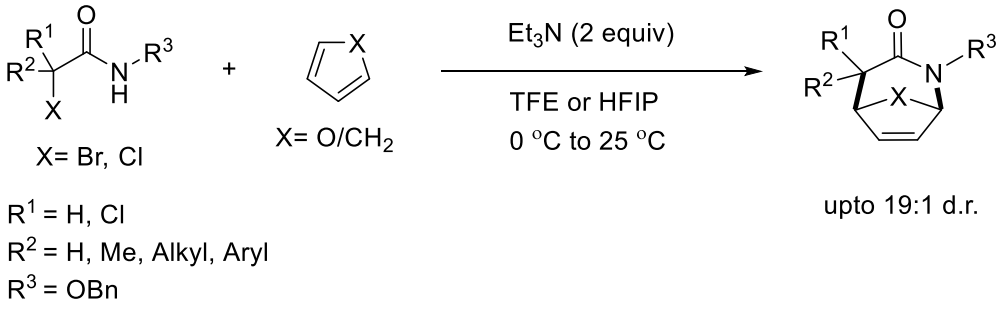
A formal (3 + 3)-cyclization process involving diaziridines and quinones was documented, resulting in the production of 1,3,4-oxadiazinanes with generally high yields. The reaction was facilitated by $Sc(OTf)_3$ and exhibited a broad substrate scope for both diaziridines and quinones. The critical role of the synergistic activation of 1,3-dipolar diaziridines and dipolar quinones was identified (Scheme 3).[15]



Scheme 3. Fe-catalyzed (3+3)-Annulation of Aziridines with Diaziridines

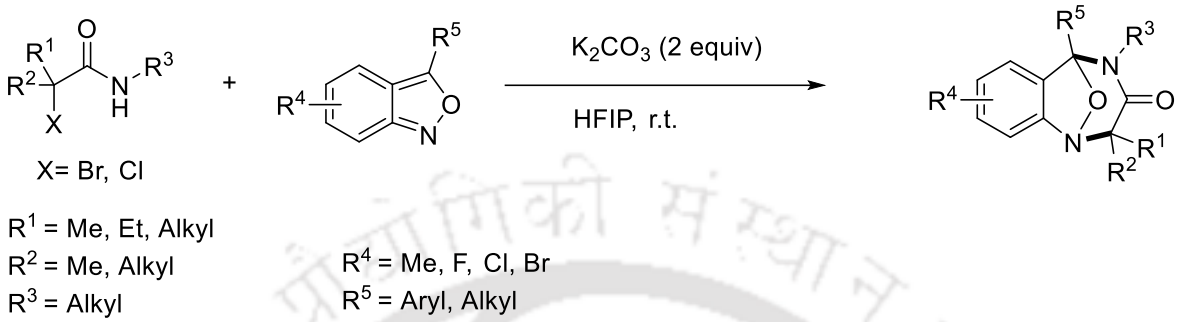
4.1.2 Base-Mediated Annulationn of *α*-Haloamides

Jeffrey and co-workers reported aza-(4+3)-cycloadditions involving putative aza-oxyallyl cationic intermediates and cyclic dienes (Scheme 4).[8] The intermediate is produced by the dehydrohalogenation of *α*-haloamides. The reaction is applicable to a range of *α*-haloamides and exhibits diastereoselectivity. Both computational and experimental evidence indicate that an *N*-alkoxy substituent contributes to the stabilization of the aza-oxyallyl cation intermediate.



Scheme 4. Aza-(4+3)-Cycloadditions of *α*-Haloamides and Cyclic Dienes

Zhao group described the synthesis multisubstituted benzodiazepine derivatives using a formal (4+3)-cycloaddition between azaoxyallyl cations and anthranils (Scheme 5).[17] These alluring polycyclic structures were typically produced under gentle conditions with high yields, through the formation of a zwitterionic intermediate.



Scheme 5. Aza-(4+3)-Cycloadditions of *α*-Haloamides and Anthranils

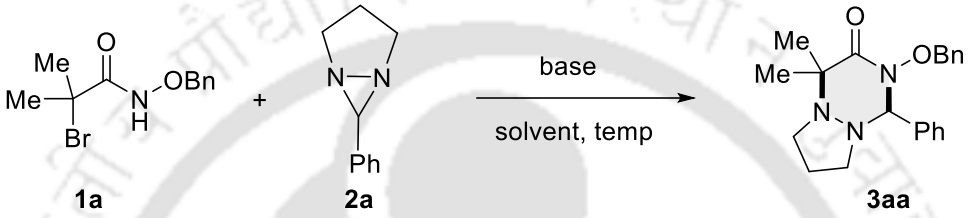
4.2 Present Study

Herein, an efficient annulation of *in situ* formed azaoxyallyl cations utilizing base with diaziridines is described to furnish 1,2,4-triazines at room temperature. At the outset, we commenced the optimization studies using N-(benzyloxy)-2-bromo-2-methylpropanamide **1a** and diaziridine **2a** as the model substrates varying the bases and solvents (Table 1). Gratifyingly, the reaction occurred to give the cycloadduct **3aa** in 79% yield when the substrates **1a** and **2a** were reacted using K_2CO_3 in CH_3CN at room temperature for 12 h. In a set of solvents examined, MeOH, $(CH_2Cl)_2$, HFIP, TFE and CH_3CN, the latter yielded the best results (entries 1-5). K_2CO_3 was found to be the base of choice, whereas Na_2CO_3 and Cs_2CO_3 provided 61% and 65% of yields, respectively (entries 5-7). In contrast, Et_3N and DIPEA gave inferior results (entries 8-9). A control experiment validated the need of the base to deliver the target heterocycle (entry 10).

Having the optimized conditions in hand, we examined the scope of the procedure for a series of diaziridines **2b-s** with *N*-(benzyloxy)-2-bromo-2-methylpropanamide **1a** as a standard substrate (Table 2). Diaziridines with substituents at the 2-position of the aryl ring having methyl **2b** and nitro **2c** groups gave the target products **3ab** and **3ac** in 65% and 59% yields, respectively. Further, the reaction of bromo **2d** and nitro **2e** substituted diaziridines at the 3-position furnished **3ad** and **3ae** in 69% and 61% yields, respectively. Similar result was observed with the diaziridines bearing electron-donating and -deficient groups at the C4-position of the aryl ring, such as bromo **2f**, cyano **2g**, methoxy **2h**, nitro **2i** and *tert*-butyl **2j**

substituents, affording the target heterocycles **3af-aj** in 60-78% yields. The structure of **3af** was determined using the X-ray analysis (CCDC 2225274). Further, trimethoxy substituted diaziridine **2k** participated to give **3ak** in 75% of yield. Intriguingly, the heteroaryl diaziridines **2l** and **2m** were found to be amenable, delivering **3al** and **3am** in 65% and 61% yields, respectively. Moreover, polycyclic diaziridines bearing 2-naphthyl **2n** and 2-fluorenyl **2o** functionalities underwent reaction to furnish **3an** and **3ao**, in 72% and 70% yields, respectively. In addition, 3,3-dimethyl bearing diaziridine **2p** was found to be compatible, affording **3ap** in

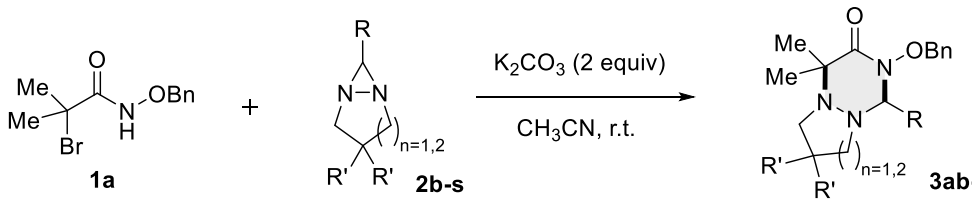
Table 1. Optimization of the Reaction Conditions[a]

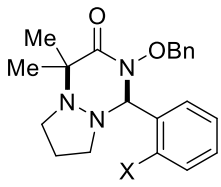


Entry	Base	Solvent	Yield (%)[b]
1	Na_2CO_3	MeOH	25
2	Na_2CO_3	$(CH_2Cl)_2$	43
3	Na_2CO_3	HFIP	54
4	Na_2CO_3	TFE	33
5	Na_2CO_3	CH_3CN	61
6	K_2CO_3	CH_3CN	79
7	Cs_2CO_3	CH_3CN	65
8	Et_3N	CH_3CN	trace
9	DIPEA	CH_3CN	trace
10	-	CH_3CN	n.d.

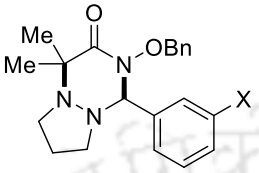
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), base (0.4 mmol), solvent (2 mL), r.t., 12 h. [b]Isolated yield. n.d.= not detected.

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

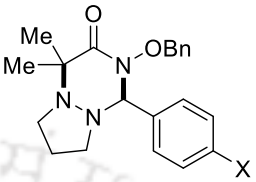




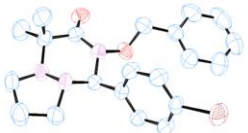
X= Me, **3ab**, 65%
= NO_2, **3ac**, 59 %



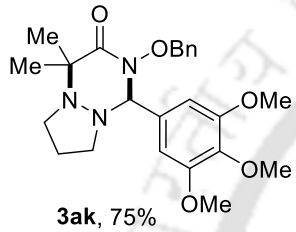
X= Br, **3ad**, 69%
= NO_2, **3ae**, 61%



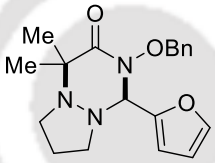
X= Br, **3af**, 73%
= CN, **3ag**, 63%
= OMe, **3ah**, 78%
= NO_2, **3ai**, 60%
= ^{t}Bu, **3aj**, 71%



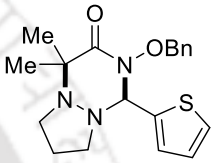
[***X-ray***] of **3af**
(CCDC 2225274)



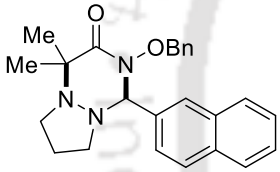
3ak, 75%



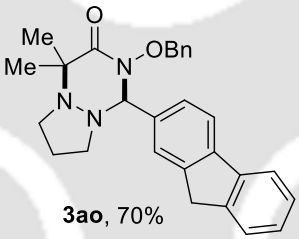
3al, 65%



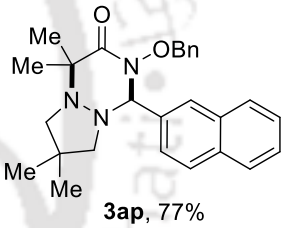
3am, 61%



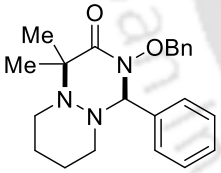
3an, 72%



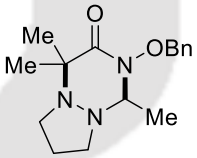
3ao, 70%



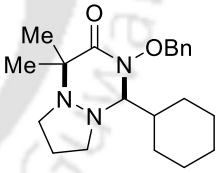
3ap, 77%



3aq, 73%



3ar, 82%



3as, n.d.

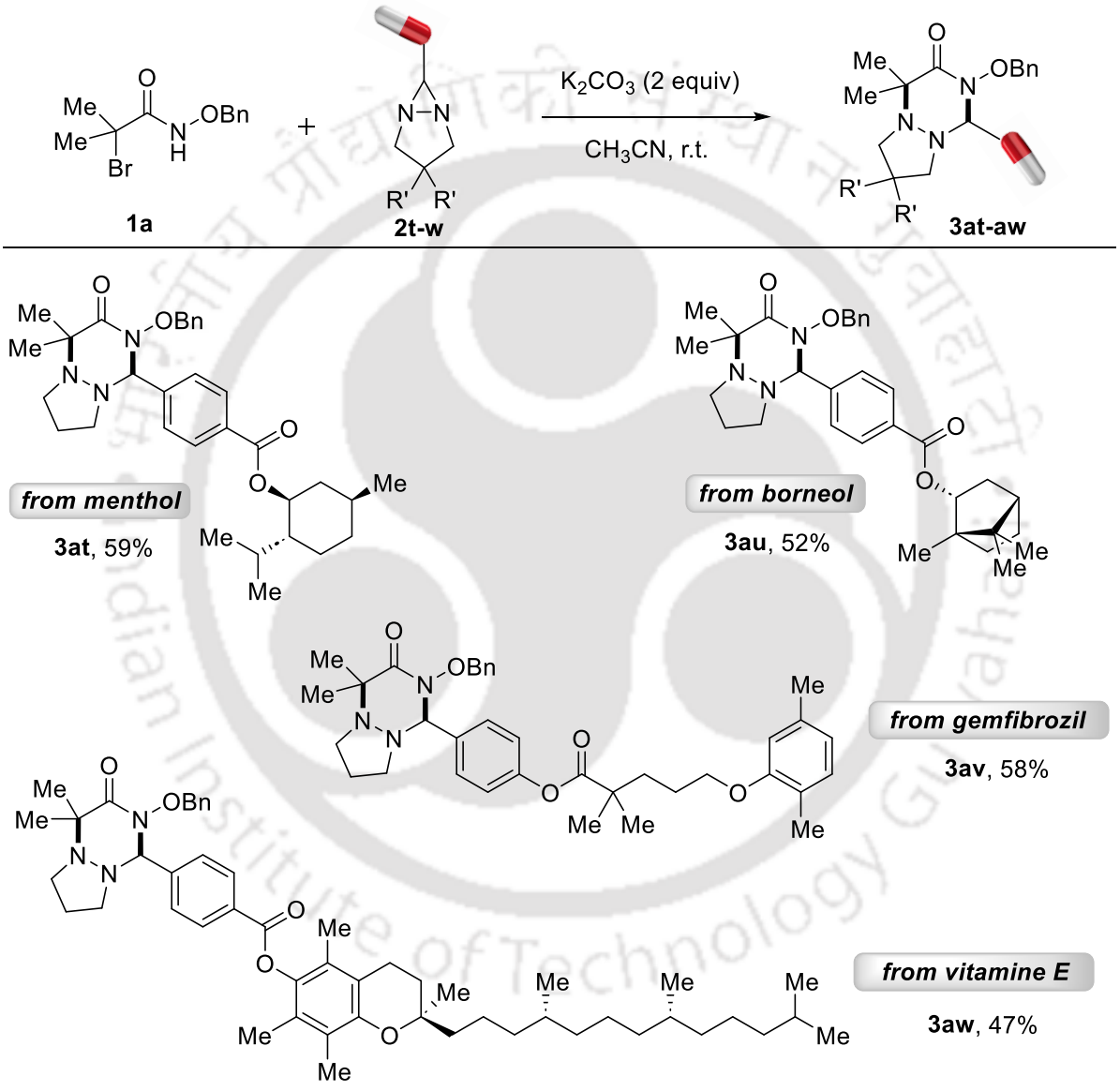
[a]Reaction conditions: **1a** (0.2 mmol), **2b-s** (0.24 mmol), K_2CO_3 (0.4 mmol), CH_3CN (2 mL), r.t., 12 h. [b]Isolated yield. n.d.= not detected.

77% yield. A similar result was observed with **2q** bearing a six membered ring, producing **3aq** in 73% yield. Further, diaziridine **2r** with methyl group underwent reaction to deliver **3ar** in 82% yield, whereas cyclohexyl substituted **2s** was an unsuccessful substrate and the formation of **3as** was not observed.

To reveal the synthetic potential, we further examined the substrate scope of diaziridines with diverse natural products and biologically active molecules (Table 3). For examples, the annulation of diaziridine **2t** with k-opioid receptor agonist L- menthol could be accomplished to provide **3at** in 59% of yield, whereas (-)-borneol derived diaziridine **2u** reacted to afford

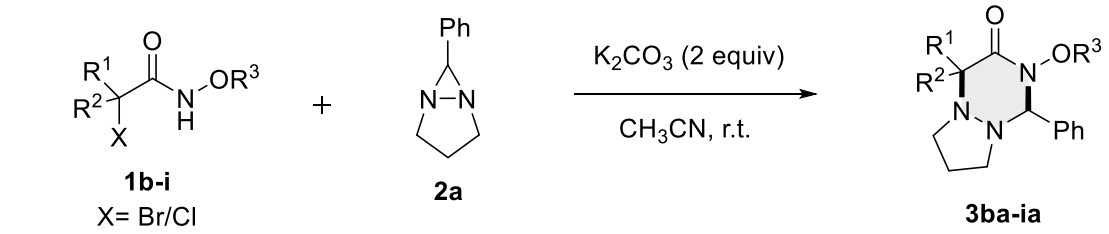
3au in 52% yield. Likewise, the annulation of gemfibrozil derived diaziridine **2v** could be achieved to afford **3av** in 58% yield, whereas the vitamin E (tocopherol) derivative **2w** was found to be compatible, producing **3aw** in 47% yield.

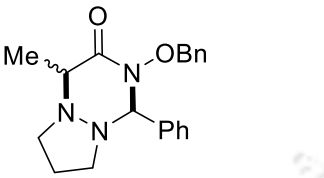
Table 3. Substrate Scope of Diaziridines Tethered with Biologically Active Molecules[a,b]



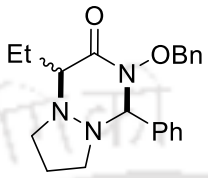
[a]Reaction conditions: **1a** (0.2 mmol), **2t-w** (0.24 mmol), K_2CO_3 (0.4 mmol), CH_3CN (2 mL), r.t., 12 h; [b]Isolated yield.

Table 4. Substrate Scope of α-Halohydroxamates[a,b]

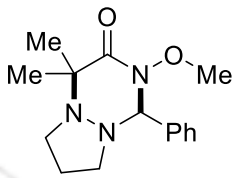




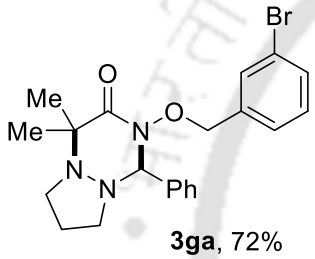
X = Br, **3ba**, 82%, dr= 12:1
= Cl, **3ca**, 80%, dr= 15:1



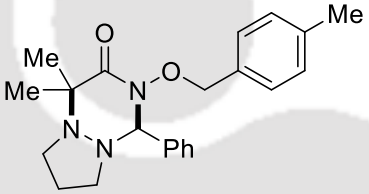
3da, 83%, dr= 7.6:1



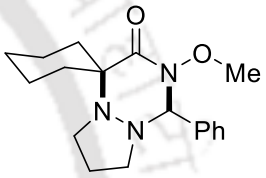
R^3 = OMe, **3ea**, trace
= OEt, **3fa**, 54%



3ga, 72%



3ha, 75%

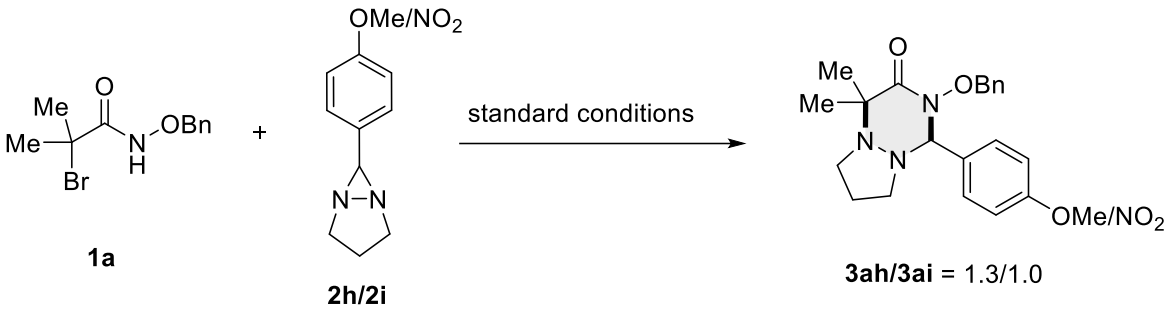


3ia, 75%

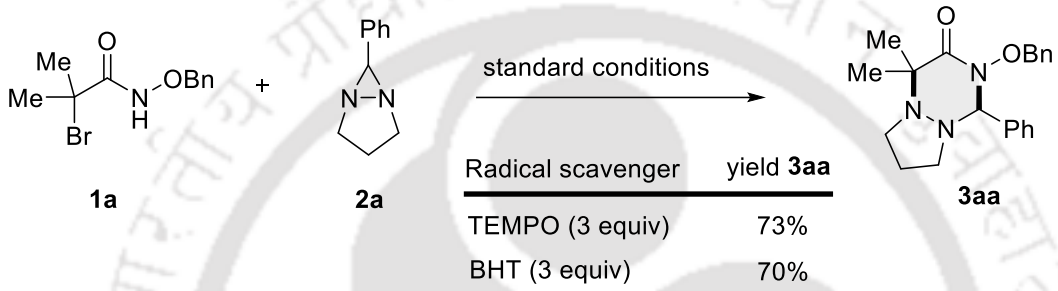
[a]Reaction conditions: **1b-i** (0.2 mmol), **2a** (0.24 mmol), K_2CO_3 (0.4 mmol), CH_3CN (2 mL), r.t., 12 h; [b]Isolated yield.

These findings led to further diversification of the procedure employing α-halohydroxamates **1b-h** using **2a** as the standard substrate (Table 4). α-Bromoamide with a monomethyl group **1b** reacted to provide **3ba** in 82% yield and 12:1 diastereomers. When the bromo group replaced with chloro **1c**, the reaction occurred to give **3ca** in 80% yield and 15:1 diastereomers. In addition, the monoethyl counterpart **1d** reacted to furnish **3da** in 83% yield and 7.6:1 diastereomers. In contrast, when the *N*-benzyloxy group was substituted with *N*-methyloxy **1e**, inferior result was obtained, whereas ethyl group **1f** was compatible, giving **3fa** in 54% yield. Furthermore, the α-bromoamides with varied substitutions such as 3-bromo **1g** and 4-methyl **1h** delightfully afforded **3ga** and **3ha** in 72% and 75% yield, respectively. These results suggest that *N*-alkoxy substituent has a significant effect on the reaction efficiency. However, the substrate **1i** with cyclohexyl substituent failed to undergo cycloaddition, which may be due to the non-planarity of the cation intermediate.

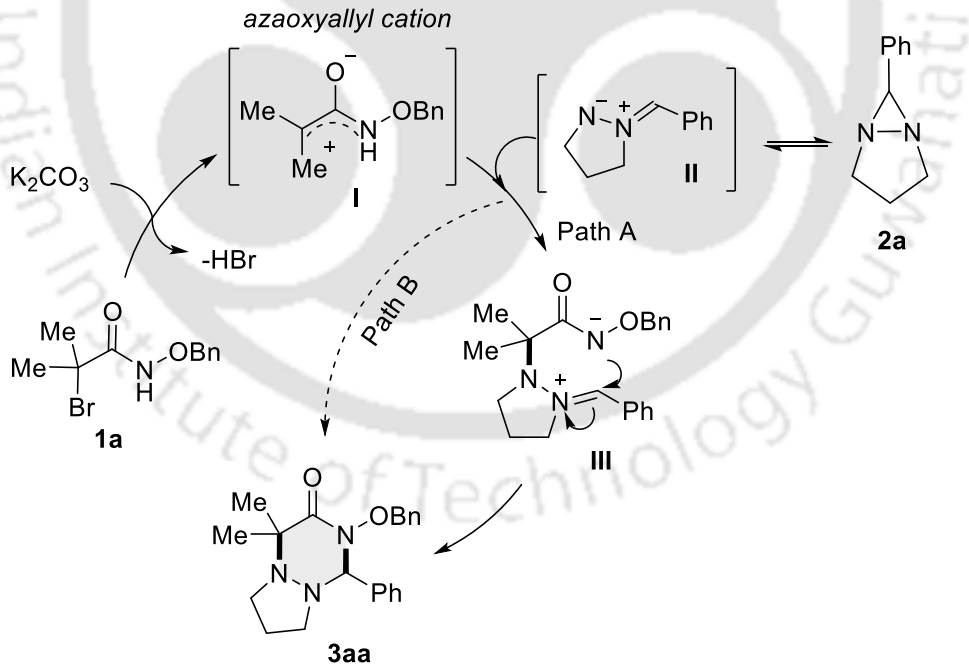
a) Intermolecular competitive experiment



b) Radical scavenger experiments



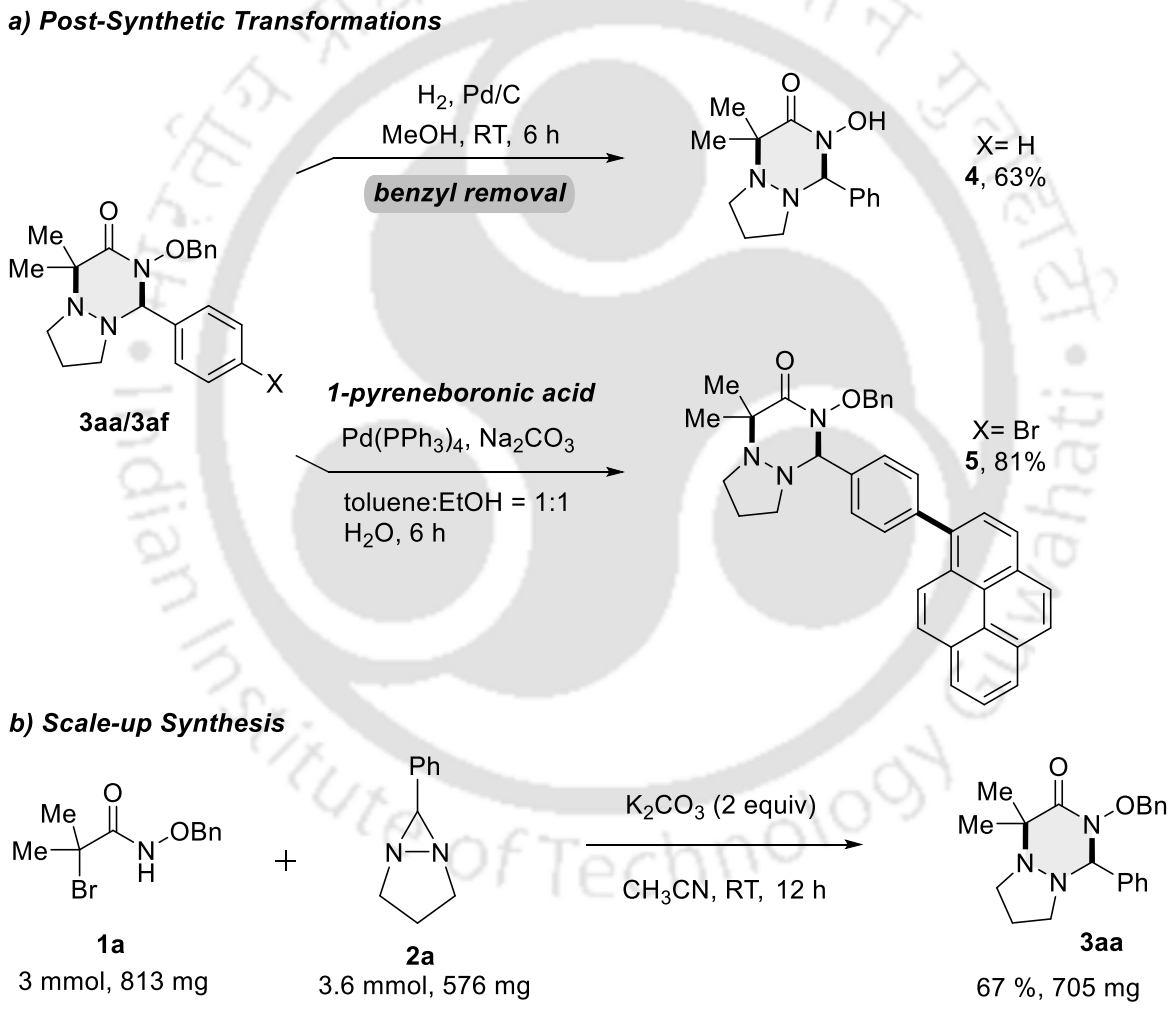
Scheme 6. Mechanistic Studies.



Scheme 7. Plausible Reaction Pathway.

To get insight into the reaction pathway, the reaction of **1a** with diaziridines bearing methoxy **2h** and nitro **2i** substituents was examined (Scheme 6a). The substrate with electron donating group exhibited slightly enhanced reactivity compared to that bearing electron withdrawing

group, which might be due to facilitation for the formation of azo-methine imine by the electron rich substituent. In addition, as above, the reaction of **1a** and **2a** occurred in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) to afford the annulated products, which suggest that the reaction might not be involved radical pathway (Scheme 6b). Thus, the dehydrohalogenation of *α*-halohydroxamates **1** using base can lead to the formation of azaoxyallyl cation **I**, which can couple with the in situ formed azo-methine imine **II** to give **III** (Scheme 7). The latter can lead annulation to furnish the cycloadduct **3** (Path A). Further, the coupling of **I** and **II** in a concerted manner *via* a cascade C-N bond formation may lead to the formation of **3** (Path B).



Scheme 8. Scale-Up and Synthetic Transformations.

The products can be further converted into diverse scaffolds (Scheme 8). For example, the benzyl group can be removed using hydrogenation to furnish **4** in 63% yield, whereas Suzuki C-C cross-coupling of **3af** with boronic acid can deliver **5** in 81% yield. To reveal the sale-up, the coupling of **1a** with **2a** was examined in 3 mmol as the representative examples, and the

reaction occurred to deliver **3aa** in 67 % yield. However, efforts to cleave the N-O bond of **3aa** using SmI_2 and $Mo(CO)_6$ were unsuccessful.

In summary, an efficient method for the annulation of azaoxyallyl cation with diaziridines has been accomplished to produce 1,2,4-triazines at room temperature. The substrate scope, functional group diversity and transition-metal free reaction conditions are the important practical features.

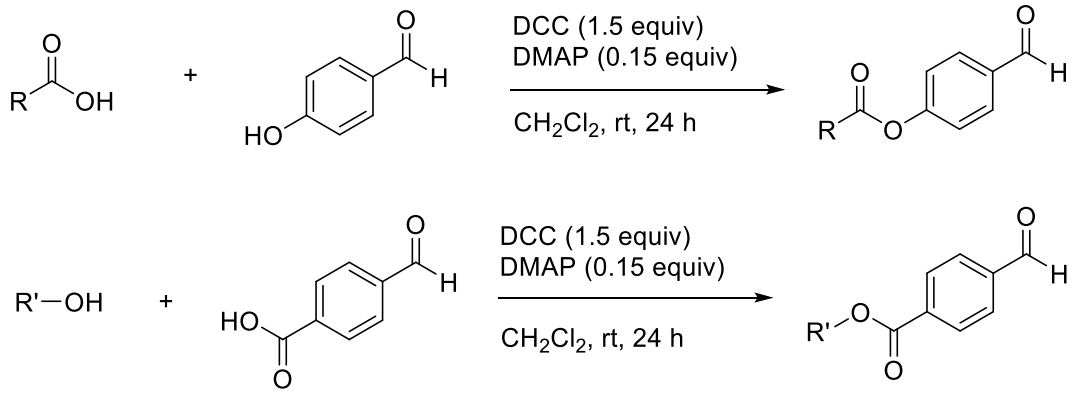
4.3 Experimental Section

General Information. Aldehydes, HFIP (≥99%), TFE (≥99%), Pd/C (Palladium on carbon, extent of labeling: 10 wt. % loading, matrix activated carbon support) and $Pd(PPh_3)_4$ (99 %) of Aldrich and TCI Chemicals were used as received. Na_2CO_3 (>99%), K_2CO_3 (98%), Cs_2CO_3 (99%), DIPEA (≥99%) and Et_3N (>99%) were procured from Merck and used as received. Methanol, 1,2-dichloroethane and acetronitrile were dried prior as per the standard procedure. Diaziridines and *α*-halohydroxamates were prepared according to the reported procedure. Merck silica gel G/GF254 plates were used for analytical TLC and Rankem silica gel (60-120 mesh) was utilized for column chromatography. NMR spectra were recorded with Bruker Avance III 600, 500 and 400 MHz spectrometers using $CDCl_3$ as solvent and Me_4Si as an internal standard. Chemical shifts (δ) and spin-spin coupling constant (*J*) are reported in ppm and in Hz, respectively, and other data are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, dd = doublet of doublets. Melting points were determined using a Büchi B-540 apparatus and are uncorrected. FT-IR spectra were collected on Perkin Elmer IR spectrometer. Q-Tof ESI-MS instrument was used for recording mass spectra. Single crystal X-ray data was collected on a Bruker SMART APEX equipped with a CCD area detector using Mo/K*α* radiation and the structure was solved by direct method using *SHELXT-2018/2* (Göttingen, Germany).

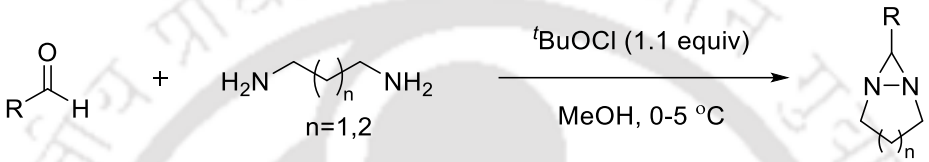
General Procedure for the Synthesis of 1t-w.

Step 1: General Procedure for the Synthesis of Aldehydes

First, carboxylic acid (1 mmol), dicyclohexylcarbodiimide (DCC) (309 mg, 1.5 mmol), 4-dimethylaminepyridine (DMAP) (18 mg, 0.15 mmol) and alcohol or phenol (1.2 mmol) were stirred in CH_2Cl_2 (10 mL) for 12 h at room temperature. The reaction mixture was then passed through as short pad of celite. The solvent was evaporated and the residue was purified on silica gel chromatography using ethyl acetate/hexane as an eluent.



Step 2: General Procedure for the Synthesis of Diaziridines



t-BuOCl (119 mg, 1.1 mmol) in MeOH (1 mL) was added dropwise to the stirring solution of 1,3-diaminopropane (148 mg, 2 mmol) in MeOH (10 mL) at 0 to 5 ºC. Then the aldehyde (1 mmol) in MeOH (1-2 mL) was added and the stirring was continued for an additional 24 h at 0 to 5 ºC. The solvent was evaporated and the residue was dissolved in $CHCl_3$ (10 mL). The solution was washed with water (10 mL) and dried (Na_2SO_4). Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate and hexane as an eluent.

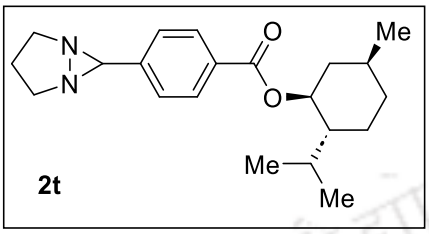
General Procedure for the Synthesis of 3. *α*-Halohydroxamates **1** (0.2 mmol), diaziridines **2** (0.24 mmol) and K_2CO_3 (55 mg, 0.4 mmol) were stirred in CH_3CN (2 mL) at room temperature for 12 h. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. The solvent was evaporated and the residue was dissolved ethyl acetate (10 mL). The solution was washed with water (5 mL) and dried (Na_2SO_4). Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate and hexane as an eluent.

Scale-up Synthesis of 3aa. *α*-Halohydroxamates **1a** (813 mg, 3 mmol), diaziridines **2a** (576 mg, 3.6 mmol) and K_2CO_3 (828 mg, 6 mmol) were subjected to the above described general procedure to produce **3aa** in 67% (705 mg) of yield.

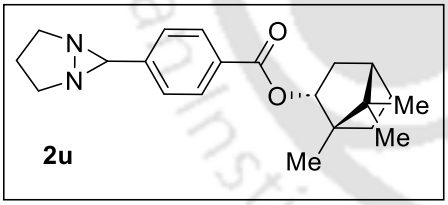
Intermolecular Competitive Experiment Employing 2h and 2i. *N*-(Benzyloxy)-2-bromo-2-methylpropanamide **1a** (54 mg, 0.2 mmol), **2h** (45 mg, 0.24 mmol), **2i** (49 mg, 0.24 mmol) and

K_2CO_3 (55 mg, 0.4 mmol) were stirred in CH_3CN (2 mL) at room temperature for 12 h. The solvent was evaporated and the work-up and purification were performed as described in the above general procedure to afford **3ah** and **3ai** in 40% and 31% yields, respectively.

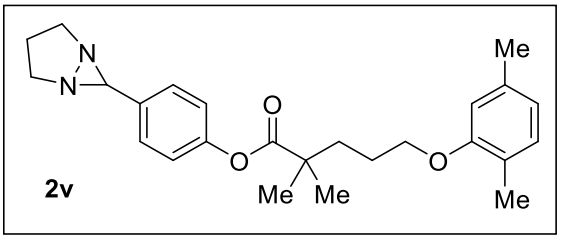
4.4 Characterization Data



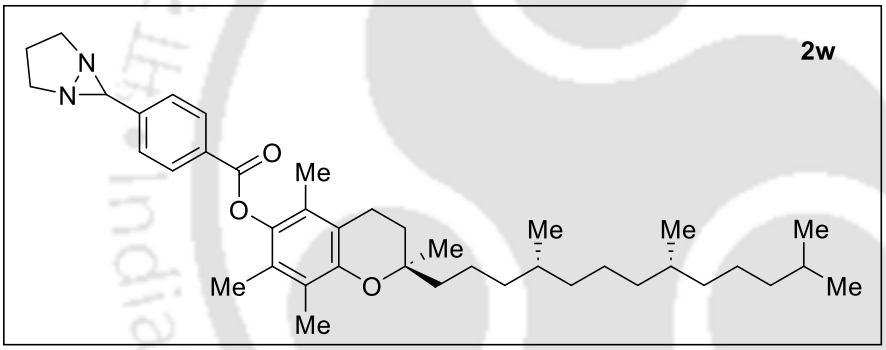
(1S,2R,5S)-2-Isopropyl-5-methylcyclohexyl 4-(1,5-diaza-bicyclo[3.1.0]hexan-6-yl)benzoate 2t. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.29; colorless solid; mp 68-69 °C; yield 77% (197 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 4.95-4.88 (m, 1H), 3.61 (dd, *J* = 12.0, 8.45 Hz, 2H), 3.20-3.12 (m, 3H), 2.13 (d, *J* = 12.0 Hz, 1H), 1.96-1.87 (m, 3H), 1.76-1.66 (m, 3H), 1.60-1.51 (m, 2H), 1.11 (t, *J* = 11.6 Hz, 2H), 0.91 (t, *J* = 7.2 Hz, 6H), 0.78 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 142.0, 131.1, 129.6, 127.4, 75.0, 56.3, 52.47, 52.45, 47.4, 41.1, 34.4, 31.5, 26.7, 23.9, 22.1, 21.7, 20.8, 16.7; FT-IR (Neat) 2954, 2870, 1712, 1689, 1455, 1370, 1271, 1113, 1099, 1019 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{31}N_2O_2$: 343.2380, found: 343.2382.



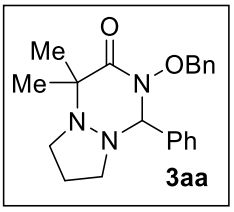
(1S,2R,4S)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 4-(1,5-diazabicyclo[3.1.0]hexan-6-yl)benzoate 2u. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.25; thick liquid; yield 69% (175 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 5.12-5.08 (m, 1H), 3.64-3.58 (m, 2H), 3.20-3.12 (m, 3H), 2.50-2.42 (m, 1H), 2.15-2.08 (m, 1H), 1.97-1.87 (m, 2H), 1.84-1.76 (m, 1H), 1.73 (t, *J* = 4.4 Hz, 1H), 1.44-1.36 (m, 1H), 1.34-1.27 (m, 1H), 1.13 (dd, *J* = 13.6, 3.2 Hz, 1H), 0.96 (s, 3H), 0.91 (d, *J* = 4.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 142.1, 131.1, 129.5, 127.4, 80.7, 56.3, 52.4, 49.2, 48.0, 45.1, 37.0, 28.2, 27.5, 21.7, 19.8, 19.0, 13.7; FT-IR (Neat) 2953, 2877, 1713, 1613, 1453, 1307, 1272, 1117, 1019 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{29}N_2O_2$: 341.2224, found: 341.2225.



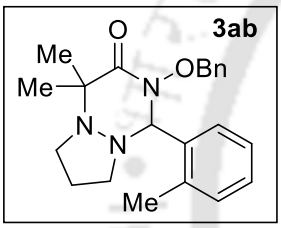
4-(1,5-Diazabicyclo[3.1.0]hexan-6-yl)phenyl 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoate 2v. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.28; thick liquid; yield 63% (192 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 3H), 6.66 (d, *J* = 7.2 Hz, 1H), 6.61 (s, 1H), 3.98-3.96 (m, 2H), 3.60-3.54 (m, 2H), 3.17-3.09 (m, 3H), 2.29 (s, 3H), 2.16 (s, 3H), 1.93-1.84 (m, 6H), 1.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 157.0, 151.4, 136.5, 134.5, 130.4, 128.4, 123.7, 121.5, 120.8, 112.1, 67.9, 56.3, 52.3, 42.5, 37.2, 25.3, 25.2, 21.8, 21.5, 15.8; FT-IR (Neat) 2927, 2875, 1747, 1613, 1508, 1263, 1194, 1160, 1112, 1045 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{33}N_2O_3$: 409.2486, found: 409.2491.



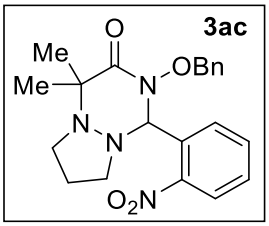
(R)-2,5,7,8-Tetramethyl -2-((4R,8R)-4,8,12-trimethyltridecyl)chroman-6-yl 4-(1,5-diazabicyclo[3.1.0]hexan-6-yl) benzoate 2w. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.26; colorless solid; mp 87-88 °C; yield 65% (293 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 3.65-3.60 (m, 2H), 3.22-3.14 (m, 3H), 2.60 (t, *J* = 6.8 Hz, 2H), 2.11 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H), 1.95-1.77 (m, 4H), 1.55-1.47 (m, 2H), 1.39-1.33 (m, 3H), 1.30-1.20 (m, 12H), 1.16-1.03 (m, 7H), 0.87-0.83 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 149.5, 142.8, 140.6, 130.2, 129.7, 127.6, 126.9, 125.2, 123.1, 117.5, 75.1, 56.1, 52.4, 39.4, 37.56, 37.51, 37.4, 37.3, 32.89, 32.88, 28.0, 24.92, 24.91, 24.5, 23.8, 22.8, 22.7, 21.7, 21.1, 20.7, 19.87, 19.80, 19.77, 19.75, 19.71, 13.1, 12.2, 11.9; FT-IR (Neat) 2925, 2868, 1730, 1614, 1459, 1270, 1235, 1171, 1090, 1018 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{40}H_{60}N_2NaO_3$: 639.4496, found: 639.4502.



2-(Benzyloxy)-4,4-dimethyl-1-phenyltetrahydro-6H pyrazolo[1,2-a] [1, 2,4] triazin-3(4H)-one 3aa. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.49; colorless solid; mp 89-90 □C; yield 79% (55 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 6.5 Hz, 2H), 7.35-7.31 (m, 3H), 7.17-7.11 (m, 3H), 6.90-6.88 (m, 2H), 4.83 (d, *J* = 9.0 Hz, 1H), 4.72 (s, 1H), 4.01 (d, *J* = 9.0 Hz, 1H), 2.99-2.94 (m, 1H), 2.81-2.76 (m, 1H), 2.72-2.68 (m, 1H), 2.37 (q, *J* = 8.5 Hz, 1H), 1.93-1.82 (m, 2H), 1.48 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 134.9, 129.7, 129.6, 129.3, 128.56, 128.51, 128.3, 86.4, 77.3, 64.0, 50.9, 45.3, 23.6, 23.4, 17.8; FT-IR (Neat) 2978, 2935, 1672, 1455, 1384, 1364, 1211, 1182, 1044, 1028 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{26}N_3O_2$: 352.2020, found: 352.2022.

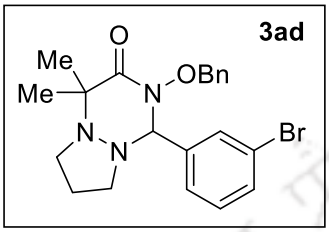


2-(Benzyloxy)-4,4-dimethyl-1-(o-tolyl)tetrahydro-6H-pyrazolo[1,2-a] [1,2,4]triazin-3(4H)-one 3ab. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.45; thick liquid; yield 65% (47 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (m, 1H), 7.32-7.28 (m, 2H), 7.22-7.19 (m, 4H), 6.92 (d, *J* = 6.0 Hz, 2H), 5.24 (s, 1H), 4.86 (d, *J* = 8.0 Hz, 1H), 3.87 (d, *J* = 7.6 Hz, 1H), 3.07-3.01 (m, 1H), 2.89-2.83 (m, 2H), 2.43-2.36 (m, 4H), 2.01-1.91 (m, 2H), 1.56 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 138.2, 134.8, 134.5, 130.4, 129.6, 129.0, 128.9, 128.5, 128.2, 126.3, 80.9, 77.5, 63.9, 50.5, 45.2, 23.55, 23.51, 19.7, 17.9; FT-IR (Neat) 2975, 2872, 1682, 1455, 1376, 1351, 1280, 1230, 1206, 1010 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{28}N_3O_2$: 366.2176, found: 366.2180.

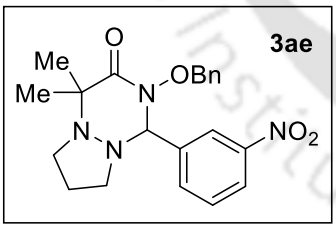


2-(Benzyloxy)-4,4-dimethyl-1-(2-nitrophenyl)tetrahydro-6H-pyrazo- lo[1,2-a][1,2,4]triazin-3(4H)-one 3ac. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.41; thick liquid; yield 59% (46 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.62-7.58 (m, 1H), 7.52-7.48 (m, 1H), 7.25-7.21 (m, 3H),

7.14-7.11 (m, 2H), 5.68 (s, 1H), 4.91 (d, *J* = 9.2 Hz, 1H), 4.40 (d, *J* = 9.2 Hz, 1H), 3.05-2.99 (m, 1H), 2.88-2.82 (m, 1H), 2.76-2.73 (m, 2H), 2.06-1.98 (m, 1H), 1.96-1.87 (m, 1H), 1.52 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 151.1, 134.4, 132.6, 131.2, 130.0, 129.6, 128.7, 128.4, 123.7, 76.8, 64.3, 50.1, 45.1, 24.1, 24.0, 23.3, 18.5; FT-IR (Neat) 2977, 2880, 1676, 1527, 1454, 1353, 1280, 1202, 1090, 1009 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{25}N_4O_4$: 397.1870, found: 397.1881.

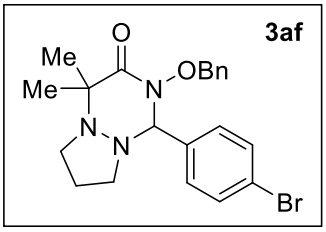


2-(Benzyloxy)-1-(3-bromophenyl)-4,4-dimethyltetrahydro-6H-pyrazolo[1,2-a][1,2,4]triazin-3(4H)-one 3ad. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.44; thick liquid; yield 69% (59 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.32-7.24 (m, 4H), 7.03 (d, *J* = 6.0 Hz, 2H), 4.92 (d, *J* = 9.0 Hz, 1H), 4.70 (s, 1H), 4.13 (d, *J* = 9.0 Hz, 1H), 3.04-3.00 (m, 1H), 2.86-2.81 (q, *J* = 8.0 Hz, 1H), 2.79-2.76 (m, 1H), 2.40 (q, *J* = 8.0 Hz, 1H), 2.00-1.91 (m, 2H), 1.53 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 138.9, 134.7, 132.7, 132.2, 130.1, 129.7, 128.7, 128.4, 128.0, 122.5, 85.7, 77.2, 64.0, 51.0, 45.2, 23.6, 23.4, 17.8; FT-IR (Neat) 2976, 2880, 1683, 1574, 1454, 1377, 1352, 1280, 1205, 1068 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{25}BrN_3O_2$: 430.1125, found: 430.1132.

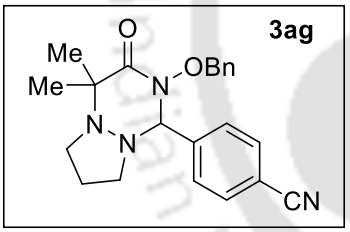


2-(Benzyloxy)-4,4-dimethyl-1-(3-nitrophenyl)tetrahydro-6H-pyrazolo[1,2-a][1,2,4]triazin-3(4H)-one 3ae. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.42; thick liquid; yield 61% (48 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18-8.71 (m, 2H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.50-7.46 (m, 1H), 7.21-7.13 (m, 3H), 6.95-6.93 (m, 2H), 4.85 (d, *J* = 10.0 Hz, 1H), 4.74 (s, 1H), 4.21 (d, *J* = 9.6 Hz, 1H), 2.99-2.93 (m, 1H), 2.81-2.75 (m, 1H), 2.64-2.59 (m, 1H), 2.35 (q, *J* = 8.4 Hz, 1H), 1.95-1.81 (m, 2H), 1.48 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 148.3, 138.8, 135.3, 134.7, 129.6, 129.4, 128.8, 128.5, 124.5, 124.1, 85.4, 77.2, 64.2, 50.9, 45.1, 23.7, 23.3, 17.9; FT-IR (Neat) 2977, 2878,

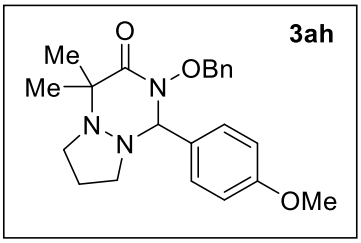
1677, 1530, 1455, 1349, 1282, 1204, 1092, 1010 cm^{-1}; HRMS (ESI) m/z [M+H]+ calcd for $C_{21}H_{25}N_4O_4$: 397.1870, found: 397.1867.



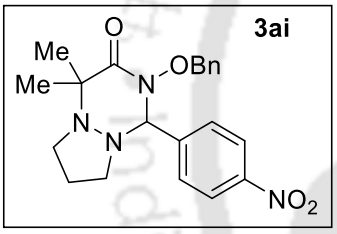
2-(Benzyloxy)-1-(4-bromophenyl)-4,4-dimethyltetrahydro-6H-pyrazolo[1,2-a][1,2,4]triazin-3(4H)-one 3af. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.44; colorless solid; mp 127-128 °C; yield 73% (62 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.19-7.15 (m, 3H), 6.95 (d, *J* = 7.5 Hz, 2H), 4.83 (d, *J* = 9.0 Hz, 1H), 4.64 (s, 1H), 4.08 (d, *J* = 9.5 Hz, 1H), 2.97-2.92 (m, 1H), 2.79-2.74 (m, 1H), 2.68-2.64 (m, 1H), 2.32 (q, *J* = 8.5 Hz, 1H), 1.92-1.81 (m, 2H), 1.45 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.7, 135.6, 134.8, 131.7, 130.9, 129.7, 128.7, 128.4, 123.6, 85.8, 77.2, 64.0, 50.9, 45.2, 23.6, 23.4, 17.7; FT-IR (Neat) 2977, 2938, 2883, 1686, 1591, 1487, 1352, 1291, 1206, 1011 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{25}BrN_3O_2$: 430.1125, found: 430.1130.



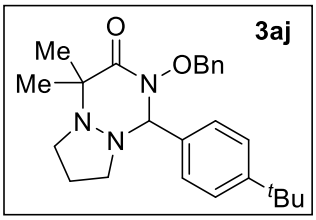
4-(2-(benzyloxy)-4,4-dimethyl-3-oxohexahydro-6*H*-pyrazolo[1,2-*a*][1,2,4]triazin-1-yl)benzonitrile 3ag. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.41; thick liquid; yield 63% (47 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.21-7.15 (m, 3H), 6.95 (d, *J* = 7.5 Hz, 2H), 4.85 (d, *J* = 10.0 Hz, 1H), 4.74 (s, 1H), 4.18 (d, *J* = 9.5 Hz, 1H), 2.98-2.93 (m, 1H), 2.78 (q, *J* = 9.0 Hz, 1H), 2.59 (t, *J* = 7.5 Hz, 1H), 2.33 (q, *J* = 8.5 Hz, 1H), 1.94-1.89 (m, 1H), 1.86-1.81 (m, 1H), 1.47 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 148.7, 143.5, 134.7, 130.1, 129.6, 128.8, 128.7, 128.4, 123.6, 85.3, 77.2, 64.3, 50.8, 45.1, 23.8, 23.3, 17.8; FT-IR (Neat) 2936, 2919, 2812, 2021, 1621, 1530, 1476, 1356, 1101, 1034 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{25}N_4O_2$: 377.1972, found: 377.1974.



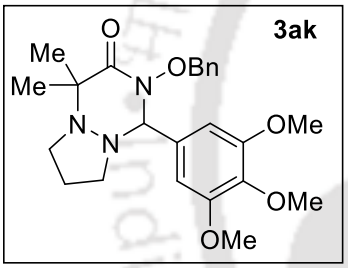
2-(benzyloxy)-1-(4-methoxyphenyl)-4,4-dimethyltetrahydro-6- H-pyrazolo[1,2-a][1,2,4]triazin-3(4H)-one 3ah. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.43; thick liquid; yield 78% (59 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.0 Hz, 2H), 7.17-7.13 (m, 3H), 6.96-6.94 (m, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 4.81 (d, *J* = 9.0 Hz, 1H), 4.66 (s, 1H), 4.02 (d, *J* = 9.0 Hz, 1H), 3.77 (s, 3H), 2.97-2.93 (m, 1H), 2.80-2.74 (m, 1H), 2.72-2.68 (m, 1H), 2.34 (q, *J* = 8.5 Hz, 1H), 1.92-1.81 (m, 2H), 1.46 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 160.6, 135.0, 130.4, 129.7, 128.7, 128.5, 128.3, 113.8, 86.0, 63.9, 55.5, 50.9, 45.3, 23.6, 23.4, 17.7; FT-IR (Neat) 2975, 2838, 1681, 1611, 1514, 1455, 1351, 1247, 1170, 1030 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{28}N_3O_3$: 382.2125, found: 382.2123.



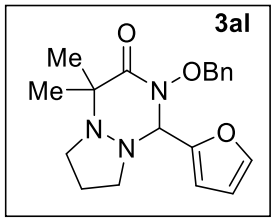
2-(Benzyloxy)-4,4-dimethyl-1-(4-nitrophenyl)tetrahydro-6H-pyrazolo[1,2-a][1,2,4]triazin-3(4H)-one 3ai. Analytical TLC on silica gel, 2:3 ethyl acetate/hexane; R_f = 0.40; colorless solid; mp 97-98 °C; yield 60% (47 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.22-7.14 (m, 3H), 6.95 (d, *J* = 7.0 Hz, 2H), 4.85 (d, *J* = 10.0 Hz, 1H), 4.74 (s, 1H), 4.19 (d, *J* = 9.5 Hz, 1H), 2.98-2.93 (m, 1H), 2.80-2.75 (m, 1H), 2.62-2.57 (m, 1H), 2.33 (q, *J* = 8.5 Hz, 1H), 1.94-1.90 (m, 1H), 1.87-1.82 (m, 1H), 1.47 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 148.7, 143.5, 134.7, 130.1, 129.6, 128.8, 128.5, 123.6, 85.3, 77.2, 64.3, 50.8, 45.1, 23.8, 23.3, 17.8; FT-IR (Neat) 2977, 2850, 1682, 1608, 1524, 1454, 1348, 1284, 1205, 1015 cm^{-1}; HRMS (ESI) m/z [M+H]+ calcd for $C_{21}H_{25}N_4O_4$: 397.1870, found: 397.1876.



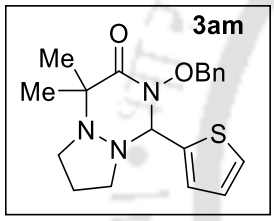
2-(Benzyloxy)-1-(4-(tert-butyl)phenyl)-4,4-dimethyltetrahy-dro-6H-pyrazolo[1,2-a][1,2,4]triazin-3(4H)-one 3aj. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.42; thick liquid; yield 71% (57 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.16-7.09 (m, 3H), 6.80 (d, *J* = 7.0 Hz, 2H), 4.87 (d, *J* = 8.5 Hz, 1H), 4.69 (s, 1H), 3.96 (d, *J* = 9.0 Hz, 1H), 2.98-2.94 (m, 1H), 2.80-2.72 (m, 2H), 2.36 (q, *J* = 9.0 Hz, 1H), 1.93-1.83 (m, 2H), 1.48 (s, 3H), 1.34 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.6, 152.8, 134.7, 133.3, 129.8, 128.9, 128.5, 128.2, 125.3, 86.2, 77.2, 63.8, 51.0, 45.2, 34.8, 31.5, 23.49, 23.45, 17.7; FT-IR (Neat) 2963, 2869, 1684, 1455, 1366, 1351, 1284, 1206, 1107, 1023 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{34}N_3O_2$: 408.2646, found: 408.2661.



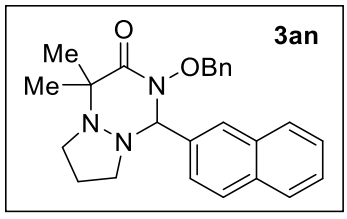
2-(Benzyloxy)-4,4-dimethyl-1-(3,4,5-trimethoxyphenyl)tetra-hydro-6H-pyrazolo[1,2-a][1,2,4]triazin-3(4H)-one 3ak. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.41; thick liquid; yield 75% (66 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.21 (m, 3H), 7.03 (dd, *J* = 7.2, 1.6 Hz, 2H), 6.75 (s, 2H), 4.96 (d, *J* = 9.2 Hz, 1H), 4.65 (s, 1H), 4.12 (d, *J* = 9.2 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 6H), 3.06-3.01 (m, 1H), 2.88-2.82 (m, 2H), 2.42 (q, *J* = 8.8 Hz, 1H), 2.02-1.92 (m, 2H), 1.54 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 153.2, 139.0, 134.9, 132.0, 129.7, 128.6, 128.3, 106.2, 86.5, 64.3, 63.9, 61.1, 56.3, 50.9, 45.2, 23.6, 23.4, 17.8; FT-IR (Neat) 2975, 2937, 2848, 1684, 1594, 1504, 1460, 1422, 1351, 1233, 1126, 1008 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{32}N_3O_5$: 442.2336, found: 442.2336.



2-(Benzyloxy)-1-(furan-2-yl)-4,4-dimethyltetrahydro-6H-pyrazolo-[1,2-a][1,2,4]triazin-3(4H)-one 3al. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.43; thick liquid; yield 65% (44 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.28-7.26 (m, 3H), 7.19-7.17 (m, 2H), 6.55 (d, *J* = 3.0 Hz, 1H), 6.45-6.44 (m, 1H), 4.96 (d, *J* = 9.0 Hz, 1H), 4.93 (s, 1H), 4.27 (d, *J* = 9.0 Hz, 1H), 3.01-2.97 (m, 1H), 2.90-2.84 (m, 2H), 2.54 (q, *J* = 9.0 Hz, 1H), 2.02-1.94 (m, 2H), 1.48 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 149.3, 143.1, 134.9, 129.7, 128.6, 128.3, 111.4, 110.7, 79.0, 77.2, 63.9, 50.9, 45.2, 23.7, 22.8, 18.1; FT-IR (Neat) 3314, 2975, 2934, 2873, 1664, 1529, 1474, 1363, 1293, 1184, 1012 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{24}N_3O_3$: 342.1812, found: 342.1815.

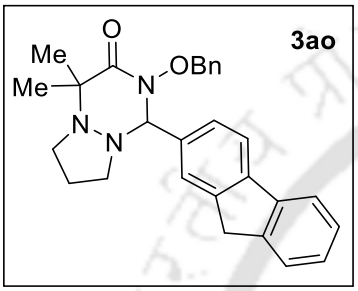


2-(Benzyloxy)-4,4-dimethyl-1-(thiophen-2-yl)tetrahydro-6H-pyrazo- lo[1,2-a][1,2,4]triazin-3(4H)-one 3am. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.43; thick liquid; yield 61% (43 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 5.0 Hz, 1H), 7.28-7.27 (m, 3H), 7.20 (d, *J* = 3.0 Hz, 1H), 7.17-7.15 (m, 2H), 7.03-7.01 (m, 1H), 5.14 (s, 1H), 4.94 (d, *J* = 9.5 Hz, 1H), 4.12 (d, *J* = 10.0 Hz, 1H), 3.01-2.96 (m, 1H), 2.91 (q, *J* = 8.5 Hz, 2H), 2.59 (s, 1H), 1.99-1.93 (m, 2H), 1.49 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 139.6, 134.9, 129.7, 129.0, 128.6, 128.3, 127.8, 126.0, 80.8, 77.4, 64.2, 64.1, 50.6, 45.2, 24.4, 23.9; FT-IR (Neat) 2976, 2935, 2880, 1674, 1454, 1373, 1305, 1231, 1208, 1020 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{24}N_3O_2S$: 358.1584, found: 358.1585.

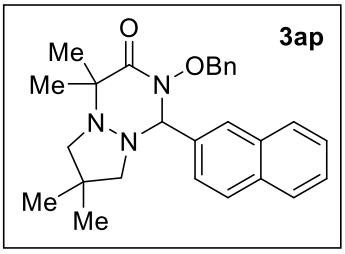


2-(Benzyloxy)-4,4-dimethyl-1-(naphthalen-2-yl)tetrahydro-6H-pyrazolo[1,2-a][1,2,4]triazin-3(4H)-one 3an. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.40; colorless solid; mp 92-93 °C; yield 72% (57 mg); ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.89-7.85 (m, 4H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.56-7.51 (m, 2H), 7.16 (t, *J* = 7.2 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 2H), 6.85 (d, *J* = 7.2 Hz, 2H), 4.93 (s, 1H), 4.91 (d, *J* = 9.2 Hz, 1H), 4.09 (d, *J* = 9.2 Hz, 1H), 3.08-3.03 (m, 1H), 2.90-2.84 (m, 1H), 2.78-2.72 (m, 1H), 2.48 (q, *J* = 8.8 Hz, 1H), 2.02-1.88 (m, 2H), 1.60 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 134.7, 134.1, 133.8, 133.0, 129.6, 129.2, 128.5, 128.4, 128.27, 128.21, 127.9, 126.7, 126.4, 125.9, 86.6, 77.2, 64.0, 51.0, 45.3, 23.6, 23.5, 17.8; FT-IR (Neat) 2976, 2935, 2880, 1681, 1454, 1376, 1308, 1281, 1207, 1015 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{28}N_3O_2$: 402.2176, found: 402.2164.

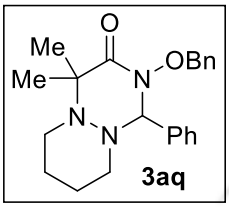


2-(Benzyloxy)-1-(9H-fluoren-3-yl)-4,4-dimethyltetrahydro-6H-pyrazolo[1,2-a][1,2,4]triazin-3(4H)-one 3ao. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.41; thick liquid; yield 70% (61 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 13.5, 7.5 Hz, 2H), 7.68 (s, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.20-7.12 (m, 3H), 6.97 (d, *J* = 7.5 Hz, 2H), 4.91 (d, *J* = 9.5 Hz, 1H), 4.84 (s, 1H), 4.14 (d, *J* = 9.0 Hz, 1H), 3.92 (s, 2H), 3.07-3.02 (m, 1H), 2.89-2.84 (m, 1H), 2.83-2.79 (m, 1H), 2.46 (q, *J* = 8.5 Hz, 1H), 2.01-1.91 (m, 2H), 1.58 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 143.7, 143.4, 143.2, 141.3, 135.0, 134.9, 129.6, 128.5, 128.2, 128.1, 127.2, 127.0, 125.9, 125.3, 120.2, 119.7, 86.7, 77.2, 64.0, 51.0, 45.3, 37.0, 27.0, 23.6, 17.8; FT-IR (Neat) 2976, 1938, 2880, 1682, 1455, 1377, 1352, 1282, 1207, 1006 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{30}N_3O_2$: 440.2333, found: 440.2334.

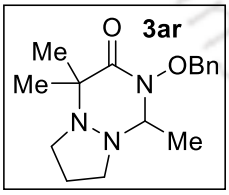


2-(Benzyloxy)-4,4,7,7-tetramethyl-1-(naphthalen-2-yl)tetrahydro-6H-pyrazolo[1,2-a][1,2,4]triazin-3(4H)-one 3ap. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.45; colorless solid; mp 130-131 °C; yield 77% (66 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88-7.84 (m, 4H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.55-7.51 (m, 2H), 7.15 (t, *J* = 7.5

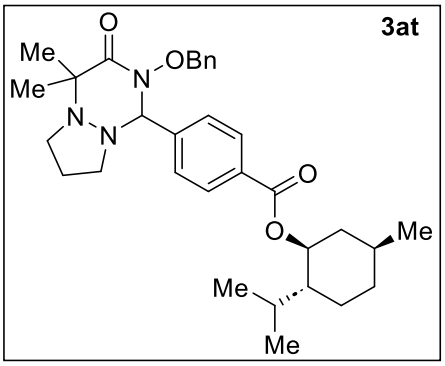
Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 2H), 6.84 (d, *J* = 7.5 Hz, 2H), 4.90-4.88 (m, 2H), 4.07 (d, *J* = 9.5 Hz, 1H), 2.81 (d, *J* = 9.0 Hz, 1H), 2.68 (d, *J* = 9.0 Hz, 1H), 2.46 (d, *J* = 9.0 Hz, 1H), 2.30 (d, *J* = 8.5 Hz, 1H), 1.60 (s, 3H), 1.39 (s, 3H), 1.11 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 134.8, 134.1, 134.0, 133.0, 129.7, 129.3, 128.49, 128.42, 128.28, 128.20, 127.9, 126.7, 126.4, 125.9, 87.0, 77.2, 64.9, 63.9, 59.7, 37.5, 28.4, 28.1, 23.5, 17.7; FT-IR (Neat) 2960, 2933, 2873, 1685, 1455, 1366, 1306, 1213, 1174, 1017 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{32}N_3O_2$: 430.2489, found: 430.2493.



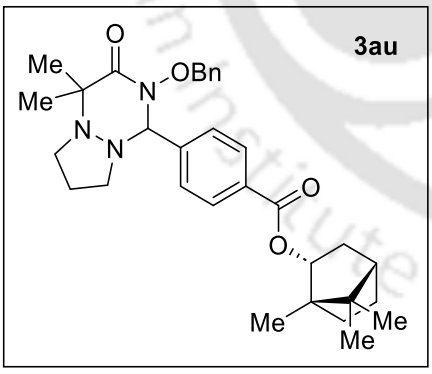
2-(Benzyloxy)-4,4-dimethyl-1-phenylhexahydropyridazino[1,2-a][1,2,4]triazin-3(4H)-one 3aq. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane; R_f = 0.39; colorless solid; mp 138-139 °C; yield 73% (53 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.54 (m, 2H), 7.44-7.42 (m, 3H), 7.27-7.22 (m, 3H), 7.05-7.02 (m, 2H), 5.78 (s, 1H), 4.94 (d, *J* = 9.2 Hz, 1H), 4.01 (d, *J* = 9.2 Hz, 1H), 2.96-2.88 (m, 1H), 2.86-2.78 (m, 2H), 2.64 (dd, *J* = 14.0, 3.2 Hz, 1H), 1.81-1.74 (m, 5H), 1.65-1.58 (m, 1H), 1.33 (s, 3H), 1.14 (d, *J* = 14.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.3, 136.9, 134.9, 129.8, 129.6, 129.1, 128.7, 128.3, 77.1, 76.4, 63.1, 48.4, 38.6, 28.0, 24.7, 22.6, 16.7; FT-IR (Neat) 2980, 2938, 1676, 1456, 1359, 1348, 1286, 1227, 1185, 1023, 1007 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{28}N_3O_2$: 366.2176, found: 366.2186.



2-(Benzyloxy)-1,4,4-trimethyltetrahydro-6H-pyrazolo[1,2-a][1,2,4]triazin-3(4H)-one 3ar. Analytical TLC on silica gel, 2:3 ethyl acetate/hexane; R_f = 0.41; thick liquid; yield 82% (47 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.38-7.33 (m, 3H), 5.03 (d, *J* = 9.6 Hz, 1H), 4.90 (d, *J* = 9.6 Hz, 1H), 4.03 (q, *J* = 6.0 Hz, 1H), 3.25-3.20 (m, 1H), 2.98-2.93 (m, 1H), 2.80-2.74 (m, 1H), 2.50-2.43 (q, *J* = 8.4 Hz, 1H), 2.04-1.96 (m, 2H), 1.37-1.35 (m, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8, 135.1, 129.6, 128.7, 128.5, 79.0, 76.9, 63.7, 51.0, 44.9, 23.6, 23.4, 17.3, 17.2; FT-IR (Neat) 2978, 2940, 2879, 1670, 1454, 1375, 1352, 1291, 1207, 1090, 1016 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{16}H_{24}N_3O_2$: 290.1863, found: 290.1869.

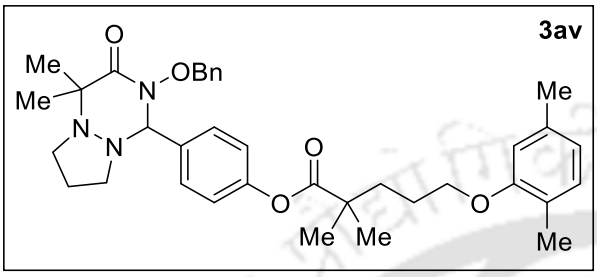


(1S,2R,5S)-2-Isopropyl-5-methylcyclohexyl 4-(2-(benzyloxy)-4,4-dimethyl-3-oxohexahydro-6H-pyrazolo[1,2-a][1,2,4]triazin-1-yl)benzoate 3at. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.43; colorless solid; mp 76-77 °C; yield 59% (62 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 8.0, 3.6 Hz, 2H), 7.57 (dd, *J* = 8.0, 4.4 Hz, 2H), 7.25-7.18 (m, 3H), 6.99 (t, *J* = 8.0 Hz, 2H), 4.98-4.89 (m, 2H), 4.79 (s, 1H), 4.17 (dd, *J* = 17.6, 9.2 Hz, 1H), 3.05-2.99 (m, 1H), 2.87-2.81 (m, 1H), 2.74-2.68 (m, 1H), 2.41 (q, *J* = 8.4 Hz, 1H), 2.16 (d, *J* = 12.0 Hz, 1H), 1.99-1.88 (m, 3H), 1.76 (d, *J* = 11.6 Hz, 2H), 1.61-1.57 (m, 2H), 1.54 (s, 3H), 1.42 (s, 3H), 1.14 (q, *J* = 11.6 Hz, 2H), 0.95-0.91 (m, 7H), 0.81 (dd, *J* = 6.8, 5.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 165.8, 141.2, 134.8, 132.1, 129.75, 129.70, 129.2, 128.6, 128.3, 85.9, 77.3, 75.3, 64.1, 50.8, 47.4, 45.2, 41.1, 34.4, 31.6, 26.8, 23.9, 23.7, 23.3, 22.1, 20.8, 17.8, 16.8; FT-IR (Neat) 2984, 2930, 2870, 1712, 1689, 1455, 1352, 1271, 1113, 1099, 1019 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{44}N_3O_4$: 534.3326, found: 534.3327.

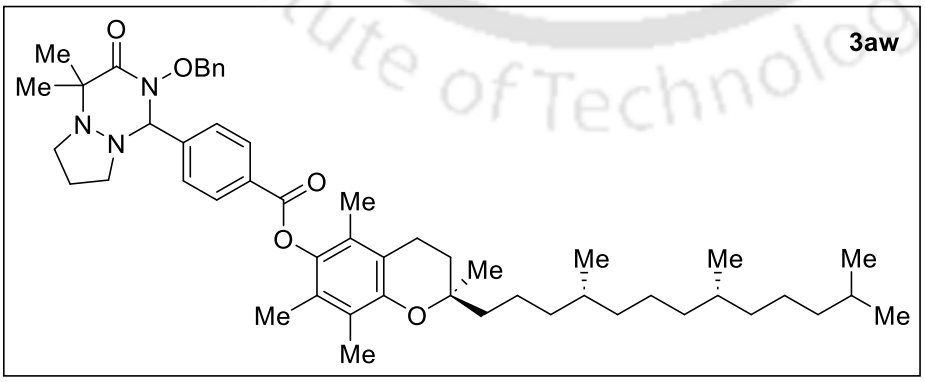


(1S,2R,4S)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 4-(2-(benzyloxy)-4,4-dimethyl-3-oxohexahydro-6H-pyrazolo[1,2-a][1,2,4]triazin-1-yl)benzoa-te 3au. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.44; thick liquid; yield 52% (55 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 6.8 Hz, 2H), 7.59 (d, *J* = 7.2 Hz, 2H), 7.25-7.20 (m, 3H), 7.01-7.00 (m, 2H), 5.15 (d, *J* = 9.6 Hz, 1H), 4.91 (d, *J* = 9.2 Hz, 1H), 4.80 (s, 1H), 4.17 (dd, *J* = 9.2, 4.8 Hz, 1H), 3.05-2.99 (m, 1H), 2.87-2.81 (m, 1H), 2.74-2.68 (m, 1H), 2.53-2.46 (m, 1H), 2.41 (q, *J* = 8.4 Hz, 1H), 2.17-2.10 (m, 1H), 2.01-1.89 (m, 2H), 1.84-1.78 (m, 1H), 1.75 (t, *J* = 4.4 Hz, 1H), 1.54 (s, 3H), 1.42 (s, 3H), 1.41-1.38 (m,

1H), 1.35-1.29 (m, 1H), 1.17-1.12 (m, 1H), 0.98 (s, 3H), 0.935-0.930 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 166.5, 141.3, 134.8, 132.1, 129.70, 129.69, 129.3, 128.6, 128.3, 85.9, 80.9, 64.1, 50.8, 49.3, 49.2, 48.0, 45.2, 45.1, 37.1, 37.0, 28.26, 28.23, 27.5, 23.7, 19.8, 19.0, 13.7; FT-IR (Neat) 2955, 2875, 1716, 1694, 1454, 1377, 1272, 1117, 1102, 1020 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{41}N_3O_4$: 532.3170, found: 532.3171.

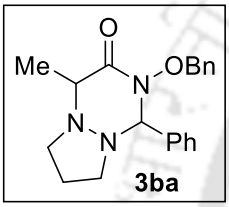


4-(2-(Benzyloxy)-4,4-dimethyl-3-oxohexahydro-6H-pyrazolo[1,2-a][1,2,4]triazin-1-yl)phenyl 5-(2,5-dimethylphenoxy)-2,2-dimethyl-pentanoate 3av. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.42; thick liquid; yield 58% (69 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.0 Hz, 2H), 7.24-7.20 (m, 3H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.03-6.98 (m, 3H), 6.67 (d, *J* = 7.6 Hz, 1H), 6.62 (s, 1H), 4.91 (d, *J* = 9.2 Hz, 1H), 4.76 (s, 1H), 4.10 (d, *J* = 8.8 Hz, 1H), 3.99 (t, *J* = 5.2 Hz , 2H), 3.05-2.99 (m, 1H), 2.87-2.81 (m, 1H), 2.80-2.74 (m, 1H), 2.40 (q, *J* = 8.8 Hz, 1H), 2.29 (s, 3H), 2.17 (s, 3H), 1.99-1.92 (m, 2H), 1.90-1.88 (m, 4H), 1.53 (s, 3H), 1.41 (s, 3H), 1.39 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 171.7, 157.0, 152.0, 136.6, 134.8, 133.9, 130.5, 130.3, 129.8, 128.6, 128.3, 123.7, 121.7, 120.9, 112.1, 85.8, 77.3, 67.9, 64.0, 50.9, 45.2, 42.6, 37.3, 25.4, 25.29, 25.28, 23.6, 23.4, 21.5, 17.8, 15.9; FT-IR (Neat) 2975, 2928, 2875, 1750, 1686, 1608, 1508, 1454, 1377, 1264, 1197, 1161, 1110, 1046 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{36}H_{46}N_3O_5$: 600.3432, found: 600.3432.

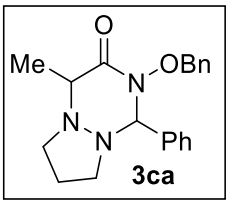


(R)-2,5,7,8-Tetramethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chroman-6-yl 4-(2-(benzyloxy)-4,4-dimethyl-3-oxohexahydro-6H-pyrazolo[1,2-a][1,2,4]triazin-1-yl)benzoate 3aw. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.41; thick liquid; yield 47% (75 mg); ^{1}H NMR (400

MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 7.6 Hz, 2H), 7.20-7.13 (m, 3H), 6.94 (dd, *J* = 7.6, 1.6 Hz, 2H), 4.89 (d, *J* = 9.2 Hz, 1H), 4.76 (s, 1H), 4.16 (d, *J* = 9.6 Hz, 1H), 2.99-2.94 (m, 1H), 2.82-2.75 (m, 1H), 2.72-2.68 (m, 1H), 2.55 (t, *J* = 6.8 Hz, 2H), 2.38 (q, *J* = 8.4 Hz, 1H), 2.05 (s, 3H), 2.00 (s, 3H), 1.96 (s, 3H), 1.93-1.83 (m, 2H), 1.79-1.72 (m, 2H), 1.49 (s, 3H), 1.47-1.42 (m, 2H), 1.36 (s, 3H), 1.34-1.30 (m, 3H), 1.26-1.14 (m, 12H), 1.09-0.96 (m, 7H), 0.80-0.77 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 164.8, 149.7, 141.9, 140.7, 134.8, 130.8, 130.3, 129.7, 129.5, 128.7, 128.4, 126.9, 125.2, 123.3, 117.7, 85.9, 77.2, 75.2, 64.2, 50.9, 45.2, 39.5, 37.73, 37.70, 37.65, 37.62, 37.57, 37.54, 37.4, 32.95, 32.93, 32.8, 28.1, 24.96, 24.94, 24.5, 23.7, 23.3, 22.8, 22.7, 21.2, 20.8, 19.9, 19.8, 19.78, 19.75, 17.8, 13.2, 12.3, 12.0; FT-IR (Neat) 2925, 2867, 1735, 1692, 1455, 1377, 1270, 1235, 1090, 1018 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{51}H_{73}N_3O_5$: 808.5623, found: 808.5623.

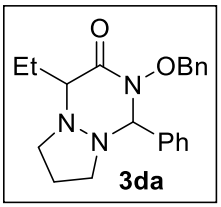


2-(Benzyloxy)-4-methyl-1-phenyltetrahydro-6H-pyrazolo[1,2a][1,2,-4]triazin-3(4H)-one 3ba. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.45; colorless solid; mp 92-93 °C; yield 82% (55 mg); major diastereomer (d.r. = 12:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 6.4 Hz, 2H), 7.45-7.39 (m, 3H), 7.23-7.18 (m, 3H), 6.96-6.94 (m, 2H), 4.96 (d, *J* = 8.8 Hz, 1H), 4.77 (s, 1H), 4.12 (d, *J* = 8.8 Hz, 1H), 3.40-3.33 (m, 2H), 2.78-2.72 (m, 1H), 2.45-2.34 (m, 2H), 2.01-1.94 (m, 2H), 1.43 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 136.0, 134.8, 129.7, 129.6, 129.2, 128.6, 128.5, 128.3, 86.1, 77.3, 64.9, 53.7, 50.9, 23.0, 14.6; FT-IR (Neat) 3032, 2979, 2834, 1687, 1454, 1372, 1356, 1288, 1259, 1148, 999 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{24}N_3O_2$: 338.1863, found: 338.1863.

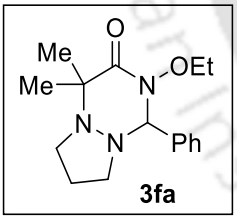


2-(Benzyloxy)-4-methyl-1-phenyltetrahydro-6H-pyrazolo[1,2-a][1,-2,4]triazin-3(4H)-one 3ca. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.45; colorless solid; mp 92-93 °C; yield 80% (53 mg); major diastereomer (d.r. = 15:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.0 Hz, 2H), 7.45-7.39 (m, 3H), 7.24-7.19 (m, 3H), 6.95 (d, *J* = 7.0 Hz, 2H), 4.96 (d, *J* = 9.0 Hz, 1H), 4.77 (s, 1H), 4.11 (d, *J* = 9.0 Hz, 1H), 3.40-3.34 (m,

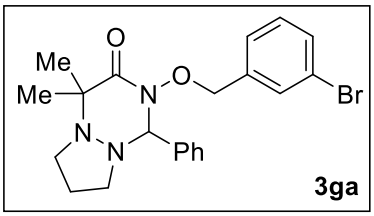
2H), 2.78-2.73 (m, 1H), 2.45-2.35 (m, 2H), 2.02-1.96 (m, 2H), 1.44 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 136.0, 134.8, 129.8, 129.7, 129.3, 128.6, 128.5, 128.3, 86.1, 77.3, 64.9, 53.7, 50.9, 23.0, 14.7; FT-IR (Neat) 3032, 2979, 2834, 1687, 1454, 1372, 1356, 1288, 1259, 1148, 999 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{24}N_3O_2$: 338.1863, found: 338.1863.



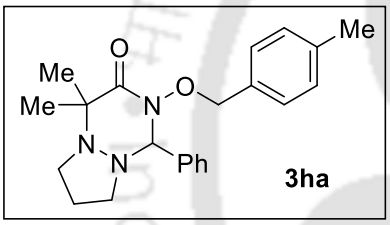
2-(Benzyloxy)-4-ethyl-1-phenyltetrahydro-6H-pyrazolo[1,2-a][1,-2,4]triazin-3(4H)-one 3da. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.44; colorless solid; mp 84-85 °C; yield 83% (58 mg); major diastereomer (d.r. = 7.6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.2 Hz, 2H), 7.42-7.37 (m, 3H), 7.26-7.19 (m, 3H), 6.98-6.95 (m, 2H), 4.97 (d, *J* = 9.6 Hz, 1H), 4.75 (s, 1H), 4.21 (d, *J* = 9.2 Hz, 1H), 3.38-3.32 (m, 2H), 2.75-2.69 (m, 1H), 2.43-2.32 (m, 2H), 2.23-2.16 (m, 1H), 2.01-1.94 (m, 2H), 1.76-1.69 (m, 1H), 1.02 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 136.0, 134.9, 129.75, 129.70, 129.2, 128.6, 128.5, 128.3, 86.0, 77.3, 69.9, 53.1, 50.7, 23.1, 22.2, 9.3; FT-IR (Neat) 2968, 2935, 2835, 1681, 1455, 1355, 1289, 1148, 1028, 1002 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{26}N_3O_2$: 352.2020, found: 352.2026.



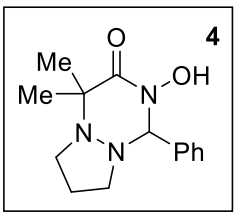
2-Ethoxy-4,4-dimethyl-1-phenyltetrahydro-6H-pyrazolo[1,2-a][1,-2,4]triazin-3(4H)-one 3fa. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.38; thick liquid; yield 54% (31 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.50 (m, 2H), 7.38-7.34 (m, 3H), 4.83 (s, 1H), 3.91-3.83 (m, 1H), 3.25-3.18 (m, 1H), 3.06-3.00 (m, 1H), 2.87-2.81 (m, 1H), 2.80-2.74 (m, 1H), 2.45 (q, *J* = 8.8 Hz, 1H), 2.01-1.90 (m, 2H), 1.51 (s, 3H), 1.39 (s, 3H), 0.87 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 136.6, 129.5, 129.1, 128.3, 86.2, 77.3, 70.8, 63.9, 51.0, 45.2, 23.6, 23.4, 17.7, 13.3; FT-IR (Neat) 2978, 2936, 2885, 1676, 1456, 1384, 1351, 1286, 1205, 1033 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{24}N_3O_2$: 290.1863, found: 290.1864.



2-((3-Bromobenzyl)oxy)-4,4-dimethyl-1-phenyltetrahydro-6H-pyrazolo[1,2-a][1,2,4]triazin-3(4H)-one 3ga. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.40; thick liquid; yield 72% (61 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.52 (m, 2H), 7.45-7.39 (m, 3H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.07 (t, *J* = 8.0 Hz, 1H), 6.97-6.92 (m, 2H), 4.87 (d, *J* = 9.2 Hz, 1H), 4.77 (s, 1H), 4.02 (d, *J* = 9.2 Hz, 1H), 3.06-3.00 (m, 1H), 2.88-2.81 (m, 1H), 2.80-2.74 (m, 1H), 2.43 (q, *J* = 8.8 Hz, 1H), 2.01-1.89 (m, 2H), 1.54 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 137.1, 136.4, 132.5, 131.6, 129.8, 129.3, 128.6, 128.1, 122.2, 86.6, 76.4, 64.0, 50.9, 45.2, 23.6, 23.4, 17.7; FT-IR (Neat) 2976, 2938, 2883, 1683, 1571, 1455, 1377, 1352, 1285, 1207, 1071 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{25}BrN_3O_2$: 430.1125, found: 430.1126.

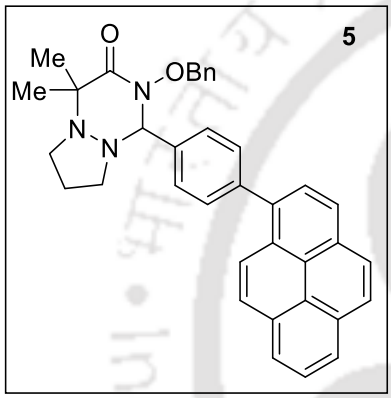


4,4-Dimethyl-2-((4-methylbenzyl)oxy)-1-phenyltetrahydro-6H-pyrazolo[1,2-a][1,2,4]triazin-3(4H)-one 3ha. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.41; colorless solid; mp 101-102 °C; yield 75% (54 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.2 Hz, 2H), 7.37-7.30 (m, 3H), 6.94 (d, *J* = 8.0 Hz, 2H), 6.78 (d, *J* = 7.6 Hz, 2H), 4.80 (d, *J* = 8.8 Hz, 1H), 4.69 (s, 1H), 3.95 (d, *J* = 8.8 Hz, 1H), 2.98-2.92 (m, 1H), 2.80-2.74 (m, 1H), 2.72-2.66 (m, 1H), 2.35 (q, *J* = 8.8 Hz, 1H), 2.20 (s, 3H), 1.93-1.81 (m, 2H), 1.47 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 138.3, 136.6, 131.9, 129.7, 129.6, 129.3, 128.9, 128.4, 86.5, 76.9, 63.9, 50.9, 45.2, 23.6, 23.4, 21.3, 17.8; FT-IR (Neat) 2925, 2853, 1684, 1519, 1456, 1376, 1353, 1286, 1206, 1012 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{28}N_3O_2$: 366.2176, found: 366.2176.



2-Hydroxy-4,4-dimethyl-1-phenyltetrahydro-6H-pyrazolo[1,2-a][1,2,4]triazin-3(4H)-one 4.[4] Pd/C (10 wt. %, 20 mol %) and **3aa** (42 mg, 0.10 mmol) were

stirred in MeOH (1.5 mL) under H_2 balloon for 6 h at room temperature. The reaction mixture was passed through a short pad of celite using EtOAc (10 mL). Evaporation of the solvent gave a residue that was purified on silica gel column chromatography. Analytical TLC on silica gel, 1:1 ethyl acetate/hexane; R_f = 0.42; colorless solid; mp 122-123 °C; yield 63% (16 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.44 (m, 2H), 7.40-7.38 (m, 3H), 4.90 (s, 1H), 3.07-3.01 (m, 1H), 2.88-2.81 (m, 1H), 2.79-2.74 (m, 1H), 2.55 (q, *J* = 8.8 Hz, 1H), 2.03-1.96 (m, 1H), 1.95-1.88 (m, 1H), 1.51 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 135.8, 129.7, 128.68, 128.62, 85.3, 63.1, 50.8, 45.1, 23.5, 23.3, 17.6; FT-IR (Neat) 3210, 2976, 2926, 2853, 1645, 1456, 1352, 1290, 1204, 1177, 1031 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{14}H_{21}N_3O$: 262.1550, found: 262.1550.



2-(Benzyloxy)-4,4-dimethyl-1-(4-(pyren-1-yl)phenyl)tetra-hydro-6H-pyrazolo[1,2-a][1,2,4]triazin-3(4H)-one 5.[5] Compound **3af** (42 mg, 0.1 mmol), pyrene-1-boronic acid (25 mg, 0.1 mmol), $Pd(PPh_3)_4$ (2.3 mg, 0.002 mmol), Na_2CO_3 (22 mg, 0.2 mmol), H_2O (50 μL) and toluene : EtOH (1:1, 2 mL) were refluxed at 100 °C for 6 h under nitrogen atmosphere. The reaction mixture was cooled to room temperature 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 to give **5**. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane; R_f = 0.44; colorless solid; mp > 200 °C; yield 81% (44 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25-8.13 (m, 4H), 8.10 (s, 2H), 8.04-7.98 (m, 3H), 7.74 (d, *J* = 7.6 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.28-7.25 (m, 3H), 7.11-7.09 (m, 2H), 5.07 (d, *J* = 9.2 Hz, 1H), 4.93 (s, 1H), 4.32 (d, *J* = 9.2 Hz, 1H), 3.11-3.06 (m, 1H), 3.00-2.94 (m, 1H), 2.92-2.88 (m, 1H), 2.57 (q, *J* = 8.8 Hz, 1H), 2.08-1.98 (m, 2H), 1.61 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 142.6, 137.1, 135.5, 135.0, 131.6, 131.0, 130.9, 130.7, 129.7, 129.4, 128.69, 128.63, 128.4, 127.8, 127.7, 127.6, 127.5, 126.2, 125.4, 125.16, 125.11, 125.0, 124.8, 86.4, 77.3, 64.1, 51.1, 45.3, 23.7, 23.5, 17.8; FT-IR (Neat) 3037, 2976, 2935, 2875, 1681, 1602,

1455, 1377, 1351, 1281, 1207, 1006 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{37}H_{34}N_3O_2$: 552.2646, found: 552.2646.

Crystal Data and Structure Refinement

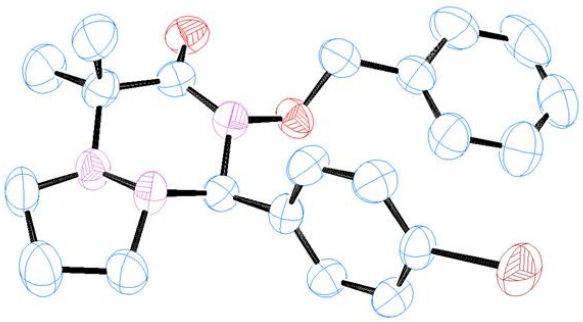


Figure S1. ORTEP diagram of 2-(Benzyloxy)-1-(4-bromophenyl)-4,4-dimethyltetrahydro-6H-pyrazolo[1,2-a][1,2,4]triazin-3(4H)-one **3af** with 50% ellipsoid (CCDC 2225274). H-Atoms omitted for clarity.

Identification code	**3af**
Empirical formula	'C21 H24 Br N3 O2'
Formula weight	430.34
Crystal habit, colour	Block /colourless
Crystal size, mm^3	0.35 x 0.31 x 0.28
Temperature, *T*/K	293 K
Wavelength, λ/Å	0.71073
Crystal system	'Orthorhombic'
Space group	'P c a 21'
Unit cell dimensions	a = 16.8943(6) Å
	b = 9.1586 (3) Å
	c = 13.1298 (4) Å
	α = 90
	β = 90
	γ = 90
Volume, *V*/$Å^3$	2031.55 (12)
Z	4
Calculated density, g cm^{-3}	1.407

Absorption coefficient, μ/mm^{-1}	2.044
F(000)	888
θ range for data collection	2.224 to 24.991°
Limiting indices	$-20 \leq h \leq 20$, $-10 \leq k \leq 10$, $-15 \leq l \leq 15$
Reflection collected / unique	3560/2836
Completeness to θ	99.9% (θ = 24.991°)
Absorption correction	None
Max. and min. transmission	0.975 and 0.980
Refinement method	'SHELXT 2018/2 (Sheldrick, 2018)'
Data / restraints / parameters	3560/1/246
Goodness−of−fit on F^2	0.921
Final R indices [I>2sigma(I)]	R1 = 0.0347, wR2 = 0.0983
R indices (all data)	R1 = 0.0536, wR2 = 0.1321

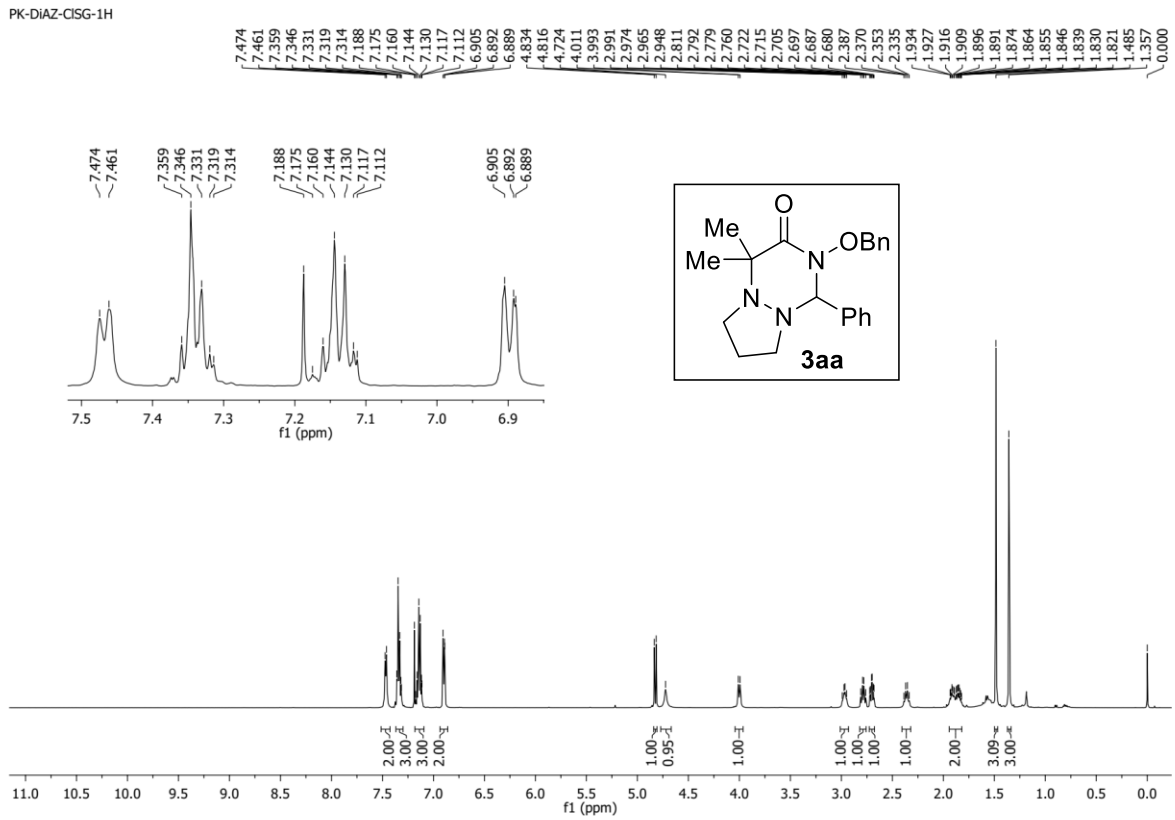
4.5 References

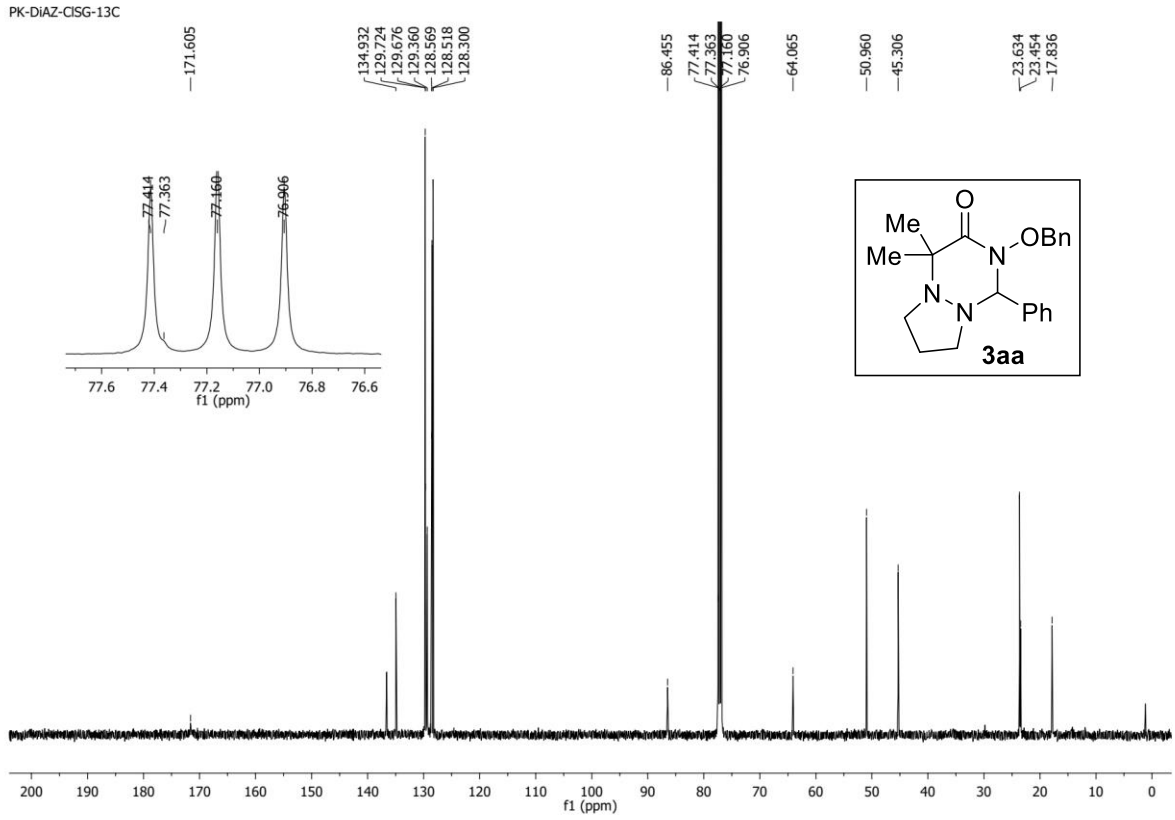
1. (a) Karpenko, I.; Deev, S.; Kiselev, O.; Charushin, V.; Rusinov, V.; Ulomsky, E.; Deeva, E.; Yanvarev, D.; Ivanov, A.; Smirnova, O.; Kochetkov, S.; Chupakhin, O.; Kukhanova, M. *Antimicrob. Agents Chemother.* **2010**, *54*, 2017. (b) Congreve, M.; Andrews, S. P.; Doré, A. S.; Hollenstein, K.; Hurrell, E.; Langmead, C. J.; Mason, J. S.; Ng, I. W.; Tehan, B.; Zhukov, A.; Weir, M.; Marshall, F. H. *J. Med. Chem.* **2012**, *55*, 1898. (c) Karczmarzyk, Z.; Wysocki, W.; Urbańczyk-Lipkowska, Z.; Kalicki, P.; Bielawska, A.; Bielawski, K.; Ławecka, J. *Chem. Pharm. Bull.* **2015**, *63*, 531. (d) Cascioferro, S.; Parrino, B.; Spanò, V.; Carbone, A.; Montalbano, A.; Barraja, P.; Diana, P.; Cirrincione, G. *Eur. J. Med. Chem.* **2017**, *142*, 328.
2. (a) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40. (b) Sheldon, R. A. *Chem. Soc. Rev*. **2012**, *41*, 1437; (c) He, J.; Shao, Q.; Wu, Q.; Yu, J.-Q. *J. Am. Chem. Soc*. **2017**, *139*, 3344.
3. (a) Coldham, I.; Hufton, R. *Chem. Rev*. **2005**, *105*, 2765. (b) Stanley, L. M.; Sibi, M. P. *Chem. Rev*. **2008**, *108*, 2887. (c) Hashimoto, T.; Maruoka, K. *Chem. Rev*. **2015**, *115*, 5366. (d) Guo, C.; Fleige, M.; Janssen-Müller, D.; Daniliuc, C. G.; Glorius, F. *Nat. Chem.* **2015**, *7*, 842.
4. (a) Adly, F. G.; Marichev, K. O.; Jensen, J. A.; Arman, H.; Doyle, M. P. *Org. Lett.* **2019**, *21*, 40. (b) Deng, Y.; Cheng, Q.-Q.; Doyle, M. *Synlett* **2017**, *28*, 1695. (c) Li, T.-Z.; Liu,

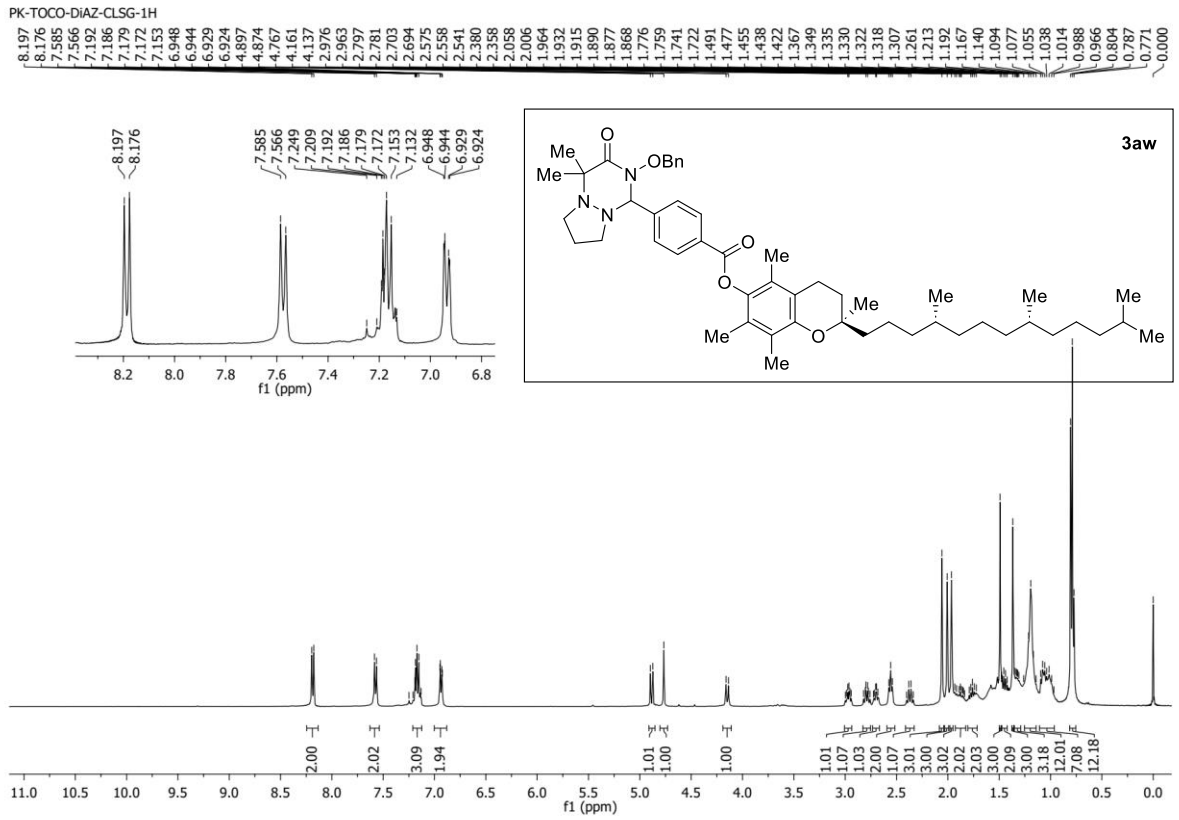
S.-J.; Sun, Y.-W.; Deng, S.; Tan, W.; Jiao, Y.; Zhang, Y.-C.; Shi, F. *Angew. Chem. Int. Ed.* **2021**, *60*, 2355.

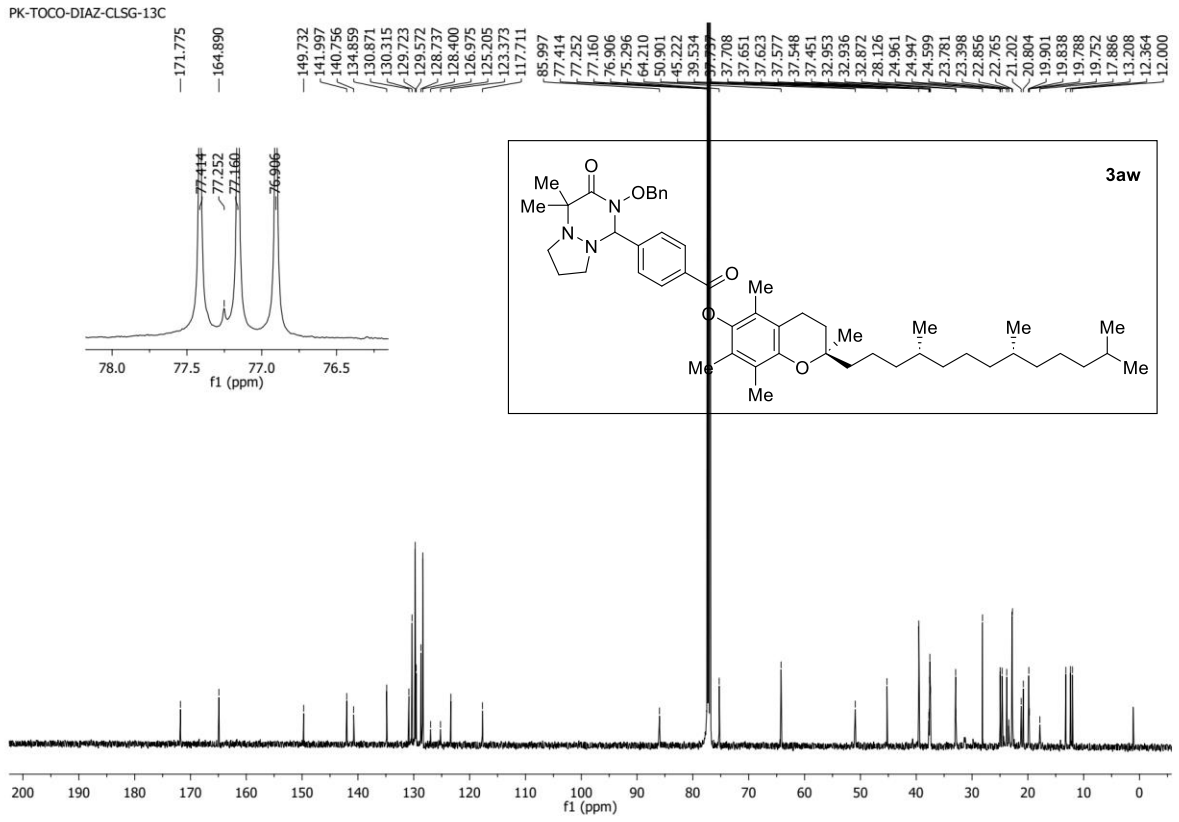
5. (a) Mack, D. J.; Njardarson, J. T. *ACS Catal.* **2013**, *3*, 272. (b) Huang, C.-Y. (dennis); Doyle, A. G. *Chem. Rev.* **2014**, *114*, 8153. (c) Fumagalli, G.; Stanton, S.; Bower, J. F. *Chem. Rev.* **2017**, *117*, 9404. (d) Liang, Y.-F.; Müller, V.; Liu, W.; Münch, A.; Stalke, D.; Ackermann, L. *Angew. Chem. Int. Ed.* **2017**, *56*, 9415. (e) Ahlburg, N. L.; Hergert, O.; Jones, P. G.; Werz, D. B. *Angew. Chem. Int. Ed.* **2023**, *62*, e202214390.
6. (a) Zheng, H.; Doyle, M. P. *Angew. Chem. Int. Ed.* **2019**, *58*, 12502. (b) Hu, H.; Xu, J.; Wang, F.; Dong, S.; Liu, X.; Feng, X. *Org. Lett.* **2020**, *22*, 93.
7. (a) Xuan, J.; Cao, X.; Cheng, X. *Chem. Commun.* **2018**, *54*, 5154. (b) El Bouakher, A.; Martel, A.; Comesse, S. *Org. Biomol. Chem.* **2019**, *17*, 8467.
8. Jeffrey, C. S.; Barnes, K. L.; Eickhoff, J. A.; Carson, C. R. *J. Am. Chem. Soc.* **2011**, *133*, 7688.
9. (a) Li, C.; Jiang, K.; Ouyang, Q.; Liu, T.-Y.; Chen, Y.-C. *Org. Lett.* **2016**, *18*, 2738. (b) Leng, H.-J.; Li, Q.-Z.; Xiang, P.; Qi, T.; Dai, Q.-S.; Jia, Z.-Q.; Gou, C.; Zhang, X.; Li, J.-L. *Org. Lett.* **2021**, *23*, 1451.
10. (a) DiPoto, M. C.; Hughes, R. P.; Wu, J. *J. Am. Chem. Soc.* **2015**, *137*, 14861. (b) Acharya, A.; Anumandla, D.; Jeffrey, C. S. *J. Am. Chem. Soc.* **2015**, *137*, 14858. (c) Ji, W.; Yao, L.; Liao, X. *Org. Lett.* **2016**, *18*, 628. (d) Zhang, K.; Yang, C.; Yao, H.; Lin, A. *Org. Lett.* **2016**, *18*, 4618. (e) Ji, D.; Sun, J. *Org. Lett.* **2018**, *20*, 2745.
11. (a) An, Y.; Xia, H.; Wu, J. *Chem. Commun.* **2016**, *52*, 10415. (b) Zhang, K.; Xu, X.; Zheng, J.; Yao, H.; Huang, Y.; Lin, A. *Org. Lett.* **2017**, *19*, 2596. (c) Baldé, B.; Force, G.; Marin, L.; Guillot, R.; Schulz, E.; Gandon, V.; Lebœuf, D. *Org. Lett.* **2018**, *20*, 7405.
12. (a) Acharya, A.; Eickhoff, J. A.; Chen, K.; Catalano, V. J.; Jeffrey, C. S. *Org. Chem. Front.* **2016**, *3*, 330. (b) Feng, J.; Zhou, M.; Lin, X.; Lu, A.; Zhang, X.; Zhao, M. *Org. Lett.* **2019**, *21*, 6245.
13. Chagarovskiy, A. O.; Vasin, V. S.; Kuznetsov, V. V.; Ivanova, O. A.; Rybakov, V. B.; Shumsky, A. N.; Makhova, N. N.; Trushkov, I. V. *Angew. Chem. Int. Ed.* **2018**, *57*, 10338.
14. Sarkar, T.; Talukdar, K.; Roy, S.; Punniyamurthy, T. *Chem. Commun.* **2020**, *56*, 3381.
15. Cortes Vazquez, J.; Davis, J.; Nesterov, V. N.; Wang, H.; Luo, W. *Org. Lett.* **2021**, *23*, 3136.
16. Feng, J.; Zhou, M.; Lin, X.; Lu, A.; Zhang, X.; Zhao, M. *Org. Lett.* **2019**, *21*, 6245.

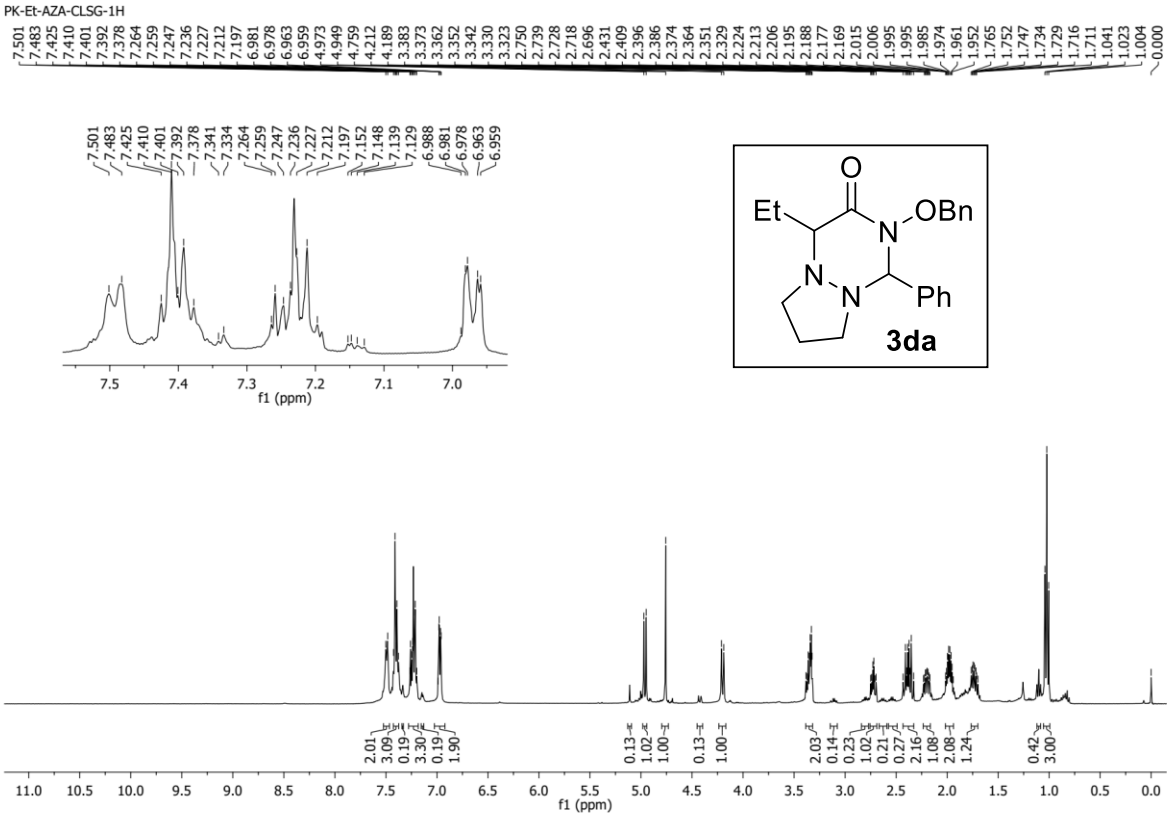
3.6 Selected NMR Spectra

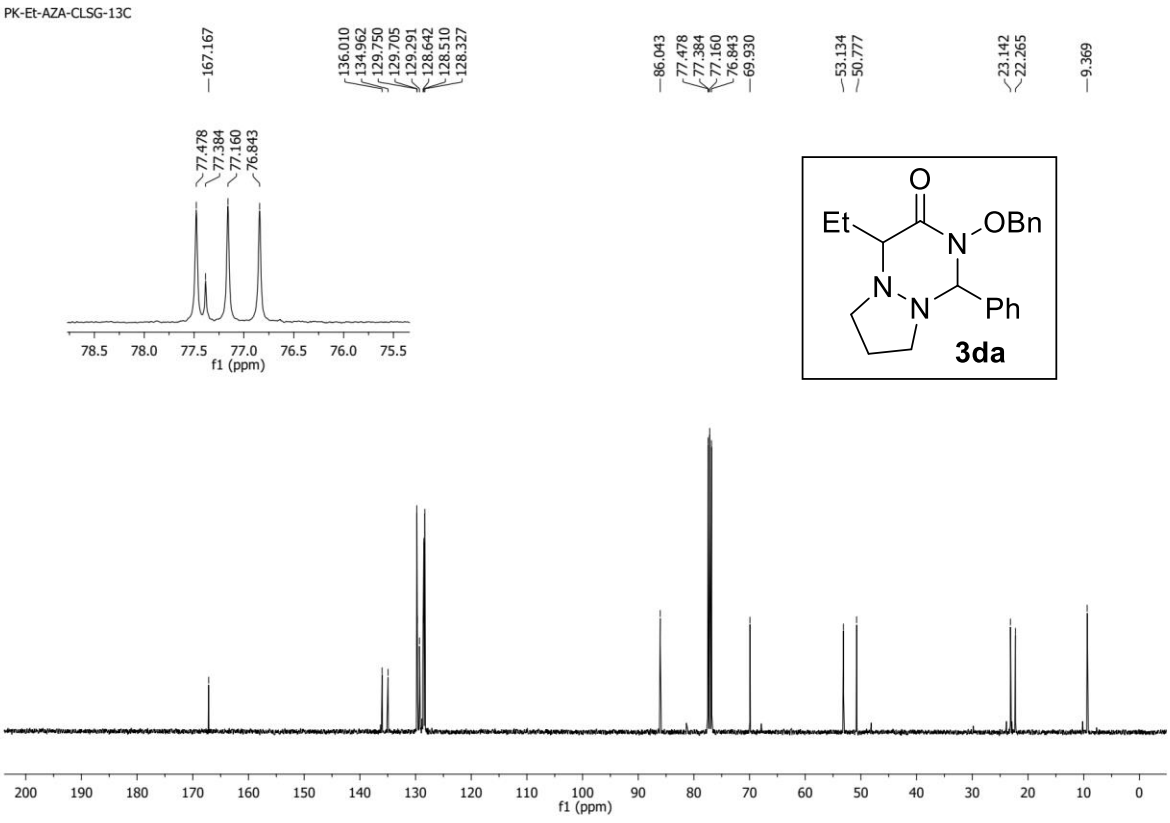




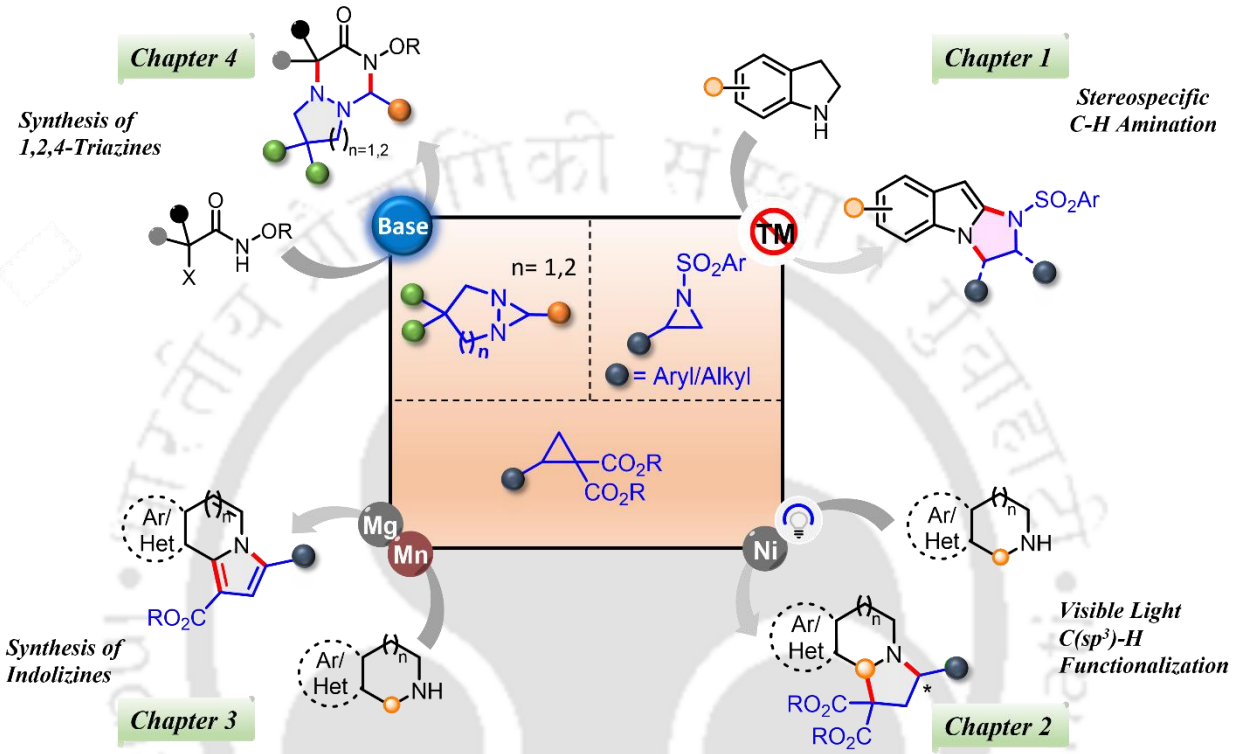








Thesis Overview



Summary

In chapter 1, we have presented an oxidative annulative coupling of indolines with *N*-sulfonyl aziridines for the construction of imidazoindoles using a combination of DDQ and NaOCl. The ring opening of aziridines occurred in neat condition followed by an intramolecular oxidative C-N bond formation to furnish imidazoindoles. The method exhibits notable tolerance towards a variety of aziridines and indolines.

In chapter 2, a $Ni(OTf)_2$ catalyzed stereospecific ring opening and visible light eosin Y catalyzed tandem C-N/C-C bond formation *via* CDC of DACs with cyclic secondary amines was developed to deliver fused pyrrolidine derivatives. This reaction provides a prospective route for direct synthesis of biologically important pyrrolidine core. Mild reaction condition, stereospecificity and broad substrate scope are the major finding of the protocol.

In chapter 3, we have demonstrated an oxidative (3+2)-cyclopentannulation of cyclic secondary amines with DACs utilizing dual action of MgI_2 and $Mn(OAc)_3 \bullet 2H_2O$ to construct synthetically important fused indolizine derivatives. The reaction involves Mg(II)-catalyzed ring opening of DACs followed by Mn(III)-mediated CDC. Decarbomethoxylation, switchable selectivity and the potential for late-stage modification of the natural products are the significant practical advantages.

In chapter 4, an (3+3)-annulation of α-halohydroxamates with diaziridines has been achieved utilizing K_2CO_3 as a base to construct 1,2,4-triazines at room temperature. The protocol established an excellent reactivity with diaziridines tethered with biologically active molecules. The elegant features of the findings include the facilitation of late-stage drug modification, broad substrate scope and mild reaction conditions.

List of Publications

1. **Pallab Karjee**, Bijoy Debnath, Santu Mandal, Sharajit Saha and Tharmalingam 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.

2. Sharajit Saha, Hemanga Bhattacharyya, **Pallab Karjee,** Bijoy Debnath, Kshitiz Verma and Tharmalingam Punniyamurthy, Expedient C-H Allylation of Sulfoxonium Ylides: Merging C-H and C-C/C-Het Bond Activation, *Chem. Commun.* **2023**. *59*, 14173.

3. Santu Mandal, Tripti Paul, **Pallab Karjee,** Madhab Barman and Tharmalingam Punniyamurthy, Site-Selective C8-Alkylation of Quinolines with Cyclopropanols: Merging C–H/C–C Bond Activation, *Org. Lett.* **2023**, *25*, 7805.

4. Anil Kumar D, **Pallab Karjee,** M. Rajendra Prasad, Tharmalingam Punniyamurthy, and Vishal Trivedi, Plasmodium Falciparum FIKK 9.1 Kinase Modeling to Screen and Identify Potent Antimalarial Agents from Chemical Library, *3 Biotech* **2023**, *13*, 277.

5. Subhajit Basak, Tripti Paul, Santu Mandal, **Pallab Karjee,** Maniya V. N. and Tharmalingam Punniyamurthy, Transition-Metal-Catalyzed Directed C8–H Carbon–Carbon Bond Formation in Quinolines and 1,2,3,4-Tetrahydroquinolines, *Synthesis* **2023**, *55*, 3454.

6. Bijoy Debnath, Tanumay Sarkar, **Pallab Karjee,** Siddhartha K. Purkayastha, Ankur K. Guha and Tharmalingam Punniyamurthy, Palladium-Catalyzed Annulative Coupling of Spirovinylcyclopropyl Oxindoles with *p*-Quinone Methides, *J. Org. Chem.* **2023**, *88*, 9704.

7. **Pallab Karjee,** Santu Mandal, Bijoy Debnath, Nirali Namdev and Tharmalingam Punniyamurthy, Expedient (3+3)-Annulation of *in Situ* Generated Azaoxyallyl Cations with Diaziridines, *Chem. Commun.* **2023**, *59*, 8270.

8. Sharajit Saha, Bijoy Debnath, Kangkan Talukdar, **Pallab Karjee,** Santu Mandal and Tharmalingam Punniyamurthy, Cascade C–H Activation/Annulation of Sulfoxonium Ylides with Vinyl Cyclopropanes: Access to Cyclopropane-Fused α-Tetralones, *Org. Lett.* **2023**, *25*, 3352.

9. Santu Mandal, **Pallab Karjee,** Sharajit Saha and Tharmalingam Punniyamurthy, Directed C8–H Allylation of Quinoline *N*-Oxides with Vinylcyclopropanes *via* Sequential C–H/C–C Activation, *Chem. Commun.* **2023**, *59*, 2823.

10. Pallab Karjee, Manmath Mishra, Bijoy Debnath and Tharmalingam Punniyamurthy, Expedient $Ni(OTf)_2$/Visible Light Photoredox-Catalyzed Annulation of Donor–Acceptor Cyclopropanes with Cyclic Secondary Amines, *Chem. Commun.* **2022**, *58*, 8670.

11. Manmath Mishra, Prabhat Kumar Maharana, **Pallab Karjee** and Tharmalingam Punniyamurthy, Expedient Cobalt-Catalyzed Stereospecific Cascade C–N and C–O Bond Formation of Styrene Oxides with Hydrazones, *Chem. Commun.* **2022**, *58*, 7090.

12. Pallab karjee, Tanumay Sarkar, Subhradeep Kar and Tharmalingam Punniyamurthy, Transition-Metal-Free Stereospecific Oxidative Annulative Coupling of Indolines with Aziridines, *J. Org. Chem.* **2020**, *85*, 8261.

Book Chapter

1. Pallab Karjee, Tanumay Sarkar, Kangkan Talukdar, Tariq A. Shah, Bijay Ketan Das and Tharmalingam Punniyamurthy, Copper-Catalyzed Sp^3 C-H Bond Functionalization. Handbook of C-H Functionalization, Ed: D Maiti, Wiley-VCH, 2022.

Conference Attended

Poster Presentation:

1. **Pallab Karjee,** Manmath Mishra, Bijoy Debnath and Tharmalingam Punniyamurthy, "Expedient $Ni(OTf)_2$/Visible Light Photoredox-Catalyzed Annulation of Donor–Acceptor Cyclopropanes with Cyclic Secondary Amines" Sustainable Chemistry 2023, IIT Indore.
2. **Pallab Karjee,** Manmath Mishra, Bijoy Debnath and Tharmalingam Punniyamurthy, "Expedient $Ni(OTf)_2$/Visible Light Photoredox-Catalyzed Annulation of Donor–Acceptor Cyclopropanes with Cyclic Secondary Amines" FICS-2022, IIT Guwahati.
3. **Pallab karjee**, Tanumay Sarkar, Subhradeep Kar and Tharmalingam Punniyamurthy, "Transition-Metal-Free Stereospecific Oxidative Annulative Coupling of Indolines with Aziridines" CRSI-NSC-28, IIT Guwahati.
4. **Pallab karjee**, Tanumay Sarkar, Subhradeep Kar and Tharmalingam Punniyamurthy, "Transition-Metal-Free Stereospecific Oxidative Annulative Coupling of Indolines with Aziridines" RIC-2022, IIT Guwahati.
5. **Pallab karjee**, Tanumay Sarkar, Subhradeep Kar and Tharmalingam Punniyamurthy, "Transition-Metal-Free Stereospecific Oxidative Annulative Coupling of Indolines with Aziridines" FOMC-2021, MNIT Jaipur.
6. **Pallab karjee**, Tanumay Sarkar, Subhradeep Kar and Tharmalingam Punniyamurthy, "Transition-Metal-Free Stereospecific Oxidative Annulative Coupling of Indolines with Aziridines" PFEOS-2021, Tezpur University.
7. **Pallab karjee**, Tanumay Sarkar, Subhradeep Kar and Tharmalingam Punniyamurthy, "Transition-Metal-Free Stereospecific Oxidative Annulative Coupling of Indolines with Aziridines" JNOST-16, IISc Bangalore.
8. **Pallab karjee**, Tanumay Sarkar, Subhradeep Kar and Tharmalingam Punniyamurthy, "Transition-Metal-Free Stereospecific Oxidative Annulative Coupling of Indolines with Aziridines" CSDDT-2020, VNIT Nagpur.

भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati