Exploiting Ring Strain in C-C and C-Heteroatom Bond Formation: Access to Spiro and Fused Indole-Based Heterocycles

A Thesis Submitted

in Partial Fulfilment of the Requirements

for the Degree of

DOCTOR OF PHILOSOPHY

by

Subhradeep Kar

Roll No. 226122022

Department of Chemistry
Indian Institute of Technology Guwahati
Guwahati 781039
September 2025

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 Indian Institute of Technology Guwahati, Guwahati, India under the supervision of Prof. Tharmalingam Punniyamurthy, Department of Chemistry and Prof. Vishal Trivedi, Department of Bioscience and Bioengineering.

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

Guwahati
September 2025

Subhradeep Kar

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

CERTIFICATE

This is to certify that the thesis entitled "***Exploiting Ring Strain in C-C and C-Heteroatom Bond Formation: Access to Spiro and Fused Indole-Based Heterocycles***" being submitted by Ms. Subhradeep Kar (Roll No. 226122022) for the award of Ph.D. degree in Department of Chemistry to the Indian Institute of Technology Guwahati, is her own research work which was carried out by her under our supervision. She has fulfilled all the requirements according to the rules of this institute, and regarding the investigations embodied in her thesis, this work has not been submitted elsewhere for a degree.

Prof. Vishal Trivedi
Co-supervisor
Department of Biosciences and Bioengineering
IIT Guwahati
Assam- 781039
India

Prof. Tharmalingam Punniyamurthy
Thesis Supervisor (Convener)
Department of Chemistry
IIT Guwahati
Assam- 781039
India

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Jai Shri Radhe!!

Subhradeep Kar

List of Abbreviations

Ar	aryl
acac	acetylacetonate
Ac	acetyl
Ac_2O	acetic anhydride
AcOH	acetic acid
Å	angstrom (10^{-8} cm)
BHT	butylated hydroxytoluene
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
Cp*	1,2,3,4,5-pentamethylcyclopentadiene
CCDC	cambridge crystallographic data center
DABCO	1,4-diazabicyclo[2.2.2]octane
DACs	donor acceptor cyclopropanes
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DFT	density functional theory
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMSO	dimethylsulfoxide
DME	dimethoxyethane
DMF	N,N-dimethylformamide
dppe	1,2-Bis(diphenylphosphino)ethane
dppb	1,4-Bis(diphenylphosphino)butane
dr	diastereomeric ratio
EDG	electron donating group
equiv	equivalent
ee	enantiomeric excess
Et	ethyl
EtOH	ethanol
ESI	electrospray ionization
EWG	electron wthdrawing group

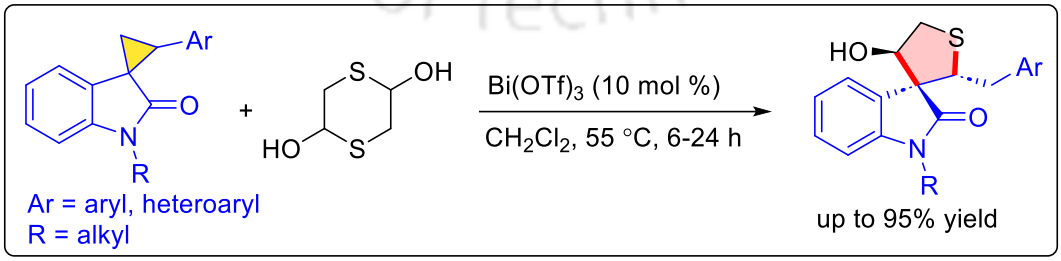
FT-IR	fourier transform infrared spectroscopy
HFIP	hexafluoroisopropanol
Het	heterocyclic
HRMS	high-resolution mass spectrometry
HPLC	high-performance liquid chromatography
Hz	hertz
^{i}Pr	isopropyl
^{i}Bu	isobutyl
kcal	kilocalorie
$LiAlH_4$	lithium aluminium hydride
m-CPBA	meta-chloroperbenzoicacid
m/z	mass to charge ratio
mp	melting point
mL	milliliter
MS	molecular sieves
MHz	megahertz
NBD	norbornadiene
nm	nanometer
NMR	nuclear magnetic resonance
^{n}Pr	propyl
^{n}Bu	butyl
Me	methyl
ORTEP	oak ridge thermal ellipsoid plot
PMB	para-methoxybenzyl
PG	protecting group
R_f	retardation factor
rt	room temperature
TFE	2,2,2-trifluoroethanol
TfOH	trifluoromethanesulfonic acid
TEMPO	2,2,6,6-tetramethylpiperidin-1-oxyl
THF	tetrahydrofuran
TLC	thin layer chromatography
µL	microlitre

Abstract

The thesis is divided into four chapters. The first chapter describes a Bi(III)-catalyzed 1,2-reactivity of spirocyclopropyl oxindoles with dithiane diols as the sulfur surrogate to furnish spirotetrahydrothiophene scaffolds with functional group diversity. The second chapter deals with a Cu(II)-catalyzed stereoselective tandem (4+3)-annulation of 4-alkylidene indole malonates with aziridines followed by a base-promoted annulation towards construction of fused azepinoindole motifs. The third chapter covers a Cu(I)-catalyzed (4+3)-cycloaddition of 4-indolyl carbinols with aziridines in a stereospecific manner, furnishing optically active azepinoindole scaffolds. The fourth chapter focuses on a Co(II)-catalyzed cascade (4+3)-coupling of 4-vinyl indoles with oxiranes and a subsequent base-promoted cyclization to afford oxepinoindole cores following a stereospecific reaction pathway.

Chapter I. Bi(III)-Catalyzed Formal (3+2)-Cycloaddition of Spirocyclopropyl Oxindoles with Dithianediol to Access Spiroheterocycles

The ring-expansion of spiro DACs derived from oxindole, has attracted considerable attention in recent decades owing to their widespread occurrence in powerful pharmacophores. However, apart from the well-established conventional behaviour, wherein cyclopropanes have been recognized as 1,3-dipoles, the exploration of intriguing even-numbered 1,2-dipolar synthons remains a dynamically and continually advanced area of research. Previous studies in this domain have primarily focused on the stoichiometric utilization of $GaCl_3$ and $MgBr_2$ in reactions involving DACs, while unveiling such reactivity under catalysis in case of spirocyclopropane remained unexplored. The present chapter describes an efficient Bi(III)-catalyzed unprecedented 1,2-reactivity of spirocyclopropyl oxindoles with dithiane diols to afford an assembly of spirotetrahydrothiophene scaffolds under mild reaction conditions (Scheme 1).

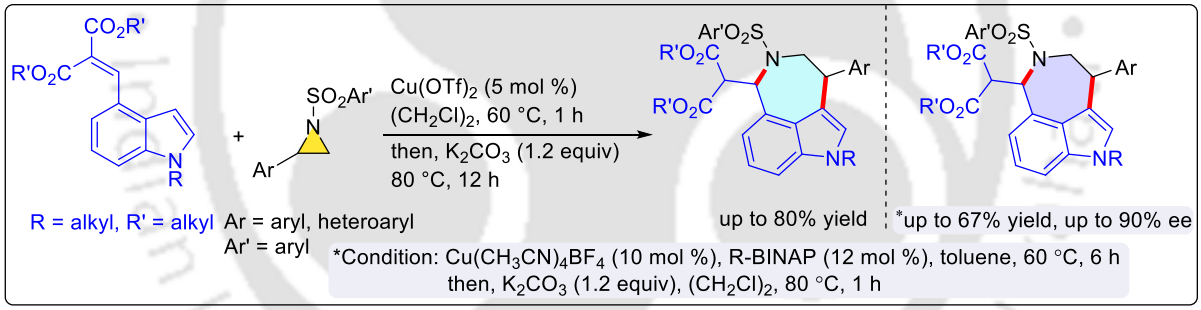


Org. Lett. **2022**, 24, 4965.

Scheme 1. Bi(III)-Catalyzed Formal (3+2)-Cycloaddition of Spirocyclopropyl Oxindoles with Dithianediol

Chapter II. Stereoselective Cu(II)-Catalyzed Tandem (4+3)-Annulation of Aziridines to Access Fused Azepinoindoles

The recurring presence of seven-membered aza-heterocycles as central frameworks in multifarious natural products and pharmaceutical agents underlines the need to devise robust synthetic methodologies towards their efficient access. Relative instability, challenging non-bonding interactions, and adverse entropic and enthalpic contributions have collectively impeded the development of effective strategies for assembling these medium-sized heterocyclic motifs. Whilst classical approaches are generally multicomponent or involve manifold steps, the strategic development of atom- and step-economic synthetic approaches is of considerable importance. Thereby, utilizing aziridines as versatile 1,3-zwitterions, the current chapter focuses on regioselective ring-opening of aziridines with C4-substituted indoles, followed by a base-promoted annulation to afford fused azepinoindole derivatives (Scheme 2). Remarkably, this strategy has been successfully applied to a preliminary asymmetric version that advances smoothly under stereoselective conditions to afford optically active units.



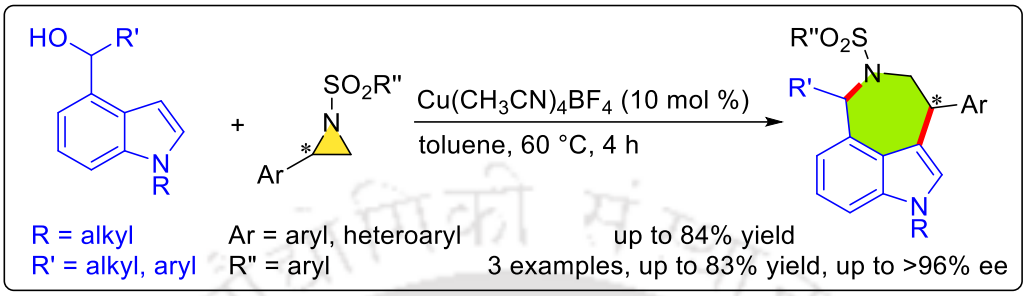
Org. Lett. **2023**, *25*, 8850.

Scheme 2. Cu(II)-Catalyzed Tandem (4+3)-Annulation of Aziridines

Chapter III. Cu(I)-Catalyzed (4+3)-Cycloaddition of 4-Indolylcarbinols with Aziridines to Access Functionalized Azepinoindoles

Indolyl carbinols have been documented as dynamic pro-electrophiles in dehydrative nucleophilic substitution reactions for accessing a diverse array of synthetically valuable structural skeletons. In this line, 2-indolyl carbinols as well as 3-indolyl carbinols have been widely exploited as synthons in diverse (3+n)- and (4+n)-cycloaddition reactions. However, the utilization of 4-indolyl carbinols as versatile alkylideneindoleninium ion precursors for reaction with strained ring systems remained an unexplored strategy. This chapter presents a stereospecific and scalable Cu(I)-catalyzed dehydrative (4+3)-cycloaddition of 4-indolyl

carbinols and N-sulfonyl aziridines, effectively yielding biologically relevant azepinoindole frameworks while minimizing the formation of the undesired Mannich-type (3+2)-cycloadduct (Scheme 3). With optically active aziridines, a series of enantioenriched cycloadducts could be obtained in up to >96% ee.

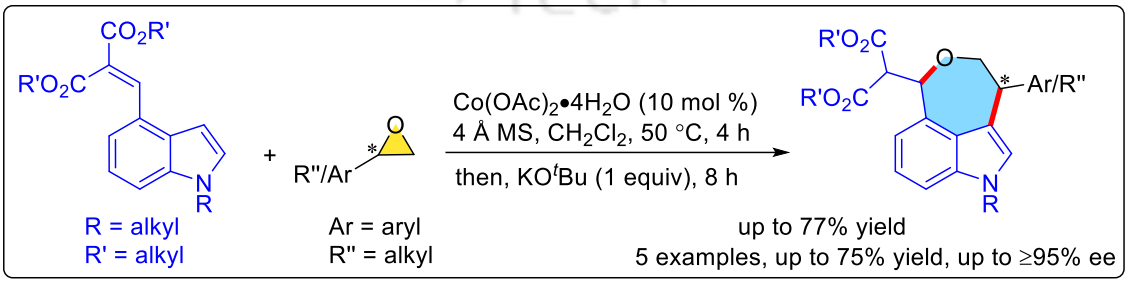


Chem. Commun. **2024**, *60,* 12008. Highlighted in *Synfacts* **2024**, *60,* 1276.

Scheme 3. Stereospecific Cu(I)-Catalyzed (4+3)-Cycloaddition of 4-Indolyl Carbinols

Chapter IV. Co(II)-Catalyzed Cascade (4+3)-Annulation of 4-Vinyl Indoles with Oxiranes: Stereospecific Access to Oxepinoindoles

Among the various oxygen-containing heterocycles, oxepinoindoles stand out as recurring subunits in natural products and pharmaceuticals. Despite substantial advancements in crafting other indole-fused systems, approaches for obtaining tetrahydrooxepino[5,4,3-cd]indole motifs are relatively limited. In this regard, utility of epoxides as precursors for synthesizing seven membered oxygen-embedded rings stands elusive. Thereby, utilizing them as versatile 1,3-dipolar synthons for the (4+3)-annulation strategy could provide access to rapid construction of diverse oxepino scaffolds via domino ring-opening/cyclisation pathway. This chapter outlines a Co(II)-catalyzed cascade (4+3)-annulation of 4-vinyl indoles with epoxides in a stereoselective fashion and with enantioenriched oxiranes, a series of optically active substrates could be synthesized in up to ≥95% ee (Scheme 4).



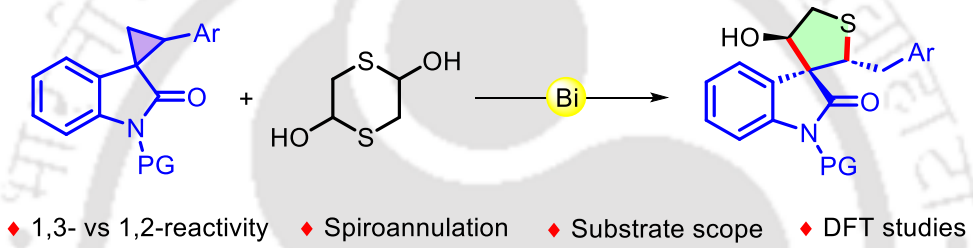
Chem. Commun. DOI: 10.1039/D5CC06979C.

Scheme 4. Co(II)-Catalyzed Cascade (4+3)-Annulation of Oxiranes with 4-Vinyl Indoles

Contents

Chapter I

Bi(III)-Catalyzed Formal (3+2)-Cycloaddition of Spirocyclopropyl Oxindoles with Dithianediol to Access Spiroheterocycles

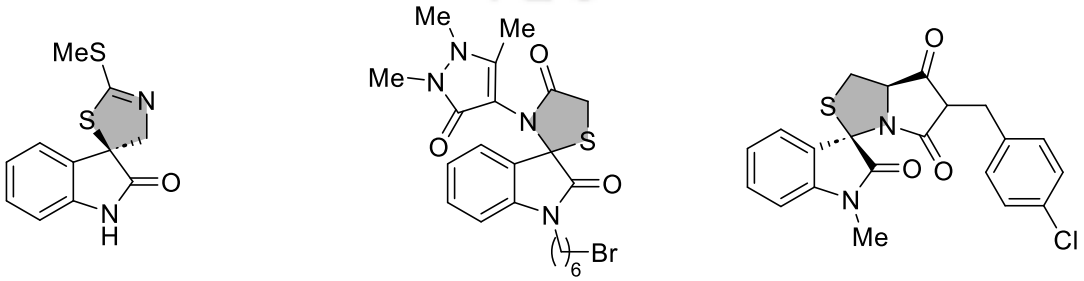


♦ 1,3- vs 1,2-reactivity ♦ Spiroannulation ♦ Substrate scope ♦ DFT studies

Org. Lett. **2022**, *24*, 4965.

Bi(III)-Catalyzed Formal (3+2)-Cycloaddition of Spirocyclopropyl Oxindoles with Dithianediol to Access Spiroheterocycles

Cyclopropanes, the smallest carbocycles, are known for their multifaceted reactivity as three-atom synthons in synthetic organic chemistry.[1] However, despite their inherent ring strain, the cyclopropane ring necessitates the installation of suitable donor and acceptor units at vicinal positions that would favour polarization and hence, cleavage of the C-C bond under suitable reaction conditions. Again, herein, majority of the reactions come down to the use of DACs as source of 1,3-zwitterions. Further, given the abundance of the oxindole core in potent pharmacophores and bio-active compounds, the ring enlargement of the oxindole derived spiro DACs has demanded significant attention in recent years (Figure 1).[2] The conformational constraints imposed by a spiro ring fusion often leads to improved biological activities, and therefore, considerable efforts are being made for their inclusive synthesis. Owing to the involvement of a spiro all-carbon quaternary stereocenter, the catalytic stereoselective synthesis of spirocyclic systems is still a long-standing challenge. Whilst the presence of geminal ester or ketone groups in cyclopropanes effectively stabilizes the zwitterionic intermediate *via* bidentate chelation, achieving such well-organized catalyst-substrate complex in case of spirocyclopropane with only monodentate amide coordination becomes a major challenge. Moreover, in addition to the classical 1,3-zwitterionic reactivity, DACs have recently been documented to exhibit a new 1,2-reactivity.[3] Whilst majority of these reactions are based on the stoichiometric use of $GaCl_3$ and $MgBr_2$, the exploitation of spiro DACs to exhibit such an even numbered dipolar system under catalysis, remained unexplored. Herein, we report an efficient Bi(III)-catalyzed 1,2-reactivity of spirocyclopropyl oxindoles with dithianediols to access spirotetrahydrothiophene frameworks under mild reaction conditions.



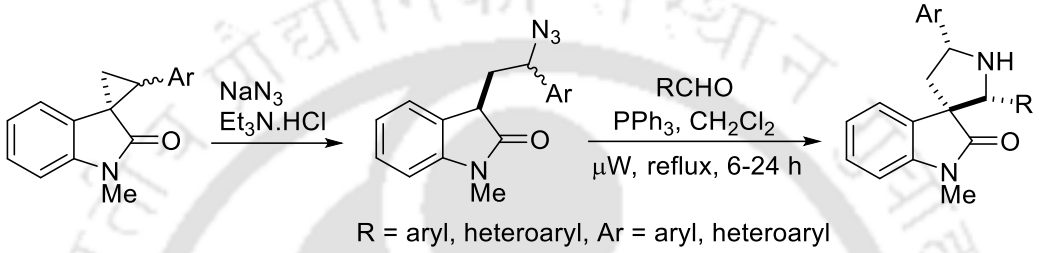
Spirobrassinin ***Antimicrobial agent*** ***p53 modulator***

Figure 1. Representative Examples of Biologically Active Spiroheterocyclic Derivatives

1.1 Literature

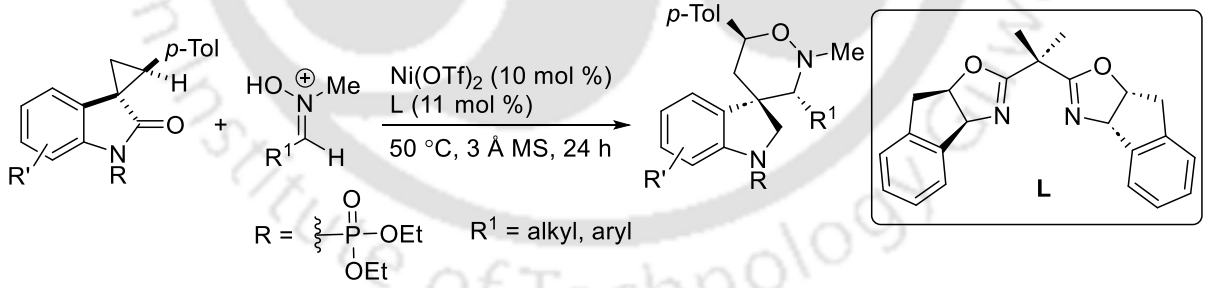
1.1.1 Reactivity of Spirocyclopropyl Oxindoles

Melnikov and co-workers reported a cascade transformation of 3-(2-azidoethyl)-oxindoles via Staudinger/aza-Wittig/Mannich reactions to achieve a one-pot assembly of spiro[pyrrolidine-3,3'-oxindole] (Scheme 1).[4] The described protocol exhibited excellent compatibility towards a series of substituted oxindoles along with various aromatic and heteroaromatic aldehydes, generating the spirocyclic pyrrolidone cores in good yields and diastereoselectivity.



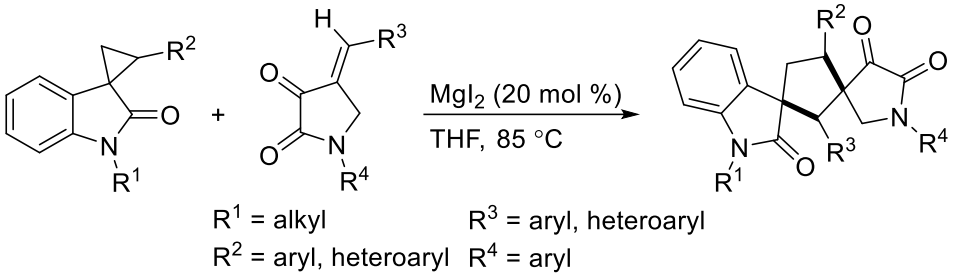
Scheme 1. 3-(2-Azidoethyl)oxindoles as Building Blocks for One-Pot Assembly of Spiro[pyrrolidine-3,3′-oxindoles]

The Zhou group reported a Ni-catalyzed diastereo- and enantioselective (3+3)-cycloaddition of N-protected spirocyclopropyl oxindoles with diverse aldo- and keto-nitrones, providing facile access to optically-active spirocyclic tetrahydro-1,2-oxazines (Scheme 2).[5]



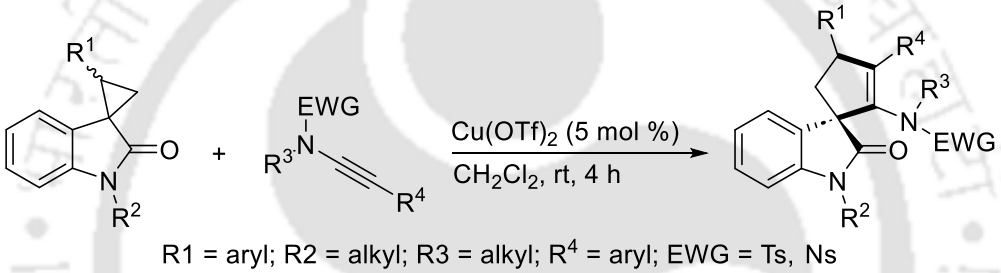
Scheme 2. Ni-Catalyzed Diastereo- and Enantioselective (3+3)-Cycloaddition of Spirocyclopropyl Oxindoles

The Saha group disclosed a Mg-catalyzed annulation of spirocyclic DACs with exo-heterocyclic olefins to deliver a spectrum of structurally varied pyrazolone tethered bis-spirocyclopentane oxindole frameworks and 2,3-dioxopyrrolidine cores in good to excellent yields (Scheme 3).[6]



Scheme 3. Mg-Catalyzed Annulation of Spiro-Cyclopropanes with exo-Heterocyclic Olefins

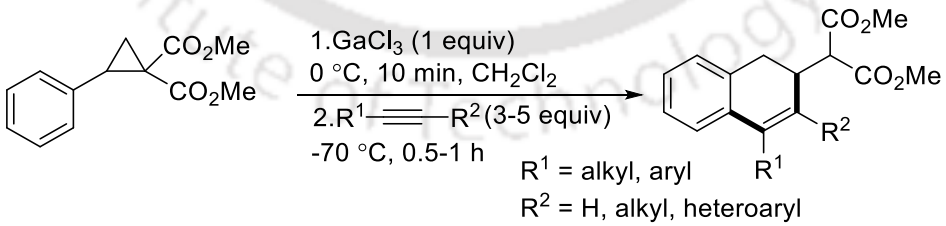
The Zhang group presented a Cu-catalyzed (3+2)-annulation of oxindole derived spiro DACs with ynamides for accessing spirocyclopenteneoxindoles (Scheme 4).[7] Under mild reaction conditions, the protocol exhibited broad substrate scope, delivering the desired heterocycles in good to excellent yields and diastereoselectivities.



Scheme 4. Cu-Catalyzed (3+2)-annulation of Spiro DACs with Ynamides

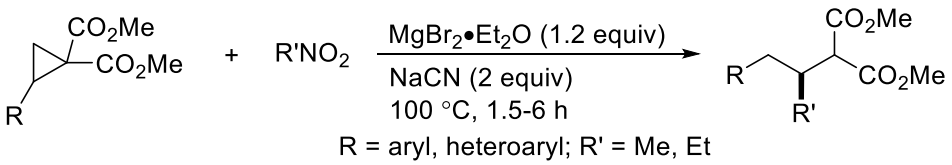
1.1.2 1, 2-Reactivity of Cyclopropanes

A (4+2)-annulation strategy utilizing the 1,2-zwitterionic reactivity of DACs was elaborated by Tomilov and co-workers (Scheme 5).[3d] DACs were subjected to reaction with acetylenes in the presence of $GaCl_3$, resulting dihydronaphthalenes with high regio- and diastereoselectivity.



Scheme 5. (4+2)-Annulation of DACs with Acetylene using 1,2-Reactivity

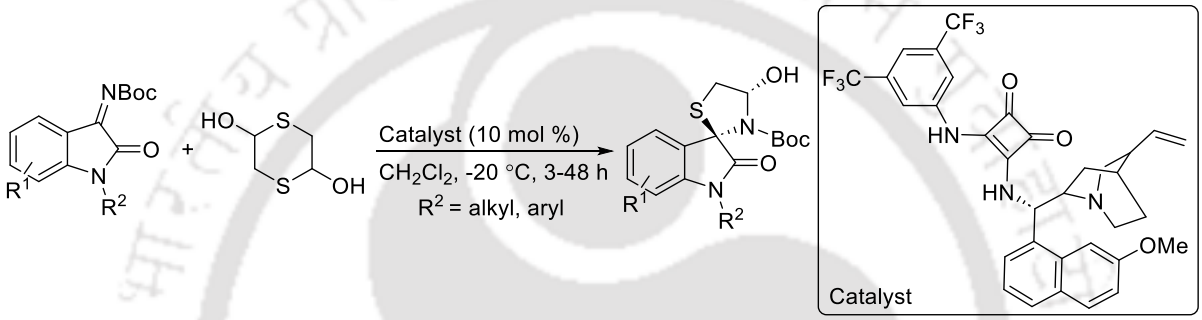
Melnikov and co-workers demonstrated the modified 1,2-reactivity of DACs towards nitroalkanes as versatile nucleophiles (Scheme 6).[3c] Under suitable reaction conditions, the 1,2-zwitterion were amenable to nucleophilic trapping leading to the formation of a series of highly functionalized substrates.



Scheme 6. Modified 1,2-Reactivity of DACs towards Nitroalkanes

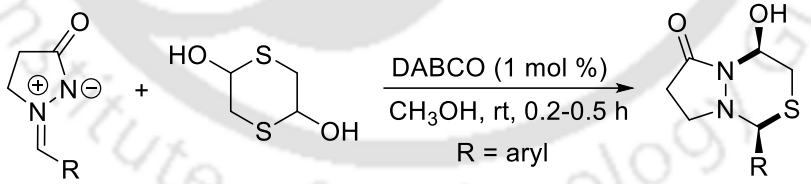
1.1.3 Reactivity of 1,4-Dithiane-2,5-diol

Li and co-workers reported an asymmetric (3+2)-cycloaddition of isatin derived ketimines with dithiane diol (Scheme 7).[8] The protocol has been further extended towards developing thiazolidines as selective inhibitors of mycobacterium tuberculosis.



Scheme 7. Asymmetric (3+2)-Annulation of Ketimines with Dithiane Diol

A DABCO catalyzed diastereoselective (3+3)-cycloaddition of dithiane diol with azomethine imine was reported by the Wang group to afford substituted heterocycles with fused dinitrogen units (Scheme 8).[9] The diastereoselectivity was controlled by the anomeric effect.



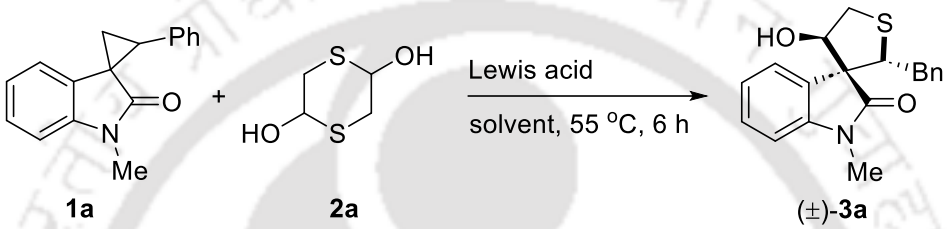
Scheme 8. Diastereoselective (3+3)-Annulation of Azomethine Imines with Dithiane Diol

Considering the literature precedents and existing research gap pertaining to the utilisation of spiro DACs as 1,2-zwitterionic synthons, we advanced our study exploring the reaction of N-protected spirocyclopropyl oxindoles with dithianediols to construct sulphur containing spiroheterocycles in a diastereoselective manner. Key aspects of this work include the 1,2-reactivity of the spiro-cyclopropane framework, substrate scope and mechanistic insights with DFT investigations.

1.2 Present Study

Herein, a Bi(III)-catalyzed formal (3+2)-cycloaddition of spirocyclopropyl oxindoles is described with dithiane diols to deliver spirotetrahydrothiophene motifs. In presence of bismuth, the spirocyclopropane demonstrated generation of a 1,2-zwitterion rather than the classical 1,3-zwitterionic synthon. In this regard, we commenced our optimization studies using spirocyclopropyl oxindole **1a** and 1,4-dithiane-2,5-diol **2a** as the model substrates in presence of a series of Lewis acids and solvents (Table 1). Preliminary investigation using a

Table 1. Optimization of the Reaction Conditions[a,b,c,d]



Entry	Lewis acid	Solvent	Yield (**3a**, %)[b]
1[c]	$GaCl_3$	CH_2Cl_2	n.d.
2[c]	$MgBr_2$	CH_2Cl_2	trace
3[c]	$ZnCl_2$	CH_2Cl_2	trace
4[c]	$CoBr_2$	CH_2Cl_2	14
5[c]	$CuCl_2$	CH_2Cl_2	23
6[c]	$Cu(ClO_4)_2•6H_2O$	CH_2Cl_2	31
7[c]	$Cu(OTf)_2$	CH_2Cl_2	77
8	$Cu(OTf)_2$	CH_2Cl_2	73
9	AgOTf	CH_2Cl_2	16
10	$Sc(OTf)_3$	CH_2Cl_2	n.d.
11	$Yb(OTf)_3$	CH_2Cl_2	n.d.
12	$Bi(OTf)_3$	CH_2Cl_2	81
13	$Bi(NO_3)_3•5H_2O$	CH_2Cl_2	23

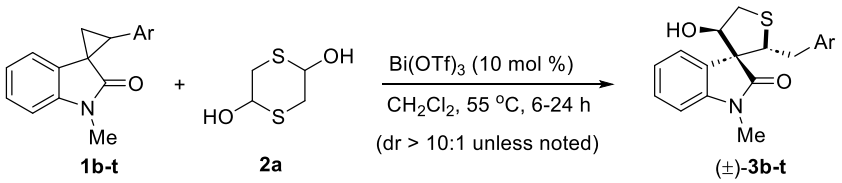
14	$Bi(OTf)_3$	$(CH_2Cl)_2$	55
15	$Bi(OTf)_3$	MeOH	n.d.
16	$Bi(OTf)_3$	Toluene	12
17	$Bi(OTf)_3$	THF	trace
18	$Bi(OTf)_3$	DMF	n.d.
19	$Bi(OTf)_3$	CH_3CN	21
20[d]	$Bi(OTf)_3$	CH_2Cl_2	27

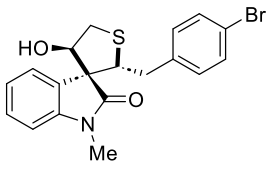
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.1 mmol), Lewis acid (10 mol %), solvent (2 mL), 55 °C, 6 h. [b]Isolated yield. [c]With 1 equiv of Lewis acid. [d]Reaction temperature (40 °C). n.d. = not detected.

stoichiometric amount of $GaCl_3$[3b] and $MgBr_2$[3c] in CH_2Cl_2 at 55 °C resulted **3a** only in a trace amount (entries 1-2). Subsequent screening with $Cu(OTf)_2$ facilitated the annulation effectively, delivering a 77% yield, whereas $ZnCl_2$, $CoBr_2$, $CuCl_2$ and $Cu(ClO4)_2$•$6H_2O$ exhibited comparatively inferior outcomes (entries 3-7). Encouraged by the success of the stoichiometric annulation, we were interested in developing the catalytic version of the protocol. Gratifyingly, with 10 mol % $Cu(OTf)_2$, the cycloaddition proceeded effectively, delivering (±)-**3a** in 73% yield (entry 8). Further screening of other metal triflates in a catalytic amount revealed that employing $Bi(OTf)_3$ increased the yield of (±)-**3a** to 81%, while, AgOTf, $Sc(OTf)_3$ and $Yb(OTf)_3$ yielded inferior results (entry 9-12). Examining other bismuth salts such as $Bi(NO_3)_3$•$5H_2O$ and a series of other solvents *viz*., $(CH_2Cl)_2$, CH_3OH, toluene, THF, DMF and CH_3CN proved less efficient compared to the established standard condition (entries 13-19). A decrement in the reaction temperature to 40 °C also produced similar results (entry 20). The stereochemistry of (±)-**3a** was confirmed using a single-crystal X-ray analysis (CCDC = 2133256).

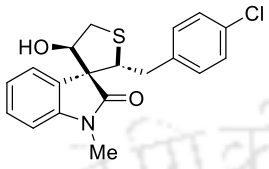
With optimal reaction conditions in hand, the scope of the protocol was examined for a series of spiro cyclopropanes **1b-t** with 1,4-dithiane-2,5-diol **2a** as the standard substrate (Table 2). Gratifyingly, cyclopropanes bearing substituents at the 4-position of the aryl ring such as bromo **1b**, chloro **1c**, fluoro **1d**, methyl **1e**, methoxy **1f**, phenyl **1h** and tert-butyl **1i** groups were well tolerated affording (±)-**3b-i** in 71-88% yields, whereas strong electron-withdrawing nitro **1g** remained an unsuccessful substrate. Next, cyclopropanes bearing substituents such as bromo

Table 2. Scope of Spirocyclopropanes with **2a**[a,b,c]

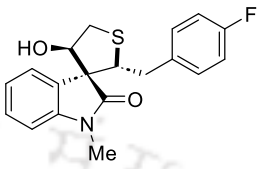




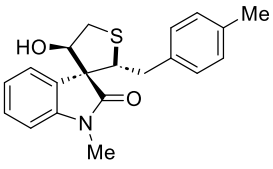
(±)-**3b**, 71%, 6 h



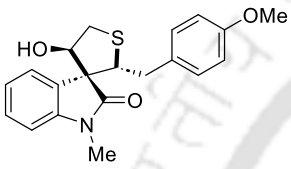
(±)-**3c**, 74%, 6 h



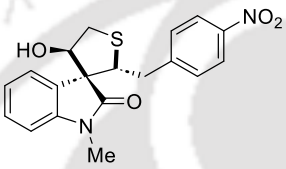
(±)-**3d**, 72%, 7 h



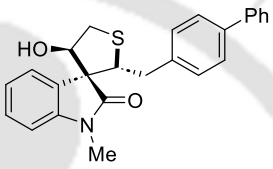
(±)-**3e**, 84%, 6 h



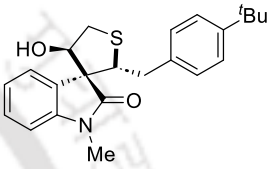
(±)-**3f**, 88%, 6 h



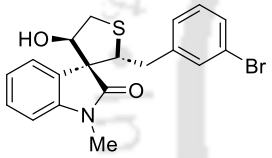
(±)-**3g**, n.r., 24 h



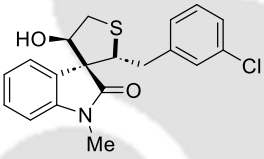
(±)-**3h**, 85%, 6 h



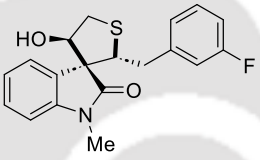
(±)-**3i**, 84%, 8 h



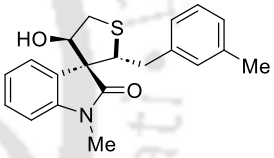
(±)-**3j**, 71%, 18 h



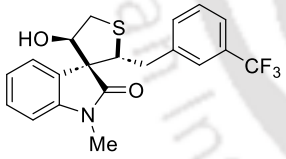
(±)-**3k**, 59%, >9:1 dr,12 h



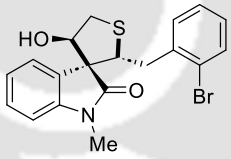
(±)-**3l**, 64%, >7:1 dr,12 h



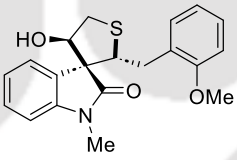
(±)-**3m**, 68%, 8 h



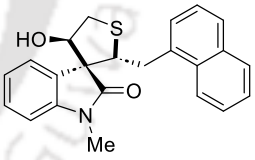
(±)-**3n**, 52%,18 h



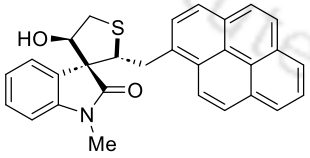
(±)-**3o**, trace, 24 h



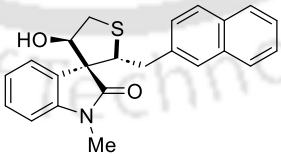
(±)-**3p**, 90%, 6 h



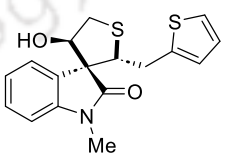
(±)-**3q**, 62%, 18 h



(±)-**3r**, 54%, >6:1 dr, 18 h



(±)-**3s**, 51%, 8 h



(±)-**3t**, 61%, >9:1 dr, 8 h

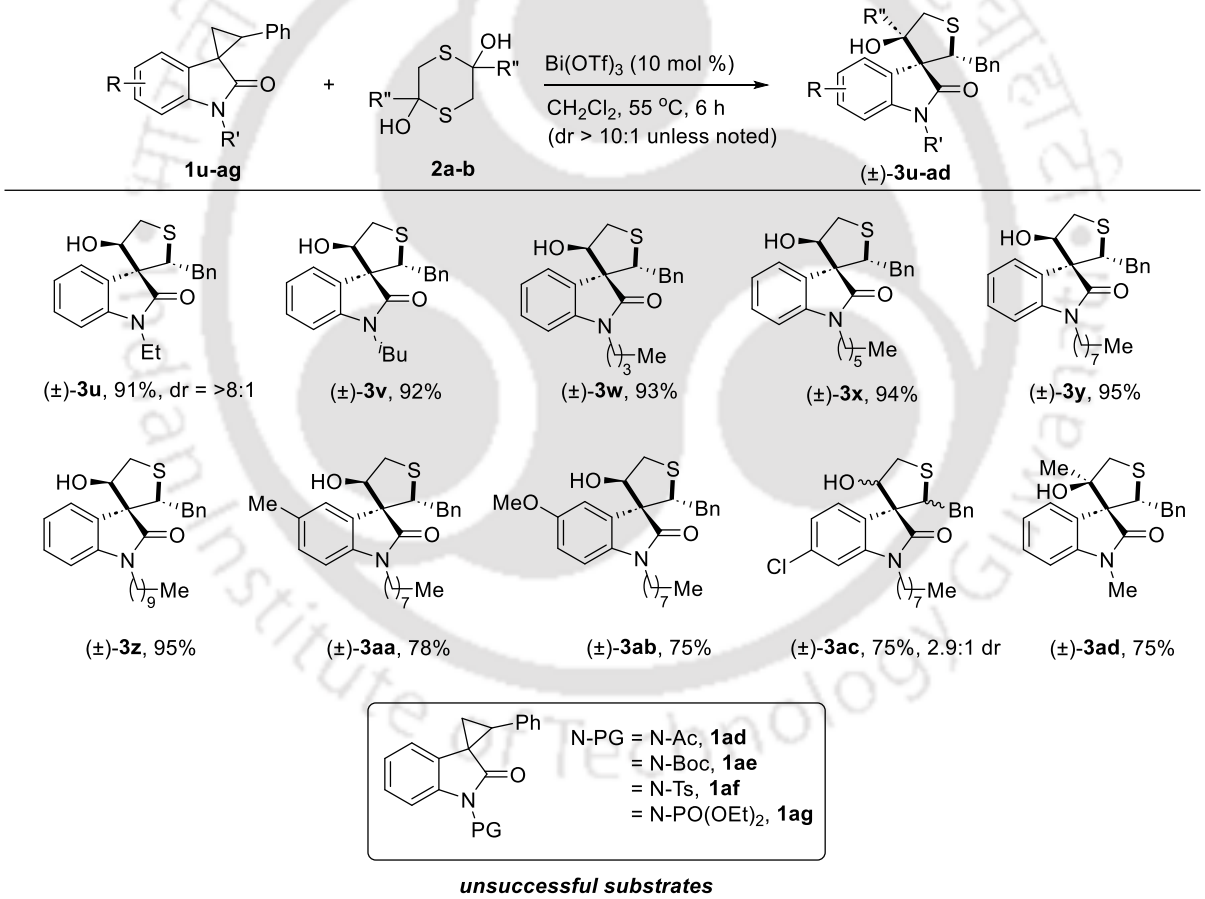
[a]Reaction conditions: **1b-t** (0.2 mmol), **2a** (0.1 mmol), $Bi(OTf)_3$ (10 mol %), CH_2Cl_2 (2 mL), 55 °C. [b]Isolated yield. [c]The dr was determined by ^1H NMR analysis.

1j, chloro **1k**, fluoro **1l**, methyl **1m** and trifluoromethyl **1n** at the 3-position of the aryl ring delivered (±)-**3j-n** in 52-71% yields. Intriguingly, cyclopropane bearing methoxy **1p** at the 2-position afforded (±)-**3p** in 90% yield, while the bromo analogue **1o** gave only a trace amount

of (±)-**3o** due to significant steric encumbrance. In addition, cyclopropanes having 1-naphthyl **1q**, 1-pyryl **1r** and 2-naphthyl **1s** substituents reacted to furnish (±)-**3q-s** in 51-62% yields. 2-Thienyl cyclopropane **1t** gave (±)-**3t** in 61% yield. These results indicated that a broad array of cyclopropanes comprising diverse substitution patterns were compatible under the optimized conditions.

The scope of the reaction was further expanded to encompass a series of oxindole derivatives **1u-ag** employing 1,4-dithiane-2,5-diol **2a** as the model substrate (Table 3). N-Alkyl oxindoles with ethyl **1u**, iso-butyl **1v** and *n*-butyl **1w** protecting groups reacted smoothly to afford (±)-**3u-w** in 91-93% yields. In parallel, oxindoles functionalized with extended long chain alkyl

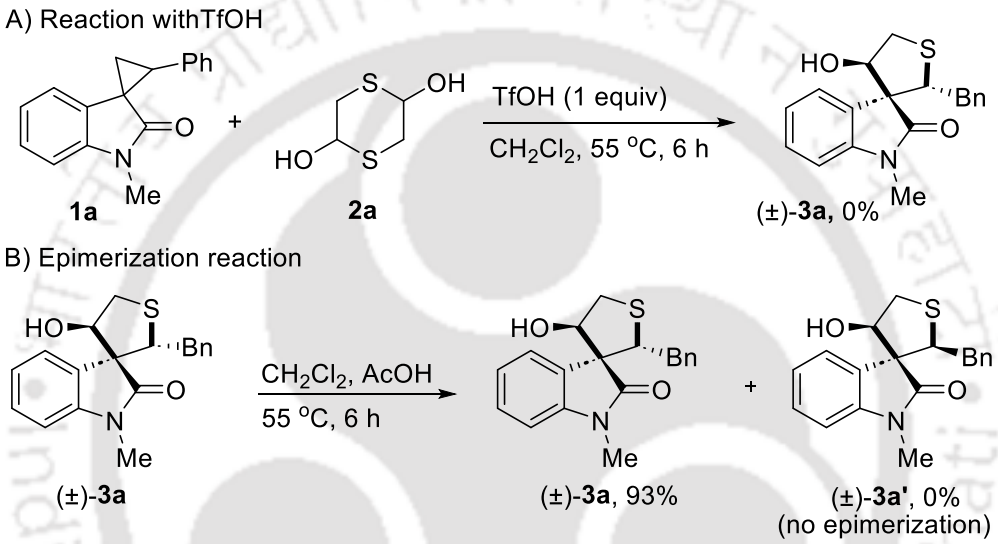
Table 3. Scope of Oxindoles and Dithianediols[a,b,c]



[a]Reaction conditions: **1u-ag** (0.2 mmol), **2a** or **2b** (0.1 mmol), $Bi(OTf)_3$ (10 mol %), CH_2Cl_2 (2 mL), 55 °C, 6 h. [b]Isolated yield. [c]The dr was determined by ^1H NMR analysis.

groups such as hexyl **1x**, octyl **1y** and decyl **1z** underwent coupling successfully to afford the desired cycloadducts (±)-**3x-z** in 94-95% yields. Further, oxindoles with substitution on the

aryl ring of the indole core, with 5-methyl **1aa** and 5-methoxy **1ab** reacted efficiently to afford (±)-**3aa** and (±)-**3ab** in 78 and 75% yields, respectively. The 6-chloro substituted oxindole delivered the cycloadduct (±)-**3ac** in 75% yield as a 2.9:1 mixture of diastereomers, while, 2,5-dimethyl-1,4-dithiane-2,5-diol **2b** afforded (±)-**3ad** in 75% yield. However, in contrast, spirocyclopropyl oxindoles embedded with electron-withdrawing N-protecting groups, such as acetyl **1ad**, tert-butyloxycarbonyl **1ae**, tosyl **1af** and diethoxy phosphoryl **1ag** remained non-viable substrates, possibly owing to the deactivation of the 2-pyrrolidone core in presence of the strong EWGs.

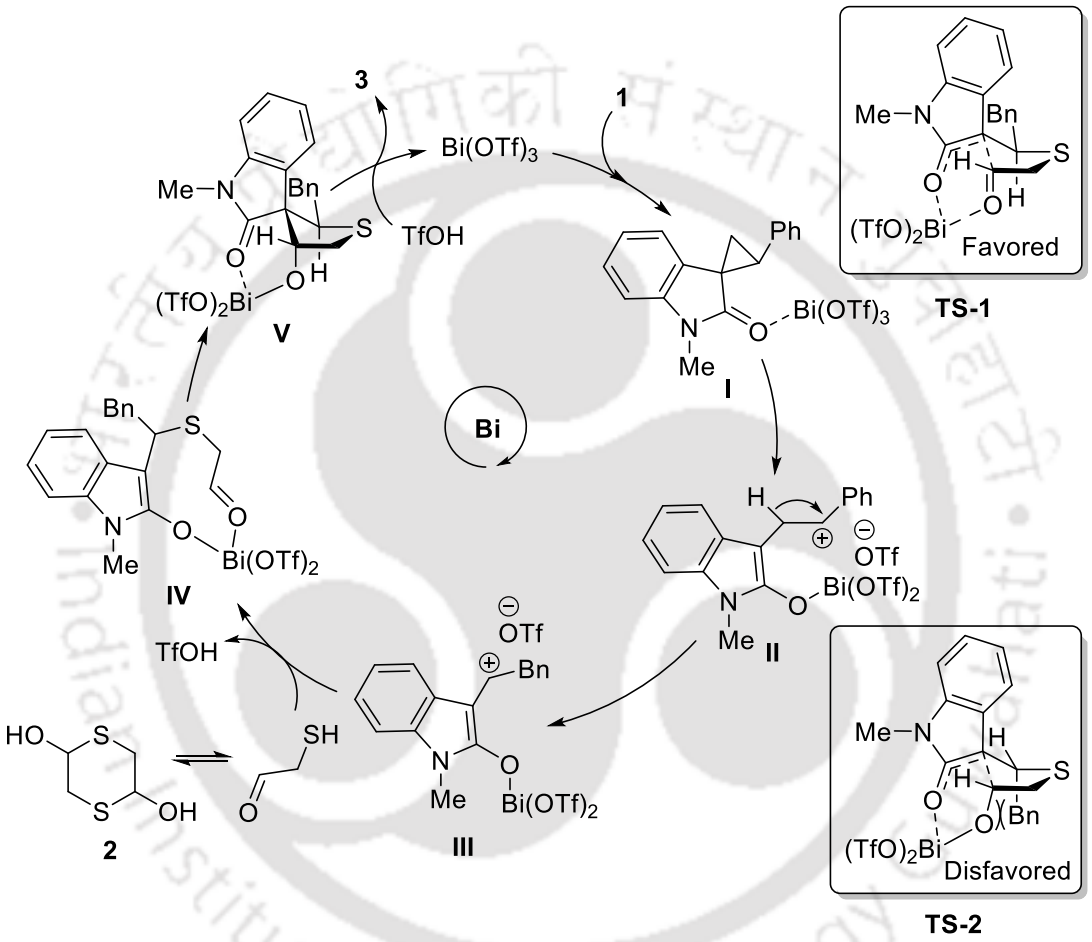


Scheme 9. Mechanistic Investigations

A set of control experiments was carried out to elucidate the reaction pathway (Scheme 9). Reaction with TfOH under otherwise standard conditions failed to deliver the target product, thereby, precluding the role of TfOH as a result of possible hydrolysis of the metal triflate and confirming the catalytic role of Bi(III) in the activation of the cyclopropyl ring (Scheme 9A). Further, epimerization of (±)-**3a** using AcOH as a representable example showed that (±)-**3a** was recovered with absolute trans-selectivity and epimerization was not detected, thereby concluding the relative thermodynamic preference of the trans-isomer over cis (Scheme 9B).[10]

In accordance with the experimental results and literature precedents,[3] the chelation of $Bi(OTf)_3$ with the carbonyl group of oxindole **1** generates intermediate **I**, wherein the regioselective ring opening of cyclopropane occurs to furnish **II** by stabilizing the negative charge (Scheme 10). Subsequent 1,2-hydride shift generates the stable 1,2-dipolar complex **III**.[3] The in situ generated mercaptoaldehyde monomer then undergoes nucleophilic addition

with **III** to deliver **IV**. Cyclization of **IV** occurs to deliver the target heterocycle with regeneration of the active catalyst. The observed diastereoselectivity can be attributed to the preferential formation of the transition-state **TS-1**, wherein the occupancy of the benzyl group at the pseudo-equatorial position facilitates formation of the target cycloadduct with trans-selectivity.[4] Alternatively, the generation of the cis-isomer via **TS-2** is disfavoured owing to steric factors.



Scheme 10. Plausible Mechanism

Computational studies further rationalized the reaction pathway. Figure 2 showcases the energy profile associated with the formation of the predominant isomer calculated at 298 K in gas phase. Chelation of $Bi(OTf)_3$ with **1** produces a stable **int-I** with O-Bi distance of 2.102 Å and this process is exergonic by 2.4 kcal/mol. **Int-I** then forms **int-II** via **TS-I**, involving an energy barrier of 9.1 kcal/mol. The C-C bond in **TS-I** instigates to break down with a distance of 2.783 Å. A following hydride shift results in the formation of the **int-III** via a transition-state **TS-II**. This step involves a barrier of 8.2 kcal/mol. Upon addition of **2**, **int-IV** is generated

with a barrier of 9.0 kcal/mol wherein both the carbonyl oxygen atoms remain coordinated with $Bi(OTf)_2$. In **TS-III**, the C…S distance is calculated as 2.314 Å. Sequential cyclization leads to the formation of **int-V** through a 5-membered cyclic transition-state **TS-IV**, with an associated energy barrier of 7.4 kcal/mol. Ultimately, **int-V** affords the trans-isomer accompanied by the release of $Bi(OTf)_3$. This process is exergonic by -0.9 kcal/mol. Consequently, the trans product is preferentially formed due to the low activation barriers. This conclusion is consistent with the experimental findings.

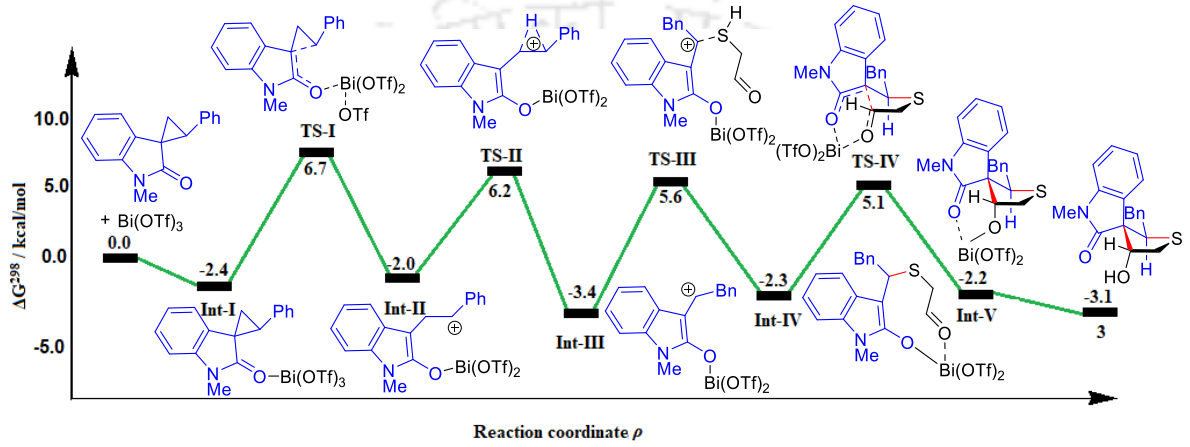
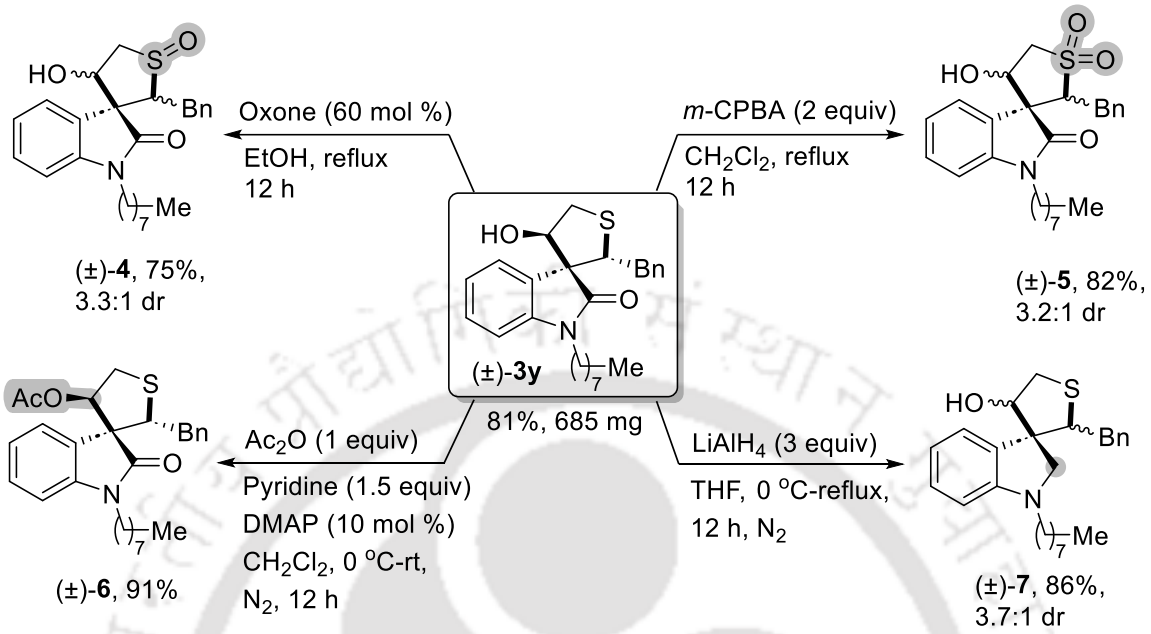


Figure 2. Calculated energy profile (ΔG298 in kcal/mol) for the annulation of spirocyclopropyl oxindole with dithianediol. Energy values are given in kcal/mol.

Post-synthetic transformations were carried out to highlight the synthetic utility of the protocol. Initially, scale-up was performed on a 2 mmol scale taking **1y** and **2a** as the representative examples to afford (±)-**3y** in 81% yield, which was further subjected to series of transformations (Scheme 11). For example, using Oxone, (±)-**3y** was oxidized to sulfoxide (±)-**4** in 75% yield with a 3.3:1 mixture of diastereomers, whereas using *m*-CPBA, sulfone (±)-**5** was produced in 82% yield with a 3.2:1 mixture of diastereomers. In addition, acetylation of the hydroxyl group of (±)-**3y** could be achieved to furnish (±)-**6** in 91% yield. Further, the reduction of the amide motif with $LiAlH_4$ could be achieved to deliver (±)-**7** in 86% yield as a 3.7:1 mixture of diastereomers.

In conclusion, we have reported herein an effective synthetic strategy towards building a library of structurally diverse all-carbon quaternary spiro-tetrahydrothiophene cores *via* annulation of spiro DACs with dithiane diol as the sulphur surrogate. The protocol exhibits the *de novo* use of spiro DACs as a source of 1,2-zwitterion under Bi-catalysis. The experimental

results and mechanism have been substantiated by DFT calculations. The extensive substrate scope, functional group versatilities and mechanistic insights are the salient features.



Scheme 11. Post-Synthetic Transformations

1.3 Experimental Section

General Information. Aldehydes, 2-oxindole (97%), $Bi(OTf)_3$ (>98%), 1,4-dithiane-2,5-diol (97%), 2,5-dihydroxy-2,5-dimethyl-1,4-dithiane (>95%), $LiAlH_4$ (95%) and *m*-CPBA (77%) were purchased from Aldrich and used as received. Isatins were purchased from TCI Chemicals and Oxone was purchased from Spectrochem. SRL silica gel G/GF 254 plates were used for analytical TLC and SRL silica gel (100-200 mesh) was used for column chromatography. NMR (^1H, ^{13}C, ^{19}F and ^{31}P) spectra were recorded with Bruker Avance III 600 MHz, Ascend 400 and 500 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. Quadrupole time-of-flight electrospray ionization (ESI) mass spectrometry instrument (model HAB 273) and Xevo XS mass spectrometer were used for recording mass spectra. Single crystal X-ray data of **3a** was collected on BRUKER D8 VENTURE SC-XRD system equipped with Apex II CCD diffractometer using Mo/Kα radiation and the structure was solved by direct method using *SHELXL-2016* (Sheldrick, 2016).

General Procedure for the Annulation of Spirocyclopropyl Oxindoles with Dithianediols. A mixture of spirocyclopropyl oxindole **1** (0.2 mmol, 1 equiv), 1,4-dithianediol **2** (0.1 mmol, 0.5 equiv) and $Bi(OTf)_3$ (0.02 mmol, 0.1 equiv) in CH_2Cl_2 (2 mL) was stirred at 55 °C in an oil bath. The progress of the reaction was monitored by TLC using ethyl acetate and hexane. After completion, the reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (2 X 5 mL) and passed through a short pad of celite using CH_2Cl_2 (10 mL). Evaporation of the solvent gave a residue that was purified by silica gel column chromatography using ethyl acetate and hexane as eluent to afford (±)-**3**.

Procedure for Epimerization Reaction.[11] AcOH (0.1 mmol, 6 µL) was added to a stirring solution of (±)-**3a** (0.1 mmol, 42 mg) in CH_2Cl_2 (2 mL) and the reaction mixture was stirred at 55 °C for 6 h. The reaction mixture was then quenched using saturated $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 X 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using ethyl acetate and hexane as eluent to give (±)-**3a** in 93% yield (39 mg).

Scale-up Synthesis of (±)-3y. A mixture of spirocyclopropyl oxindole **1y** (2 mmol, 1 equiv, 694 mg), 1,4-dithianediol **2a** (1 mmol, 0.5 equiv, 152 mg) and $Bi(OTf)_3$ (0.2 mmol, 0.1 equiv, 130 mg) in CH_2Cl_2 (10 mL) was stirred at 55 °C in an oil bath for 18 h. After completion, the reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (15 mL) and passed through a short pad of celite using CH_2Cl_2 (15 mL). The purification of the product was performed as described in the general procedure to afford (±)-**3y** in 81% yield (685 mg).

Synthesis of (±)-4.[12] The cycloadduct (±)-**3y** (0.1 mmol, 42 mg) and Oxone (0.06 mmol, 37 mg) in ethanol (2 mL) were stirred at 60 °C for 12 h. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. After completion, the reaction mixture was cooled and diluted with ethyl acetate (10 mL). The organic layer was successively washed with brine (2 X 5 mL) and extracted with ethyl acetate (3 X 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using ethyl acetate and hexane as eluent to give (±)-**4.**

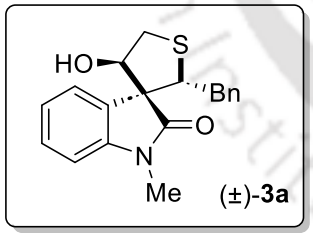
Synthesis of (±)-5.[13] The cycloadduct (±)-**3y** (0.1 mmol, 42 mg) and *m*-CPBA (0.2 mmol, 34 mg) in CH_2Cl_2 (2 mL) were heated to reflux for 12 h. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. After completion, the reaction mixture was cooled, diluted with CH_2Cl_2 (10 mL). The organic layer was successively washed

with saturated aq. $NaHCO_3$ solution (2 X 5 mL) and extracted with CH_2Cl_2 (3 X 10 mL). Drying Na_2SO_4 and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using ethyl acetate and hexane as eluent to give (±)-**5**.

Synthesis of (±)-6.[14] Ac_2O (0.1 mmol, 10 mg) was added to a stirring solution of the cycloadduct **3y** (0.1 mmol, 43 mg), pyridine (0.15 mmol, 12 mg) and DMAP (0.01 mmol, 1.2 mg) in CH_2Cl_2 (2 ml) at 0 °C under nitrogen atmosphere. The reaction mixture was gradually warmed to room temperature and stirred for 12 h. After completion, the reaction mixture was quenched by using saturated aq. $NaHCO_3$ (10 mL) and was extracted with CH_2Cl_2 (3 X 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using ethyl acetate and hexane as eluent to afford (±)-**6**.

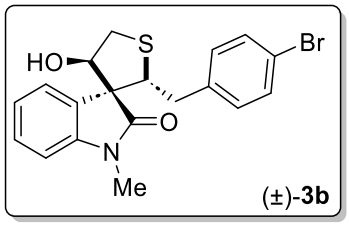
Synthesis of (±)-7.[15] $LiAlH_4$ (0.3 mmol, 11.4 mg) was added to a stirring solution of the cycloadduct (±)-**3y** (0.1 mmol, 42 mg) in anhydrous THF (2 mL) at 0 °C under nitrogen atmosphere. The reaction mixture was then heated to reflux at 80 °C for 12 h. After completion, the reaction was cooled to room temperature, quenched with saturated aq. NH_4Cl (5 mL) and extracted with ethyl acetate (3 X 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using ethyl acetate and hexane as eluent to afford (±)-**7**.

1.4 Characterization Data of the Products

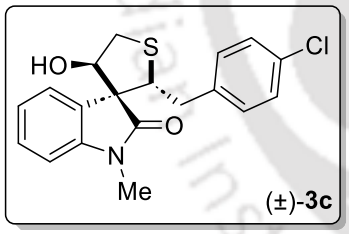


2'-Benzyl-4'-hydroxy-1-methyl-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-3a. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.56; brown solid; mp 102-103 °C ; yield 81% (53 mg); major diastereomer (>10:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66-7.64 (m, 1H), 7.44-7.41 (m, 1H), 7.23-7.20 (m, 1H), 7.11 (s, 3H), 6.83-6.82 (m, 1H), 6.67-6.66 (m, 2H), 4.68 (s, 1H), 4.60-4.57 (m, 1H), 4.19 (s, 1H), 3.44-3.41 (m, 1H), 3.20-3.17 (m, 1H), 2.84-2.81 (m, 4H), 2.43-2.38 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 143.7, 137.7, 129.4, 128.9, 128.0, 126.8, 126.1, 125.9, 123.3, 108.8, 80.9, 62.3, 52.4, 38.7, 36.9, 26.1; HRMS

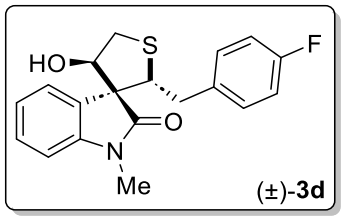
(ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{20}NO_2S$: 326.1209, found: 326.1212; FT-IR (KBr) 3412, 2937, 1684, 1609, 1469, 1374, 753, 699 cm^{-1}.



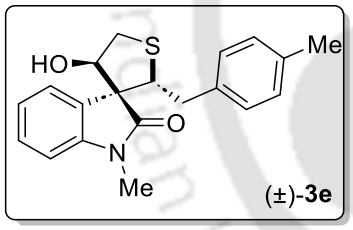
2'-(4-Bromobenzyl)-4'-hydroxy-1-methyl-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-3b. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.54; colorless solid; mp 108-109 °C; yield 71% (57 mg); major diastereomer (>10:1 dr); ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.2 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.24-7.19 (m, 3H), 6.84 (d, *J* = 8 Hz, 1H), 6.54 (d, *J* = 8.4 Hz, 2H), 4.55-4.51 (m, 1H), 4.19-4.18 (m, 1H), 3.44-3.40 (m, 1H), 3.20 (d, *J* =12 Hz, 1H), 2.86 (s, 3H), 2.79-2.74 (m, 1H), 2.40-2.34 (m, 1H) (The OH is not visible); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 143.6, 136.6, 131.0, 130.7, 129.5, 125.9, 123.4, 120.7, 108.8, 80.8, 62.3, 52.1, 38.7, 36.4, 26.2; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{19}BrNO_2S$: 404.0314, found: 404.0316; FT-IR (KBr) 3422, 2934, 1690, 1610, 1489, 1469, 1375, 1071, 1011, 756 cm^{-1}.



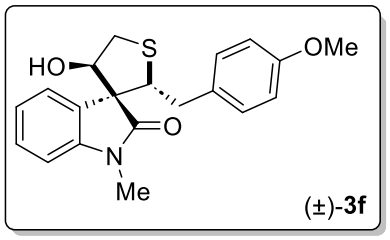
2'-(4-chlorobenzyl)-4'-hydroxy-1-methyl-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-3c. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.48; yellow solid; mp 100-101 °C; yield 74% (53 mg); major diastereomer (>10:1 dr); ^1H NMR (600 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.2 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.59 (d, *J* = 7.8 Hz, 2H), 4.64 (s, 1H), 4.54-4.52 (m, 1H), 4.19-4.18 (m, 1H), 3.44-3.41 (m, 1H), 3.19 (d, *J* = 11.4 Hz, 1H), 2.86 (s, 3H), 2.79-2.76 (m, 1H), 2.40-2.36 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 143.6, 136.1, 132.6, 130.3, 129.5, 128.1, 125.9, 123.4, 108.8, 80.8, 62.3, 52.2, 38.7, 36.3, 26.2; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{19}ClNO_2S$: 360.0820, found: 360.0835; FT-IR (KBr) 3418, 2936, 1689, 1491, 1374, 755 cm^{-1}.



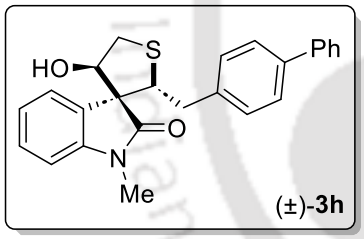
2'-(4-Fluorobenzyl)-4'-hydroxy-1-methyl-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-3d. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.50; light yellow solid; mp 89-90 °C; yield 72% (49 mg); major diastereomer (>10:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.23-7.20 (m, 1H), 6.85-6.78 (m, 3H), 6.64-6.62 (m, 2H), 4.62 (s, 1H), 4.56-4.52 (m, 1H), 4.20-4.19 (m, 1H), 3.44-3.41 (m, 1H), 3.20 (d, *J* = 11.5 Hz, 1H), 2.88 (s, 3H) 2.79-2.75 (m, 1H), 2.42-2.37 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 162.7 ($J_{C\text{-}F}$ = 243.5 Hz), 143.6, 133.5 ($J_{C\text{-}F}$ = 4.1 Hz), 130.4 ($J_{C\text{-}F}$ = 7.7 Hz), 129.5, 126.0, 125.9, 123.4, 114.9 ($J_{C\text{-}F}$ = 21.1 Hz), 108.8, 80.9, 62.4, 52.5, 38.7, 36.1, 26.2; ^{19}F NMR (471 MHz, $CDCl_3$) δ -116.0; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{19}FNO_2S$: 344.1115, found: 344.1115; FT-IR (KBr) 3425, 2937, 1690, 1610, 1509, 1469, 1374, 1220, 757, 749 cm^{-1}.



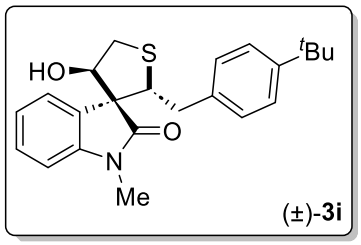
4'-Hydroxy-1-methyl-2'-(4-methylbenzyl)-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-3e. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.58; colorless solid; mp 99-100 °C ; yield 84% (57 mg); major diastereomer (>10:1 dr); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 2H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.56 (d, *J* = 7.8 Hz, 2H), 4.69 (s, 1H), 4.57-4.54 (m, 1H), 4.19-4.18 (m, 1H), 3.43-3.40 (m, 1H), 3.19 (d, *J* = 12 Hz, 1H), 2.82 (s, 3H), 2.78-2.75 (m, 1H), 2.38-2.34 (m, 1H), 2.24 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.0, 143.7, 136.2, 134.6, 129.3, 128.7, 128.6, 126.1, 125.9, 123.3, 108.8, 80.8, 62.3, 52.6, 38.6, 36.4, 26.1, 21.1; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{22}NO_2S$: 340.1366, found: 340.1382; FT-IR (KBr) 3416, 2937, 1686, 1610, 1469, 1373, 756, 747 cm^{-1}.



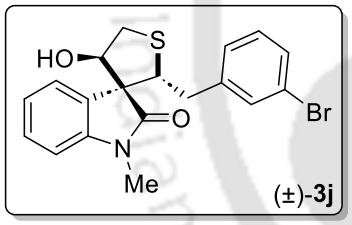
4'-Hydroxy-2'-(4-methoxybenzyl)-1-methyl-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-3f. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.42; brown solid; mp 104-105 °C; yield 88% (63 mg); major diastereomer (>10:1 dr); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.2 Hz, 1H), 7.43 (m, 1H), 7.22 (m, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.66-6.64 (m, 2H), 6.58-6.56 (m, 2H), 4.69 (s, 1H), 4.55-4.53 (m, 1H), 4.19-4.18 (m, 1H), 3.73 (s, 3H), 3.43-3.40 (m, 1H), 3.19 (d, *J* = 12 Hz, 1H), 2.85 (s, 3H), 2.77-2.74 (m, 1H), 2.37-2.33 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 158.4, 143.7, 129.9, 129.8, 129.3, 126.1, 125.9, 123.3, 113.4, 108.8, 80.8, 62.3, 55.3, 52.7, 38.6, 36.0, 26.2; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{22}NO_3S$: 356.1315, found: 356.1322; FT-IR (KBr) 3417, 2936, 1686, 1610, 1511, 1469, 1374, 1245, 757, 748 cm^{-1}.



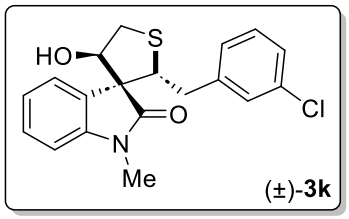
2'-([1,1'-Biphenyl]-4-ylmethyl)-4'-hydroxy-1-methyl-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-3h. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.47; colorless solid; mp 166-167 °C; yield 85% (69 mg); major diastereomer (>10:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.5 Hz, 1H), 7.52-7.51 (m, 2H), 7.44-7.39 (m, 3H), 7.35-7.30 (m, 3H), 7.25-7.21 (m, 1H), 6.82 (d, *J* = 8 Hz, 1H), 6.73 (d, *J* = 8.5 Hz, 2H), 4.70 (s, 1H), 4.65-4.61 (m, 1H), 4.20 (s, 1H), 3.46 (d, *J* = 11.5 Hz, 1H), 3.21 (d, *J* = 11.5 Hz, 1H), 2.91-2.86 (m, 1H), 2.78 (s, 3H), 2.47-2.43 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 143.8, 140.9, 139.6, 136.7, 129.4, 128.9, 127.3, 127.0, 126.6, 126.1, 125.9, 123.3, 108.8, 80.9, 62.3, 52.3, 38.8, 36.7, 26.1; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{25}H_{24}NO_2S$: 402.1522, found: 402.1536; FT-IR (KBr) 3418, 2933, 1688, 1611, 1469, 1374, 758 cm^{-1}.



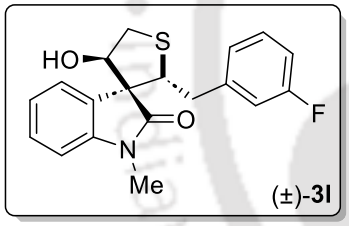
2'-(4-(*tert*-butyl)benzyl)-4'-hydroxy-1-methyl-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-3i. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.55; colorless solid; mp 129-130 °C; yield 84% (64 mg); major diastereomer (>10:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.23-7.20 (m, 1H), 7.14-7.12 (m, 2H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.58-6.56 (m, 2H), 4.60-4.56 (m, 1H), 4.19-4.18 (m, 1H), 3.45-3.41 (m, 1H), 3.20 (d, *J* = 11.6 Hz, 1H), 2.84-2.79 (m, 1H), 2.77(s, 3H), 2.39-2.33 (m, 1H), 1.26 (m, 9H), (The OH is not visible); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 149.4, 143.7, 134.5, 129.3, 128.5, 126.1, 125.9, 124.8, 123.3, 108.7, 80.9, 62.2, 52.4, 38.7, 36.4, 34.5, 31.4, 26.1; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{28}NO_2S$: 382.1835, found: 382.1834; FT-IR (KBr) 3416, 2959, 1687, 1610, 1469, 1374, 755, 745 cm^{-1}.



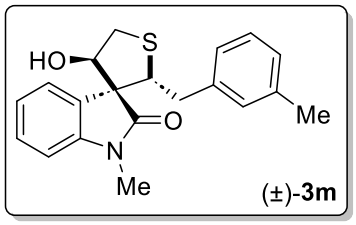
2'-(3-Bromobenzyl)-4'-hydroxy-1-methyl-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-3j. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.48; yellow solid; mp 119-120 °C; yield 71% (57 mg); major diastereomer (>10:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.24-7.22 (m, 2H), 7.07-7.04 (m, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 8 Hz, 1H), 6.48 (s, 1H), 4.63 (s, 1H), 4.54-4.50 (m, 1H), 4.19 (s, 1H), 3.44 (d, *J* = 11.5 Hz, 1H), 3.20 (d, *J* = 12 Hz, 1H), 2.89 (s, 3H) 2.84-2.80 (m, 1H), 2.40-2.35 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 143.6, 139.9, 131.9, 129.9, 129.8, 129.6, 127.7, 125.88, 125.84, 123.5, 121.9, 109.1, 80.9, 62.3, 52.0, 38.7, 36.7, 26.2; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{19}BrNO_2S$: 404.0314, found: 404.0320; FT-IR (KBr) 3423, 2935, 1690, 1610, 1470, 1374, 750 cm^{-1}.



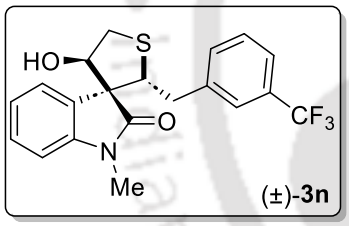
2'-(3-Chlorobenzyl)-4'-hydroxy-1-methyl-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-3k. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.49; brown solid; mp 110-111 °C; yield 59% (42 mg); major diastereomer (>9:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.25-7.21 (m, 1H), 7.11-7.09 (m, 2H), 6.90 (d, *J* = 8 Hz, 1H), 6.79-6.77 (m, 1H), 6.38 (s, 1H), 4.54-4.51 (m, 1H), 4.199-4.192 (m, 1H), 3.45-3.41 (m, 1H), 3.20 (d, *J* = 12 Hz, 1H), 2.89 (s, 3H), 2.83-2.78 (m, 1H), 2.41-2.36 (m, 1H), (The OH is not visible); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 143.6, 139.7, 133.6, 129.6, 129.5, 129.0, 127.2, 127.0, 125.9, 125.8, 123.5, 109.0, 80.9, 62.3, 52.1, 38.7, 36.7, 26.2; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{19}ClNO_2S$: 360.0820, found: 360.0824; FT-IR (KBr) 3417, 2932, 1688, 1610, 1470, 1353, 755, 684 cm^{-1}.



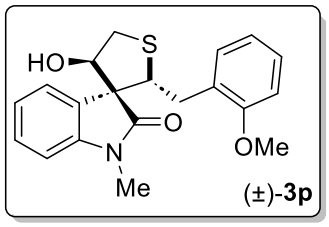
2'-(3-Fluorobenzyl)-4'-hydroxy-1-methyl-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-3l. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.46; yellow solid; mp 104-105 °C; yield 64% (44 mg); major diastereomer (>7:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 8 Hz, 1H), 7.24-7.21 (m, 1H), 7.13-7.09 (m, 1H), 6.88 (d, *J* = 7.5 Hz, 1H), 6.83 – 6.79 (m, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 6.29 (d, *J* = 9.5 Hz, 1H), 4.55-4.52 (m, 1H), 4.209-4.203 (m, 1H), 3.44-3.41 (m, 1H), 3.20 (d, *J* = 11.5 Hz, 1H), 2.90 (s, 3H) 2.80-2.76 (m, 1H), 2.43-2.39 (m, 1H), (The OH is not visible); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 163.5 (J_{C-F} = 243.8 Hz), 143.7, 140.4 (J_{C-F} = 7.6 Hz), 129.6 (J_{C-F} = 8 Hz), 129.59, 125.97, 125.93, 124.65 (J_{C-F} = 4.3 Hz), 123.4, 115.8 (J_{C-F} = 21.2 Hz), 113.7 (J_{C-F} = 20.7 Hz), 108.9, 80.8, 62.4, 52.3, 38.7, 36.7, 26.2; ^{19}F NMR (471 MHz, $CDCl_3$) δ -113.6; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{19}FNO_2S$: 344.1115, found: 344.1120. FT-IR (KBr) 3425, 2933, 1690, 1611, 1470, 1375, 1354, 757, 749 cm^{-1}.



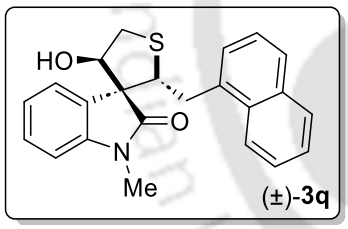
4'-Hydroxy-1-methyl-2'-(3-methylbenzyl)-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-3m. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.56; yellow solid; mp 114-115 °C; yield 68% (46 mg); major diastereomer (>10:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.23-7.20 (m, 1H), 7.04-7.00 (m, 1H), 6.92-6.91 (m, 1H), 6.83 (d, *J* = 7 Hz, 1H), 6.56(d, *J* = 7.5 Hz, 1H), 6.38 (s, 1H), 4.69 (s, 1H), 4.58-4.55 (m, 1H), 4.20-4.18 (m, 1H), 3.44-3.41 (m, 1H), 3.19 (d, *J* = 12 Hz, 1H), 2.83 (s, 3H), 2.80-2.75 (m, 1H), 2.40-2.35 (m, 1H), 2.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 143.8, 137.6, 137.5, 129.7, 129.3, 127.9, 127.5, 126.2, 125.9, 123.3, 108.6, 80.9, 62.3, 52.4, 38.7, 36.9, 26.1, 21.3; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{22}NO_2S$: 340.1366, found: 340.1384; FT-IR (KBr) 3417, 2937, 1686, 1609, 1469, 1374, 756, 747 cm^{-1}.



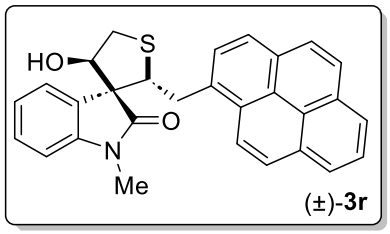
4'-Hydroxy-1-methyl-2'-(3-(trifluoromethyl)benzyl)-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-3n. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.40; colorless solid; mp 127-128 °C; yield 52% (41 mg); major diastereomer (>10:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.39-7.37 (m, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.25-7.22 (m, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 8 Hz, 1H), 6.63 (s, 1H), 4.60-4.57 (m, 1H), 4.198-4.191 (m, 1H), 3.46-3.43 (m, 1H), 3.21 (d, *J* = 12 Hz, 1H), 2.91-2.87 (m, 1H), 2.80 (s, 3H), 2.51-2.46 (m, 1H), (The OH is not visible); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 143.4, 138.6, 132.4, 130.7 (J_{C-F} = 31.7 Hz), 129.6, 128.7, 127.3 (J_{C-F} = 270.6 Hz), 125.8, 125.7, 125.6 (J_{C-F} = 3.6 Hz), 123.8 (J_{C-F} = 3.7 Hz), 123.5, 109.1, 80.9, 62.3, 51.8, 38.7, 36.8, 26.0; ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.4; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{19}F_3NO_2S$: 394.1083, found: 394.1093; FT-IR (KBr) 3425, 2939, 1692, 1611, 1493, 1470, 1330, 1163, 1123, 1073, 749 cm^{-1}.



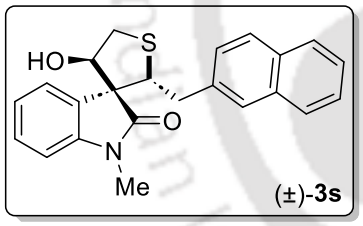
4'-Hydroxy-2'-(2-methoxybenzyl)-1-methyl-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-3p. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane R_f = 0.43; colorless solid; mp 116-117 °C; yield 90% (64 mg); major diastereomer (>10:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.09-7.06 (m, 1H), 6.81 (d, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 8 Hz, 1H), 6.55 (t, *J* = 7.5 Hz, 1H), 6.07-6.05 (m, 1H) 4.83-4.80 (m, 1H), 4.67 (s, 1H), 4.15-4.14 (m, 1H), 3.76 (s, 3H), 3.43-3.40 (m, 1H), 3.17 (d, *J* = 12 Hz, 1H), 2.94-2.90 (m, 1H), 2.79 (s, 3H), 2.42-2.37 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 158.1, 143.9, 130.3, 129.2, 128.2, 126.5, 126.1, 126.0, 123.2, 119.4, 110.1, 108.7, 81.0, 62.4, 55.3, 49.4, 38.6, 32.6, 26.0; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{22}NO_3S$: 356.1315, found: 356.1316. FT-IR (KBr) 3417, 2936, 1687, 1610, 1493, 1468, 1375, 1246, 754 cm^{-1}.



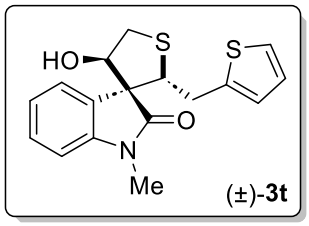
4'-Hydroxy-1-methyl-2'-(naphthalen-1-ylmethyl)-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-3q. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.43; colorless solid; mp 135-136 °C; yield 62% (46 mg); major diastereomer (>10:1 dr); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79-7.76 (m, 2H), 7.67-7.64 (m, 2H), 7.45-7.40 (m, 3H), 7.28-7.27 (m, 1H), 7.19 (t, *J* = 7.2 Hz, 1H) 6.81 (d, *J* = 7.8 Hz, 1H), 6.70 (d, *J* = 6.6 Hz, 1H), 4.82 (t, *J* = 7.8 Hz, 1H), 4.19-4.18 (m, 1H), 3.46-3.43 (m, 1H), 3.19-3.16 (m, 2H), 2.97-2.93 (m, 1H), 2.79 (s, 3H), (The OH is not visible); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 143.8, 134.1, 133.7, 131.7, 129.4, 128.6, 127.7, 126.7, 126.2, 126.1, 125.9, 125.7, 124.9, 123.5, 123.4, 109.0, 80.8, 62.5, 51.7, 38.6, 33.4, 26.2; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{22}NO_2S$: 376.1366, found: 376.1366; FT-IR (KBr) 3416, 2917, 1686, 1610, 1469, 1353, 745 cm^{-1}.



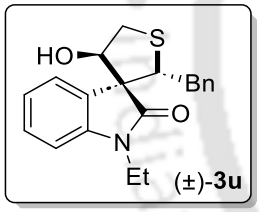
4'-Hydroxy-1-methyl-2'-(pyren-1-ylmethyl)-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-3r. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.47; yellow solid; mp 142-143 °C; yield 54% (48 mg); major diastereomer (>6:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.5 Hz, 2H), 8.02-7.95 (m, 4H), 7.92 (d, *J* = 7.5 Hz, 1H), 7.84-7.83 (m, 2H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.28-7.27 (m, 1H), 6.71 (d, *J* = 7.5 Hz, 1H), 4.98-4.95 (m, 1H), 4.187-4.180 (m, 1H), 3.50-3.45 (m, 2H), 3.26-3.24 (m, 1H), 3.21 (d, *J* = 12 Hz, 1H), 2.47 (s, 3H), (The OH is not visible); ^{13}C (125 MHz, $CDCl_3$) δ 176.5, 143.8, 131.9, 131.4, 130.8, 130.5, 129.5, 129.0, 127.66, 127.63, 127.4, 127.3, 126.3, 126.04, 126.02, 125.1, 124.9, 124.8, 124.2, 123.5, 122.9, 109.1, 80.9, 62.5, 52.7, 38.7, 33.8, 25.9; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{29}H_{24}NO_2S$: 450.1522, found: 450.1516; FT-IR (KBr) 3423, 2935, 1688, 1610, 1469, 1374, 846, 756 cm^{-1}.



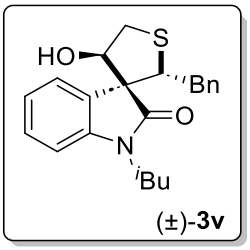
4'-Hydroxy-1-methyl-2'-(naphthalen-2-ylmethyl)-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-3s. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane R_f = 0.42; colorless solid; mp 146-147 °C; yield 51% (38 mg); major diastereomer (>10:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75-7.73 (m, 1H), 7.71-7.69 (m, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.51-7.49 (m, 1H), 7.48-7.45 (m, 1H), 7.41-7.38 (m, 2H), 7.29-7.27 (m, 1H), 7.06-7.04 (m, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.70 (s, 1H), 4.68-4.65 (m, 2H), 4.16-4.15 (m, 1H), 3.47-3.44 (m, 1H), 3.21 (d, *J* = 12.0 Hz, 1H), 3.06-3.02 (m, 1H), 2.63-2.58 (m, 1H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 143.8, 134.9, 133.0, 132.5, 129.3, 127.7, 127.6, 127.4, 127.2, 126.1, 126.0, 125.9, 125.7, 123.4, 108.8, 80.9, 62.3, 51.8, 38.8, 37.3, 25.7; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{22}NO_2S$: 376.1366, found: 376.1367; FT-IR (KBr) 3415, 2928, 1689, 1611, 1469, 1374, 747 cm^{-1}.



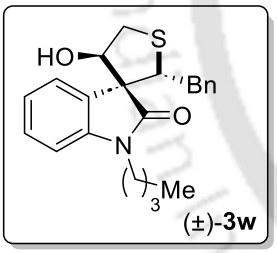
4'-Hydroxy-1-methyl-2'-(thiophen-2-ylmethyl)-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-3t. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.42; brown solid; mp 117-118 ºC; yield 61% (40 mg); major diastereomer (>9:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7 Hz, 1H), 7.44-7.40 (m, 1H), 7.22-7.19 (m, 1H), 7.06-7.04 (m, 1H), 6.89 (d, *J* = 8 Hz, 1H), 6.77-6.76 (m, 1H), 6.31-6.30 (m, 1H), 4.70 (s, 1H), 4.57-4.54 (m, 1H), 4.23-4.22 (m, 1H), 3.45-3.41 (m, 1H), 3.21-3.18 (m, 1H), 2.99 (s, 3H), 2.92-2.88 (m, 1H), 2.71-2.66 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.9, 143.8, 140.2, 129.5, 126.4, 125.8, 125.7, 125.5, 124.3, 123.4, 108.8, 80.8, 62.4, 52.9, 38.7, 31.1, 26.4; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{18}NO_2S_2$: 332.0773, found: 332.0769; FT-IR (KBr) 3423, 2916, 2849, 1694, 1611, 1470, 1375, 1265, 1189, 745 cm^{-1}.



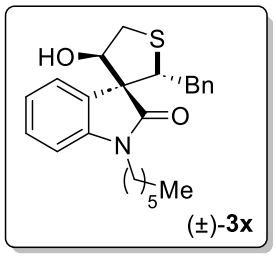
2'-Benzyl-1-ethyl-4'-hydroxy-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-3u. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.58; thick yellow liquid; yield 91% (62 mg); major diastereomer (>8:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.12-7.10 (m, 3H), 6.87 (d, *J* = 8 Hz, 1H), 6.75-6.73 (m, 2H), 4.59 (t, *J* = 8.0 Hz, 1H), 4.207-4.200 (m, 1H), 3.48-3.35 (m, 3H), 3.19 (d, *J* = 12 Hz, 1H), 2.76-2.72 (m, 1H) 2.46-2.42 (m, 1H), 1.06 (t, *J* = 7.5 Hz, 3H), (The OH is not visible); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 142.8, 138.0, 129.3, 128.8, 128.2, 126.8, 126.4, 126.1, 123.1, 108.9, 81.0, 62.4, 52.5, 38.6, 36.9, 35.1, 12.7; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{22}NO_2S$: 340.1366, found: 340.1388; FT-IR (neat) 3411, 2935, 1684, 1609, 1466, 1372, 755, 699 cm^{-1}.



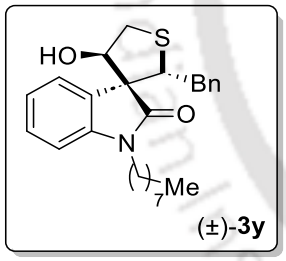
2'-Benzyl-4'-hydroxy-1-isobutyl-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-3v. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.59; thick yellow liquid; yield 92% (78 mg); major diastereomer (>10:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.21-7.18 (m, 1H), 7.14-7.12 (m, 3H), 6.87 (d, *J* = 8 Hz, 1H), 6.78-6.76 (m, 2H), 4.70 (s, 1H), 4.56 (t, *J* = 8 Hz, 1H), 4.21-4.20 (m, 1H), 3.44-3.41 (m, 1H), 3.29-3.25 (m, 1H), 3.19 (d, *J* = 11.5 Hz, 1H), 3.12-3.08 (m, 1H), 2.73-2.68 (m, 1H) 2.48-2.44 (m, 1H), 2.06-1.97 (m, 1H), 0.92 (d, *J* = 7 Hz, 3H), 0.85 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.3, 143.4, 138.1, 129.2, 128.8, 128.1, 126.8, 126.3, 126.0, 123.1, 109.4, 81.0, 62.5, 52.7, 47.6, 38.6, 36.9, 27.0, 20.4, 20.1; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{22}H_{26}NO_2S$: 368.1679, found: 368.1679; FT-IR (neat) 3416, 2925, 1686, 1610, 1466, 1376, 735, 700 cm^{-1}.



2'-Benzyl-1-butyl-4'-hydroxy-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-3w. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; thick brown liquid; yield 93% (68 mg); major diastereomer (>10:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.21-7.18 (m, 1H), 7.13-7.11 (m, 3H), 6.87 (d, *J* = 8 Hz, 1H), 6.76-6.74 (m, 2H), 4.72 (s, 1H), 4.57 (t, *J* = 8 Hz, 1H), 4.20-4.19 (m, 1H), 3.46-3.40 (m, 2H), 3.32-3.25 (m, 1H), 3.19 (d, *J* = 11.5 Hz, 1H), 2.74-2.70 (m, 1H) 2.46-2.42 (m, 1H), 1.53-1.42 (m, 2H), 1.30-1.26 (m, 2H), 0.90 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 143.1, 138.0, 129.2, 128.8, 128.1, 126.8, 126.4, 126.0, 123.1, 109.1, 80.9, 62.4, 52.6, 40.0, 38.6, 36.9, 29.8, 29.5, 20.2, 13.7; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{22}H_{26}NO_2S$: 368.1679, found: 368.1679; FT-IR (neat) 3415, 2929, 2870, 1683, 1608, 1487, 1466, 1364, 747, 699 cm^{-1}.

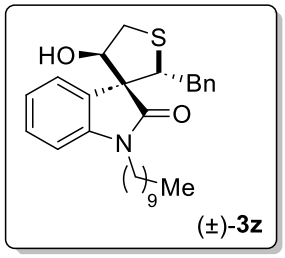


2'-Benzyl-1-hexyl-4'-hydroxy-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-3x. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.61; thick brown liquid; yield 94% (74 mg); major diastereomer (>10:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.5 Hz, 1H), 7.42-7.38 (m,1H), 7.22-7.18 (m, 1H), 7.13-7.11 (m, 3H), 6.87 (d, *J* = 8 Hz, 1H), 6.76-6.74 (m, 2H), 4.57 (t, *J* = 7.5 Hz, 1H), 4.20-4.19 (m, 1H), 3.45-3.39 (m, 2H), 3.32-3.26 (m, 1H), 3.19 (d, *J* = 12 Hz, 1H), 2.74-2.70 (m, 1H), 2.47-2.42 (m, 1H), 1.50-1.41 (m, 2H), 1.27-1.25 (m, 6H), 0.88-0.84 (m, 3H), (The OH is not visible); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 143.1, 138.1, 129.3, 128.8, 128.2, 126.8, 126.4, 126.1, 123.1, 109.1, 81.0, 62.5, 52.7, 40.3, 38.6, 36.9, 31.4, 27.4, 26.6, 22.6, 14.0; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{24}H_{30}NO_2S$: 396.1992, found: 396.2003; FT-IR (neat) 3416, 2926, 2855, 1684, 1609, 1466, 1367, 751, 699 cm^{-1}.

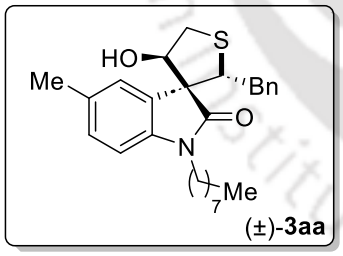


2'-Benzyl-4'-hydroxy-1-octyl-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-3y. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.62; thick yellow liquid; yield 95% (80 mg); major diastereomer (>10:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.5 Hz, 1H), 7.42-7.38 (m, 1H), 7.21-7.18 (m, 1H), 7.13-7.10 (m, 3H), 6.87 (d, *J* = 8 Hz, 1H), 6.76-6.74 (m, 2H), 4.72 (s, 1H), 4.57 (t, *J* = 8 Hz, 1H), 4.20-4.19 (m, 1H), 3.45-3.39 (m, 2H), 3.32-3.26 (m, 1H), 3.19 (d, *J* = 11.5 Hz, 1H), 2.74-2.69 (m, 1H) 2.47-2.42 (m, 1H), 1.52-1.39 (m, 2H), 1.27-1.23 (m, 10H), 0.86 (t, *J* = 7 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.9, 143.1, 138.0, 129.3, 128.8, 128.1, 126.8, 126.3, 126.0, 123.1, 109.1, 80.9, 62.4, 52.6, 40.3, 38.6, 36.9, 31.8, 29.27, 29.26, 27.4, 26.9, 22.7, 14.2; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for

$C_{26}H_{34}NO_2S$: 424.2305, found: 424.2306; FT-IR (neat) 3418, 2926, 2854, 1686, 1609, 1466, 1368, 754, 699 cm^{-1}.

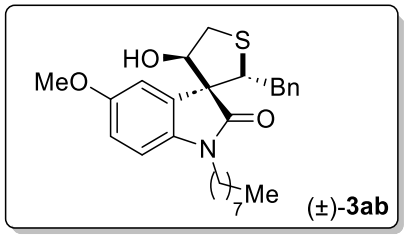


2'-Benzyl-1-decyl-4'-hydroxy-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-3z. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.65; thick yellow liquid; yield 95% (86 mg); major diastereomer (>10:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 8 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.13-7.10 (m, 3H), 6.87 (d, *J* = 8 Hz, 1H), 6.76-6.74 (m, 2H), 4.72 (s, 1H), 4.57 (t, *J* = 8 Hz, 1H), 4.20-4.19 (m, 1H), 3.45-3.39 (m, 2H), 3.32-3.27 (m, 1H), 3.19 (d, *J* = 12 Hz, 1H), 2.74-2.69 (m, 1H) 2.47-2.42 (m, 1H), 1.52-1.42 (m, 2H), 1.26-1.23 (m, 14H), 0.87 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 143.1, 138.1, 129.3, 128.8, 128.2, 126.8, 126.4, 126.1, 123.1, 109.1, 80.9, 62.5, 52.7, 40.3, 38.6, 36.9, 31.9, 29.6, 29.4, 29.3, 27.4, 26.9, 22.7, 14.2 (one carbon is overlapped); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{28}H_{38}NO_2S$: 452.2618, found: 452.2636; FT-IR (neat) 3418, 2922, 2852, 1685, 1609, 1465, 1366, 752, 698 cm^{-1}.

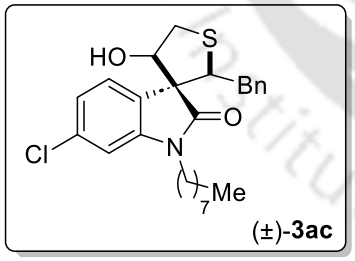


2'-Benzyl-1-octyl-4'-hydroxy-5-methyl-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-3aa. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.50; thick liquid; yield 78% (68 mg); major diastereomer (>10:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.21 (d, *J* = 8 Hz, 1H), 7.13-7.11 (m, 3H), 6.78-6.75 (m, 3H), 4.79 (s, 1H), 4.56 (t, *J* = 7.5 Hz, 1H), 4.19-4.18 (m, 1H), 3.45-3.37 (m, 2H), 3.31-3.25 (m, 1H), 3.18 (d, *J* = 11.5 Hz, 1H), 2.73-2.69 (m, 1H), 2.47-2.42 (m, 4H), 1.52-1.41 (m, 2H), 1.28-1.23 (m, 10H), 0.87-0.84 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 140.7, 138.1, 132.8, 129.5, 128.8, 128.1, 126.8, 126.7, 126.4, 108.8, 80.9, 62.5, 52.7, 40.3, 38.6, 36.9, 31.8, 29.2, 27.4, 26.9, 22.75, 22.73, 21.5, 14.1;

HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{27}H_{36}NO_2S$: 438.2461, found: 438.2460; FT-IR (neat) 3412, 2925, 2855, 1682, 1616, 1599, 1492, 1454, 1355, 1166, 1048, 807, 744, 701 cm^{-1}.

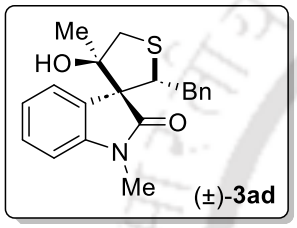


2'-Benzyl-1-octyl-4'-hydroxy-5-methoxy-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-3ab. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.44; thick liquid; yield 75% (68 mg); major diastereomer (>10:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.31 (m, 1H), 7.14-7.12 (m, 3H), 6.93-6.91 (m, 1H), 6.80-6.76 (m, 3H), 4.80 (s, 1H), 4.56 (t, *J* = 8 Hz, 1H), 4.209-4.201 (m, 1H), 3.87 (s, 3H), 3.43-3.37 (m, 2H), 3.32-3.25 (m, 1H), 3.17 (d, *J* = 12 Hz, 1H), 2.74-2.70 (m, 1H), 2.49-2.44 (m, 1H), 1.52-1.42 (m, 2H), 1.28-1.23 (m, 10H), 0.87-0.84 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4, 156.4, 138.1, 136.5, 128.8, 128.1, 127.7, 126.8, 113.7, 113.2, 109.3, 80.8, 62.8, 56.0, 52.7, 40.4, 38.4, 36.8, 31.8, 29.2, 27.4, 26.9, 22.7, 14.1; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{27}H_{36}NO_3S$: 454.2410, found: 454.2408; FT-IR (neat) 3406, 2925, 2854, 1681, 1597, 1489, 1455, 1434, 1351, 1030, 803, 698 cm^{-1}.

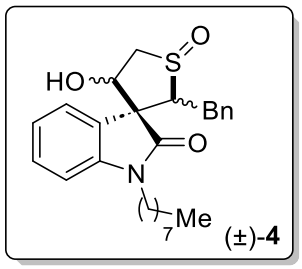


2'-Benzyl-6-chloro-4'-hydroxy-1-octyl-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-3ac. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.44; thick yellow liquid; yield 75% (68 mg); mixture of diastereomers (>2.9:1 dr); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.8 Hz, 0.34H, minor), 7.59 (d, *J* = 7.8 Hz, 1H, major), 7.18-7.17 (m, 1.22H, major + minor), 7.14-7.12 (m, 3.39H, major + minor), 6.848-6.844 (m, 1H, major), 6.817-6.814 (m, 0.34H, minor), 6.78-6.76 (m, 2.38H, major + minor), 4.75-4.72 (m, 0.34H, minor), 4.56 (t, *J* = 7.8 Hz, 1H, major), 4.28 (t, *J* = 7.8 Hz, 0.34H, minor), 4.17-4.16 (m, 1H, major), 3.42-3.34

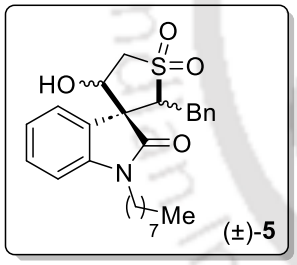
(m, 2.34H, major + minor), 3.32-3.29 (m, 0.34H, minor), 3.26-3.21 (m, 1.34H, major + minor), 3.19 (d, J = 12 Hz, 1H, major), 3.03 (t, J = 10.2 Hz, 0.34H, minor), 2.75-2.72 (m, 1H, major), 2.63-2.59 (m, 0.34H, minor), 2.48-2.46 (m, 0.34H, minor), 2.45-2.40 (m, 1H, major), 1.49-1.39 (m, 2.69H, major + minor), 1.28-1.23 (m, 13.41H, major + minor), 0.87-0.85 (m, 4H, major + minor), (The OH is not visible); ^{13}C NMR (150 MHz, $CDCl_3$) δ (major + minor) 176.9, 176.0, 145.8, 144.3, 137.8, 137.1, 135.38, 135.30, 128.9, 128.7, 128.2, 127.02, 127.00, 126.9, 124.7, 123.0, 122.8, 122.4, 109.7, 109.4, 80.8, 80.5, 62.4, 62.2, 60.5, 52.5, 49.5, 40.4, 38.5, 38.3, 36.8, 34.5, 31.88, 31.85, 29.3, 29.28, 29.26, 29.21, 27.4, 27.3, 26.9, 26.8, 22.7, 21.2, 14.3, 14.2; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{26}H_{33}ClNO_2S$: 458.1915, found: 458.1918; FT-IR (neat) 3430, 2925, 2854, 1694, 1605, 1488, 1454, 1365, 1076, 813, 700 cm^{-1}.



2'-Benzyl-4'-hydroxy-1,4'-dimethyl-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-3ad. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.55; thick liquid; yield 75% (51 mg); major diastereomer (>10:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, J = 7.5 Hz, 1H), 7.37-7.33 (m, 1H), 7.19-7.15 (m, 1H), 7.06-7.02 (m, 3H), 6.76 (d, J = 7.5 Hz, 1H), 6.59-6.57 (m, 2H), 4.85-4.84 (m, 1H), 4.63-4.59 (m, 1H), 3.18-3.15 (m, 1H), 3.08-3.03 (m, 1H), 2.72-2.69 (m, 4H), 2.31-2.26 (m, 1H), 0.77 (s, 3H), (The OH is not visible); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.3, 144.0, 137.5, 129.1, 128.9, 128.0, 126.77, 126.70, 125.5, 123.4, 108.7, 86.2, 64.9, 53.3, 42.9, 37.5, 26.0, 22.7; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{22}NO_2S$: 340.1366, found: 340.1366; FT-IR (neat) 3408, 3058, 3027, 2928, 2852, 1686, 1610, 1469, 1453, 1372, 1351, 1093, 1027, 755, 742, 698, 543, 498 cm^{-1}.

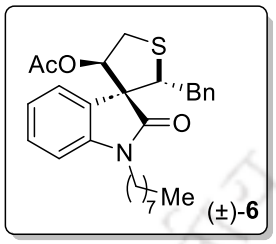


2'-Benzyl-4'-hydroxy-1-octyl-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one 1'-oxide (±)-4. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.40; mixture of diastereomers (3.3:1 dr); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.2 Hz, 1H, major), 7.70 (d, *J* = 7.2 Hz, 0.30H, minor), 7.39-7.36 (m, 1.30H, major + minor), 7.21-7.19 (m, 1.30H, major + minor), 7.11-7.10 (m, 3H, major), 6.82-6.81 (m, 0.30H, minor), 6.79 (d, *J* = 7.8 Hz, 1H, major), 6.77-6.73 (m, 2H, major), 4.60-4.59 (m, 0.30H, minor), 4.49 (t, *J* = 3.6 Hz, 1H, major), 4.14-4.11 (m, 1H, major), 3.98-3.95 (m, 1H, major), 3.70 (t, *J* = 8.4 Hz, 0.30H, minor), 3.54-3.50 (m, 0.30H, minor), 3.50-3.45 (m, 0.30H, minor), 3.44-3.40 (m, 1H, major), 3.39-3.35 (m, 0.6H, minor), 3.27-3.22 (m, 2H, major), 3.09-3.06 (m, 1H, major), 2.67-2.63 (m, 0.30H, minor), 2.51-2.47 (m, 1H, major), 2.35-2.33 (m, 0.30H), 1.48-1.38 (m, 2.61H, major + minor), 1.28-1.24 (m, 13H, major + minor), 0.87-0.85 (m, 3.90H, major + minor), (The OH is not visible); ^{13}C NMR (150 MHz, $CDCl_3$) δ (major) 176.5, 143.1, 136.1, 129.4, 129.3, 128.3, 128.2, 126.9, 126.0, 123.3, 109.1, 79.6, 64.6, 62.3, 62.0, 40.4, 31.8, 29.9, 29.28, 29.25, 27.4, 26.9, 22.7, 14.2; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{26}H_{34}NO_3S$: 440.2254, found: 440.2252; FT-IR (neat) 3385, 3060, 2927, 2855, 1710, 1611, 1489, 1467, 1370, 1026, 746, 699 cm^{-1}.

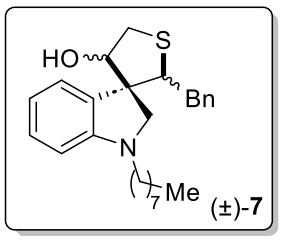


2'-Benzyl-4'-hydroxy-1-octyl-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one 1',1'-dioxide (±)-5. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.52; mixture of diastereomers (3.2:1 dr); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74-7.70 (m, 1.30H, major + minor), 7.44-7.42 (m, 1H, major), 7.33-7.30 (m, 0.30H, minor), 7.29-7.27 (m, 0.30H, minor), 7.22-7.20 (m, 1H, major), 7.15-7.02 (m, 3.91H, major + minor), 6.81-6.76 (m, 1.31H, major + minor), 6.62-6.57 (m, 2.47H, major + minor), 4.83-4.80 (m, 1H, major), 4.39-4.37 (m, 0.31H, minor), 4.20-4.19 (m, 0.31H, minor), 4.13-4.10 (m, 1H, major), 4.02 (d, *J* = 7.8 Hz, 0.31H, minor), 3.81-3.77 (m, 1H, major), 3.73-3.70 (m, 0.31H, minor), 3.65-3.63 (m, 0.31H, minor), 3.58-3.55 (m, 0.31H, minor), 3.45-3.41 (m, 1H, major), 3.30-3.25 (m, 1H, major + minor), 3.21-3.15 (m, 1.31H, major + minor), 3.07-3.03 (m, 1H, major + minor), 2.59-2.49 (m, 1.31H, major + minor), 1.39-1.29 (m, 2.64H, major + minor), 1.28-1.22 (m, 13.31H, major + minor), 0.87-0.84

(m, 3.93H, major + minor), (The OH is not visible); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major + minor) 175.2, 174.4, 144.8, 143.2, 134.2, 134.1, 130.26, 130.21, 129.33, 129.31, 128.9, 128.7, 128.3, 127.3, 127.2, 126.6, 126.2, 123.5, 122.9, 122.2, 109.6, 109.2, 71.9, 71.4, 68.1, 63.2, 60.5, 58.4, 57.4, 56.7, 40.58, 40.52, 31.86, 31.83, 30.0, 29.8, 29.4, 29.26, 29.22, 29.20, 27.7, 27.3, 27.2, 27.1, 26.8, 22.7, 14.3, 14.1; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{26}H_{34}NO_4S$: 456.2203, found: 456.2204; FT-IR (neat) 3423, 2925, 2854, 1692, 1610, 1466, 1370, 1309, 1097, 1214, 1124, 748, 697, 544, 510, 500 cm^{-1}.



2'-Benzyl-1-octyl-2-oxo-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-4'-yl acetate (±)-6. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.42; thick liquid; yield 91% (42 mg); major diastereomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.5 Hz, 1H), 7.39-7.35 (m, 1H), 7.17-7.11 (m, 4H), 6.87-6.83 (m, 3H), 5.389-5.380 (m, 1H), 4.54-4.51 (m, 1H), 3.58-3.54 (m, 1H), 3.48-3.42 (m, 1H), 3.35-3.29 (m, 1H), 3.07 (d, *J* = 12.5 Hz, 1H), 2.66-2.61 (m, 1H), 2.55-2.51 (m, 1H), 2.12 (s, 3H), 1.52-1.45 (m, 2H), 1.29-1.24 (m, 10H), 0.87-0.84 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 170.1, 143.5, 138.3, 129.3, 128.9, 128.2, 126.7, 126.1, 125.6, 122.4, 108.7, 80.8, 62.0, 53.1, 40.4, 37.2, 36.3, 31.9, 29.33, 29.31, 27.3, 27.0, 22.7, 21.2, 14.2; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{28}H_{36}NO_3S$: 466.2410, found: 466.2410; FT-IR (neat) 3028, 2925, 2854, 1746, 1711, 1608, 1487, 1466, 1360, 1224, 1109, 1021, 752, 699, 486 cm^{-1}.



2'-Benzyl-1-octyl-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-4'-ol (±)-7. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; thick liquid; yield 86% (35 mg); yellow thick liquid; mixture of diastereomers (3.7:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* =

7.5 Hz, 1H, major), 7.24-7.20 (m, 2H, major), 7.19-7.14 (m, 2H, major), 7.13-7.11 (m, 2H, major), 6.71 (t, J = 7.5 Hz, 1H, major), 6.65-6.64 (m , 0.27H, minor), 6.50-6.49 (m, 1H, major), 4.45 (s, 0.27H, minor), 4.26 (s, 1H, major) 4.07 (d, J = 9.5 Hz, 0.27H, minor), 3.82-3.76 (m, 2H, major), 3.72-3.68 (m, 0.30H, minor), 3.49-3.46 (m, 0.27H, minor), 3.40-3.37 (m, 1H, major), 3.16-3.06 (m, 2.54H, major + minor), 3.04-2.98 (m, 1H, major), 2.97-2.90 (m, 1H, major), 2.89-2.83 (m, 0.27H, minor), 2.82-2.79 (m, 1H, major), 2.73-2.68 (m, 1H, major), 1.58-1.51 (m, 2.55H, major + minor), 1.37-1.23 (m, 12.73H, major + minor), 0.89-0.87 (m, 3.81H, major + minor), (The OH is not visible); ^{13}C NMR (150 MHz, $CDCl_3$) δ (major + minor) 153.3, 140.2, 138.1, 129.4, 129.1, 129.0, 128.93, 128.91, 128.5, 128.2, 127.1, 127.0, 126.5, 125.8, 124.8, 117.3, 116.8, 108.1, 107.5, 80.8, 79.0, 78.3, 63.8, 62.2, 58.6, 57.3, 56.1, 52.7, 48.8, 48.5, 38.3, 36.8, 33.8, 31.9, 29.8, 29.57, 29.54, 29.4, 27.37, 27.34, 27.1, 27.0, 22.8, 14.2 (four carbons of the minor isomer are overlapped) ; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{26}H_{36}NOS$: 410.2512, found: 410.2511; FT-IR (neat) 3382, 3027, 2923, 2852, 1739, 1601, 1489, 1460, 1371, 1262, 1156, 802, 740, 698, 489 cm^{-1}.

Crystal Structure and Data of (±)-3a

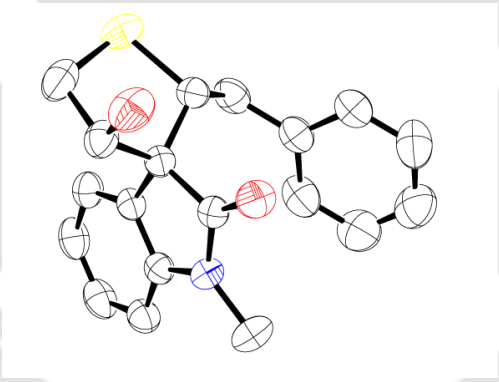


Figure 3. ORTEP diagram of 2'-benzyl-4'-hydroxy-1-methyl-4',5'-dihydro-2'H-spiro[indoline-3,3'-thiophen]-2-one (±)-**3a** (CCDC 2133256) with 50% ellipsoid. H-omitted for clarity.

Identification code	**(±)-3a**
Empirical formula	'C19 H19 N O2 S'
Formula weight	325.41
Crystal habit, colour	Needle/Colorless
Temperature, T/K	296 K
Wavelength, λ/Å	0.71073
Crystal system	'triclinic'
Space group	'P -1'

Unit cell dimensions	a = 8.9051(7) Å b = 9.7038(9) Å c = 10.1516(10) Å α = 109.993(3) β = 93.704(3) γ = 95.566(3)
Volume, V/Å^3	815.98(13)
Z	2
Calculated density, Mg·m^{-3}	1.324
Absorption coefficient, μ/mm^{-1}	0.208
F(000)	344
θ range for data collection	2.14 to 25°
Limiting indices	-10 ≤ h ≤ 10, –11 ≤ k ≤ 11, –12 ≤ l ≤ 12
Reflection collected / unique	2874/2153
Completeness to θ	100%
Max. and min. transmission	0.969 and 0.951
Refinement method	' SHELXL-2016/6 (Sheldrick, 2016) '
Data / restraints / parameters	2874/0/ 210
Goodness–of–fit on F^2	1.281
Final R indices [I>2sigma(I)]	R1 = 0.0753, wR2 = 0.2108
R indices (all data)	R1 = 0.0959, wR2 = 0.2304

1.5 References

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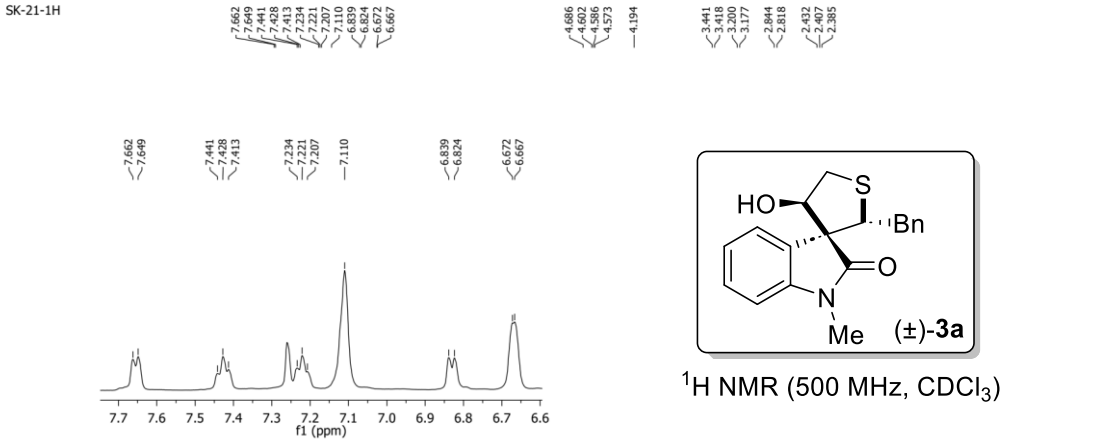
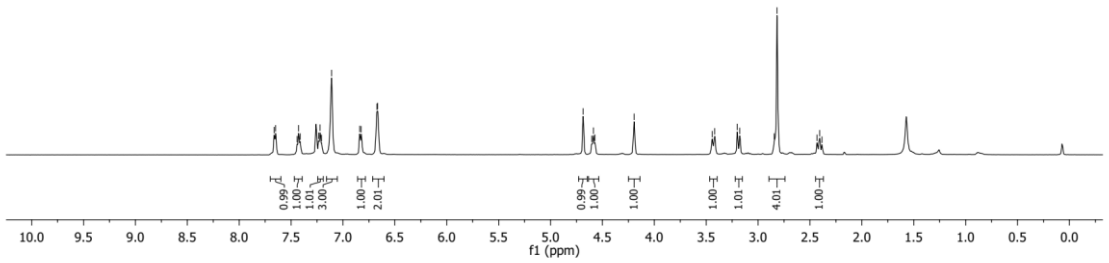
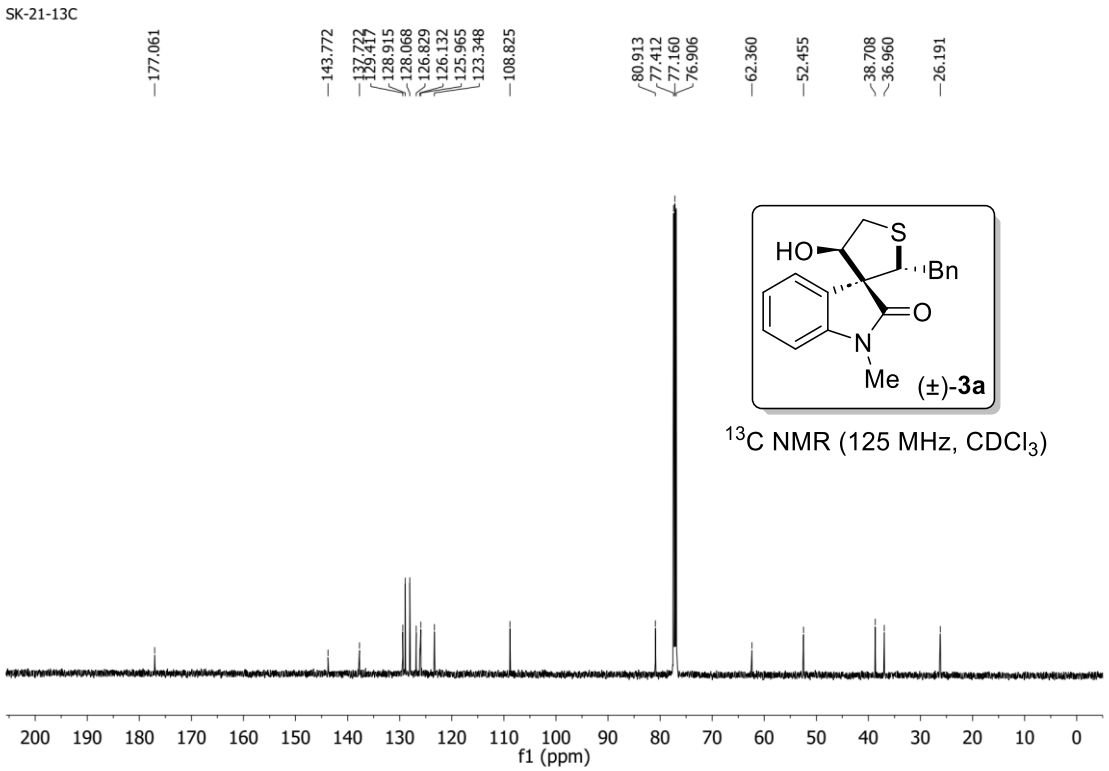
1.6 Selected NMR Spectra



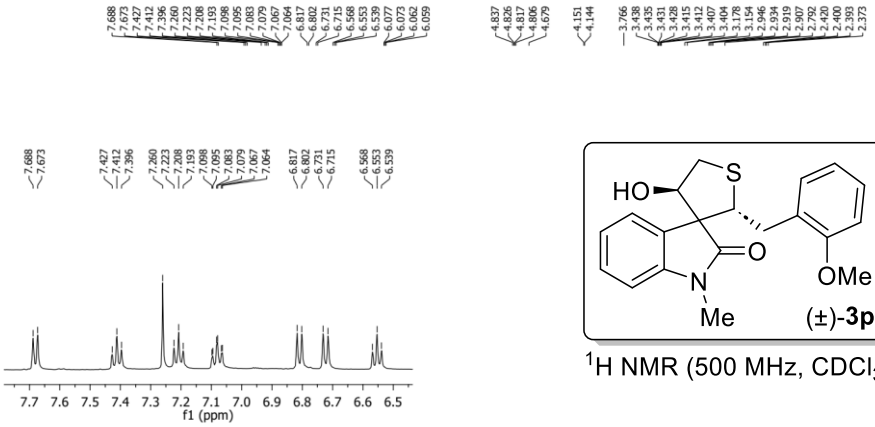
^{1}H NMR (500 MHz, $CDCl_3$)





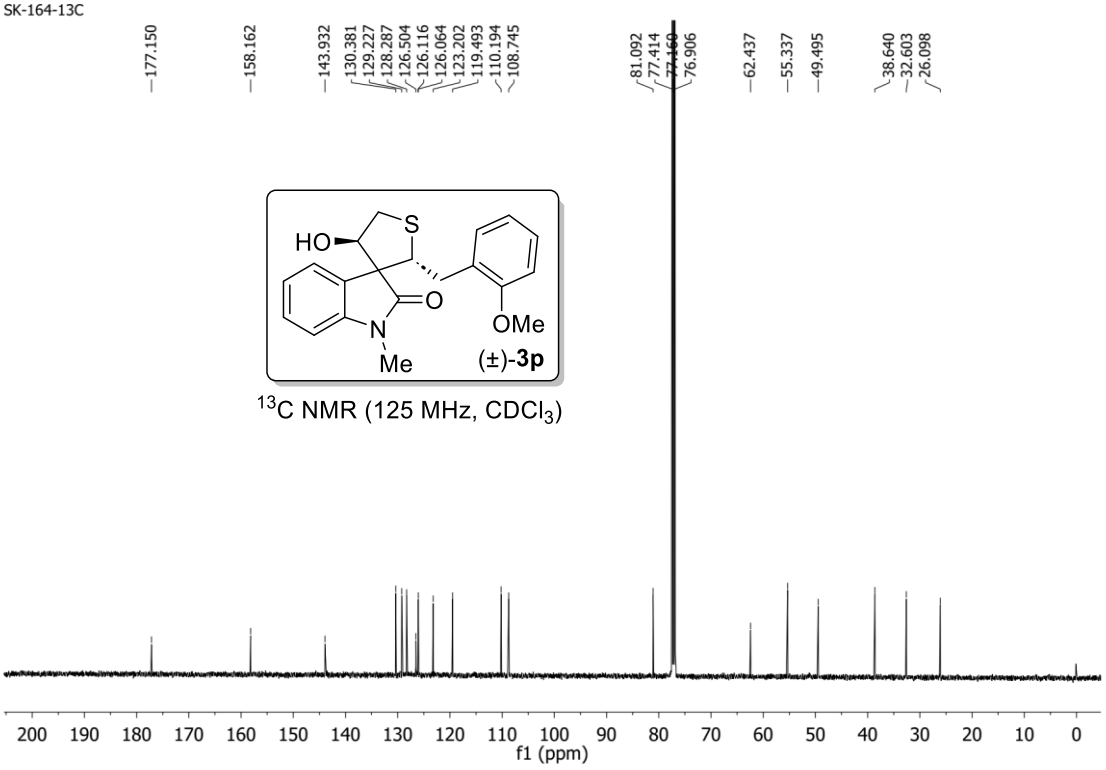
^{13}C NMR (125 MHz, $CDCl_3$)

SK-164-1H

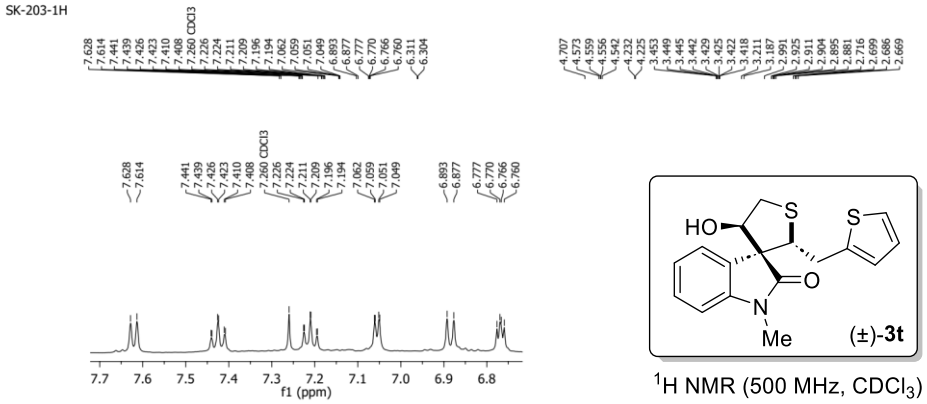


^{1}H NMR (500 MHz, $CDCl_3$)

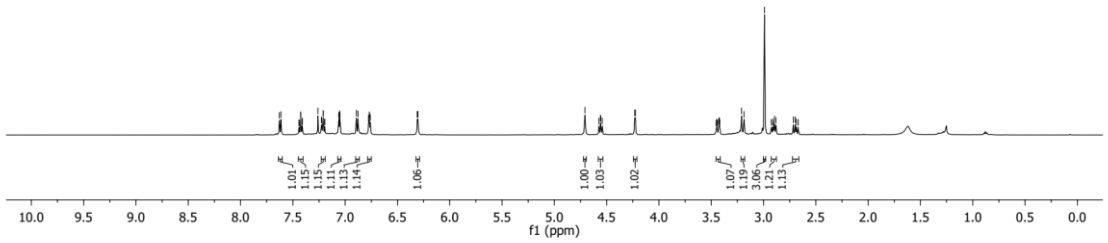
SK-164-13C

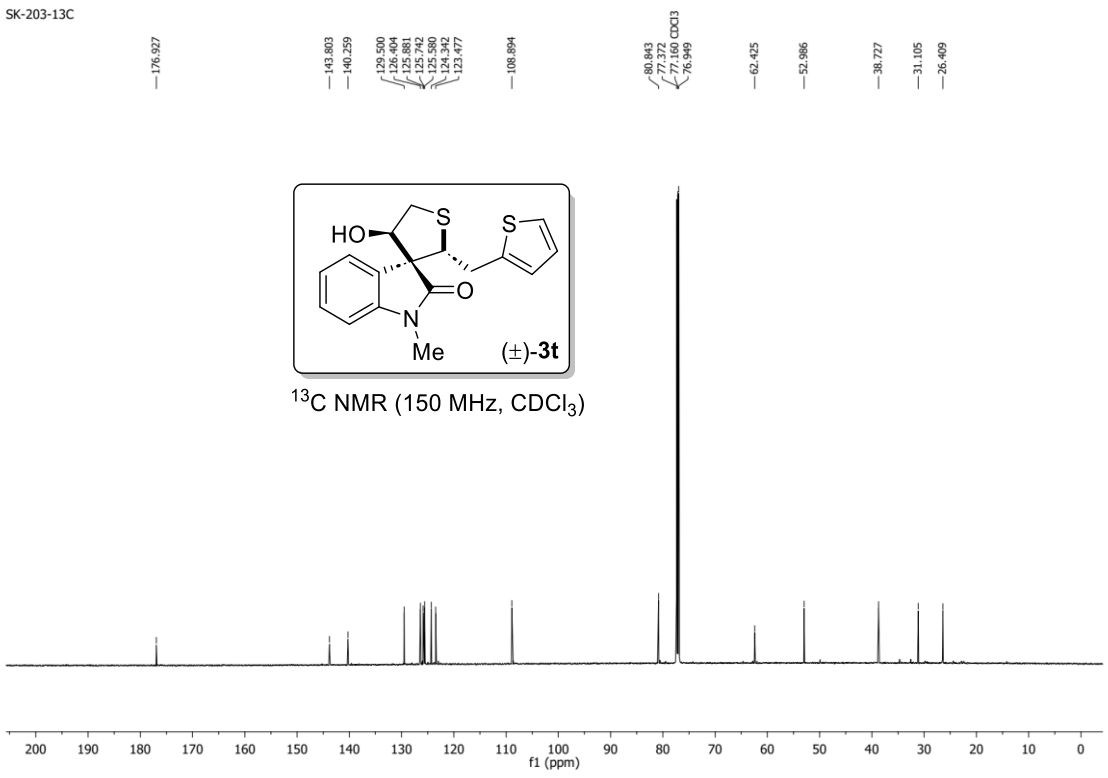


^{13}C NMR (125 MHz, $CDCl_3$)



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

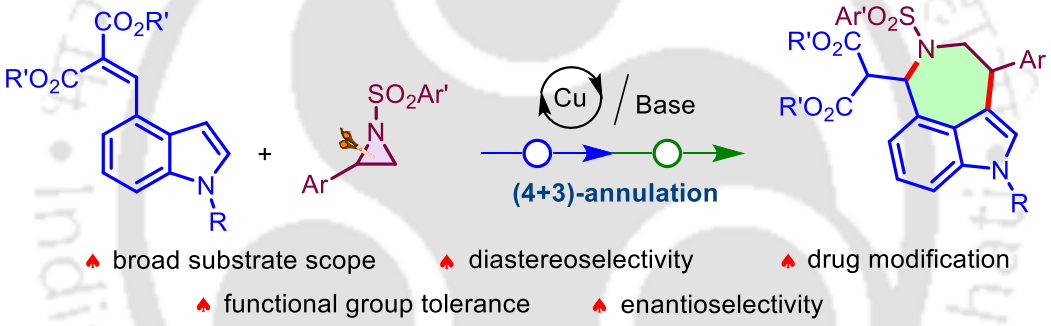




^{13}C NMR (150 MHz, $CDCl_3$)

Chapter II

Stereoselective Cu(II)-Catalyzed Tandem (4+3)-Annulation of Aziridines to Access Fused Azepinoindoles



♠ broad substrate scope ♠ diastereoselectivity ♠ drug modification

♠ functional group tolerance ♠ enantioselectivity

Org. Lett. **2023**, *25*, 8850.

Stereoselective Cu(II)-Catalyzed Tandem (4+3)-Annulation of Aziridines to Access Fused Azepinoindoles

Amongst the innumerable heterocycles that constitute the core-motif in natural products and pharmaceuticals, aza-heterocycles have garnered significant attention and are highly valued for their prominent roles in the field of chemical biology.[1] Unambiguously, in this domain, the never-ending documentation of seven-membered aza-heterocycles has led to significant research progresses that serve as pertinent guidelines for the generation of annulation strategies towards their wide ranging synthesis (Figure 1).[2] Although significant progress has been achieved in synthesising five- and six-membered ring systems, strategies for constructing seven-membered rings, particularly, nitrogen-containing heterocycles, are still comparatively underdeveloped.[3,4] This can be owed to their relative instability, non-bonding interactions as well as unfavourable entropic and enthalpic factors.[4] Consequently, the synthesis of fused azepine analogues using readily available precursors, while minimising both atom-usage and reaction steps continues to be a highly sought-after goal. In this context, utilizing strained rings as viable building blocks[5], molecular complexities can be achieved by exploiting their ability to act as a 1,3-zwitterion in presence of Lewis acids. Thus, aziridines, the smallest aza-heterocycles, can be used as nitrogen-embedded three atom synthons for accessing heterocycles *via* concerted cycloaddition or cascade ring-opening/cyclization pathway.[6] Thus, introducing a Michael acceptor at the C4-position of indole can facilitate a regioselective ring-opening, followed by a base-induced cyclization, yielding a variety of fused azepinoindole frameworks. This chapter, thus, focuses on a stereoselective Cu-catalyzed tandem (4+3)-annulation of aziridines with 4-vinyl indoles, suppressing a (3+2) Friedel-Crafts/Mannich cascade. The key features include the substrate scope, drug modification and a study on the asymmetric version that gave the desired optically active products in up to 90% ee.

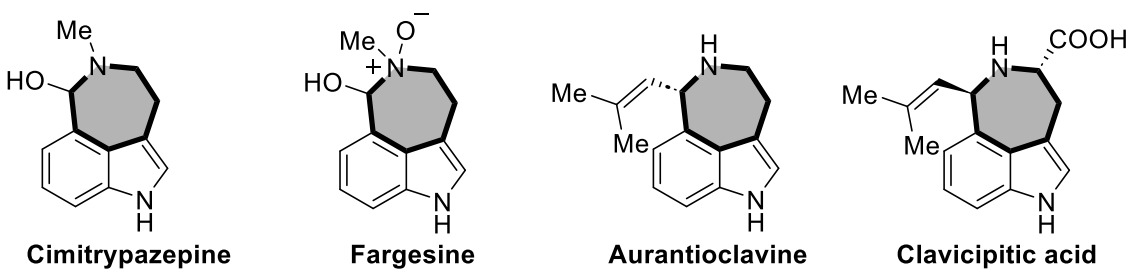
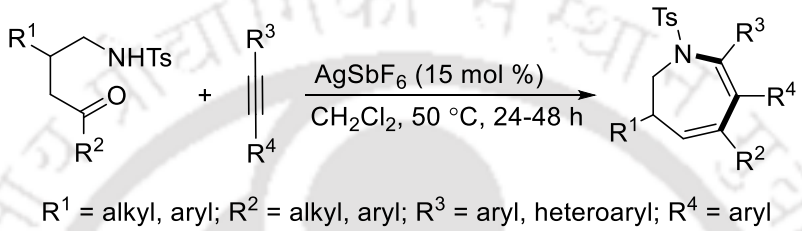


Figure 1. Representative Examples of Bio-active Azepinoindole Alkaloids

2.1 Literature

2.1.1 Ag-Catalyzed (5+2)-Cycloaddition

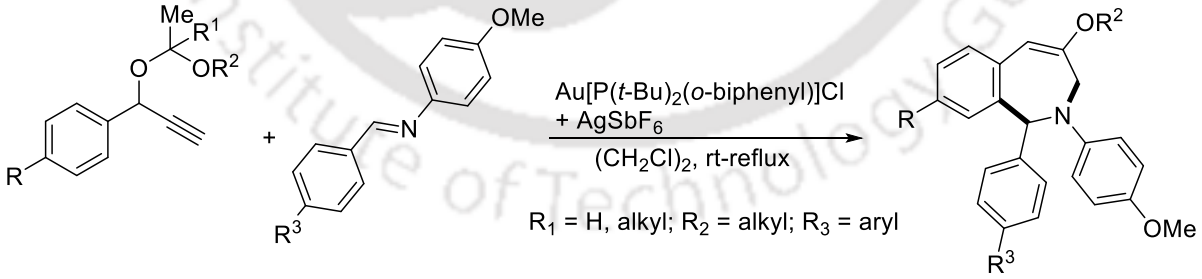
Li and co-workers developed an efficient method for generating 2,3-dihydro-1H-azepines, through the Ag-catalyzed (5+2)-cycloaddition of γ-amino ketones with alkynes (Scheme 1).[7] This intermolecular (5+2)-cycloaddition exhibits broad substrate scope, forming four chemical bonds in a single step, generating seven-membered ring systems through the release of H_2O as the by-product.



Scheme 1. Ag-Catalyzed (5+2)-Cycloaddition of γ-Amino Ketones with Alkynes

2.1.2 Au-Catalyzed (5+2)-Cycloaddition

The Fiksdahl group presented a Au(I)-catalyzed formal (2+5)-cycloaddition of phenylpropargyl acetals and benzaldimines to afford benz[*c*]azepin-4-ol (Scheme 2).[8] The protocol involves a cascade reaction, including a nucleophilic benzaldimine N-attack on the reactive phenylpropargyl-gold(I) carbenoid complex. A successive deauration promotes ring closure by 1,7-electrocyclization through an intramolecular Pictet-Spengler-type reaction.

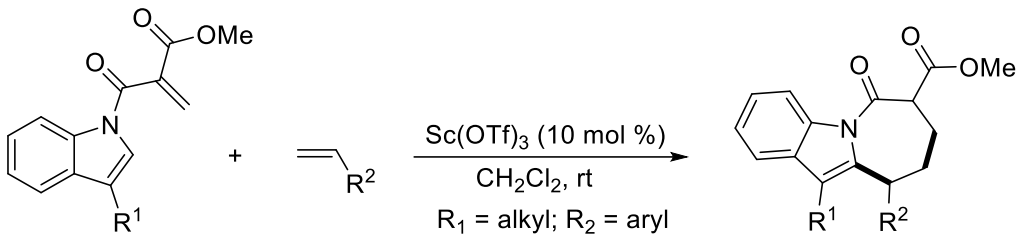


Scheme 2. Au-Catalyzed Formal (5+2)-Cycloaddition of Phenylpropargyl Acetals with Aldimines

2.1.3 Sc-Catalyzed (5+2)-Cycloaddition

The France group developed a tandem (5+2)-cycloaddition to access azepino[1,2-a]indoles under Sc-catalysis (Scheme 3).[9] The reaction goes *via* an initial formal (2+2)-cycloaddition

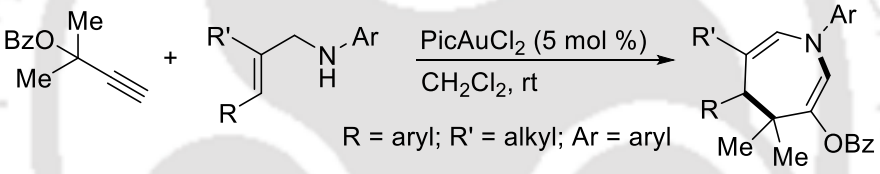
followed by a cyclobutane ring-opening cyclization. The substrates were obtained in good to excellent yields and diastereomeric ratios.



Scheme 3. Sc-Catalyzed (5+2)-Cycloaddition to Access Azepino[1,2-*a*]indoles

2.1.4 Au-Catalyzed Intermolecular (4+3)-Annulation

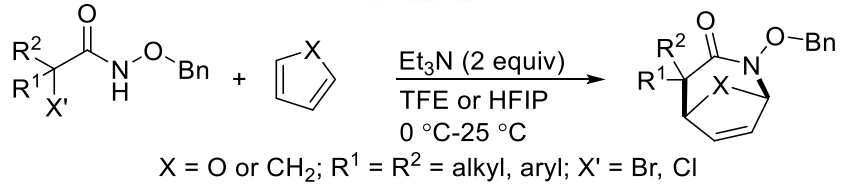
Toste and co-workers demonstrated a Au(III)-catalyzed intermolecular (4+3)-annulation of propargyl esters and imines (Scheme 4).[10] The outlined method emphasizes the formation of an allyl-gold intermediate generated from a gold stabilized vinylcarbenoid and its subsequent electrophilic trapping to afford the seven-membered nitrogen containing heterocycles.



Scheme 4. Synthesis of Azepines by Au-Catalyzed (4+3)-Annulation

2.1.5 Aza-(4+3)-Cycloaddition involving Aza-Oxyallyl Cations

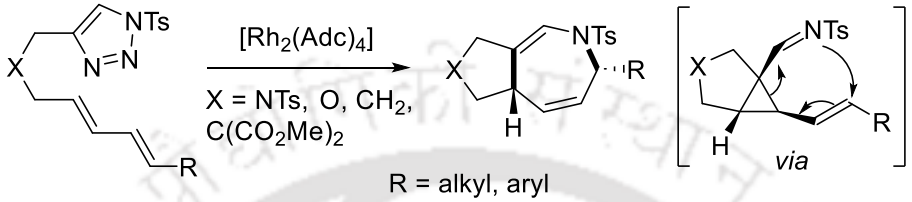
The Jeffery group portrayed an aza-(4+3)-cycloaddition of azaoxyallyl cationic intermediates and cyclic dienes (Scheme 5).[11] The generation of the active reaction intermediate by dehydrohalogenation of haloamides and its further reaction leads to generating diversified bridged seven-membered heterocycles in moderate to good yields and diastereoselectivities.



Scheme 5. Aza-(4+3)-Cycloaddition of Putative Aza-oxyallyl Cationic Intermediates

2.1.6 Tandem Rh-Catalyzed Intramolecular Cyclization of Dienyltriazoles

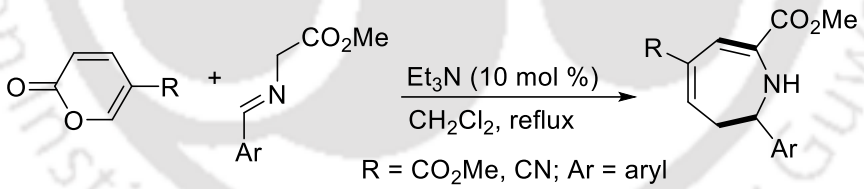
The Sarpong group disclosed a Rh-catalyzed intramolecular cyclization for producing fused dihydroazepines from 1-sulfonyl-1,2,3-triazoles (Scheme 6).[12] The reaction goes *via* the formation of a transient 1-imino-2-vinylcyclopropane intermediate generated through the intramolecular cyclopropanation of an *α*-imino Rh(II)carbenoid. A subsequent 1-aza-Cope rearrangement generates the target fused dihydroazepine derivatives.



Scheme 6. Synthesis of Fused Azepines Using Rh(II)-Catalyzed Cyclopropanation/1-Aza-Cope Rearrangement

2.1.7 Formal (4+3)-Annulation of Methyl Coumalates with Imine Esters

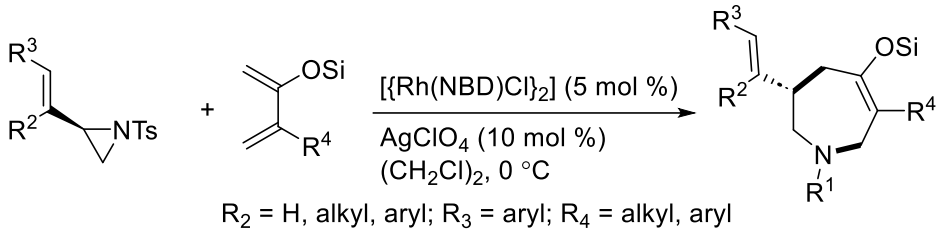
A tandem formal (4+3)-cycloaddition/decarboxylation/isomerization of methyl coumalates with imine esters was developed by the Wang group. Utilizing Et_3N as a mild base, the reaction proceeds efficiently to afford a series of densely functionalized seven-membered heterocyclic azepine derivatives (Scheme 7).[13]



Scheme 7. Formal (4+3)-Annulation/Decarboxylation/Isomerization of Methyl Coumalates with Imine Esters

2.1.8 Rh-Catalyzed Intermolecular Aza-(4+3)-Cycloaddition of Vinyl Aziridines and Dienes

The Zhang group demonstrated an intermolecular (4+3)-annulation of vinyl aziridines with silyl dienol ethers under Rh-catalysis to afford functionalized azepines (Scheme 8).[14] The use of readily accessible substrates, mild reaction conditions and selectivity are the salient features of the protocol.



Scheme 8. Rh-Catalyzed Intermolecular (4+3)-Annulation of Vinyl Aziridines

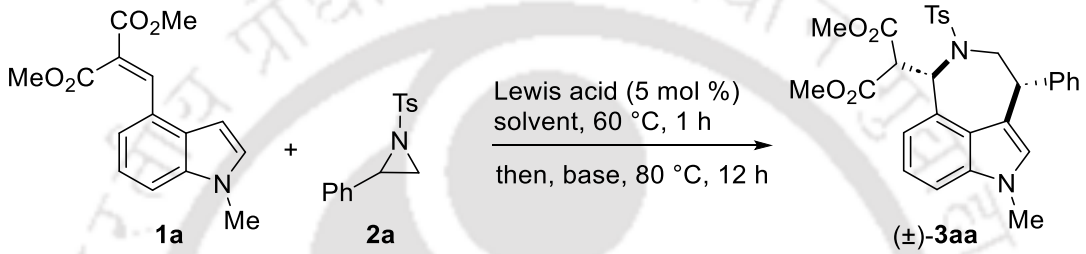
In view of the literature reports presented above and the research gap pertaining to the synthesis of seven-membered N-heterocycles, we aimed towards the strategic utilization of strained ring systems as versatile building blocks. The combination of ring strain and intrinsic reactivity inherent to these frameworks would provide an opportunity to design efficient methodologies for obtaining structurally diverse indole fused azepine motifs. Through this study, we seek to achieve diastereoselective access to complex heterocyclic architectures and thereby expanding the synthetic scope for compounds of significant potential in medicinal chemistry.

2.2 Present Study

This chapter describes a stereoselective (4+3)-cycloaddition of 4-vinyl indoles with aziridines to afford tricyclic fused azepinoindoles. We commenced our optimization employing indole **1a** and 2-phenyl-1-tosyl aziridine **2a** as the representative substrates utilizing a series of Lewis acids, bases, and solvents (Table 1). Initial studies showed that (±)-**3aa** was obtained in 52% yield when the reaction was performed with 5 mol % $Yb(OTf)_3$ and 1.2 equiv K_2CO_3 in $(CH_2Cl)_2$ as the solvent (entry 1). Further screening using $Cu(OTf)_2$, $Sc(OTf)_3$ and $Zn(OTf)_2$ showed that with the former, the yield was enhanced to 75% with >10:1 dr, while others did not confer any noticeable change (entries 2-4). Examining a series of other Cu(II) salts viz., $Cu(OAc)_2$, $CuBr_2$, $CuCl_2$ and $Cu(acac)_2$ revealed that in all these cases, the yield was quite inferior in comparison to $Cu(OTf)_2$ (entries 5-8). In view of the reactivity enhancement property of chelating ligands in copper-catalyzed reactions,[15] we surveyed a series of ligands **L1-4** with $Cu(OTf)_2$ as the optimized Lewis acid (entries 9-12). However, ligand employment failed to deliver any prominent outcome. Next, amongst the bases studied, K_2CO_3 demonstrated superior results over Na_2CO_3, Cs_2CO_3, *t*-BuOK, DBU and DABCO (entries 13-17). Solvents like CH_2Cl_2, THF, toluene, CH_3CN and CH_3OH proved ineffective, producing <65% yield (entries 18-22). Control experiments carried out in the absence of any catalyst or base ruled out any possibility of the ring-opening/annulation transformation (entries 23-24).

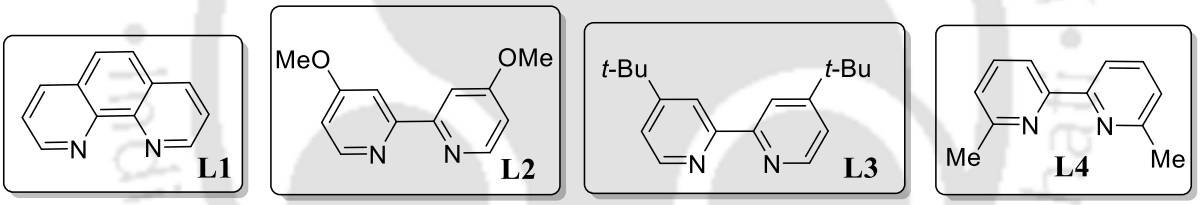
With established optimized conditions, the scope of the methodology was subsequently applied to a series of aziridines **2b-x** with **1a** as the standard substrate (Table 2). Aziridine **2b** bearing 2-fluoro substituent underwent reaction to afford (±)-**3ab** in 69% yield. Further, aziridines substituted at the 3-position of the aryl ring with bromo **2c**, chloro **2d**, and methyl **2e** afforded (±)-**3ac-ae** in 63-67% yields and up to >14:1 dr. Strong electron-withdrawing **2f** coupled efficiently to give (±)-**3af** in 77% yield (>13:1 dr). Comparable outcomes were observed with aziridines bearing substituents at the 4-position of the aryl ring with bromo **2g**, fluoro **2h**, methyl **2i**, acetoxy **2j**, phenyl **2k**, and trifluoromethyl **2l**, giving (±)-**3ag-al** in 68-80

Table 1. Optimization of the Reaction Conditions[a,b,c]



Entry	Lewis acid (5 mol %)	Base	Solvent	Yield (%)[b]
1	$Yb(OTf)_3$	K_2CO_3	$(CH_2Cl)_2$	52
2	$Sc(OTf)_3$	K_2CO_3	$(CH_2Cl)_2$	71
3	**$Cu(OTf)_2$**	**K_2CO_3**	**$(CH_2Cl)_2$**	**75**
4	$Zn(OTf)_2$	K_2CO_3	$(CH_2Cl)_2$	47
5	$Cu(OAc)_2$	K_2CO_3	$(CH_2Cl)_2$	n.d.
6	$CuBr_2$	K_2CO_3	$(CH_2Cl)_2$	trace
7	$CuCl_2$	K_2CO_3	$(CH_2Cl)_2$	n.d.
8	$Cu(acac)_2$	K_2CO_3	$(CH_2Cl)_2$	15
9	$Cu(OTf)_2$, **L1**	K_2CO_3	$(CH_2Cl)_2$	trace
10	$Cu(OTf)_2$, **L2**	K_2CO_3	$(CH_2Cl)_2$	trace
11	$Cu(OTf)_2$, **L3**	K_2CO_3	$(CH_2Cl)_2$	25
12	$Cu(OTf)_2$, **L4**	K_2CO_3	$(CH_2Cl)_2$	trace
13	$Cu(OTf)_2$	Na_2CO_3	$(CH_2Cl)_2$	23

14	$Cu(OTf)_2$	Cs_2CO_3	$(CH_2Cl)_2$	trace
15	$Cu(OTf)_2$	*t*-BuOK	$(CH_2Cl)_2$	n.d.
16	$Cu(OTf)_2$	DBU	$(CH_2Cl)_2$	48
17	$Cu(OTf)_2$	DABCO	$(CH_2Cl)_2$	53
18[c]	$Cu(OTf)_2$	K_2CO_3	CH_2Cl_2	31
19	$Cu(OTf)_2$	K_2CO_3	THF	34
20	$Cu(OTf)_2$	K_2CO_3	Toluene	56
21	$Cu(OTf)_2$	K_2CO_3	CH_3CN	65
22	$Cu(OTf)_2$	K_2CO_3	CH_3OH	trace
23	$Cu(OTf)_2$	-	$(CH_2Cl)_2$	n.d.
24	-	K_2CO_3	$(CH_2Cl)_2$	n.d.

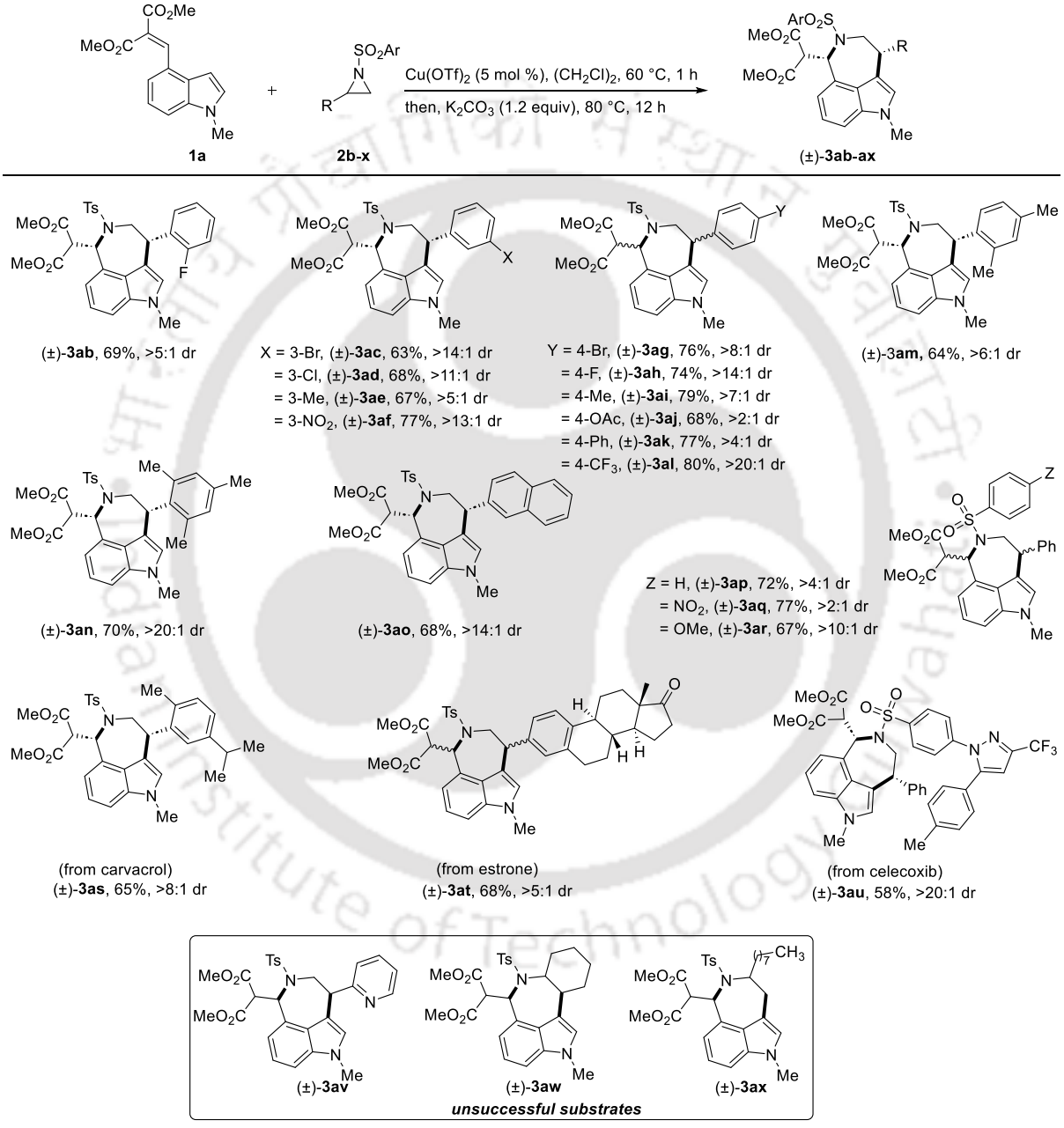


[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), $Cu(OTf)_2$ (5 mol %), $(CH_2Cl)_2$ (2 mL), 60 °C, 1 h; then, K_2CO_3 (0.12 mmol), 80 °C, 12 h. [b]Isolated yield. [c]Reaction temperature (50 °C). n.d. = not detected.

% yields with up to >20:1 dr. The stereochemistry of (±)-**3ag** was determined using a single crystal X-ray analysis (CCDC 2299116). Moreover, di- and trimethyl substituted aziridines **2m** and **2n** were amenable, delivering (±)-**3am** and (±)-**3an** in 64 and 70% yields, respectively. Notably, 2-naphthyl substituted aziridine **2o** resulted (±)-**3ao** in 68% yield (>14:1 dr). Next, the reaction conditions were applied to a set of aziridines bearing different N-sulfonyl aryl substitutions. N-sulfonylphenyl **2p** delivered (±)-**3ap** in 72% yield, while aziridines with substitution at the 4-position of the N-sulfonyl aryl ring with nitro **2q** and methoxy **2r** groups were tolerated to give the annulated (±)-**3aq** and (±)-**3ar** in 77% and 67% yields, respectively. Further, aziridines derived from bio-active and drug molecules, such as, the anti-oxidant carvacrol derivative **2s** and estrone **2t** afforded the target (±)-**3as** and (±)-**3at** in 65% and 68%

yields respectively. Intriguingly, aziridine derived from nonsteroidal anti-inflammatory drug celecoxib **2u** reacted efficiently to furnish (±)-**3au** in 58%. On the contrary, 2-pyridyl aziridine **2v**, meso-cyclohexyl derived **2w** and octyl derived **2x** remained unsuccessful in affording the target heterocycles.

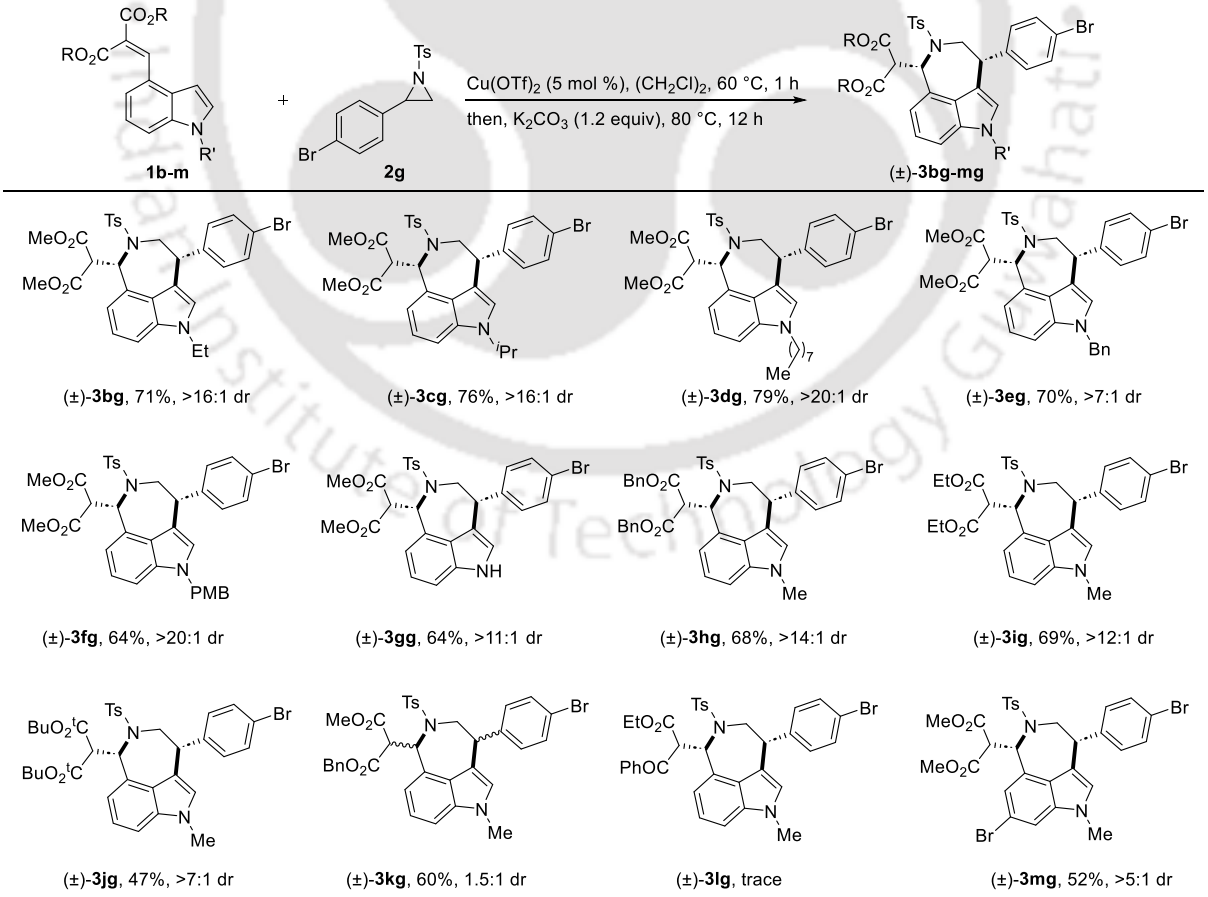
Table 2. Scope of Aziridines[a,b,c]



[a]Reaction conditions: **1a** (0.1 mmol), **2b-x** (0.12 mmol), $Cu(OTf)_2$ (5 mol %), $(CH_2Cl)_2$ (2 mL), 60 °C, 1 h; then, K_2CO_3 (0.12 mmol), 80 °C, 12 h. [b]Isolated yield. [c]The dr was assigned by ^1H NMR analysis.

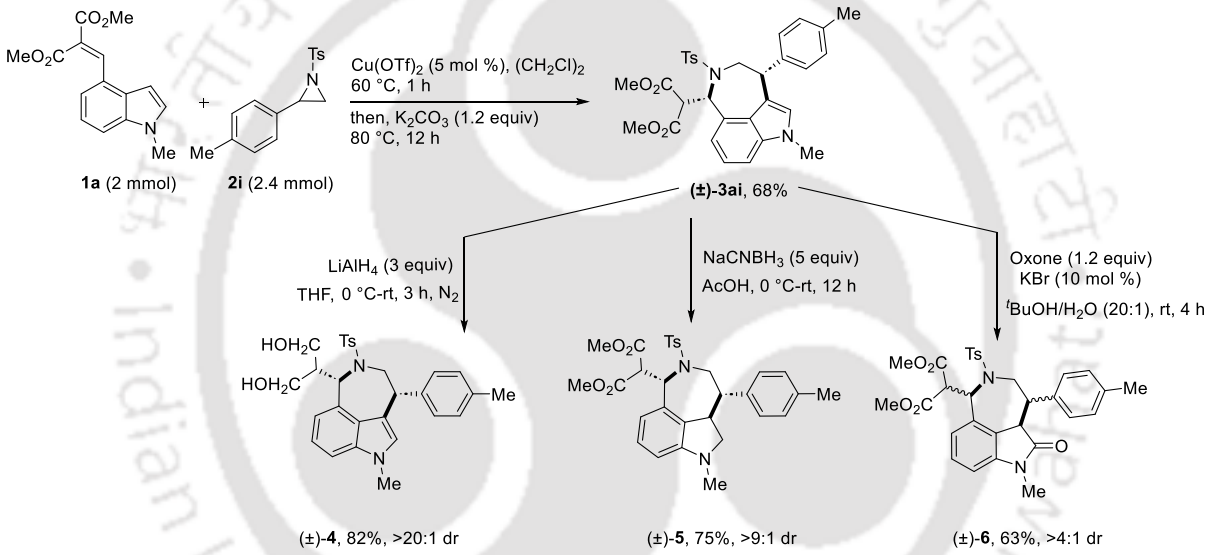
Encouraged by the effectiveness of the described annulation protocol, we moved towards variation of a series of indoles **1b-m** with **2g** as the standard substrate (Table 3). N-Alkyl substituted indoles bearing ethyl **1b**, isopropyl **1c**, and long chain octyl **1d** were compatible, furnishing (±)-**3bg-dg** in 71-79% yields and >16:1 to >20:1 dr. Moreover, N-benzyl **1e**, and N-PMB **1f** were compatible in delivering the target (±)-**3eg** (70% yield, >7:1 dr) and (±)-**3fg** (64% yield, >20:1 dr), respectively. However, N-Boc substituted **1g** underwent deprotection under the standard reaction conditions to afford (±)-**3gg** in 64% yield and >11:1 dr. In a series of indoles **1h-j** having diverse substitution at the malonate center such as Bn, Et and ^{t}Bu, the intended products (±)-**3hg-jg** were formed in moderate to good yields and diastereomeric ratios. Significant steric interactions caused by the bulky ^{t}Bu groups led to a reduced yield in case of (±)-**3jg**. Unsymmetrically substituted alkylidene malonate **1k** was facile, delivering (±)-**3kg** in 60% yield as a 1.5:1 mixture of diastereomers, while (±)-**3lg** containing a *β*-keto ester malonate was obtained only in a trace amount. Moreover, indole bearing substitution on the benzene core with 5-bromo reacted to give (±)-**3mg** in 52% yield and >5:1 dr.

Table 3. Scope of Indoles[a,b,c]



[a]Reaction conditions: **1b-m** (0.1 mmol), **2g** (0.12 mmol), $Cu(OTf)_2$ (5 mol %), $(CH_2Cl)_2$ (2 mL), 60 °C, 1 h; then, K_2CO_3 (0.12 mmol), 80 °C, 12 h. [b]Isolated yield. [c]The dr was assigned by ^1H NMR analysis.

Next, we moved towards studying the applicability of the annulated product by performing scale-up synthesis and post synthetic transformations (Scheme 9). The reaction carried out on a 2 mmol scale utilising **1a** and **2i** as the representative examples, afforded (±)-**3ai** in 68% yield. Reduction of the diester in presence of $LiAlH_4$ gave the diol (±)-**4** in 82% yield with a >20:1 dr. Using $NaCNBH_3$, (±)-**3ai** could be reduced to the indoline (±)-**5** in 75% yield. Further, an Oxone oxidation in presence of KBr resulted transformation of (±)-**3ai** to (±)-**6** (63% yield, >4:1 dr).

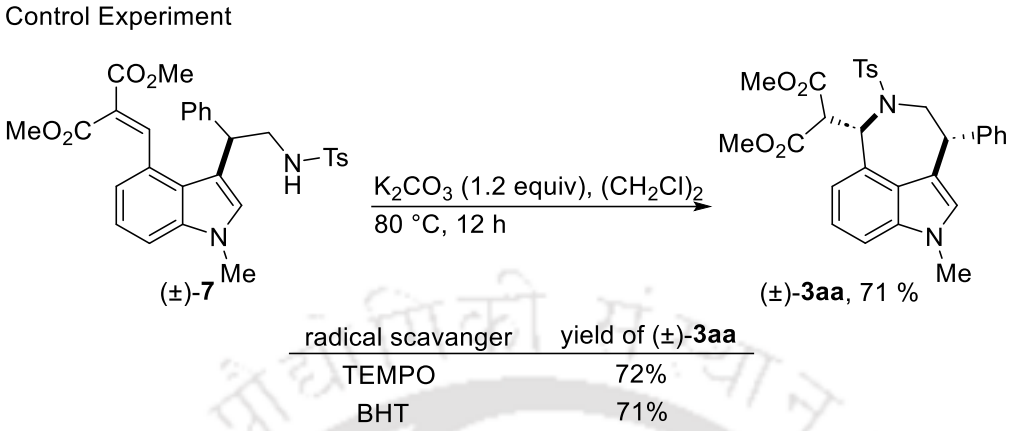


Scheme 9. Scale-up and Post-Synthetic Transformations

Control experiments carried out in presence of radical scavengers, BHT and TEMPO did not show significant decrement in the overall yield, thus, suggesting an ionic pathway (Scheme 10). Also, (±)-**7** was isolated and subjected to the optimised reaction conditions, resulting (±)-**3aa** in 71% yield, thus confirming a cascade pathway that goes through the ring-opening intermediate (±)-**7**.

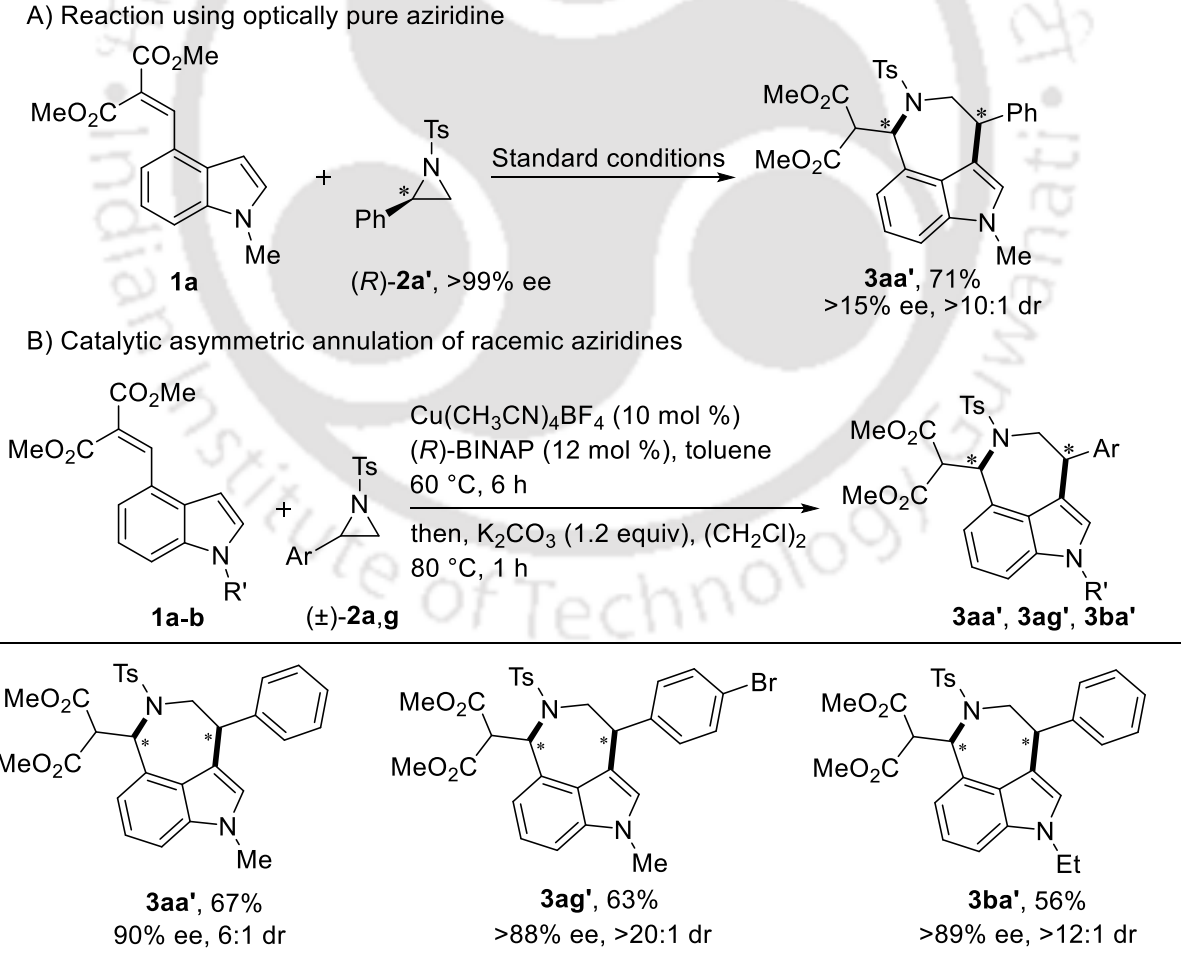
Next, the stereochemical aspects of the protocol were studied by performing the reaction of (±)-**1a** with (*R*)-2-phenyl-1-tosylaziridine **2a'** as the representative substrate (Table 5A). Annulation occurred to deliver **3aa'** in >15% ee, which suggests that the reaction of aziridines

involves predominantly S_N1 pathway. We next shifted our focus towards examining the enantioselective version (Table 5B). Gratifyingly, a study using (*R*)-BINAP as the ligand with



Scheme 10. Mechanistic Investigations

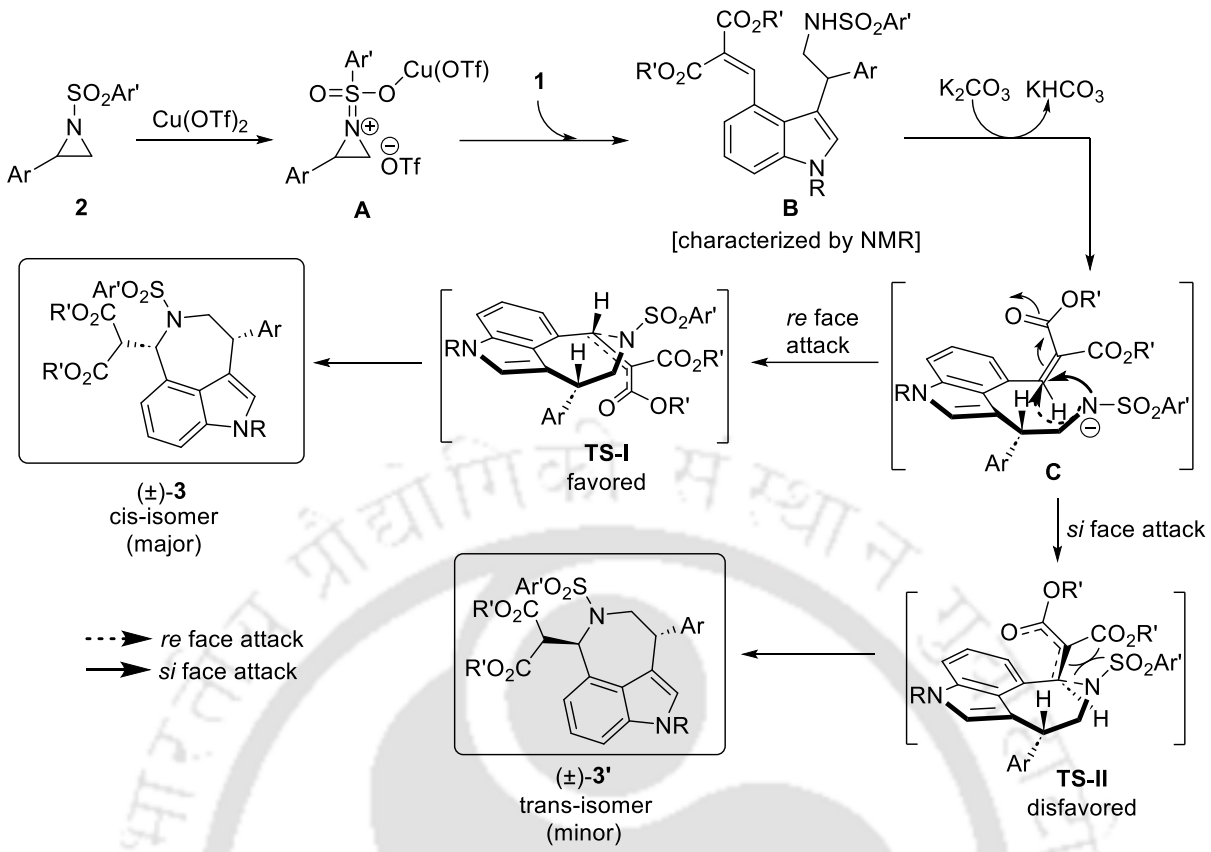
Table 5. Catalytic Asymmetric Synthesis[a,b,c]



[a]Reaction conditions: **1a-b** (0.1 mmol), **2a**, **g** (0.12 mmol), $Cu(CH_3CN)_4BF_4$ (10 mol %), (*R*)-BINAP (12 mol %), toluene, 60 °C, 5 h; then, K_2CO_3 (0.12 mmol), $(CH_2Cl)_2$, 80 °C, 1 h. [b]Isolated yield. [c]The dr and ee were assigned by HPLC analysis.

$Cu(CH_3CN)_4BF_4$, employing (±)-**1a** and (±)-**2a** as the representative substrates, afforded **3aa'** in 90% ee and 6:1 dr.[16] The generality of the enantioselective reaction was further exemplified using indoles (±)-**1a-b** and aziridines (±)-**2a** and (±)-**2g**, to deliver the target scaffolds **3ag'** and **3ba'** in 88% ee (>20:1 dr) and 89% ee (>12:1 dr), respectively. These initial results indicate potential for further application of the procedure towards the construction of the optically active azepinoindole motifs.

Mechanistic studies and literature precedents[17] suggest that initial activation of the aziridine ring in presence of the Lewis acid generates intermediate **A** that can further lead to a Friedel-Crafts reaction of **1** to generate the open chain intermediate **B** (Scheme 11). Successively, a base promoted deprotonation produces the transient intermediate **C**. The intramolecular aza-Micheal addition of **C** on the alkylidene malonate delivers the target heterocycle **3**. The obtained diastereoselectivity can be explained by comparing the two possible transition states. In **TS-I**, selective aza-Micheal addition of the aziridine to the re-face of the alkylidene malonate delivers (±)-**3** as the major cis-isomer, while severe gauche interactions between the N-tosyl group and ester moiety disfavours the formation of the trans-isomer (±)-**3′**.



Scheme 11. Plausible Mechanism

In conclusion, we have described a highly efficient approach for the cascade (4+3)-annulation of aziridines with 4-alkylidene indole malonates to achieve varied azepinoindole motifs in good to high yields with good functional group tolerance and diastereoselectivities. Diversification of drug molecules and natural products as well as a preliminary asymmetric study proceeded smoothly to deliver the optically active annulated products.

2.3 Experimental Section

General Information. 1H-Indole-4-carbaldehyde, styrenes, malonates, $Cu(OTf)_2$, $Cu(CH_3CN)_4BF_4$, (*R*)-BINAP, $LiAlH_4$, $NaCNBH_3$ and Oxone were purchased from Aldrich and used as received. Chloramine-T trihydrate and K_2CO_3 were purchased from Merck, and used as received. The solvents were dried prior to use according to the standard procedure. SRL silica gel G/GF 254 plates were used for analytical TLC and SRL silica gel (100-200 mesh) was used for column chromatography. NMR (^1H, ^{13}C and ^{19}F) 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 of (±)-**3ag** 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-2019/1 (Göttingen, Germany). HPLC analysis has been carried out using Waters-2489 with Daicel Chiralcel AD-H column utilizing *iso*-propanol and hexane as eluent.

General Procedure for the Synthesis of Cycloadducts (±)-3aa-mg. Indole **1** (0.1 mmol, 1 equiv), aziridine **2** (0.12 mmol, 1.2 equiv) and $Cu(OTf)_2$ (0.005 mmol, 0.05 equiv, 2 mg) were stirred in $(CH_2Cl)_2$ (2 mL) at 60 °C for 1 h under nitrogen atmosphere. Then, K_2CO_3 (0.12 mmol, 1.2 equiv, 16 mg) was added and the resulting mixture was stirred at 80 °C for 12 h under nitrogen atmosphere. The reaction progress was monitored by TLC using ethyl acetate and hexane as an eluent. After completion, as monitored by TLC, the reaction mixture was allowed to cool to room temperature and diluted with CH_2Cl_2 (5 mL) and passed through a short pad of Celite using CH_2Cl_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 to afford (±)-**3**.

General Procedure for the Catalytic Asymmetric Synthesis of 3aa′, 3ag′ and 3ba′. To an oven dried round bottom flask, was added $Cu(CH_3CN)_4BF_4$ (0.01 mmol, 0.1 equiv, 3 mg) and (*R*)-BINAP (0.012 mmol, 0.12 equiv, 7 mg) under nitrogen atmosphere. Toluene (3 mL) was added and the mixture was allowed to stir at room temperature for 40 minutes. Then, aziridine **2** (0.12 mmol, 1.2 equiv) and indole **1** (0.1 mmol, 1 equiv) were added and the resulting mixture was allowed to stir at 60 °C for 5 h. After 5 h, the reaction mixture was diluted with EtOAc (5 mL) and passed through a short pad of Celite using EtOAc (10 mL). The solvent was evaporated and then, K_2CO_3 (0.24 mmol, 1.2 equiv) and $(CH_2Cl)_2$ (2 mL) were added and the reaction mixture was allowed to stir at 80 °C for 1h under nitrogen atmosphere. After completion, the reaction mixture was allowed to cool to room temperature and diluted with CH_2Cl_2 (5 mL) and passed through a short pad of Celite using CH_2Cl_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 to afford the **3′**. The enantiomeric excess was determined using chiral HPLC.

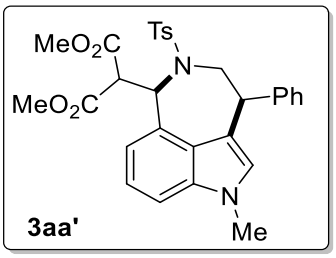
Scale-up Synthesis of (±)-**3ai**. Indole **1a** (2 mmol, 1 equiv, 546 mg), aziridine **2i** (2.4 mmol, 1.2 equiv, 655 mg) and $Cu(OTf)_2$ (0.01 mmol, 0.005 equiv, 36 mg) were stirred in $(CH_2Cl)_2$ (5 mL) at 60 °C for 1 h under nitrogen atmosphere. Then, K_2CO_3 (0.24 mmol, 1.2 equiv, 33 mg) was added and the resulting mixture was stirred at 80 °C for 12 h under nitrogen atmosphere. After completion, as monitored by TLC, the reaction mixture was allowed to cool to room temperature and diluted with CH_2Cl_2 (10 mL) and passed through a short pad of Celite using CH_2Cl_2 (20 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 to afford (±)-**3ai**.

Synthesis of (±)-**4**.[18] To a solution of (±)-**3ai** (0.1 mmol, 1equiv, 56 mg) in THF (2 mL) at 0 °C under nitrogen atmosphere, $LiAlH_4$ (0.3 mmol, 3 equiv, 11 mg) was added portion wise. The reaction mixture was then gradually moved to room temperature and allowed to stir for 3 h. After completion, as monitored by TLC, the reaction mixture was quenched with saturated aq. NH_4Cl (5 mL) and extracted with ethyl acetate (3 X 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using ethyl acetate and hexane as an eluent to afford (±)-**4**.

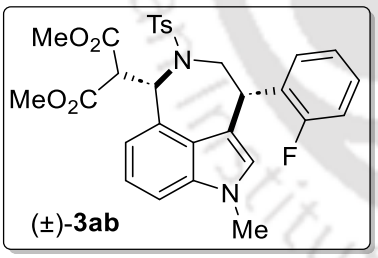
Synthesis of (±)-**5**.[19] To a solution of (±)-**3ai** (0.1 mmol, 1 equiv, 56 mg) in AcOH (5 mL) at 0 °C was added $NaBH_3CN$ (0.5 mmol, 5 equiv, 31 mg) portion wise. The reaction was allowed to stir at room temperature for 12 h. After complete consumption of the starting material, as monitored by TLC, saturated aq. NaOH (5 mL) was added slowly to the reaction mixture at 0 °C and extracted with ethyl acetate (3 X 10 mL). Subsequently, the combined organic layers were washed with brine (5 mL) and water (5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as an eluent to afford (±)-**5**.

Synthesis of (±)-**6**.[20] To a solution of (±)-**3ai** (0.1 mmol, 1 equiv, 56 mg) and KBr (0.01 mmol, 0.1 equiv, 2 mg) in $^tBuOH/H_2O$ (v/v 20:1) (2 mL) at room temperature, was added Oxone (0.12 mmol, 1.2 equiv, 37 mg) and allowed to stir for 4 h. After completion, as monitored by TLC, the reaction mixture was quenched with saturated aq. $Na_2S_2O_3$ (5 mL) and extracted with ethyl acetate (3 X 10 mL). The combined organic layers were washed with brine (5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as an eluent to afford (±)-**6**.

2.4 Characterization Data of the Products

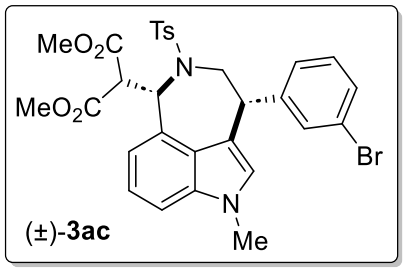


Dimethyl 2-(6-methyl-4-phenyl-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate 3aa′. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.54; colorless solid; mp 150-151 °C; yield 67% (36 mg); major diastereomer (>6:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 6.4 Hz, 2H), 7.37-7.31 (m, 5H), 7.15-7.12 (m, 3H), 7.07 (t, *J* = 6 Hz, 1H), 7.03-7.01 (m, 1H), 6.35-6.33 (m, 1H), 6.32 (s, 1H), 4.46-4.42 (m, 1H), 3.99-3.93 (m, 3H), 3.59 (s, 3H), 3.56 (s, 3H), 3.55 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 167.1, 143.2, 143.1, 138.0, 137.7, 132.2, 129.4, 128.9, 128.76, 128.75, 127.4, 127.1, 124.5, 120.8, 118.0, 116.8, 109.0, 61.2, 58.5, 52.8, 52.5, 50.8, 46.7, 32.8, 21.5; FT-IR (KBr) 2924, 2852, 1733, 1599, 1455, 1343, 1156, 1093, 810, 660, 545 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{30}H_{30}N_2NaO_6S$: 569.1717, found: 569.1717. $[\alpha]_D^{25}$ = -112.8 (c = 0.07, $CHCl_3$); HPLC: 90% ee [CHIRALCEL AD-H, hexane/^{i}PrOH = 80:20, flow rate: 1 mL/min, λ= 254 nm, t_R = 16.54 min (minor), 22.57 (major)].

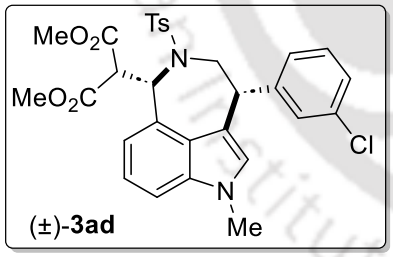


Dimethyl 2-(4-(2-fluorophenyl)-6-methyl-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3ab**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.45; red solid; mp 169-170 °C; yield 69% (39 mg); major diastereomer (>5:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8 Hz, 2H), 7.37-7.33 (m, 1H), 7.30-7.27 (m, 1H), 7.17-7.09 (m, 5H), 7.07-7.02 (m, 2H), 6.38 (d, *J* = 8 Hz, 1H), 6.33 (s, 1H), 4.77-4.70 (m, 1H), 4.02-4.00 (m, 3H), 3.61 (s, 6H), 3.39 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.4, 167.1, 143.1, 138.0, 137.8, 132.2, 130.5, 129.7, 129.4, 128.8, 128.1, 127.5, 124.49, 124.46, 121.4, 120.9, 118.1, 116.0, 115.6, 109.1, 61.3, 58.6, 52.9, 52.5, 32.8, 21.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ -115.6; FT-IR (KBr) 2953, 1733, 1490, 1455, 1434, 1343, 1237, 1157, 1092, 1044,

1020, 811, 760, 659, 546 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{30}H_{29}FN_2NaO_6S$: 587.1623, found: 587.1625.

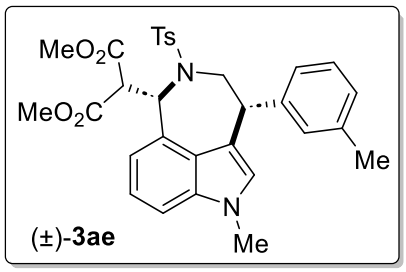


Dimethyl 2-(4-(3-bromophenyl)-6-methyl-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3ac**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.48; colorless solid; mp 154-155 °C; yield 63% (39 mg); major diastereomer (>14:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.47 (s, 1H), 7.44-7.42 (m, 1H), 7.29-7.27 (m, 1H), 7.25-7.21 (m, 1H), 7.18-7.14 (m, 3H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.04-7.02 (m, 1H), 6.354-6.352 (m, 1H), 6.33 (d, *J* = 7.6 Hz, 1H), 4.46-4.42 (m, 1H), 3.99-3.90 (m, 3H), 3.64 (s, 3H), 3.58 (s, 3H), 3.36 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 167.1, 145.7, 143.3, 137.9, 137.7, 132.2, 131.7, 130.44, 130.41, 129.5, 128.8, 127.58, 127.55, 124.5, 122.8, 121.0, 118.2, 116.1, 109.1, 61.2, 58.5, 52.9, 52.6, 50.8, 46.6, 32.9, 21.5; FT-IR (KBr) 2953, 2920, 1733, 1457, 1433, 1343, 1240, 1156, 1091, 983, 810, 747, 665, 545 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{30}H_{29}BrN_2NaO_6S$: 647.0822, found: 647.0826.

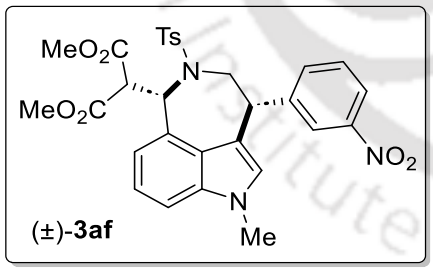


Dimethyl 2-(4-(3-chlorophenyl)-6-methyl-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3ad**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.46; colorless solid; mp 160-161 °C; yield 68% (40 mg); major diastereomer (>11:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.5 Hz, 2H), 7.32-7.28 (m, 3H), 7.24-7.22 (m, 1H), 7.18-7.14 (m, 3H), 7.09 (t, *J* = 7.5 Hz, 1H), 7.04-7.03 (m, 1H), 6.35 (s, 1H), 6.33 (d, *J* = 7.5 Hz, 1H), 4.47-4.43 (m, 1H), 3.99-3.89 (m, 3H), 3.64 (s, 3H), 3.58 (s, 3H), 3.36 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 167.1, 145.4, 143.3, 137.9, 137.7, 134.5, 132.2, 130.1, 129.5, 128.8, 127.5, 127.4, 127.1, 124.5, 121.0, 118.2, 116.1, 109.1, 61.2, 58.6, 52.9,

52.6, 50.8, 46.6, 32.9, 21.5; FT-IR (KBr) 2953, 2924, 1733, 1596, 1456, 1433, 1343, 1156, 1091, 811, 666, 593, 546 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{30}H_{29}ClN_2NaO_6S$: 603.1327, found: 603.1339.

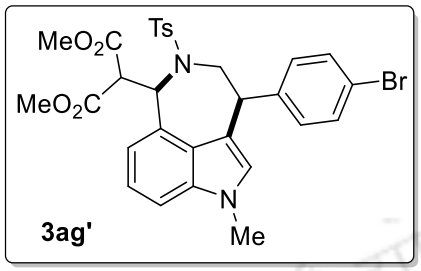


Dimethyl 2-(6-methyl-4-(m-tolyl)-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3ae**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.50; colorless solid; mp 175-176 °C; yield 67% (38 mg); major diastereomer (>5:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.5 Hz, 2H), 7.25-7.23 (m, 1H), 7.17-7.11 (m, 6H), 7.10-7.07 (m, 1H), 7.03-7.01 (m, 1H), 6.36-6.35 (m, 1H), 6.34 (d, *J* = 8 Hz, 1H), 4.43-4.40 (m, 1H), 3.96-3.89 (m, 3H), 3.62 (s, 3H), 3.57 (s, 3H), 3.38 (s, 3H), 2.37 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 167.1, 143.2, 143.1, 138.3, 138.0, 137.7, 132.3, 129.5, 129.4, 128.9, 128.6, 127.9, 127.5, 125.8, 124.5, 120.8, 118.0, 116.9, 109.0, 61.3, 58.5, 52.9, 52.5, 50.9, 46.7, 32.8, 21.59, 21.56; FT-IR (KBr) 2952, 2920, 1735, 1606, 1457, 1434, 1342, 1239, 1157, 1092, 1044, 982, 811, 747, 660, 545 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{31}H_{32}N_2NaO_6S$: 583.1873, found: 583.1878.

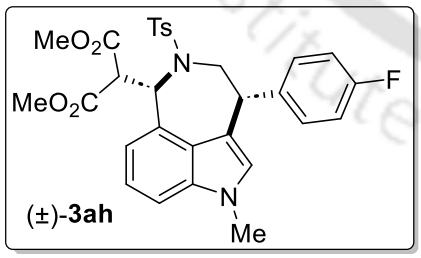


Dimethyl 2-(6-methyl-4-(3-nitrophenyl)-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3af**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.40; yellow solid; mp 170-171 °C; yield 77% (46 mg); major diastereomer (>13:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19-8.16 (m, 2H), 7.73-7.71 (m, 1H), 7.68 (d, *J* = 8 Hz, 2H), 7.55 (t, *J* = 8 Hz, 1H), 7.19-7.16 (m, 3H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.07-7.06 (m, 1H), 6.34 (d, *J* = 6.5 Hz, 1H), 6.30 (s, 1H), 4.64-4.60 (m, 1H), 4.01-3.99 (m, 2H), 3.90 (d, *J* = 6.5 Hz, 1H), 3.64 (s, 3H), 3.58 (s, 3H), 3.35 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 167.1,

148.7, 145.5, 143.5, 137.8, 137.7, 135.2, 132.2, 129.8, 129.6, 128.7, 127.5, 124.4, 123.6, 122.4, 121.3, 118.4, 115.7, 109.2, 61.0, 58.6, 52.9, 52.6, 50.7, 46.7, 33.0, 21.5; FT-IR (KBr) 2953, 2925, 1733, 1528, 1347, 1306, 1156, 1093, 812, 740, 665, 546 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{30}H_{30}N_3O_8S$: 592.1748, found: 592.1742.

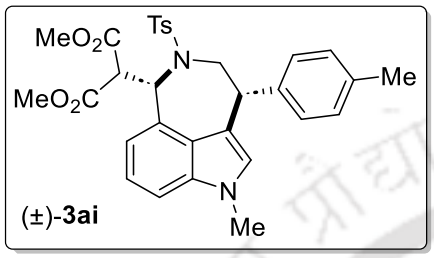


Dimethyl 2-(4-(4-bromophenyl)-6-methyl-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate 3ag′. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.52; colorless solid; mp 159-160 °C; yield 63% (39 mg); major diastereomer (>20:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8 Hz, 2H), 7.49 (d, *J* = 8 Hz, 2H), 7.25-7.21 (m, 2H), 7.17-7.13 (m, 3H), 7.08 (t, *J* = 7.2 Hz, 1H), 7.03-7.02 (m, 1H), 6.32-6.30 (m, 2H), 4.47-4.43 (m, 1H), 3.93-3.88 (m, 3H), 3.62 (s, 3H), 3.56 (s, 3H), 3.35 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 167.1, 143.3, 142.3, 137.9, 137.7, 132.2, 131.9, 130.5, 129.5, 128.8, 127.5, 124.5, 121.03, 121.01, 118.1, 116.4, 109.1, 61.1, 58.6, 52.9, 52.5, 50.7, 46.4, 32.9, 21.5; FT-IR (KBr) 2923, 2853, 1735, 1456, 1343, 1158, 1092, 1010, 814, 658, 600, 542 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{30}H_{29}BrN_2NaO_6S$: 647.0822, found: 647.0819. $[\alpha]_D^{25}$ = -67.5 (c = 0.04, $CHCl_3$); HPLC: >88% ee [CHIRALCEL AD-H, hexane/^{i}PrOH = 80:20, flow rate: 1 mL/min, λ= 254 nm, t_R = 24.20 min (major), 28.25 (minor)].

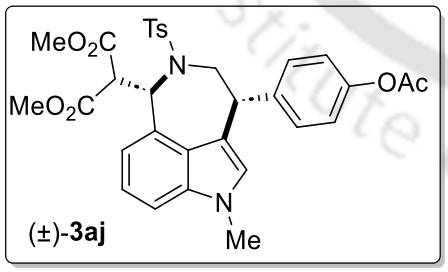


Dimethyl 2-(4-(4-fluorophenyl)-6-methyl-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3ah**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.46; colorless solid; mp 174-175 °C; yield 74% (42 mg); major diastereomer (>14:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.32-7.28 (m, 2H), 7.17-7.14 (m, 3H), 7.11-7.02 (m, 4H), 6.32-6.31 (m, 2H), 4.47-4.43 (m, 1H), 3.97-3.86 (m, 3H), 3.63 (s, 3H), 3.57

(s, 3H), 3.36 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 167.1, 163.0 (d, $J_{C\text{-}F}$ = 243.8 Hz), 143.2, 139.0 (d, $J_{C\text{-}F}$ = 3.1 Hz), 137.9, 137.7, 132.3, 130.3 (d, $J_{C\text{-}F}$ = 7.7 Hz), 129.5, 128.8, 127.5, 124.5, 121.0, 118.1, 116.8, 115.7 (d, $J_{C\text{-}F}$ = 21 Hz), 109.1, 61.1, 58.6, 52.9, 52.5, 50.9, 46.1, 32.9, 21.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ -115.6; FT-IR (KBr) 2953, 2925, 1732, 1600, 1508, 1434, 1342, 1221, 1156, 1100, 811, 747, 659, 544 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{30}H_{29}FN_2NaO_6S$: 587.1623, found: 587.1630.

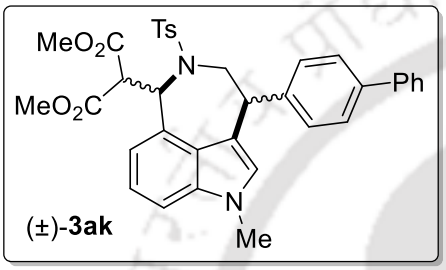


Dimethyl 2-(6-methyl-4-(*p*-tolyl)-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3ai**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.53; colorless solid; mp 184-185 °C; yield 79% (44 mg); major diastereomer (>7:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.5 Hz, 2H), 7.23-7.21 (m, 2H), 7.17-7.13 (m, 5H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.02-7.01 (m, 1H), 6.356-6.354 (m, 1H), 6.33 (d, *J* = 8 Hz, 1H), 4.43-4.40 (m, 1H), 3.97-3.87 (m, 3H), 3.62 (s, 3H), 3.56 (s, 3H), 3.37 (s, 3H), 2.37 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 167.1, 143.1, 140.3, 138.0, 137.7, 136.8, 132.3, 129.48, 129.46, 128.9, 128.7, 127.6, 124.5, 120.8, 118.0, 117.0, 109.0, 61.3, 58.5, 52.9, 52.5, 50.9, 46.3, 32.9, 21.5, 21.2; FT-IR (KBr) 2952, 2923, 1735, 1456, 1434, 1342, 1157, 1092, 816, 660, 548 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{31}H_{32}N_2NaO_6S$: 583.1873, found: 583.1874.

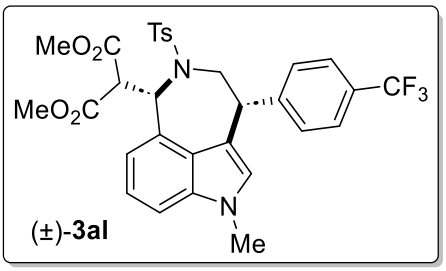


Dimethyl 2-(4-(4-acetoxyphenyl)-6-methyl-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3aj**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.44; colorless solid; mp 167-168 °C; yield 68% (41 mg); mixture of diastereomers (>2:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8 Hz, 0.8H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.36-7.33 (m, 3H), 7.17-7.15 (m, 4H), 7.10-7.07 (m, 3H), 7.03-7.02 (m, 1H), 6.87-6.86 (m, 0.4H), 6.83-6.81

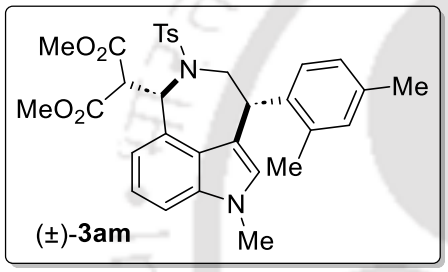
(m, 1H), 6.38 (s, 1H), 6.33 (d, J = 8 Hz, 1H), 4.84-4.79 (m, 0.4H), 4.50-4.47 (m, 1H), 3.97-3.88 (m, 3H), 3.85-3.77 (m, 1.2H), 3.69 (s, 1.2H), 3.63 (s, 3H), 3.56 (s, 3H), 3.48 (s, 1.2H), 3.36 (s, 3H), 2.44 (s, 1.2H), 2.34-2.32 (m, 6H), 2.23 (s, 1.2H),; ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.8, 169.7, 169.6, 169.1, 167.5, 167.1, 150.1, 149.7, 144.5, 143.2, 140.87, 140.84, 137.9, 137.7, 135.0, 134.5, 132.3, 129.85, 129.83, 129.5, 129.0, 128.4, 127.5, 127.3, 124.5, 123.0, 121.8, 120.96, 120.91, 118.1, 116.6, 116.5, 109.1, 107.9, 61.2, 58.5, 54.5, 53.1, 53.0, 52.9, 52.5, 50.9, 46.3, 33.2, 32.9, 21.8, 21.6, 21.3, 21.2; FT-IR (KBr) 2953, 2923, 1737, 1504, 1342, 1200, 1158, 1091, 1018, 910, 813, 748, 548 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{32}H_{32}N_2NaO_8S$: 627.1772, found: 627.1772.



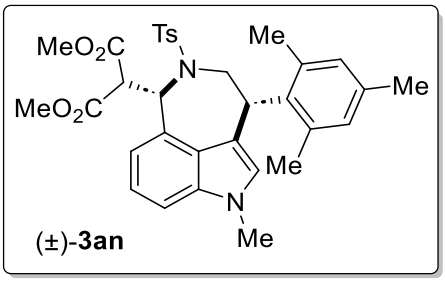
Dimethyl 2-(4-([1,1'-biphenyl]-4-yl)-6-methyl-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3ak**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.48; colorless solid; mp 166-167 °C; yield 77% (48 mg); major diastereomer (>4:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 8 Hz, 2H), 7.63-7.61 (m, 2H), 7.60-7.59 (m, 2H), 7.46 (t, J = 7.5 Hz, 2H), 7.42 (d, J = 7.5 Hz, 2H), 7.37-7.36 (m, 1H), 7.19-7.15 (m, 3H), 7.11-7.08 (m, 1H), 7.05-7.04 (m, 1H), 6.42 (s, 1H), 6.36 (d, J = 7.5 Hz, 1H), 4.53-4.50 (m, 1H), 4.01-3.95 (m, 3H), 3.64 (s, 3H), 3.58 (s, 3H), 3.38 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 167.2, 143.2, 142.3, 140.9, 140.1, 138.0, 137.8, 132.3, 129.5, 129.2, 129.0, 128.9, 127.6, 127.5, 127.4, 127.1, 124.6, 120.9, 118.1, 116.8, 109.1, 61.2, 58.6, 52.9, 52.6, 50.9, 46.5, 32.9, 21.6; FT-IR (KBr) 2953, 2925, 1733, 1486, 1434, 1342, 1240, 1156, 1092, 756, 660, 550 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{36}H_{34}N_2NaO_6S$: 645.2030, found: 645.2046.



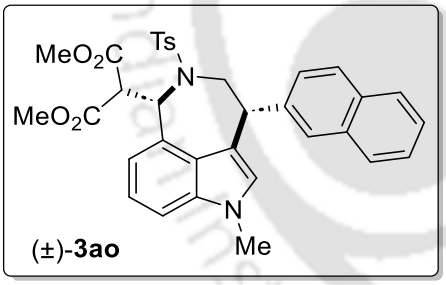
Dimethyl 2-(6-methyl-2-tosyl-4-(4-(trifluoromethyl)phenyl)-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3al**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.40; colorless solid; mp 159-160 °C; yield 80% (49 mg); major diastereomer (>20:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 8 Hz, 2H), 7.48 (d, J = 8 Hz, 2H), 7.18-7.15 (m, 3H), 7.10 (t, J = 7.5 Hz, 1H), 7.05-7.04 (m, 1H), 6.33-6.32 (m, 2H), 4.57 (t, J = 8 Hz, 1H), 3.97 (d, J = 8.5 Hz, 2H), 3.90 (d, J = 7 Hz, 1H), 3.63 (s, 3H), 3.57 (s, 3H), 3.36 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 167.1, 147.4, 143.4, 137.8, 137.7, 132.2, 129.9 (q, J_{C-F} = 32.2 Hz), 129.5, 129.2, 128.8, 127.59 (q, J_{C-F} = 270.3 Hz), 127.53, 125.8 (q, J_{C-F} = 3.6 Hz), 124.5, 121.1, 118.2, 116.1, 109.1, 61.1, 58.6, 52.9, 52.6, 50.7, 46.9, 32.9, 21.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ -62.3; FT-IR (KBr) 2953, 2925, 1735, 1617, 1457, 1324, 1157, 1112, 1066, 1017, 983, 658, 600, 550 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{30}F_3N_2O_6S$: 615.1771, found: 615.1767.



Dimethyl 2-(4-(2,4-dimethylphenyl)-6-methyl-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3am**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.52; colorless solid; mp 188-189 °C; yield 64% (37 mg); major diastereomer (>6:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 8.5 Hz, 2H), 7.18-7.16 (m, 2H), 7.13-7.11 (m, 1H), 7.11-7.09 (m, 1H), 7.07-7.03 (m, 3H), 7.00-6.98 (m, 1H), 6.37 (d, J = 8 Hz, 1H), 6.32 (s, 1H), 4.76-4.73 (m, 1H), 3.96 (d, J = 8 Hz, 1H), 3.92-3.84 (m, 2H), 3.62 (s, 3H), 3.57 (s, 3H), 3.38 (s, 3H), 2.41 (s, 3H), 2.34-2.32 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 167.1, 143.1, 138.7, 138.1, 137.7, 136.3, 132.3, 131.0, 129.3, 128.5, 128.3, 127.5, 127.3, 127.1, 124.7, 120.8, 118.0, 116.8, 109.0, 61.4, 58.5, 52.8, 52.5, 50.1, 41.1, 32.8, 21.5, 21.1, 19.6; FT-IR (KBr) 2952, 2920, 1735, 1456, 1434, 1342, 1239, 1156, 1091, 813, 747, 659, 545 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{35}N_2O_6S$: 575.2210, found: 575.2222.

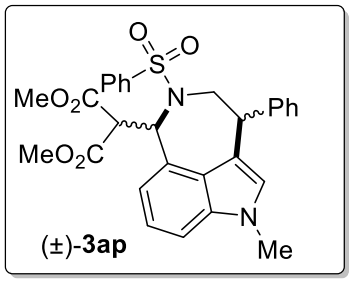


Dimethyl 2-(4-mesityl-6-methyl-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3an**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.54; colorless solid; mp 185-186 °C; yield 70% (41 mg); major diastereomer (>20:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.18-7.06 (m, 4H), 7.01-6.99 (m, 1H), 6.93 (s, 1H), 6.85 (s, 1H), 6.33-6.31 (m, 2H), 5.07-5.03 (m, 1H), 4.11-4.04 (m, 1H), 3.97 (d, *J* = 9.2 Hz, 1H), 3.85-3.80 (m, 1H), 3.62 (s, 3H), 3.51 (s, 3H), 3.41 (s, 3H), 2.40 (s, 3H), 2.32 (s, 3H), 2.30 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 167.0, 143.0, 138.1, 138.0, 137.7, 137.2, 136.3, 135.6, 132.8, 131.1, 129.3, 129.1, 127.6, 126.8, 123.9, 120.9, 118.0, 116.1, 109.1, 61.6, 58.9, 52.9, 52.6, 46.9, 41.1, 32.8, 21.7, 21.5, 21.2, 20.9; FT-IR (KBr) 2973, 1681, 1609, 1531, 1447, 1305, 1058, 748 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{33}H_{36}N_2NaO_6S$: 611.2186, found: 611.2206.

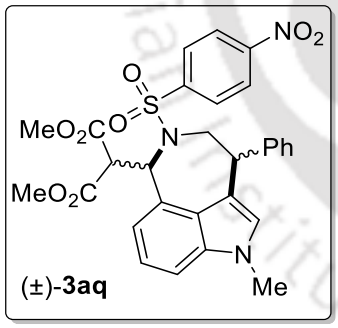


Dimethyl 2-(6-methyl-4-(naphthalen-2-yl)-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3ao**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.49; colorless solid; mp 165-166 °C; yield 68% (40 mg); major diastereomer (>14:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86-7.83 (m, 4H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.52-7.47 (m, 2H), 7.45-7.43 (m, 1H), 7.18-7.15 (m, 3H), 7.10 (t, *J* = 7.5 Hz, 1H), 7.06-7.04 (m, 1H), 6.36-6.35 (m, 2H), 4.67 (t, *J* = 8.5 Hz, 1H), 4.05-4.03 (m, 2H), 3.99 (d, *J* = 7.5 Hz, 1H), 3.60 (s, 3H), 3.55 (s, 3H), 3.40 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 167.2, 143.2, 140.5, 138.0, 137.8, 133.6, 132.8, 132.4, 129.5, 129.1, 128.5, 127.9, 127.8, 127.6, 127.5, 126.8, 126.3, 125.9, 124.6, 120.9, 118.1, 116.8, 109.1, 61.3, 58.6, 52.9, 52.6, 50.8, 47.0, 32.9, 21.5;

FT-IR (KBr) 2952, 2923, 1733, 1456, 1434, 1342, 1240, 1156, 1044, 814, 747, 662, 548 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{34}H_{32}N_2NaO_6S$: 619.1873, found: 619.1878.

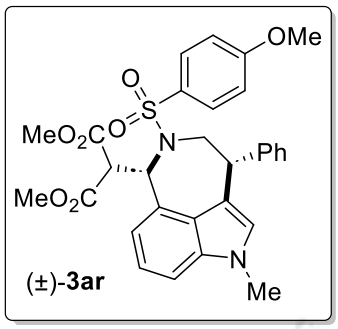


Dimethyl 2-(6-methyl-4-phenyl-2-(phenylsulfonyl)-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3ap**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.50; yellow solid; mp 150-151 °C; yield 72% (39 mg); major diastereomer (>4:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.5 Hz, 2H), 7.45-7.42 (m, 1H), 7.38-7.36 (m, 2H), 7.35-7.32 (m, 5H), 7.17-7.16 (m, 1H), 7.10-7.07 (m, 1H), 7.04-7.02 (m, 1H), 6.36 (d, *J* = 8 Hz, 1H), 6.33 (s, 1H), 4.45-4.42 (m, 1H), 3.99-3.92 (m, 3H), 3.62 (s, 3H), 3.55 (s, 3H), 3.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 167.1, 143.2, 140.9, 137.7, 132.4, 132.2, 128.98, 128.90, 128.8, 127.5, 127.2, 124.5, 121.6, 120.9, 118.1, 116.7, 109.1, 61.4, 58.5, 52.9, 52.6, 50.9, 46.7, 32.9; FT-IR (KBr) 2592, 2923, 1608, 1447, 1343, 1241, 1158, 1093, 982, 753, 589 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{29}H_{28}N_2NaO_6S$: 555.1560, found: 555.1562.

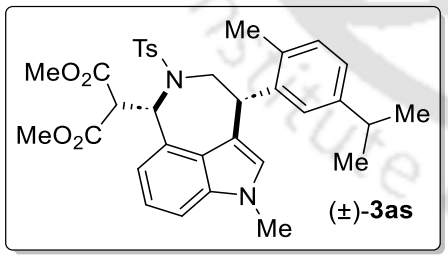


Dimethyl 2-(6-methyl-2-((4-nitrophenyl)sulfonyl)-4-phenyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3aq**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.38; yellow solid; mp 164-165 °C; yield 77% (44 mg); major diastereomer (>2:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.8 Hz, 2H), 7.94 (d, *J* = 8.8 Hz, 2H); 7.37-7.35 (m, 2H), 7.33-7.31 (m, 2H), 7.18-7.16 (m, 1H), 7.11-7.07 (m, 1H), 7.03-6.99 (m, 2H), 6.352-6.350 (m, 1H), 6.29 (d, *J* = 9.2 Hz, 1H), 4.43-4.38 (m, 1H), 4.05-4.03 (m, 1H), 3.91-3.87 (m, 2H), 3.617-3.613 (m, 6H), 3.47 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 166.8, 149.7, 146.5, 142.7, 137.7, 131.3, 129.3, 128.9, 128.74, 128.71, 127.5, 123.8, 121.0,

118.2, 116.0, 109.5, 61.8, 58.3, 53.1, 52.8, 51.0, 46.3, 32.9; FT-IR (KBr) 2953, 2923, 1736, 1530, 1349, 1308, 1162, 1093, 854, 736, 612 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{29}H_{27}N_3NaO_8S$: 600.1411, found: 600.1411.

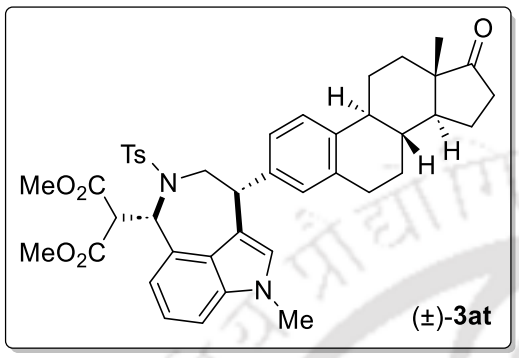


Dimethyl 2-(2-((4-methoxyphenyl)sulfonyl)-6-methyl-4-phenyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3ar**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.45; colorless solid; mp 169-170 °C; yield 67% (38 mg); major diastereomer (>10:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 9 Hz, 2H), 7.37-7.29 (m, 5H), 7.16-7.15 (m, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.02-7.01 (m, 1H), 6.81 (d, *J* = 8.5 Hz, 2H), 6.33-6.31 (m, 2H), 4.44-4.41 (m, 1H), 3.98-3.88 (m, 3H), 3.79 (s, 3H), 3.62-3.60 (m, 6H), 3.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 167.2, 162.7, 143.3, 137.7, 132.7, 132.3, 129.7, 128.9, 128.84, 128.80, 127.2, 124.6, 120.9, 118.1, 116.9, 114.0, 109.0, 61.2, 58.6, 55.6, 52.9, 52.5, 50.8, 46.6, 32.9; FT-IR (KBr) 2924, 2853, 1735, 1596, 1497, 1459, 1342, 1258, 1153, 1095, 556 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{30}H_{30}N_2NaO_7S$: 585.1666, found: 585.1669.

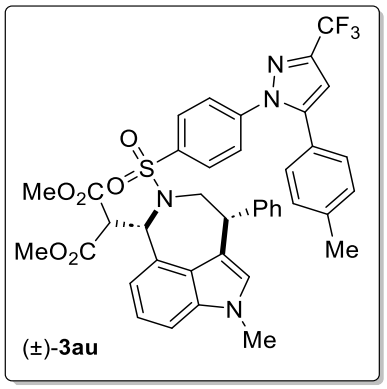


Dimethyl 2-(4-(5-isopropyl-2-methylphenyl)-6-methyl-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3as**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.49; yellow solid; mp 171-172 °C; yield 65% (39 mg); major diastereomer (>8:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8 Hz, 2H), 7.19-7.03 (m, 8H), 6.38 (d, *J* = 7.6 Hz, 1H), 6.32-6.31 (m, 1H), 4.76-4.72 (m, 1H), 3.98 (d, *J* = 8.4 Hz, 1H), 3.90-3.81 (m, 2H), 3.63 (s, 3H), 3.56 (s, 3H), 3.39 (s, 3H), 2.84-2.77 (m, 1H), 2.38 (s, 3H), 2.32 (s, 3H), 1.19-

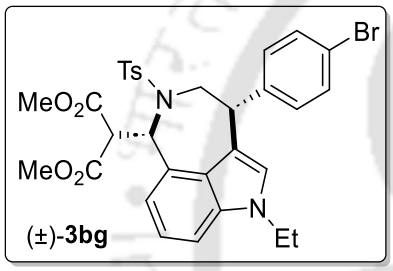
1.17 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 167.1, 146.9, 143.1, 141.4, 138.1, 137.8, 133.9, 132.4, 130.3, 129.4, 128.5, 127.5, 126.7, 124.7, 124.5, 120.9, 118.0, 116.8, 109.1, 61.4, 58.6, 52.9, 52.5, 50.0, 41.6, 33.8, 32.9, 24.2, 21.5, 19.2; FT-IR (KBr) 2955, 2925, 1736, 1456, 1434, 1343, 1157, 1091, 813, 747, 661, 549 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{34}H_{38}N_2NaO_6S$: 625.2343, found: 625.2337.



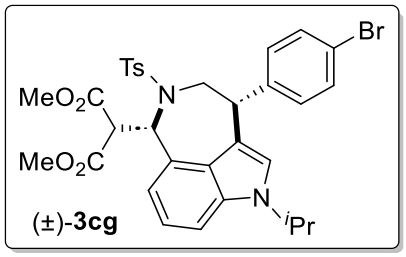
Dimethyl 2-(6-methyl-4-((8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl)-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3at**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.47; colorless solid; mp 154-155 °C; yield 68% (49 mg); major diastereomer (>5:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.17-7.00 (m, 8H), 6.40 (s, 1H), 6.32-6.29 (m, 1H), 4.44-4.39 (m, 1H), 3.96-3.93 (m, 1H), 3.90-3.84 (m, 2H), 3.63 (s, 3H), 3.56 (s, 3H), 3.386-3.382 (m, 3H), 2.93-2.91 (m, 2H), 2.55-2.48 (m, 1H), 2.46-2.42 (m, 1H), 2.33 (s, 3H), 2.20-1.97 (m, 5H), 1.70-1.62 (m, 3H), 1.53-1.45 (m, 3H), 0.94 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 221.0, 167.4, 167.1, 143.1, 140.7, 138.6, 138.0, 137.7, 136.8, 132.3, 129.4, 128.9, 127.6, 127.3, 125.7, 125.6, 124.5, 120.8, 118.0, 116.8, 109.0, 61.3, 58.5, 52.5, 51.0, 50.7, 48.1, 46.4, 44.5, 38.3, 36.0, 32.9, 31.7, 29.5, 26.7, 25.8, 21.7, 21.5, 14.0; FT-IR (KBr) 2926, 2855, 1735, 1496, 1456, 1342, 1239, 1157, 1104, 1092, 813, 747, 660, 550 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{42}H_{46}N_2NaO_7S$: 745.2918, found: 745.2924.



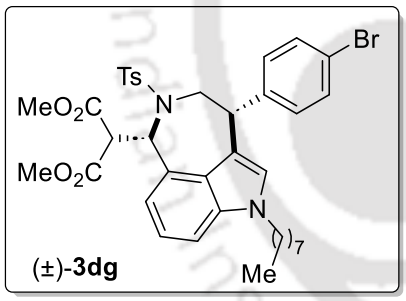
Dimethyl 2-(6-methyl-4-phenyl-2-((4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)sulfonyl)-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3au**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.43; colorless solid; mp 174-175 °C; yield 58% (44 mg); major diastereomer (>20:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.37-7.34 (m, 2H), 7.31-7.28 (m, 3H), 7.24-7.21 (m, 2H), 7.17-7.15 (m, 1H), 7.10 (t, *J* = 8 Hz, 3H), 7.01-6.98 (m, 3H), 6.68 (s, 1H), 6.34-6.32 (m, 2H), 4.38-4.34 (m, 1H), 4.05-4.00 (m, 2H), 3.94-3.87 (m, 1H), 3.64-3.62 (m, 6H), 3.43 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 167.0, 145.2, 143.0, 142.2, 140.5, 139.8, 137.7, 131.6, 129.8, 129.1, 128.8, 128.79, 128.76, 128.4, 127.3, 125.8, 125.1, 124.4, 120.9, 118.1, 116.3, 109.4, 106.3, 61.5, 58.6, 53.1, 52.7, 50.9, 46.3, 32.9, 21.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ -62.4; FT-IR (KBr) 2953, 1736, 1471, 1346, 1270, 1236, 1159, 1134, 1097, 975, 809, 758, 703, 627 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{40}H_{35}F_3N_4NaO_6S$: 779.2122, found: 779.2125.



Dimethyl 2-(4-(4-bromophenyl)-6-ethyl-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3bg**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.47; colorless solid; mp 156-157 °C; yield 71% (63 mg); major diastereomer (>16:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8 Hz, 2H), 7.49 (d, *J* = 8 Hz, 2H), 7.24-7.22 (m, 2H), 7.19-7.17 (m, 1H), 7.14 (d, *J* = 8 Hz, 2H), 7.07 (t, *J* = 7.5 Hz, 1H), 7.02-7.01 (m, 1H), 6.38 (s, 1H), 6.31 (d, *J* = 7.5 Hz, 1H), 4.49-4.45 (m, 1H), 4.06-3.96 (m, 2H), 3.92-3.87 (m, 3H), 3.56 (s, 3H), 3.36 (s, 3H), 2.32 (s, 3H), 1.32 (t, *J* = 7Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 167.1, 143.2, 142.4, 137.9, 136.8, 132.3, 131.9, 130.6, 129.4, 127.5, 127.0, 124.7, 121.0, 120.9, 118.2, 116.4, 109.1, 61.2, 58.6, 52.9, 52.5, 50.8, 46.4, 41.0, 21.5, 15.4; FT-IR (KBr) 2953, 2923, 1733, 1487, 1436, 1342, 1156, 1091, 1009, 813, 665, 544 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{31}H_{31}BrN_2NaO_6S$: 661.0978, found: 661.0958.

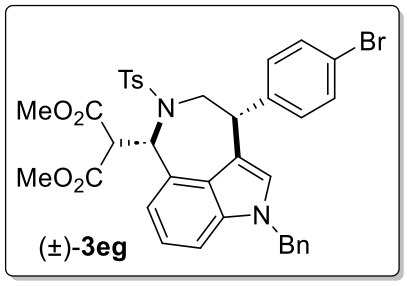


Dimethyl 2-(4-(4-bromophenyl)-6-isopropyl-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3cg**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.49; colorless solid; mp 151-152 °C; yield 76% (50 mg); major diastereomer (>16:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8 Hz, 2H), 7.24-7.20 (m, 3H), 7.12 (d, *J* = 8Hz, 2H), 7.07-7.00 (m, 2H), 6.468-6.465 (m, 1H), 6.30 (d, *J* = 8 Hz, 1H), 4.59-4.52 (m, 1H), 4.51-4.47 (m, 1H), 3.94-3.89 (m, 2H), 3.86-3.80 (m, 1H), 3.55 (s, 3H), 3.37 (s, 3H), 2.31 (s, 3H), 1.38 (q, *J* = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 167.1, 143.1, 142.5, 137.8, 136.6, 132.2, 131.9, 130.6, 129.4, 127.5, 124.6, 123.5, 120.9, 120.7, 118.2, 116.3, 109.2, 61.3, 58.5, 52.9, 52.59, 52.57, 50.9, 47.0, 46.5, 22.8, 22.6, 21.5; FT-IR (KBr) 2975, 2952, 1735, 1487, 1436, 1343, 1195, 1157, 1010, 814, 663, 548 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{32}H_{33}BrN_2NaO_6S$: 675.1135, found: 675.1133.

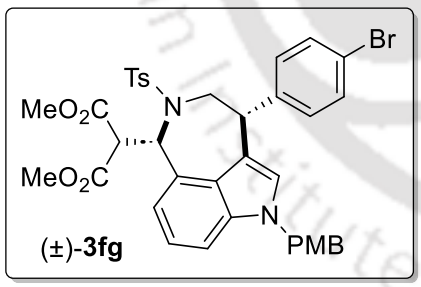


Dimethyl 2-(4-(4-bromophenyl)-6-octyl-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3dg**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.53; yellow solid; mp 161-162 °C; yield 79% (57 mg); major diastereomer (>20:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.24-7.22 (m, 2H), 7.18-7.16 (m, 1H), 7.13 (d, *J* = 8 Hz, 2H), 7.08-7.00 (m, 2H), 6.36 (s, 1H), 6.32 (d, *J* = 7.6 Hz, 1H), 4.48-4.44 (m, 1H), 4.00-3.86 (m, 5H), 3.57 (s, 3H), 3.35 (s, 3H), 2.32 (s, 3H), 1.71-1.64 (m, 2H), 1.29-1.23 (m, 10H), 0.86 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 167.1, 143.2, 142.4, 137.9, 137.0, 132.2, 131.9, 130.6, 129.4, 127.8, 127.5, 124.6, 120.9, 120.8, 118.1, 116.2, 109.2, 61.2, 58.6, 52.9, 52.5, 50.8, 46.4, 31.8, 30.1, 29.3, 29.2, 26.9,

22.7, 21.5, 14.2; FT-IR (KBr) 2926, 2855, 1736, 1487, 1435, 1344, 1157, 1010, 813, 659, 547 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{37}H_{43}BrN_2NaO_6S$: 745.1917, found: 745.1917.

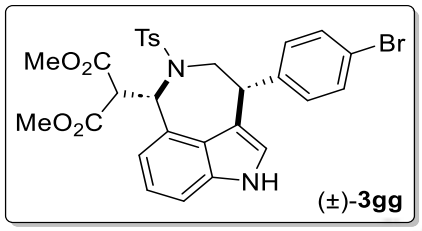


Dimethyl 2-(6-benzyl-4-(4-bromophenyl)-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3eg**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.42; yellow solid; mp 178-179 °C; yield 70% (65 mg); major diastereomer (>7:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.24-7.22 (m, 5H), 7.14-7.09 (m, 3H), 7.04-7.02 (m, 2H), 6.95-6.93 (m, 2H), 6.44-6.43 (m, 1H), 6.35 (d, *J* = 7.2 Hz, 1H), 5.24-5.09 (m, 2H), 4.50-4.46 (m, 1H), 3.95-3.88 (m, 3H), 3.58 (s, 3H), 3.32 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 167.1, 143.3, 142.3, 137.9, 137.3, 132.4, 131.9, 131.1, 130.5, 129.5, 129.2, 128.8, 128.3, 127.7, 126.9, 126.5, 124.8, 121.3, 121.0, 118.5, 117.1, 109.6, 61.1, 58.7, 52.9, 52.5, 50.8, 50.1, 46.4, 21.6; FT-IR (KBr) 2953, 2928, 1735, 1514, 1439, 1345, 1247, 1159, 1010, 660, 549 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{36}H_{33}BrN_2NaO_6S$: 723.1135, found: 723.1136.

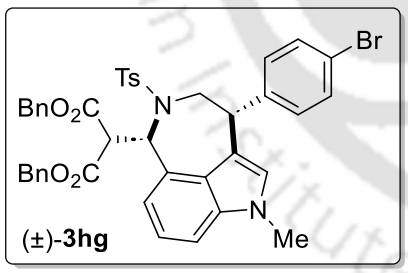


Dimethyl 2-(4-(4-bromophenyl)-6-(4-methoxybenzyl)-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3fg**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.44; colorless solid; mp 179-180 °C; yield 74% (69 mg); major diastereomer (>20:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.14-7.11 (m, 3H), 7.03-7.02 (m, 2H), 6.91-6.89 (m, 2H), 6.80-6.77 (m, 2H), 6.423-6.420 (m, 1H), 6.34 (d, *J* = 7.2 Hz, 1H), 5.17-5.13 (m, 1H), 5.05-5.01 (m, 1H), 4.49-4.45 (m, 1H), 3.94-3.87 (m, 3H), 3.76 (s, 3H), 3.58 (s, 3H), 3.32 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 167.1, 159.1, 143.2, 142.3, 137.9, 137.2, 132.3,

131.9, 130.5, 129.5, 129.3, 128.2, 127.9, 127.5, 124.8, 121.2, 121.0, 118.4, 116.9, 114.2, 109.6, 61.1, 58.6, 55.4, 52.9, 52.5, 50.8, 49.6, 46.4, 21.5; FT-IR (KBr) 2953, 2928, 1732, 1513, 1436, 1342, 1246, 1157, 1009, 814, 660, 548 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{37}H_{35}BrN_2NaO_7S$: 753.1241, found: 753.1240.

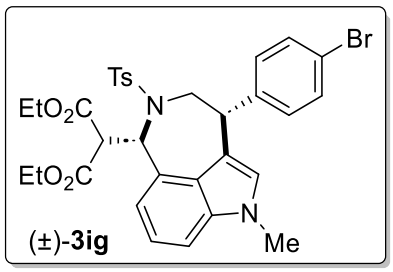


Dimethyl 2-(4-(4-bromophenyl)-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3gg**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.40; colorless solid; mp 187-188 °C; yield 64% (39 mg); major diastereomer (>11:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.68 (d, *J* = 8 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.24-7.22 (m, 3H), 7.16 (d, *J* = 8 Hz, 2H), 7.07-7.03 (m, 2H), 6.468-6.460 (m, 1H), 6.33 (d, *J* = 7.5 Hz, 1H), 4.47-4.44 (m, 1H), 3.98-3.91 (m, 2H), 3.88 (d, *J* = 7 Hz, 1H), 3.57 (s, 3H), 3.33 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 167.1, 143.3, 142.2, 137.8, 137.0, 132.1, 131.9, 130.5, 129.5, 127.5, 124.14, 124.12, 121.5, 121.0, 118.6, 118.0, 111.0, 61.1, 58.6, 52.9, 52.6, 50.7, 46.5, 21.6; FT-IR (KBr) 3393, 2953, 2925, 1735, 1487, 1434, 1342, 1157, 1092, 1010, 814, 669, 549 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{29}H_{27}BrN_2NaO_6S$: 633.0665, found: 633.0665.

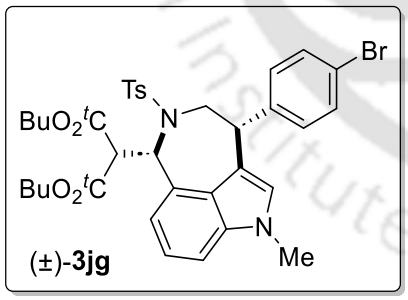


Dibenzyl 2-(4-(4-bromophenyl)-6-methyl-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3hg**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.54; colorless solid; mp 151-152 °C; yield 68% (53 mg); major diastereomer (>14:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.30-7.27 (m, 4H), 7.23-7.20 (m, 3H), 7.18-7.14 (m, 2H), 7.10-7.05 (m, 4H), 6.99 (d, *J* = 8 Hz, 2H), 6.85 (d, *J* = 7.2 Hz, 2H), 6.45 (d, *J* = 5.6 Hz, 1H), 6.29 (s, 1H), 5.08 (q, *J* = 12 Hz, 2H), 4.64-4.61 (m, 1H), 4.48-4.42 (m, 2H), 3.89-3.84 (m, 3H), 3.66 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 166.7, 143.3, 142.3, 137.7, 137.6, 135.1, 134.6, 132.4, 131.8, 130.5, 129.6,

128.7, 128.6, 128.53, 128.50, 128.3, 127.5, 124.7, 121.2, 118.3, 116.7, 108.9, 67.79, 67.75, 60.7, 59.2, 51.0, 46.9, 32.9, 21.5; FT-IR (KBr) 2924, 2850, 1732, 1456, 1341, 1157, 1009, 747, 697 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{42}H_{37}BrN_2NaO_6S$: 799.1448, found: 799.1450.

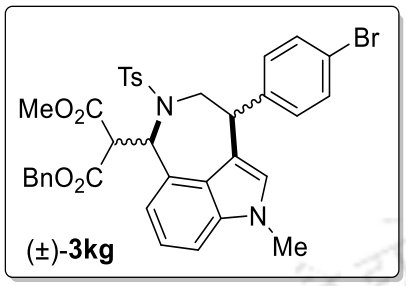


Diethyl 2-(4-(4-bromophenyl)-6-methyl-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3ig**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.52; colorless solid; mp 146-147 °C; yield 69% (45 mg); major diastereomer (>12:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8 Hz, 2H), 7.24-7.22 (m, 2H), 7.15-7.11 (m, 3H), 7.09-7.07 (m, 2H), 6.37 (d, *J* = 6.4 Hz, 1H), 6.31 (s, 1H), 4.48-4.44 (m, 1H), 4.12-4.03 (m, 2H), 4.01-3.92 (m, 2H), 3.80-3.71 (m, 3H), 3.62 (s, 3H), 2.33 (s, 3H), 1.19 (t, *J* = 7.2 Hz, 3H), 0.86 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 166.9, 143.2, 142.4, 137.9, 137.7, 132.4, 131.9, 130.5, 129.5, 128.7, 127.4, 124.7, 121.0, 120.9, 118.4, 116.6, 108.9, 62.0, 61.7, 60.7, 59.0, 50.9, 46.6, 32.9, 21.5, 14.0, 13.6; FT-IR (KBr) 2960, 2928, 1728, 1486, 1457, 1343, 1304, 1241, 1156, 1011, 815, 666, 600, 542 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{32}H_{33}BrN_2NaO_6S$: 675.1135, found: 675.1150.

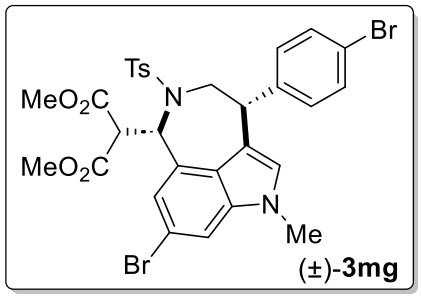


Di-*tert*-butyl 2-(4-(4-bromophenyl)-6-methyl-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3jg**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.55; colorless solid; mp 166-167 °C; yield 47% (33 mg); major diastereomer (>7:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.25-7.23 (m, 2H), 7.20-7.18 (m, 1H), 7.14-7.08 (m, 4H), 6.37 (d, *J* = 4.4 Hz, 1H), 6.28-6.27 (m, 1H), 4.49-4.45 (m, 1H), 4.13-4.06 (m, 1H), 3.97-3.93 (m, 1H), 3.60(s, 3H), 3.50 (d, *J* = 4.8 Hz, 1H), 2.31 (s, 3H), 1.44 (s, 9H), 1.01 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

166.8, 166.6, 142.9, 142.6, 138.0, 137.7, 132.7, 131.8, 130.6, 129.5, 128.5, 128.3, 124.8, 121.1, 120.8, 119.1, 116.8, 108.6, 82.2, 82.0, 61.3, 60.3, 50.9, 46.7, 32.8, 27.9, 27.4, 21.5; FT-IR (KBr) 2926, 2855, 1716, 1487, 1456, 1368, 1344, 1308, 1157, 1009, 746, 658, 549 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{36}H_{41}BrN_2NaO_6S$: 731.1761, found: 731.1766.

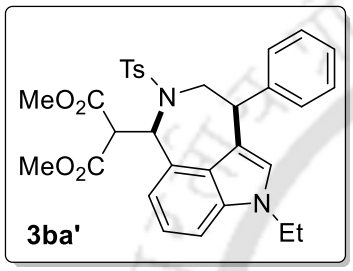


1-Benzyl 3-methyl 2-(4-(4-bromophenyl)-6-methyl-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3kg**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.47; colorless solid; mp 179-180 °C; yield 60% (42 mg); (1.5:1 mixture of diastereomers); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.64 (m, 3.30H), 7.48-7.46 (m, 1.32H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.30-7.27 (m, 3.35H), 7.23-7.19 (m, 4H), 7.18-7.15 (m, 3.61H), 7.10-7.03 (m, 5H), 7.00-6.98 (m, 2H), 6.89-6.87 (m, 2H), 6.37 (t, *J* = 6 Hz, 1.66H), 6.32-6.29 (m, 1.66H), 5.07-4.95 (m, 1.66H), 4.72-4.69 (m, 1H), 4.49-4.45 (m, 1.66H), 4.43-4.42 (m, 0.66 H), 3.94-3.82 (m, 5H), 3.66 (s, 3H), 3.62 (s, 2H), 3.59 (s, 3H), 3.28 (s, 2H), 2.34 (s, 3H), 2.29 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 167.1, 167.0, 166.8, 143.38, 143.33, 142.4, 142.2, 137.8, 137.7, 135.1, 134.6, 132.3, 131.9, 131.8, 130.5, 129.6, 129.5, 128.8, 128.7, 128.67, 128.64, 128.55, 128.51, 128.4, 128.26, 128.21, 127.52, 127.50, 124.6, 124.5, 121.2, 121.0, 120.96, 120.90, 118.3, 118.1, 116.6, 116.5, 109.0, 108.9, 67.7, 67.6, 61.0, 60.8, 58.9, 58.8, 52.9, 52.5, 51.0, 50.8, 46.8, 46.5, 32.9, 21.6, 21.5; FT-IR (KBr) 2924, 1734, 1486, 1456, 1342, 1241, 1156, 1009, 814, 747, 667, 549 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{36}H_{33}BrN_2NaO_6S$: 723.1135, found: 723.1139.

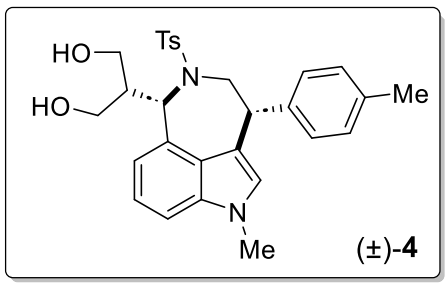


Dimethyl 2-(8-bromo-4-(4-bromophenyl)-6-methyl-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3mg**. Analytical TLC on silica gel, 1:4 ethyl

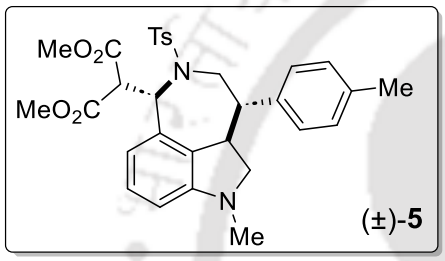
acetate/hexane R_f = 0.50; colorless solid; mp 186-187 °C; yield 52% (37 mg); major diastereomer (>5:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.328-7.325 (m, 1H), 7.22-7.14 (m, 5H), 6.323-6.320 (m, 1H), 6.21 (d, *J* = 7.2 Hz, 1H), 4.48-4.44 (m, 1H), 3.94-3.84 (m, 3H), 3.60 (s, 3H), 3.55 (s, 3H), 3.45 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 166.9, 143.5, 141.9, 138.5, 137.6, 133.9, 132.0, 130.5, 129.6, 129.5, 127.5, 123.6, 121.2, 121.1, 116.9, 114.4, 112.1, 60.6, 58.5, 53.0, 52.8, 50.6, 46.4, 33.0, 29.8, 21.6; FT-IR (KBr) 2924, 2853, 1735, 1599, 1458, 1345, 1157, 1092, 1010, 814, 670, 549 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{30}H_{28}Br_2N_2NaO_6S$: 724.9927, found: 724.9930.



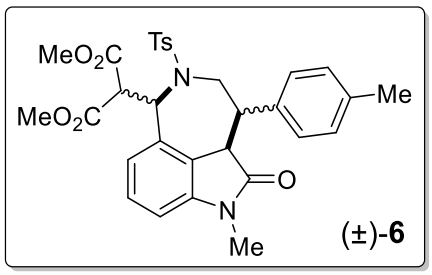
Dimethyl 2-(6-ethyl-4-phenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indol-1-yl)malonate 3ba′. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.51; colorless solid; mp 152-153 °C; yield 76% (31 mg); major diastereomer (>12:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8 Hz, 2H), 7.29-7.27 (m, 2H), 7.25-7.13 (m, 3H), 7.10-7.08 (m, 1H), 7.04-7.02 (m, 2H), 6.99-6.91 (m, 2H), 6.30 (s, 1H), 6.25 (d, *J* = 7.6 Hz, 1H), 4.40-4.36 (m, 1H), 3.95-3.80 (m, 5H), 3.48 (s, 3H), 3.28 (s, 3H), 2.23 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 167.2, 143.4, 143.1, 138.0, 136.7, 132.3, 129.4, 128.8, 128.7, 127.5, 127.1, 124.7, 120.7, 118.1, 116.9, 109.0, 61.3, 58.6, 52.9, 52.5, 50.9, 46.8, 40.9, 21.5, 15.4; FT-IR (KBr) 2951, 2926, 1733, 1485, 1436, 1340, 1156, 1089, 1010, 813, 665, 544 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{31}H_{32}N_2NaO_6S$: 583.1873, found: 583.1875; $[\alpha]_D^{25}$ = -98.9 (c = 0.19, $CHCl_3$); HPLC: >89% ee [CHIRALCEL AD-H, hexane/^{i}PrOH = 80:20, flow rate: 1 mL/min, λ= 254 nm, t_R = 16.15 min (major), 17.35 (minor)].



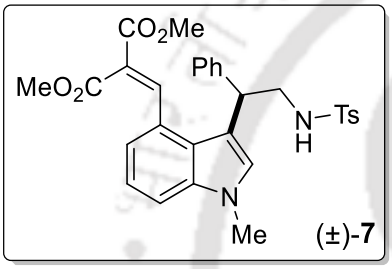
2-(6-Methyl-4-(*p*-tolyl)-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)propane-1,3-diol (±)-**4.** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.40; pale yellow solid; mp 158-159 °C; yield 82% (41 mg); major diastereomer (>20:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.4 Hz, 2H), 7.22-7.20 (m, 2H), 7.17-7.15 (m, 2H), 7.13-7.09 (m, 1H), 7.08-7.03 (m, 2H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.389-6.385 (m, 1H), 5.64 (d, *J* = 11.2 Hz, 1H), 4.45-4.41 (m, 1H), 4.29-4.24 (m, 1H), 4.05-4.02 (m, 1H), 3.98-3.89 (m, 2H), 3.76-3.73 (m, 1H), 3.61 (s, 3H), 3.55-3.48 (m, 1H), 2.36 (s, 3H), 2.21 (s, 3H), 2.01-1.99 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.1, 140.0, 137.7, 137.2, 136.9, 132.2, 129.4, 129.2, 128.7, 128.5, 127.3, 124.6, 120.8, 119.4, 116.3, 108.3, 64.7, 64.4, 58.4, 50.2, 45.5, 44.0, 32.9, 21.4, 21.2; FT-IR (KBr) 3446, 2921, 2851, 1607, 1453, 1336, 1155, 1093, 749, 662, 545 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{29}H_{32}N_2NaO_4S$: 527.1975, found: 527.1974.



Dimethyl 2-(6-methyl-4-(*p*-tolyl)-2-tosyl-2,3,4,4a,5,6-hexahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**5**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.52; colorless solid; mp 166-167 °C; yield 75% (42 mg); major diastereomer (>9:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.4 Hz, 2H), 7.16 (t, *J* = 8.4 Hz, 4H), 7.05 (d, *J* = 8 Hz, 2H), 6.69 (d, *J* = 7.6 Hz, 1H), 6.38 (d, *J* = 8 Hz, 1H), 5.85 (d, *J* = 12 Hz, 1H), 4.21 (d, *J* = 11.6 Hz, 1H), 3.95-3.87 (m, 1H), 3.84-3.75 (m, 1H), 3.62-3.53 (m, 2H), 3.50-3.49 (m, 6H), 3.24 (t, *J* = 9.2 Hz, 1H), 2.79-2.73 (m, 1H), 2.59 (s, 3H), 2.47-2.42 (m, 1H), 2.36-2.34 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 167.2, 143.1, 140.3, 138.0, 137.7, 136.8, 132.3, 129.49, 129.46, 128.9, 128.7, 127.6, 124.5, 120.8, 118.0, 117.0, 109.0, 61.3, 58.5, 52.9, 52.5, 50.9, 46.3, 32.9, 29.8, 21.5, 21.2; FT-IR (KBr) 2924, 2853, 1738, 1596, 1459, 1259, 1158, 1089, 807, 659, 542 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{31}H_{34}N_2NaO_6S$: 585.2030, found: 585.2033.



Dimethyl 2-(6-methyl-5-oxo-4-(*p*-tolyl)-2-tosyl-2,3,4,4a,5,6-hexahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**6**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.40; colorless solid; mp 189-190 °C; yield 63% (36 mg); major diastereomer (>4:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.4 Hz, 2H), 7.31 (t, *J* = 8 Hz, 1H), 7.23-7.21 (m, 1H), 7.17-7.15 (m, 5H), 6.80-6.78 (m, 1H), 6.00-5.97 (m, 1H), 5.34 (d, *J* = 12 Hz, 1H), 4.44-4.37 (m, 1H), 3.87-3.71 (m, 2H), 3.61 (s, 3H), 3.52 (s, 3H), 3.12 (s, 3H), 3.05-2.99 (m, 2H), 2.36-2.35 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 166.6, 166.4, 143.8, 142.2, 137.77, 137.70, 137.3, 133.9, 130.2, 129.6, 128.8, 128.3, 127.6, 125.8, 109.0, 62.5, 60.3, 53.9, 53.0, 52.9, 49.0, 47.7, 26.9, 21.6, 21.3; FT-IR (KBr) 2954, 2921, 1734, 1597, 1467, 1323, 1159, 1091, 812, 694, 573, 545 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{31}H_{32}N_2NaO_7S$: 599.1822, found: 599.1821.



Dimethyl 2-((1-methyl-3-(2-((4-methylphenyl)sulfonamido)-1-phenylethyl)-1*H*-indol-4-yl)methylene)malonate (±)-**7**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.30; yellow solid; mp 169-170 °C; yield 52% (37 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.33-7.26 (m, 4H), 7.25-7.19 (m, 3H), 7.15-7.10 (m, 3H), 7.04 (s, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 4.56-4.53 (m, 1H), 4.44 (t, *J* = 6.8 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.63 (s, 3H), 3.49 (t, *J* = 6.4 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 164.3, 143.6, 141.3, 137.7, 136.7, 129.8, 128.8, 128.5, 128.4, 127.3, 127.2, 126.76, 126.70, 125.5, 121.9, 119.9, 114.1, 111.5, 52.5, 52.4, 48.7, 43.3, 33.2, 21.6; FT-IR (KBr) 3290, 2954, 2924, 1728, 1601, 1435, 1260, 1157, 1073, 801, 702, 550 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{30}H_{30}N_2NaO_6S$: 569.1717, found: 569.1717.

Crystal Structure and Data of (±)-3ag

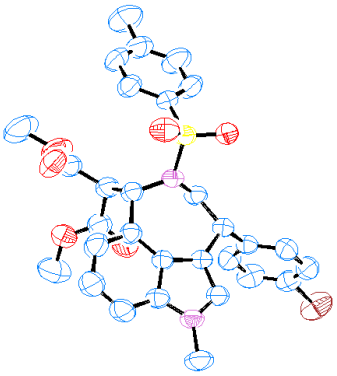


Figure S1. ORTEP diagram of dimethyl 2-(4-(4-bromophenyl)-6-methyl-2-tosyl-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-1-yl)malonate (±)-**3ag** with 50% ellipsoid (CCDC 2299116). H-Omitted for clarity.

Identification code	(±)-**3ag**
Empirical formula	'C30 H29 Br N2 O6 S'
Formula weight	625.52
Crystal habit, colour	Block/Colorless
Temperature, *T*/K	296 K
Wavelength, *λ*/Å	0.71073
Crystal system	'triclinic'
Space group	'P -1'
Unit cell dimensions	a = 9.866(6) Å b = 11.154(7) Å c = 14.703(9) Å α = 82.043(2) β = 79.967(2) γ = 65.710(2)
Volume, *V*/Å^3	1448.4(16)
Z	2
Calculated density, Mg·m^{-3}	1.434
Absorption coefficient, *μ*/mm^{-1}	1.537
F(000)	644
θ range for data collection	2.009 to 26.304°

Limiting indices	$-12 \leq h \leq 12$, $-13 \leq k \leq 13$, $-18 \leq l \leq 18$
Reflection collected / unique	5829/ 4300
Completeness to θ	99.0%
Absorption correction	None
Max. and min. transmission	0.702 and 0.677
Refinement method	'SHELXL-2019/1 (Sheldrick, 2019)'
Data / restraints / parameters	5829/0/365
Goodness–of–fit on F^2	1.029
Final R indices [I>2sigma(I)]	R1 = 0.0476, wR2 = 0.1252
R indices (all data)	R1 = 0.0697, wR2 = 0.1442

2.5 References

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Shu, X.- Z.; Tang, W.; Houk, K. N. *J. Am. Chem. Soc.* **2013**, *135*, 9271. (f) Shu, X.-Z.; Schienebeck, C. M.; Song, W.; Guzei, I. A.; Tang, W. *Angew. Chem. Int. Ed.* **2013**, *52*, 13601. (g) Shi, Z.; Grohmann, C.; Glorius, F. *Angew. Chem. Int. Ed.* **2013**, *52*, 5393.

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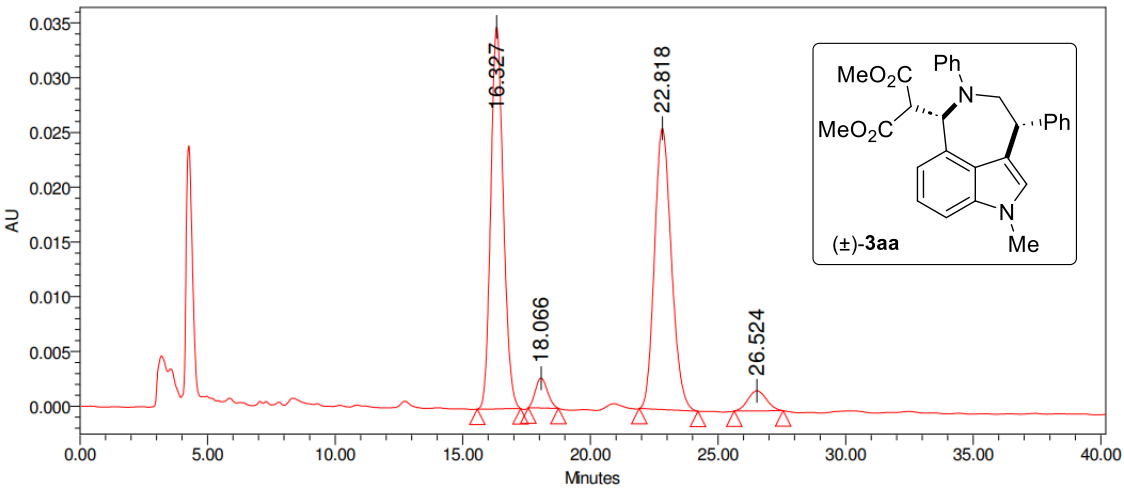
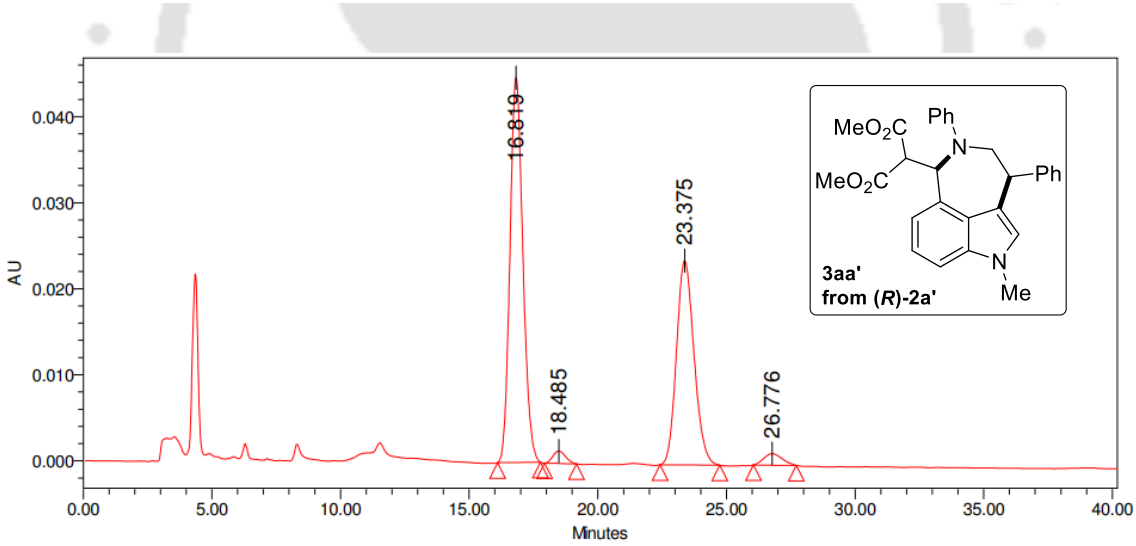
2.6 HPLC Chromatograms



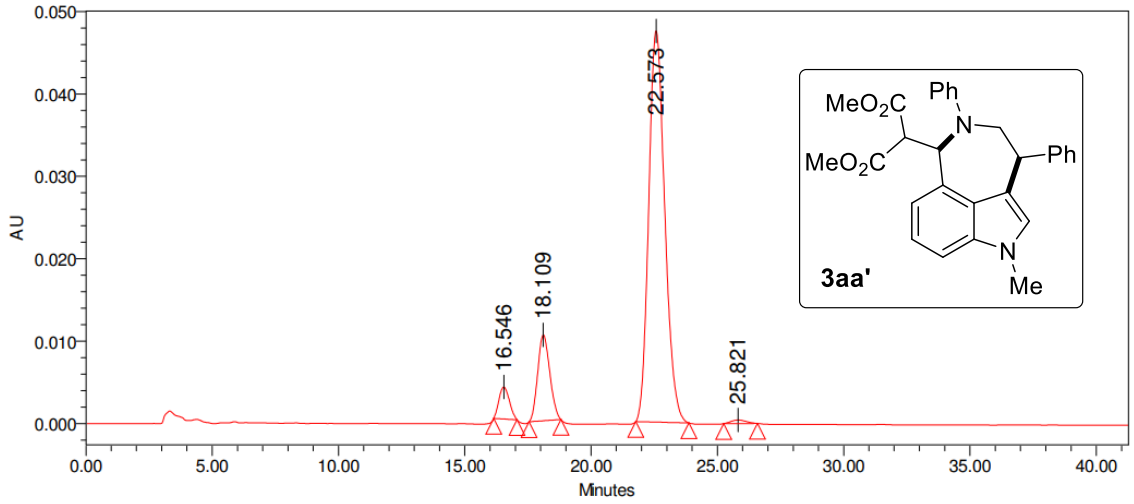
Peak Results

	Start Time (min)	End Time (min)	RT	Height (μV)	% Area
1	15.567	17.267	16.327	34885	46.50
2	17.567	18.750	18.066	2737	3.53
3	21.917	24.217	22.818	25683	46.32
4	25.633	27.550	26.524	1827	3.65



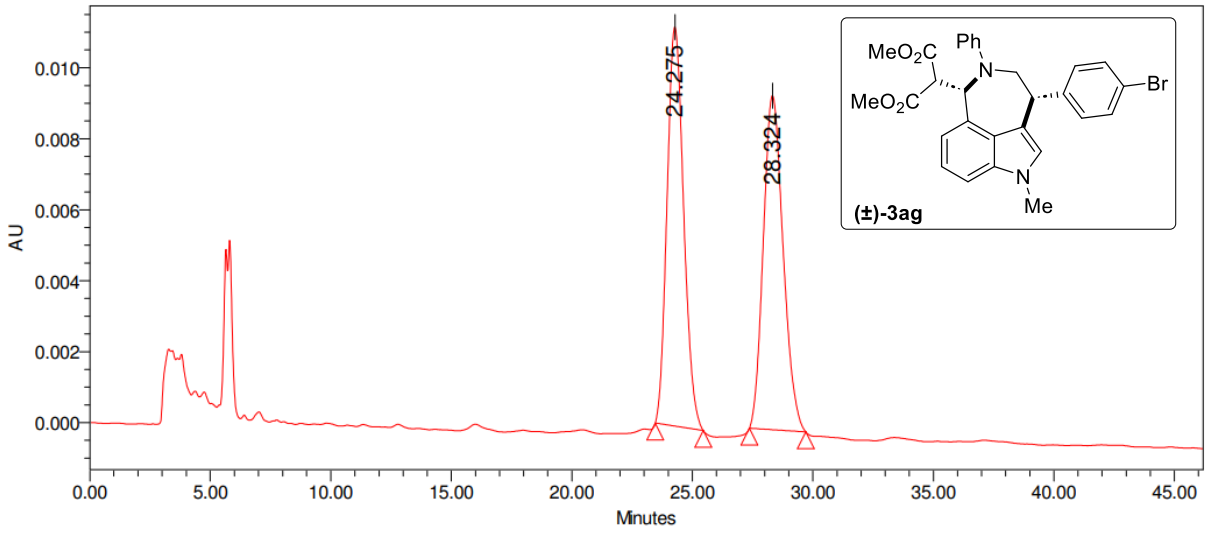
Peak Results

	Start Time (min)	End Time (min)	RT	Height (μV)	% Area
1	16.100	17.767	16.819	44736	55.68
2	17.933	19.167	18.485	1444	1.76
3	22.417	24.733	23.375	23758	40.18
4	26.050	27.717	26.776	1338	2.37



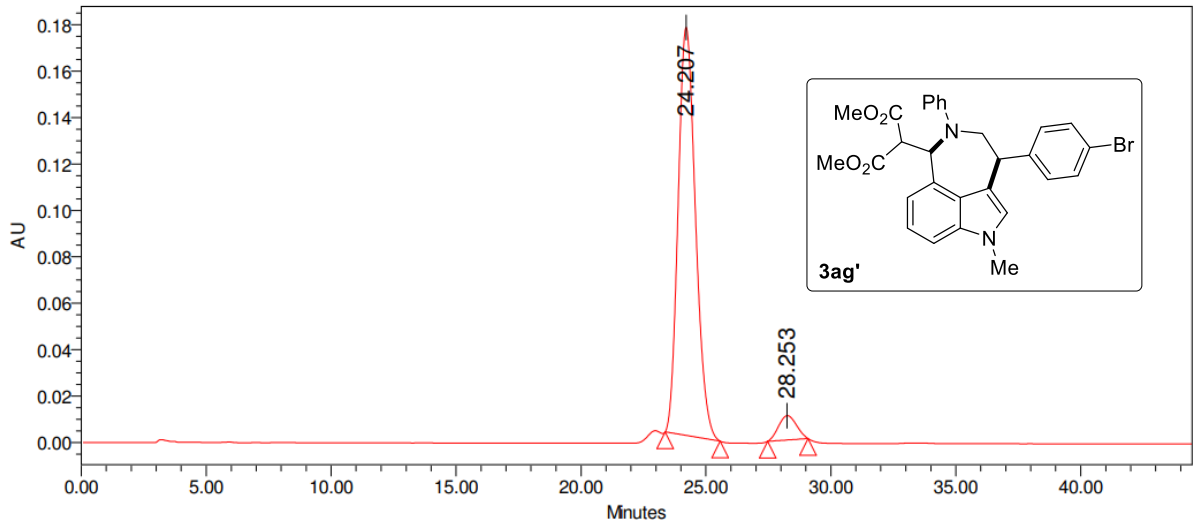
Peak Results

	Start Time (min)	End Time (min)	RT	Height (μV)	% Area
1	16.150	17.067	16.546	3881	4.30
2	17.550	18.800	18.109	10414	13.46
3	21.767	23.867	22.573	47493	81.54
4	25.250	26.583	25.821	434	0.70



Peak Results

	Start Time (min)	End Time (min)	RT	Height (μV)	% Area
1	23.467	25.450	24.275	11244	50.03
2	27.367	29.700	28.324	9414	49.97



Peak Results

	Start Time (min)	End Time (min)	RT	Height (µV)	% Area
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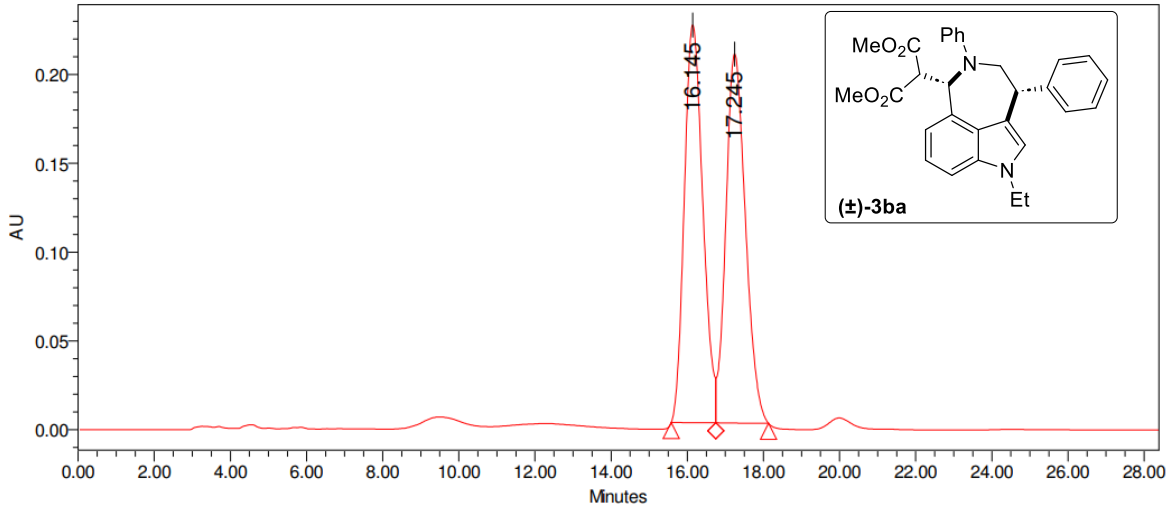
2	27.467	29.083	28.253	10501	5.77



Peak Results

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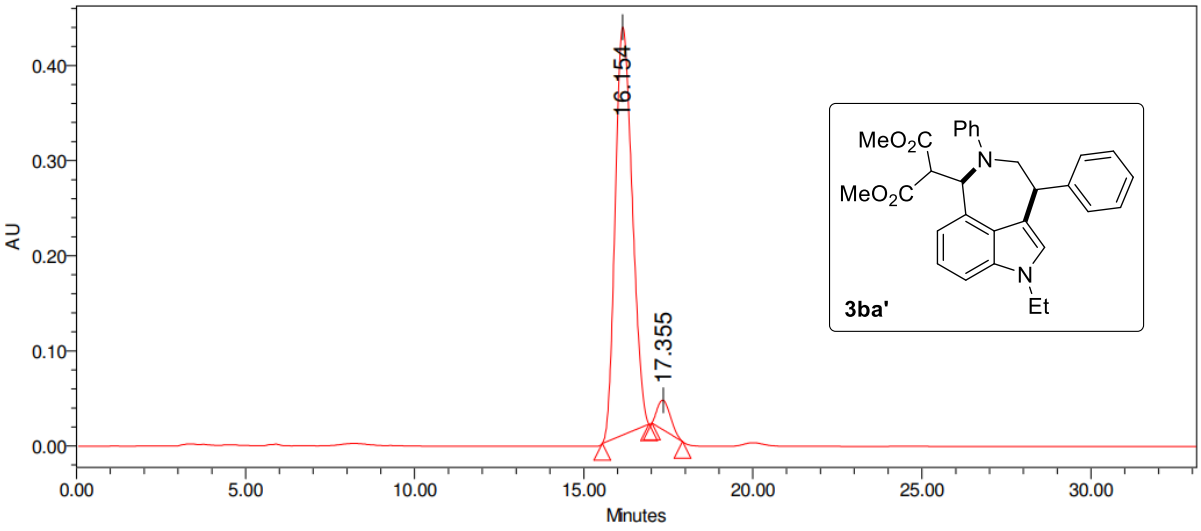

Peak Results

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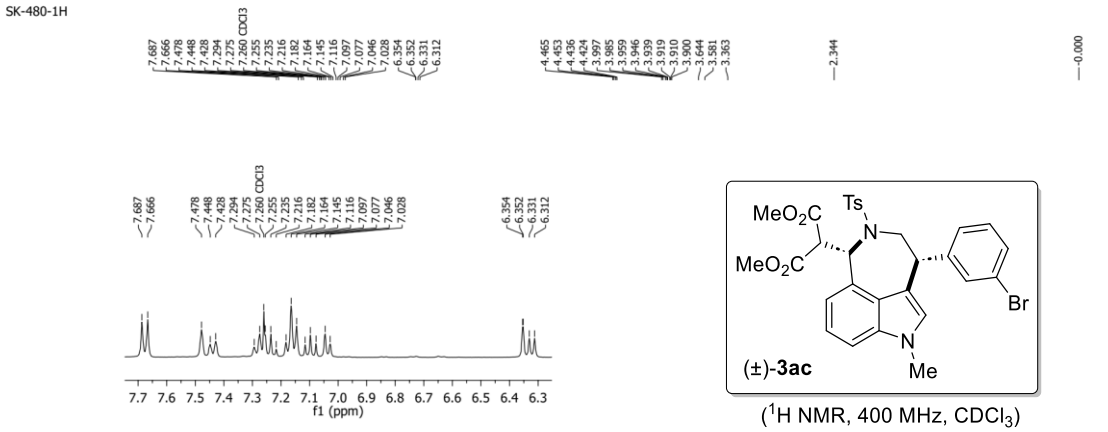
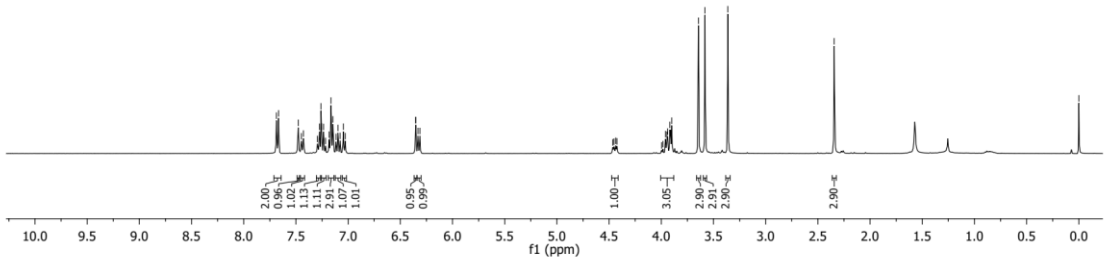
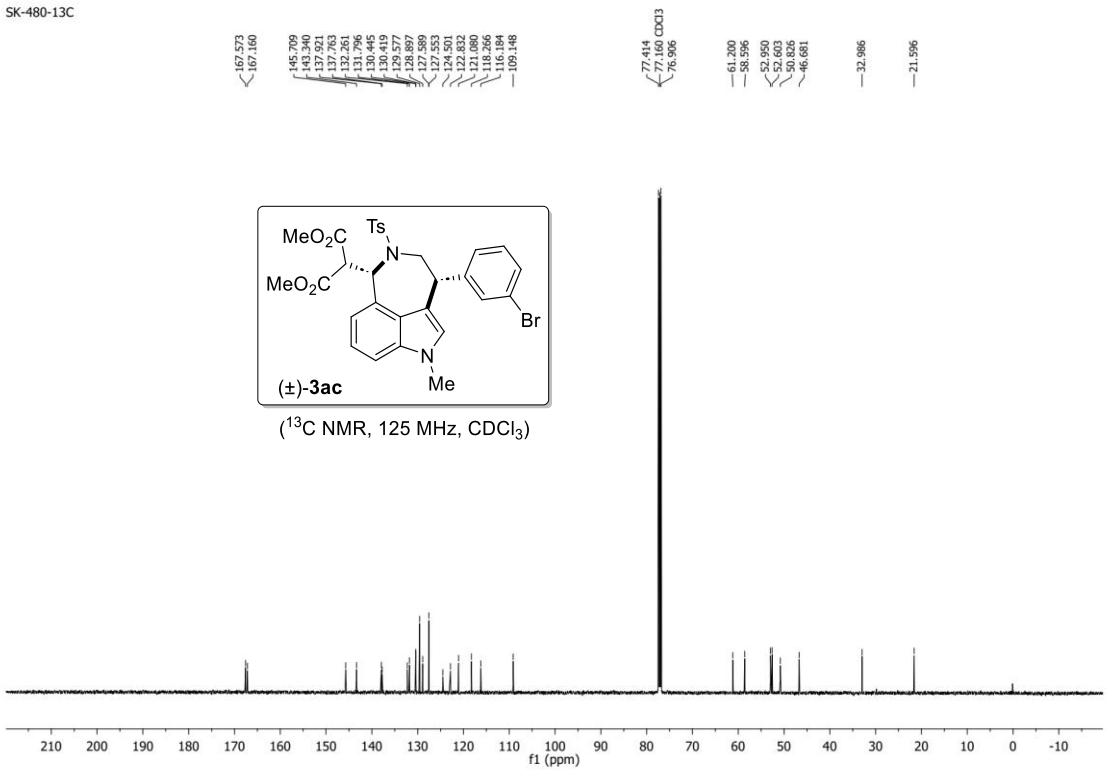
2	17.017	17.917	17.355	31153	5.32

2.7 Selected NMR Spectra

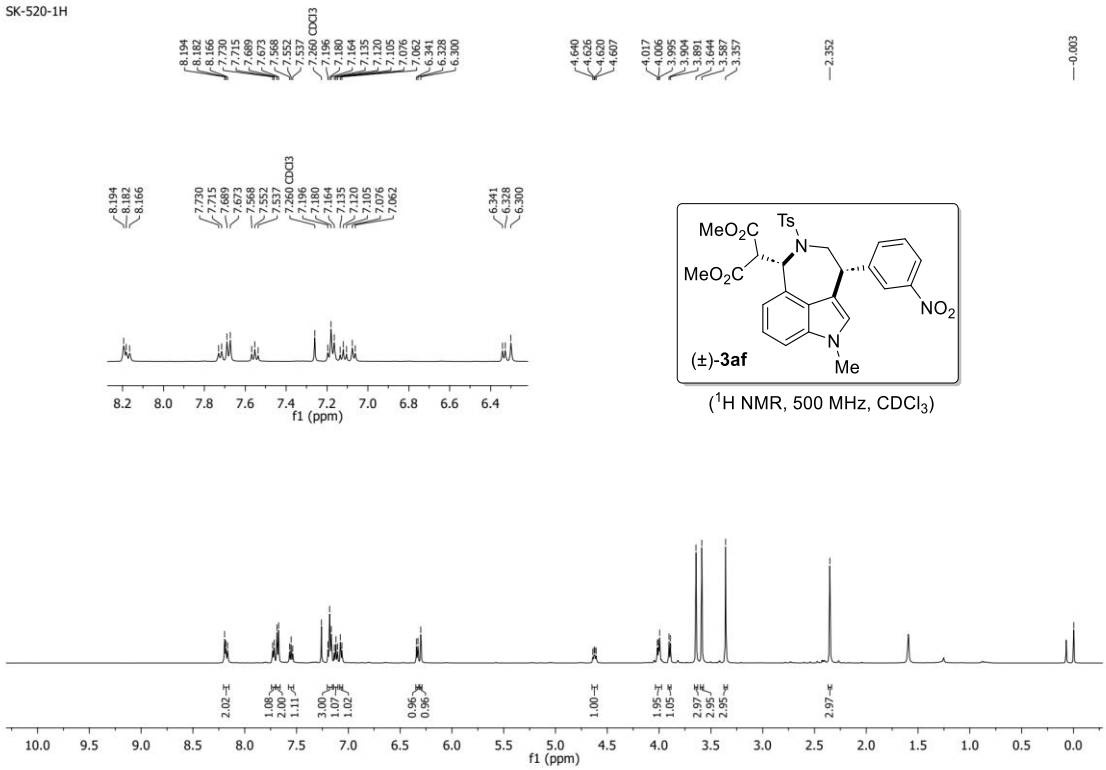


(^{1}H NMR, 400 MHz, $CDCl_3$)





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



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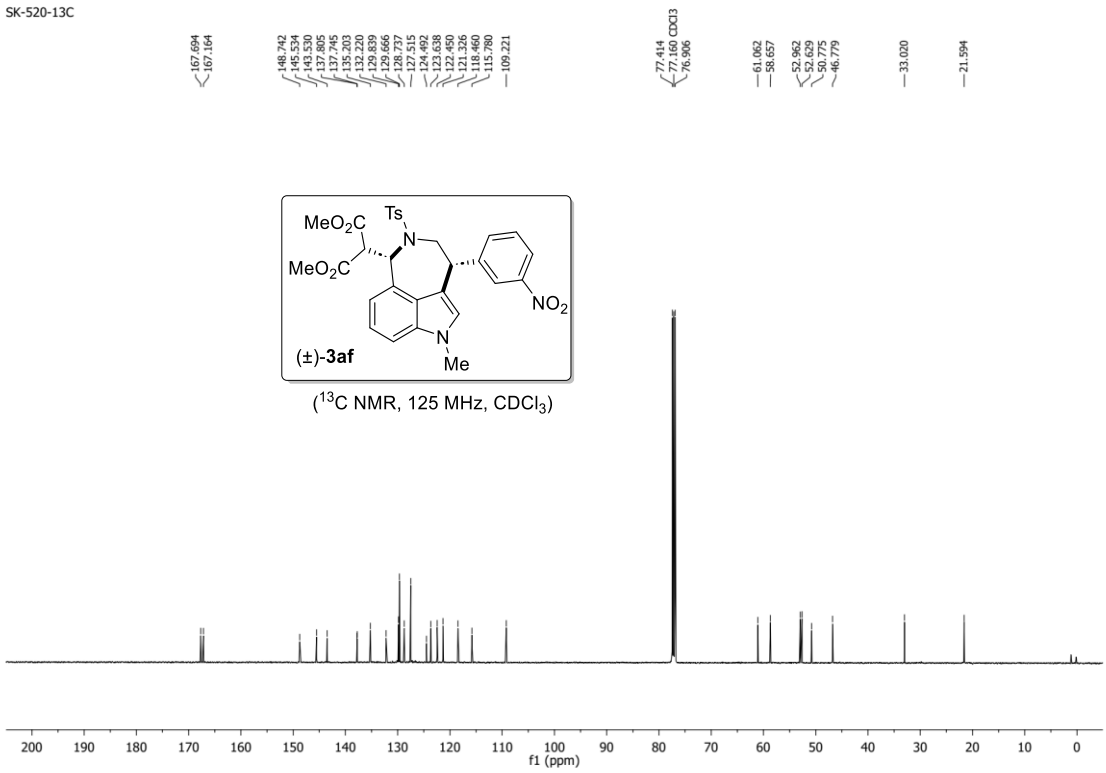
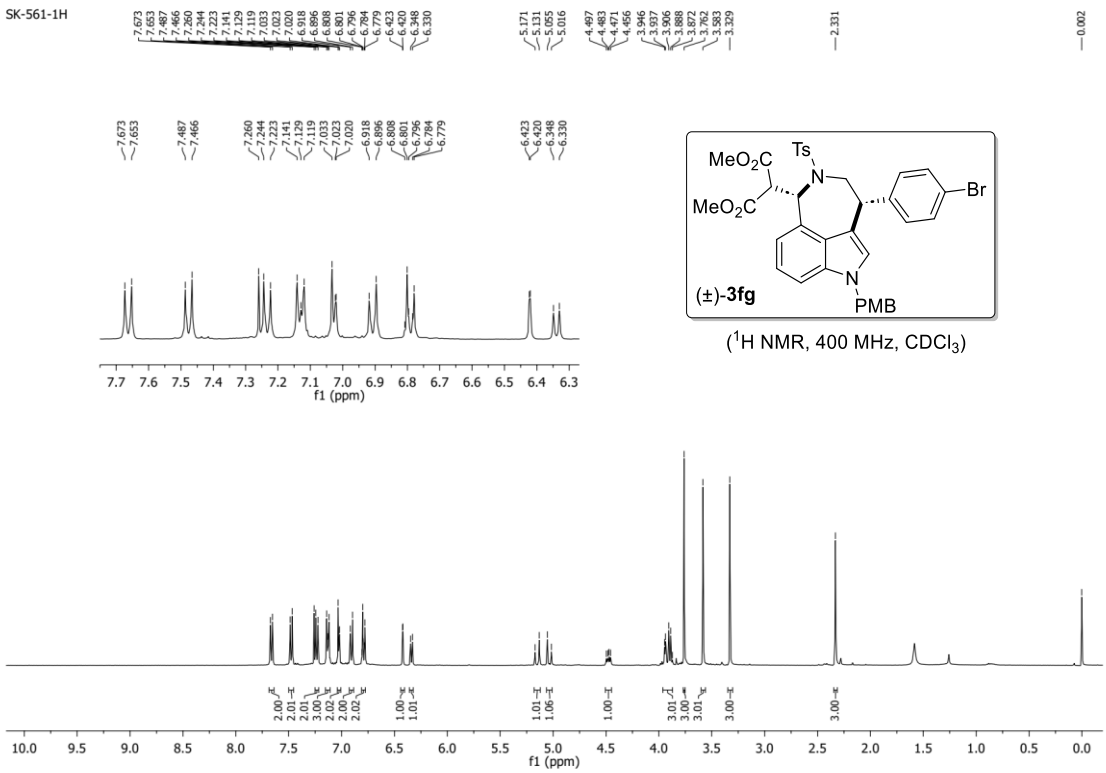
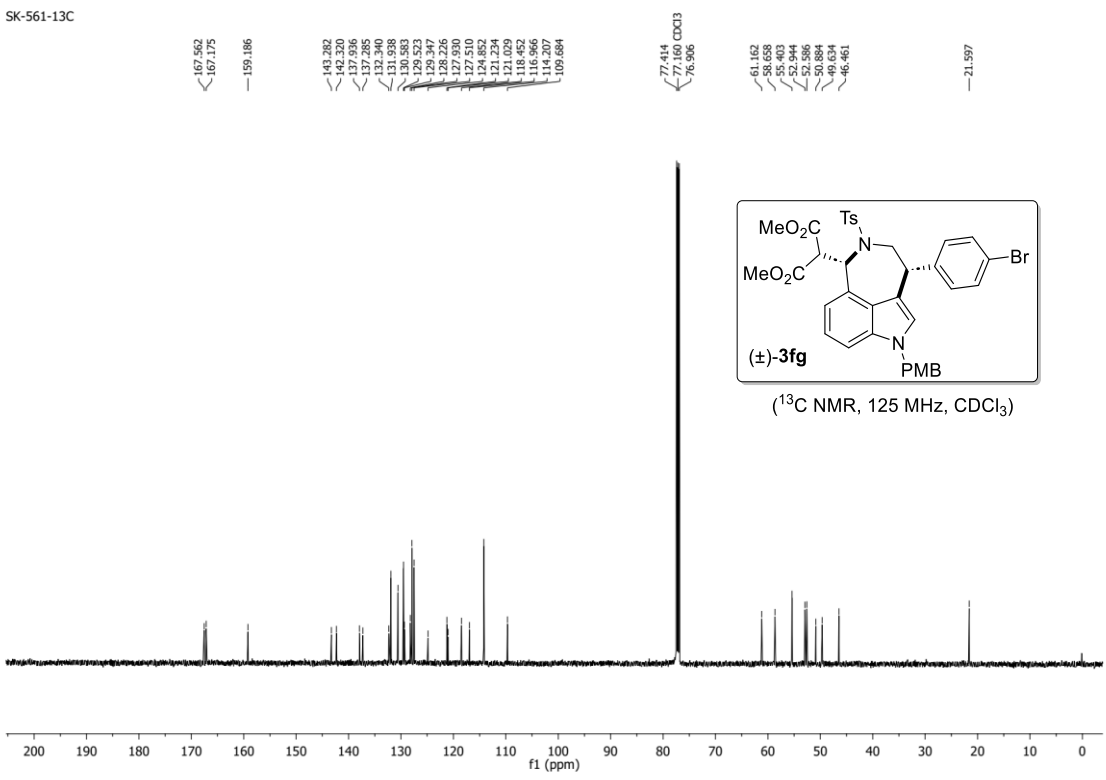


(^{13}C NMR, 125 MHz, $CDCl_3$)



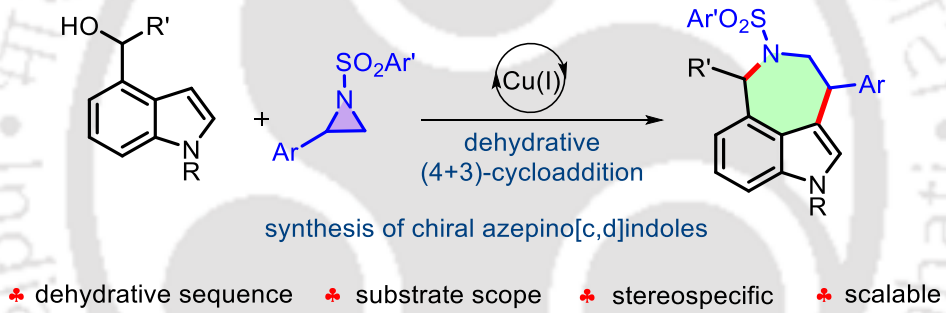
(^{1}H NMR, 400 MHz, $CDCl_3$)



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

Chapter III

Cu(I)-Catalyzed (4+3)-Cycloaddition of 4-Indolylcarbinols with Aziridines to Access Functionalized Azepinoindoles



synthesis of chiral azepino[c,d]indoles

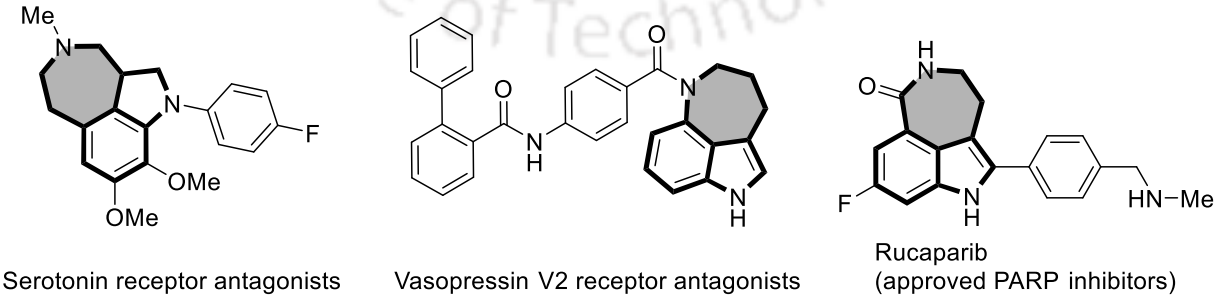
♣ dehydrative sequence ♣ substrate scope ♣ stereospecific ♣ scalable

Chem. Commun. **2024**, *60*, 12008.

Highlighted in *Synfacts* **2024**, *60*, 1276.

Cu(I)-Catalyzed (4+3)-Cycloaddition of 4-Indolylcarbinols with Aziridines to Access Functionalized Azepinoindoles

Medium-sized cyclic compounds, more specifically the seven membered ring systems, often widely found in natural products and pharmacophores are attractive targets in synthetic organic chemistry.[1] In this regard, tricyclic fused azepinoindoles have garnered prominence as intriguing areas of study owing to their miscellaneous biological interests (Figure 1).[2] However, conventional cyclization/annulation strategies are highly challenging due to difficulties arising from the unfavourable entropic and enthalpic factors as well as competing pathways that tend to prefer the formation of the smaller sized rings.[3] Thus, in recent decades, stereoselective methodologies have been developed for synthesizing cyclic medium-sized rings. Contextually, the (4+3)-cycloaddition is recognised as a foremost approach in this arena.[4] Further, utilizing aziridines, strained aza-rings, as versatile coupling partners could expedite the rapid assembly of nitrogen-containing heterocyclic cores *via* cycloaddition or ring-opening/annulation in presence of suitable Lewis acids.[5] Moreover, indolyl carbinols are known to serve as alkylideneindoleninium ion precursors for the development of structurally important synthetic architectures.[6] The Lewis acid catalyzed annulation of 4-indolylmethanols with strained rings remained an unexplored pathway. Thus, employing them as dynamic pro-electrophiles in dehydrative nucleophilic substitution for reaction with N-tosyl aziridines, presents a promising strategy for accessing a wide array of structurally diverse azepinoindoles. This chapter focuses on a Cu(I)-catalyzed dehydrative (4+3)-cycloaddition, suppressing the (3+2)-cycloadduct, in a stereoselective manner. The optically active substrates could be achieved in up to >96% ee values.



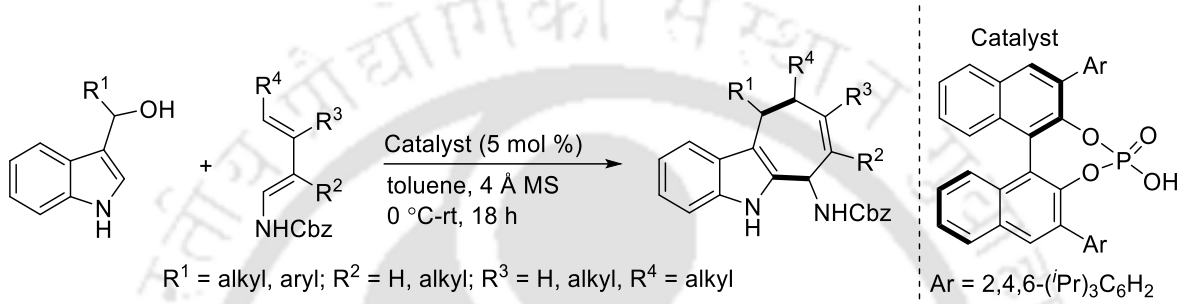
Serotonin receptor antagonists | Vasopressin V2 receptor antagonists | Rucaparib (approved PARP inhibitors)

Figure 1. Pharmacologically Relevant Azepinoindole Motifs.

3.1 Literature

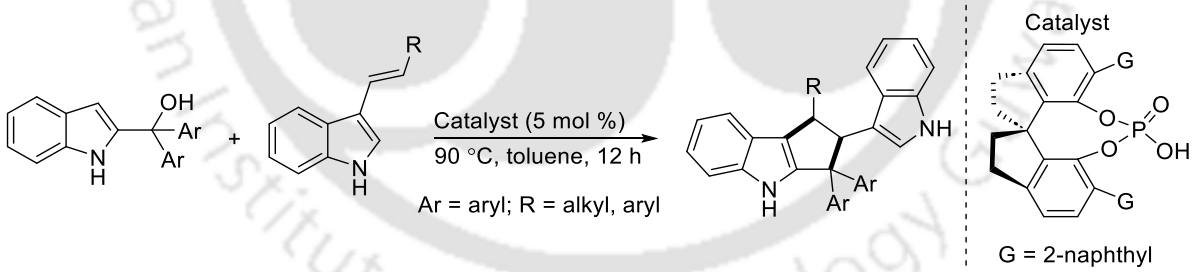
3.1.1 Reactivity of Indolyl Carbinols

Masson and co-workers developed a highly stereoselective (4+3)-cycloaddition of 1,3-dine-1-carbamates with 3-indolyl methanols in presence of a suitable chiral phosphoric acid to deliver 6-aminotetrahydrocyclohepta[*b*]indoles in good yields (Scheme 1).[6b] Mechanistic studies reveal the formation of an ion pair between the chiral phosphate and the carbocation, which implies that the cycloaddition occurs in a cascade manner.



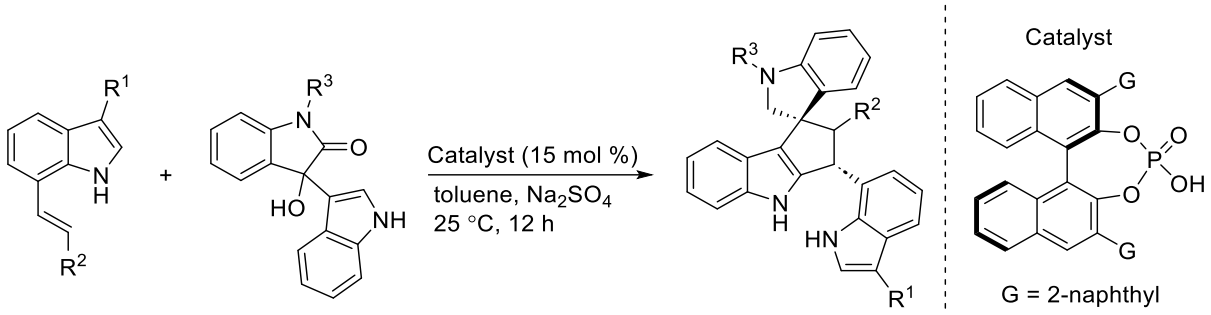
Scheme 1. Stereoselective (4+3)-Cycloaddition with 1,3-Diene-1-carbamates

The Shi group documented an asymmetric (3+2)-cycloaddition of 2-indolylmethanols with 3-vinyl indoles in presence of suitably substituted chiral phosphoric acid (Scheme 2).[7] Using this strategy, the cyclopenta[*b*]indole motifs could be obtained in high yields.



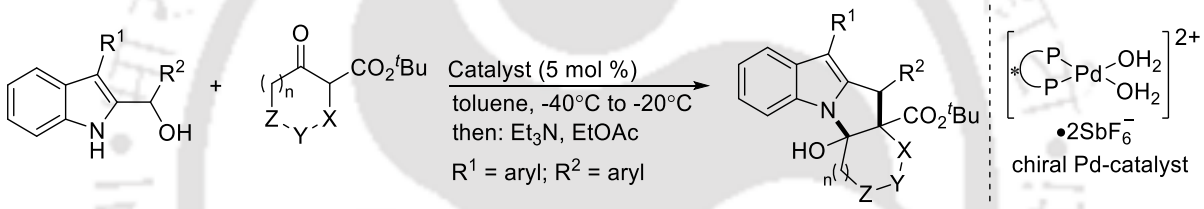
Scheme 2. Asymmetric [3+2] Cycloaddition of 2-Indolylmethanols

They again reported an organocatalytic asymmetric cascade reaction of 7-vinylindoles with isatin derived 3-indolylmethanols in a diastereo- and enantioselective manner to afford C7-functionalized indoles along with the construction of cyclopenta[*b*]indole and spirooxindole frameworks (Scheme 3).[8] Analysis of the reaction mechanism and activation mode indicated the involvement of a vinylogous Michael addition/Friedel-Crafts pathway, which is characterized by the simultaneous H-bonding activation of both the reactants.



Scheme 3. Organocatalytic Asymmetric Cascade Reactions of 7-Vinylindoles

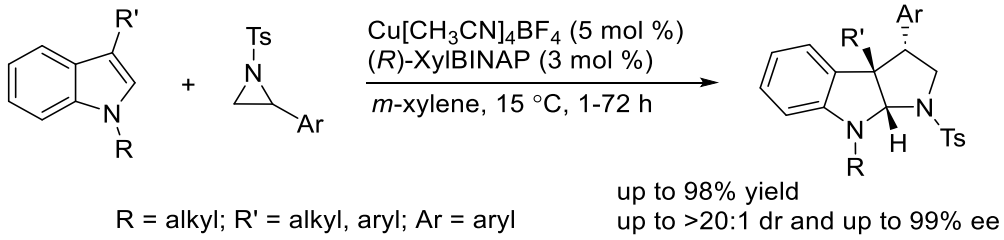
The Schneider group reported a highly stereoselective dual cooperative catalytic strategy wherein a single chiral palladium catalyst could activate both the substrates, simultaneously forming a highly reactive chiral Pd-enolate as well as a vinylogous iminium ion. Substituted pyrrolo[1,2-a]indoles with stereocenters could be obtained in excellent enantioselectivities (Scheme 4).[6d]



Scheme 4. Enantioselective (3+2)-Cycloannulation of *β*-Keto Esters with Alkylidene 2H-Indoles

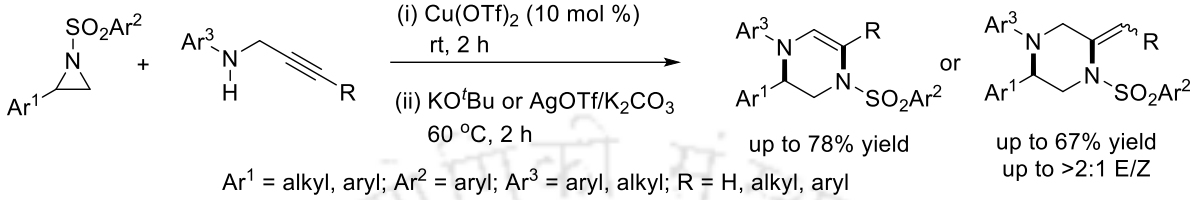
3.1.2 Reactivity of Aziridines

The Chai group described a Cu(I)-catalyzed (3+2)-annulation of indoles with N-tosylaziridines using Cu(I)/chiral diphosphine complexes as the catalytic system to afford variedly substituted chiral pyrroloindolines in a highly stereoselective manner under mild reaction conditions (Scheme 5).[5a]



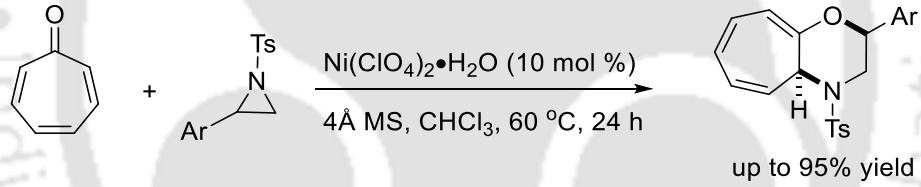
Scheme 5. Copper(I)-Catalyzed Kinetic Resolution of N-Sulfonylaziridines with Indoles

Our group developed a stereospecific Cu(II)-catalyzed nucleophilic ring opening/cyclization cascade of N-sulfonylaziridines with propargylamines (Scheme 6).[5b] The reaction pathway follows a hydroamination/isomerization sequence, occuring *via* 6-*exo-dig* cyclization to deliver functionally diverse piperazine and tetrahydropyrazine frameworks. Additionally, reaction of optically active aziridines yielded enantioenriched cycloadducts in high ee values.



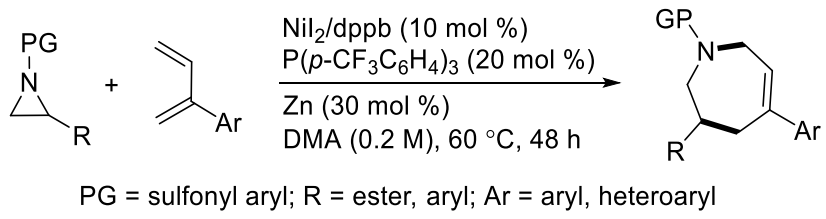
Scheme 6. Cascade Ring Opening/Cyclization of N-Sulfonylaziridines with Propargylamines

The Chai group described a Ni(II)-catalyzed (8+3)-cycloaddition of tropones with N-tosylaziridines to afford fused oxazines (Scheme 7).[5c] The reaction was well tolerated towards steric and electronic substituents on the aziridine ring to furnish the cycloadducts in good yields and selectivity.



Scheme 7. (8+3)-Cycloaddition of Tropones with Aziridines

The Wang group demonstrated a Ni-catalyzed dynamic kinetic activation for the catalyst-controlled activation of aziridines (Scheme 8).[5d] Cleavage of the more sterically hindered C-N bond generates the 1,3-radical anion intermediate, which, participates in a highly regioselective 1,4-Heck/allylic substitution cascade with 1,3-dienes, resulting in a radical-polar crossover (4+3) cycloaddition.



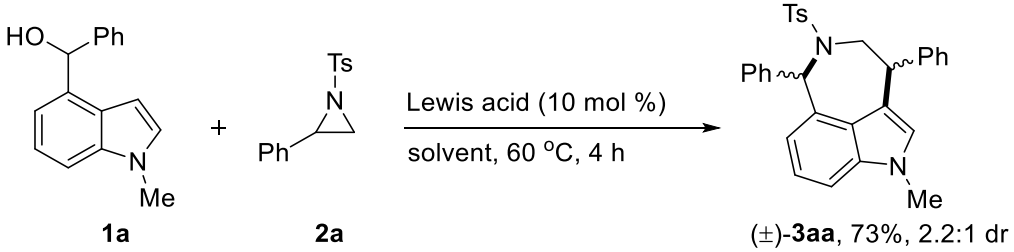
Scheme 8. Kinetic Activation of Aziridines for Radical-Polar Crossover (4+3)-Cycloaddition

In view of the previous reports highlighting the utility of indolyl carbinols as effective synthons for the assembly of indole-based molecular frameworks, we observed a notable gap in the literature concerning their positional variants. Specifically, the potential of 4-indolyl carbinols as efficient 4-atom synthons has remained largely unexplored. This is particularly striking in the context of cycloaddition reaction with strained ring systems, wherein, their unique electronic and structural features could be harnessed to unlock new reactivity patterns. Our study, thus, aims to systematically investigate the application of 4-indolyl carbinols in such transformations, enabling the synthesis of a broad array of indole-fused azepine architectures.

3.2 Present Study

Herein we have presented a Cu(I)-catalyzed (4+3)-cycloaddition of 4-indolylcarbinols with aziridines to furnish azepinoindoles in a stereoselective fashion depicting broad substrate scope and chirality transfer. We began our initial optimization studies using indole-4-yl methanol **1a** and N-sulfonyl aziridine **2a** as the model substrates (Table 1). In a series of Lewis acids examined, $Cu(OTf)_2$ in $(CH_2Cl)_2$ at 60 °C produced (±)-**3aa**, although in a low yield of 31% (entry 1). Variating Lewis acids, such as $Sc(OTf)_3$, $Ni(OTf)_2$ and $LiClO_4•3H_2O$, however, failed to give notable outcomes (entries 2-4). Inspired by the preliminary results, we moved towards screening of a series of other copper salts (entries 5-8). To our delight, $[Cu(CH_3CN)_4]BF_4$ depicted a moderate increase in yield to 58%, while with $[Cu(CH_3CN)_4]PF_6$, the yield was 45% (entry 8). Further analysis of a set of solvents revealed that toluene proved superior over CH_2Cl_2, CH_3CN, THF, CH_3OH, *m*-xylene, demonstrating an increase in the overall yield to 73% (entries 9-14). Efforts to enhance the yield through ligand utilization proved unsuccessful (entries 15-18). Moreover, the reaction proceeded sluggishly at lower temperatures; however, elevating the temperature to 100 °C resulted in a yield of 62% (entries 19-20). A control experiment confirmed that the catalyst played a crucial role in delivering the target heterocycle (entry 21). The structure of (±)-**3aa** was determined by single crystal X-ray analysis (CCDC 2368687).

Table 1. Optimization of the Reaction Conditions[a]

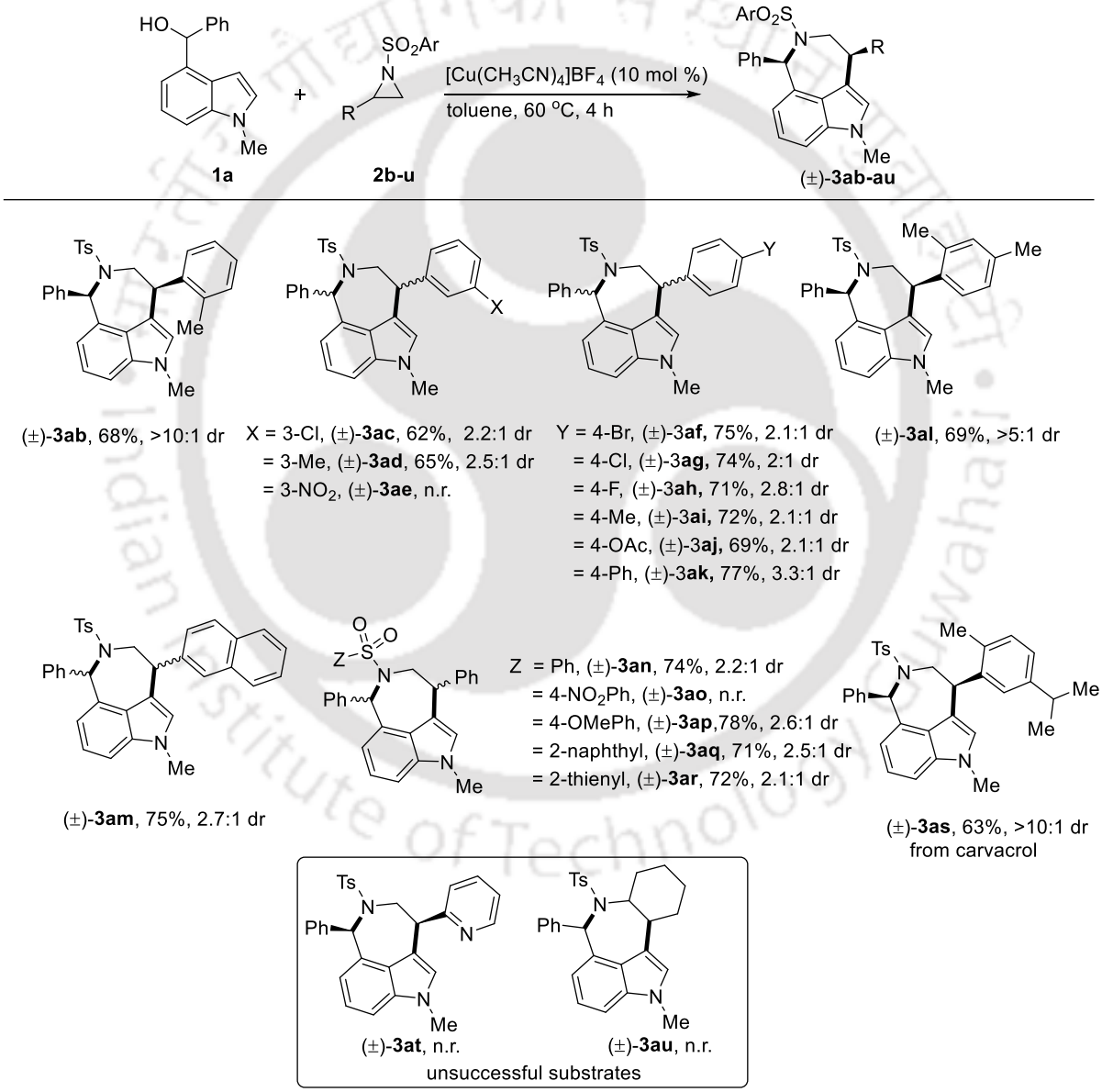


Entry	Lewis acid	Ligand	Solvent	Yield (%)[b]
1	$Cu(OTf)_2$	-	$(CH_2Cl)_2$	31
2	$Sc(OTf)_3$	-	$(CH_2Cl)_2$	23
3	$Ni(OTf)_2$	-	$(CH_2Cl)_2$	trace
4	$LiClO_4•3H_2O$	-	$(CH_2Cl)_2$	n.d.
5	$CuCl_2$	-	$(CH_2Cl)_2$	trace
6	$CuBr_2$	-	$(CH_2Cl)_2$	trace
7	$[Cu(CH_3CN)_4]BF_4$	-	$(CH_2Cl)_2$	58
8	$[Cu(CH_3CN)_4]PF_6$	-	$(CH_2Cl)_2$	45
[c]9	$[Cu(CH_3CN)_4]BF_4$	-	CH_2Cl_2	25
10	$[Cu(CH_3CN)_4]BF_4$	-	CH_3CN	n.r.
11	**$[Cu(CH_3CN)_4]BF_4$**	**-**	**toluene**	**73**
12	$[Cu(CH_3CN)_4]BF_4$	-	THF	41
13	$[Cu(CH_3CN)_4]BF_4$	-	CH_3OH	n.r.
14	$[Cu(CH_3CN)_4]BF_4$	-	*m*-xylene	54
15	$[Cu(CH_3CN)_4]BF_4$	dppe	toluene	63
16	$[Cu(CH_3CN)_4]BF_4$	dppb	toluene	25
17	$[Cu(CH_3CN)_4]BF_4$	PPh_3	toluene	n.r.
18	$[Cu(CH_3CN)_4]BF_4$	2,2′-bipyridyl	toluene	n.r.
[d]19	$[Cu(CH_3CN)_4]BF_4$	-	toluene	31
[e]20	$[Cu(CH_3CN)_4]BF_4$	-	toluene	62
21	-	-	toluene	n.r.

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), Lewis acid (10 mol %), Ligand (10 mol %), solvent (1 mL), 60 °C, 4 h. [b]Isolated yield. n.r. = no reaction. [c]Reaction temperature 40 °C. [d]Reaction temperature 50 °C. [e]Reaction temperature 100 °C.

Under the optimized reaction conditions, the viability of the protocol was assessed for diverse sulfonylated aziridines **2b-u** with **1a** as the standard substrate (Table 2). A series of aziridines bearing substituents at different positions on the aryl ring were well tolerated. For example, 2-methyl substituted **2b** reacted to give (±)-**3ab** in 68% yield with >10:1 dr.[9] Besides, aziridines bearing substituents at the 3-position of the aryl ring with chloro **2c** and methyl **2d**, afforded (±)-**3ac-ad** in 62% and 65% yields, respectively. However, strong electron-withdrawing nitro **2e** failed to react under the standard conditions. Further, aziridines having substituents at the

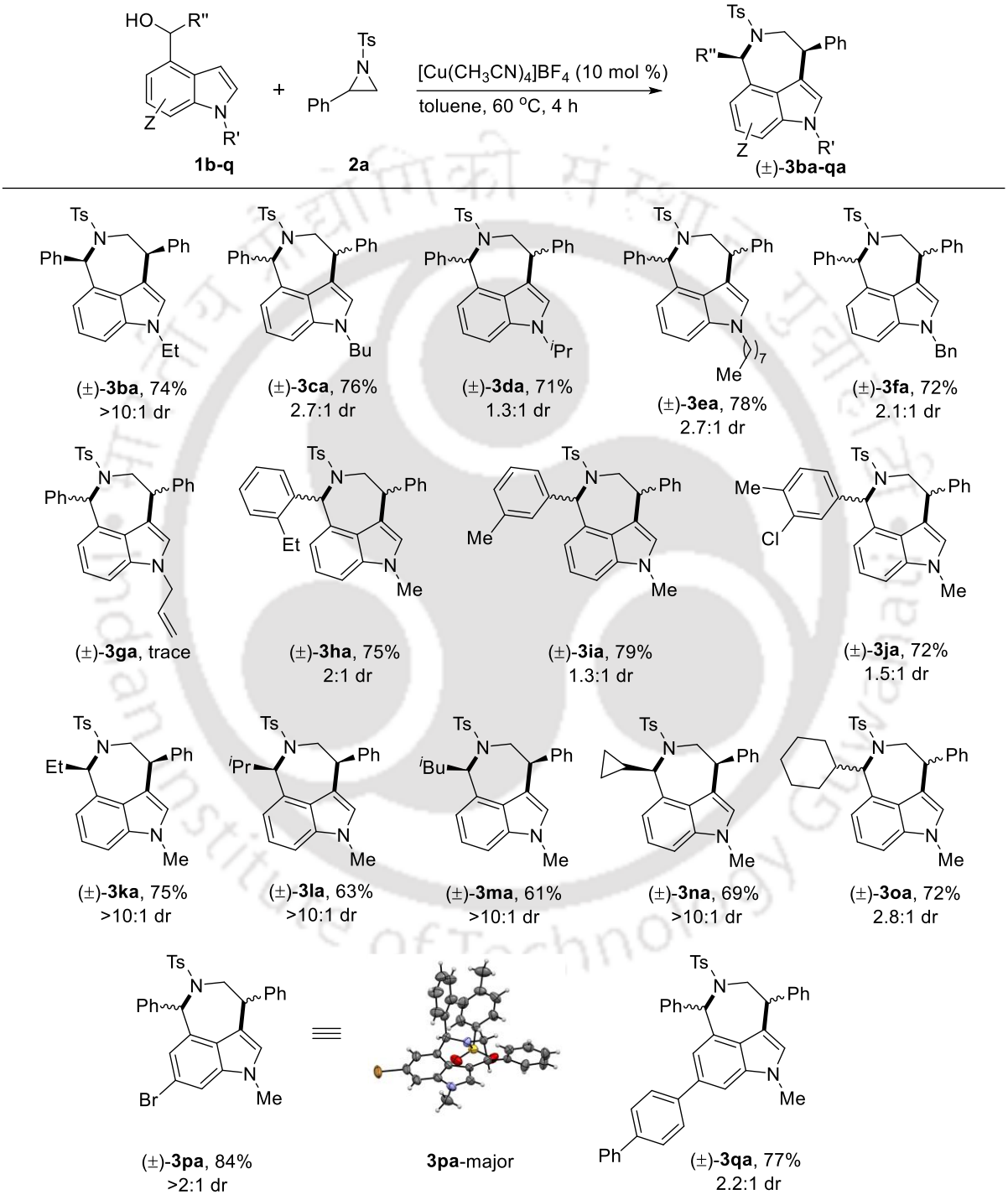
Table 2. Substrate Scope of Aziridines [a,b,c]



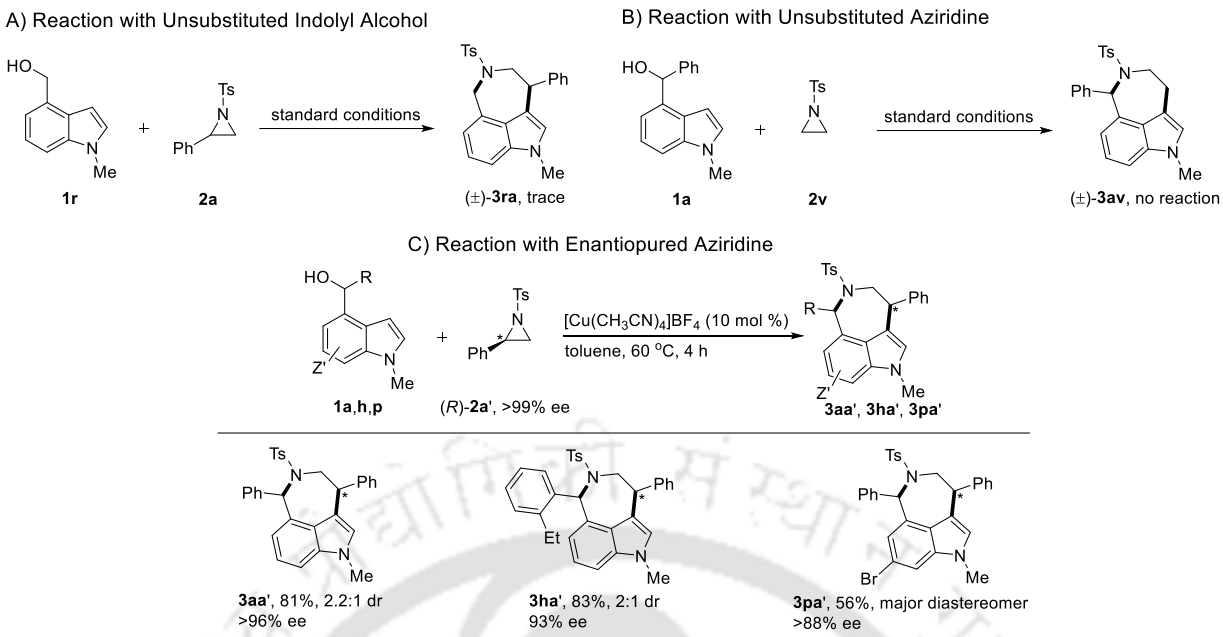
[a]Reaction conditions: **1a** (0.1 mmol), **2b-u** (0.12 mmol), $[Cu(CH_3CN)_4]BF_4$ (10 mol %), toluene (1 mL), 60 ºC, 4 h. [b]Isolated yield. [c]The dr was assigned by ^1H NMR analysis.

4-position with bromo **2f**, chloro **2g**, fluoro **2h**, methyl **2i**, acetoxy **2j** and phenyl **2k** groups reacted efficiently to deliver the cycloadducts (±)-**3af-ak** in 69-77% yields and up to >3:1 dr. Remarkably, disubstituted aziridine **2l** and 2-naphthyl derived aziridine **2m** proved amenable

Table 3. Substrate Scope of Indoles[a,b,c]



[a]Reaction conditions: **1b-q** (0.1 mmol), **2a** (0.12 mmol), $[Cu(CH_3CN)_4]BF_4$ (10 mol %), toluene (1 mL), 60 ºC, 4 h. [b]Isolated yield. [c]The dr was assigned by ^1H NMR analysis.



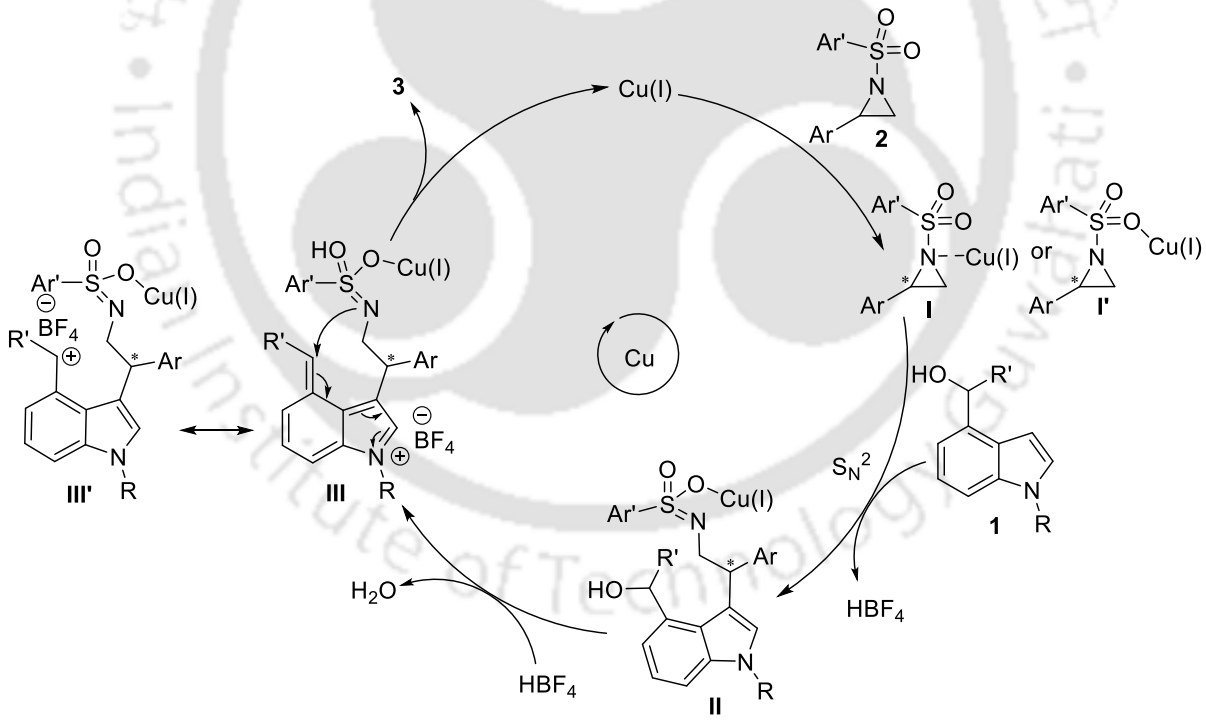
Scheme 9. Mechanistic Studies

in delivering (±)-**3al** and (±)-**3am** in 69% and 75% yields, respectively. The applicability of the reaction was expanded by varying the N-sulfonylaryl substitutions. N-Sulfonylphenyl **2n** and 4-methoxy-N-sulfonylphenyl **2p** reacted to give (±)-**3an** and (±)-**3ap** in 74% and 78% yields, respectively (>2:1 dr). Further, 2-naphthyl **2q** and 2-thienyl **2r** furnished (±)-**3aq** and (±)-**3ar** in up to 72% yields, while **2o** remained an unsuccessful substrate. Delightedly, bioactive anti-oxidant carvacrol derived aziridine **2s** reacted to give (±)-**3as** in 63% yield with >10:1 dr. However, 2-pyridyl **2t** and meso-cyclohexyl **2u** remained ineffective substrates.

Later, we advanced towards investigating the cycloaddition across a range of structurally varied indoles **1b-q** with **2a** as the representative substrate (Table 3). Among various N-alkyl indole derivatives bearing ethyl **1b**, butyl **1c**, isopropyl **1d** and long chain octyl **1e**, the target products (±)-**3ba-ea** were obtained in 71-78% yields and up to >10:1 dr. N-Benzyl substituted **1f** reacted to furnish (±)-**3fa** in 72% (>2:1 dr), while N-allyl **1g** gave a trace amount of (±)-**3ga**. To broaden the scope of our investigation, we assessed the compatibility of a range of 4-indolyl carbinols **1h-o** bearing diverse substitution at the carbinol center. Intriguingly, aryl substituted derivatives having functionalization at the 2-position **1h**, 3-position **1i**, as well as disubstituted **1j** delivered (±)-**3ha-ja** in 72-79% yields. Moreover, alkyl substitution at the carbinol center with substituents such as, ethyl **1k**, isopropyl **1l**, isobutyl **1m**, cyclopropyl **1n** and cyclohexyl **1o** reacted efficiently to give (±)-**3ka-3oa** in 61-75% yields. Finally, greater structural diversity can be attained by modifying indoles with specific substituents at the 6-position of the aryl ring, such as 6-Br **1p** and 6-biphenyl **1q**, resulting (±)-**3pa** and (±)-**3qa** in 84% and 77% yields,

respectively. The major diastereomer of (±)-**3pa** was isolated, whose structure was determined from single crystal X-ray analysis (CCDC 2368691).

To shed light into the reaction pathway, the reaction of an unsubstituted indolyl carbinol **1r** was carried out with **2a**. The target cycloadduct (±)-**3ra** was formed only in a trace amount owing to the comparatively lower stabilisation of the intermediate carbocation leading to the product formation (Scheme 9A). Further, no reaction was observed when indolyl carbinol **1a** was treated with an unsubstituted N-tosyl aziridine **2v**, thus, indicating the necessity of a suitable aryl substitution at the 2-position of the aziridine ring (Scheme 9B). Further, to depict the stereochemical outcomes, the reaction of indoles **1a**, **1h** and **1p** was carried out with optically active (*R*)-**2a′** (Scheme 9C). Under the standard reaction conditions, **1a** reacted to give **3aa′** in >96% ee and >2:1 dr. Further, indole **1h** bearing 2-ethylphenyl substitution at the carbinol center afforded **3ha′** in 93% ee with 2:1 dr, while **1p** furnished **3pa′** in slightly reduced 88% ee.[10] These findings indicate that the protocol is stereospecific towards furnishing optically pure azepines with commendable chirality transfer.

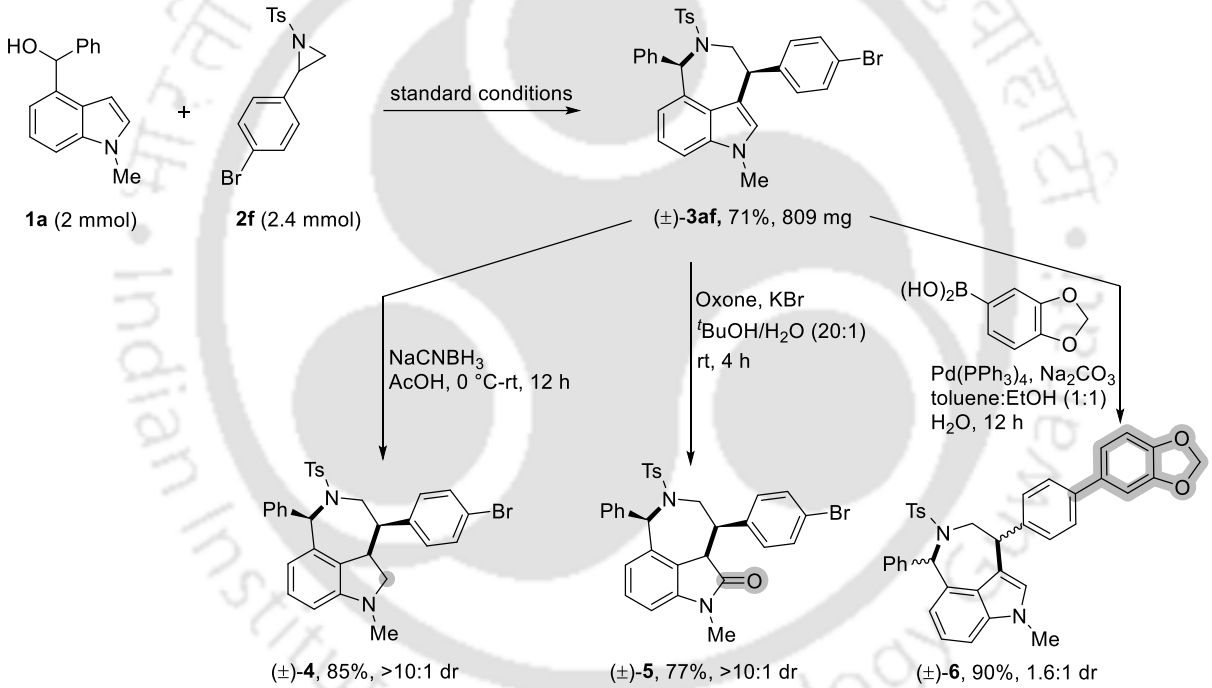


Scheme 10. Plausible Mechanism

Considering literature precedents[6d,11] and mechanistic studies, a plausible catalytic cycle has been reported (Scheme 10). Initial activation of the aziridine **2** in presence of the Lewis acid generates the intermediate **I** or **I′** which can lead to S_N2 attack by the C3-position of indole **1** to give the Friedel-Crafts type intermediate **II**. Selective coordination of the -OH functionality

with the Lewis acid leads to activation of **II**, directing dehydrative elimination to afford the carbocation **III′** or its delocalized resonating indol-4-yl cationic species **III**. The generated alkylideneindoleninium, can undergo a Michael-type addition by the tethered aziridine nitrogen to furnish **3** and regenerate the catalyst to complete the catalytic cycle.

To further demonstrate the synthetic utility of the protocol, a scale-up synthesis was carried out on a 2 mmol scale using indole **1a** and N-tosyl aziridine **2f** as model substrates (Scheme 11). The reaction occurred to furnish (±)-**3af** in 71% yield, which was subjected to various post synthetic transformations. For example, using $NaCNBH_3$ in AcOH, (±)-**3af** was reduced to the indoline (±)-**4** in 85%, while an Oxone mediated oxidation afforded the oxindole (±)-**5** in 77% yield and >10:1 dr. In addition, a Pd-catalyzed Suzuki coupling with benzo[*d*][1,3]dioxol-5-yl boronic acid delivered the dioxol tethered azepinoindole (±)-**6** in 90% yield and 1.6:1 dr.



Scheme 11. Scale-up and Post-Synthetic Utilities

In conclusion, we have described a well-designed protocol for the (4+3)-cycloaddition of 4-indolylcarbinols with N-sulfonyl aziridines, utilizing inexpensive and weakly Lewis acidic Cu(I) as the catalyst. An assembly of azepinoindoles were synthesized with good functional group diversity. The described protocol allows for a stereospecific reaction pathway, furnishing optically active azepinoindoles in up to >96% ee.

3.3 Experimental Section

General Information. 1*H*-Indole-4-carbaldehyde, styrenes, $Cu(CH_3CN)_4BF_4$, $LiAlH_4$, $NaCNBH_3$ and Oxone were purchased from Aldrich and used as received. Chloramine-T hydrate was purchased from Merck, and used as received. The solvents were dried prior to use according to the standard procedure. SRL silica gel G/GF 254 plates were used for analytical TLC and SRL silica gel (100-200 mesh) was used for column chromatography. NMR (^1H, ^{13}C and ^{19}F) 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 of (±)-**3aa** and (±)-**3pa-major** 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-2018/3* (Göttingen, Germany). HPLC analysis has been carried out using Waters-2489 with YMC Chiral ART Cellulose-SC column utilizing *iso*-propanol and hexane as eluent. Optical rotation was determined using a Rudolph Autopol I Automatic Polarimeter at mentioned temperatures.

General Procedure for the Synthesis of (±)-**3aa-qa**. Indole **1** (0.1 mmol, 1 equiv), aziridine **2** (0.12 mmol, 1.2 equiv) and $Cu(CH_3CN)_4BF_4$ (0.01 mmol, 0.10 equiv, 3 mg) were stirred in toluene (2 mL) at 60 °C for 4 h under calcium chloride tube. After completion, as monitored by TLC, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (5 mL) and passed through a short pad of celite using ethyl acetate (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 eluent to afford (±)-**3**.

General Procedure for the Enantiospecific Synthesis of 3aa′, 3ha′ and 3pa′. Indole **1** (0.1 mmol, 1 equiv), (*R*)-2-phenyl-1-tosylaziridine **2a′** (0.12 mmol, 1.2 equiv, 32 mg) and $Cu(CH_3CN)_4BF_4$ (0.01 mmol, 0.10 equiv, 3 mg) were stirred in toluene (2 mL) at 60 °C for 4 h under calcium chloride tube. The purification was performed as above presented general procedure. The enantiomeric excess was determined using chiral HPLC.

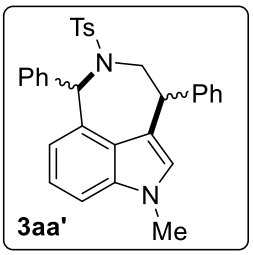
Scale-up Synthesis of (±)-**3af**. Indole **1a** (2 mmol, 1 equiv, 474 mg), aziridine **2f** (2.4 mmol, 1.2 equiv, 840 mg) and $Cu(CH_3CN)_4BF_4$ (0.2 mmol, 0.10 equiv, 63 mg) were stirred in toluene (5 mL) at 60 °C for 4 h under calcium chloride tube. After completion, as monitored by TLC, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (10 mL) and passed through a short pad of celite using ethyl acetate (15 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 to afford (±)-**3af**.

Synthesis of (±)-**4**.[12] To a solution of (±)-**3af** (0.1 mmol, 1 equiv, 57 mg) in AcOH (5 mL) at 0 °C, was added $NaBH_3CN$ (0.5 mmol, 5 equiv, 31 mg) portion wise. The reaction was allowed to stir at room temperature for 12 h. After complete consumption of the starting material, saturated aq. NaOH (5 mL) was added slowly to the reaction mixture at 0 °C and extracted with ethyl acetate (3 X 10 mL). Subsequently, the combined organic layers were washed with brine (5 mL) and water (5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as eluent to afford (±)-**4**.

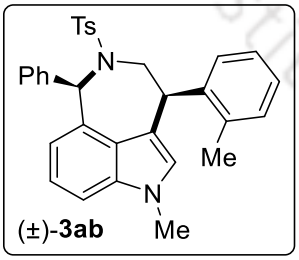
Synthesis of (±)-**5**.[13] To a solution of (±)-**3af** (0.1 mmol, 1 equiv, 57 mg) and KBr (0.01 mmol, 0.1 equiv, 2 mg) in $^tBuOH/H_2O$ (v/v 20:1) (2 mL) at room temperature, was added Oxone (0.12 mmol, 1.2 equiv, 37 mg) and allowed to stir for 4 h. After completion, as monitored by TLC, the reaction mixture was quenched with saturated aq. $Na_2S_2O_3$ (5 mL) and extracted with ethyl acetate (3 X 10 mL). The combined organic layers were washed with brine (5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as eluent to afford (±)-**5**.

Synthesis of (±)-**6**.[14] To a solution of (±)-**3af** (0.1 mmol, 1 equiv, 57 mg) in toluene/EtOH (1:1, 3 mL), was added the benzo[d][1,3]dioxol-5-ylboronic acid (0.1 mmol, 1 equiv, 16 mg), $Pd(PPh_3)_4$ (3 mol %, 3 mg), Na_2CO_3 (0.1 mmol, 1 equiv, 11 mg) and H_2O (100 µL). The mixture was stirred at 100 °C for 12 h under a nitrogen atmosphere. After 12 h, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (10 mL) and washed with brine (1 X 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as eluent to give (±)-**6**.

3.4 Characterization Data of the Products

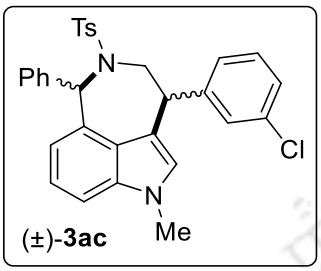


6-Methyl-1,4-diphenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole 3aa′. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; colorless solid; mp 154-155 °C; yield 73% (36 mg); mixture of diastereomers (2.2:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8 Hz, 2H), 7.31-7.30 (m, 1H), 7.25-7.19 (m, 6.20H), 7.16-7.15 (m, 7.17H), 7.12-7.10 (m, 2.70H), 7.00-6.99 (m, 1H), 6.89-6.86 (m, 3.21H), 6.83-6.82 (m, 0.73H), 6.73 (s, 1H), 6.67 (s, 0.39H), 6.35 (s, 1H), 5.92 (s, 0.38H), 4.52-4.49 (m, 1H), 4.15-4.10 (m, 0.43H), 3.78-3.74 (m, 1.41H), 3.66 (s, 3H), 3.63-3.61 (m, 0.41H), 3.53 (s, 1H), 3.38-3.32 (m, 1H), 2.33 (s, 3H), 2.26 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.7, 142.8, 141.8, 141.1, 140.6, 140.3, 138.8, 137.7, 137.6, 136.9, 133.3, 132.5, 129.4, 129.1, 129.0, 128.7, 128.69, 128.60, 128.3, 128.0, 127.6, 127.5, 127.3, 126.9, 126.7, 126.6, 126.1, 125.8, 121.9, 121.2, 119.6, 119.1, 117.17, 117.13, 108.6, 108.2, 65.1, 63.4, 53.0, 50.5, 46.4, 42.9, 32.9, 32.6, 21.58, 21.51; FT-IR (KBr) 2924, 1733, 1343, 1156, 1091, 660, 545 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{29}N_2O_2S$: 493.1944, found: 493.1956; $[\alpha]_D^{25}$ = +100 (c = 0.01, $CHCl_3$); HPLC: *ee* for major diastereomer = >96% *ee* [YMC Chiral ART Cellulose-SC column, hexane/^{i}PrOH = 90:10, flow rate: 1 mL/min, λ= 254 nm, t_R = 25.71 min (major), 30.48 min (minor)].

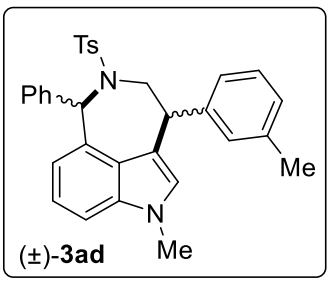


6-Methyl-1-phenyl-4-(*o*-tolyl)-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-3ab. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.54; colorless solid; mp 157-158 °C; yield 68% (34 mg); major diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.68 (m, 2H), 7.23-7.18 (m, 2H), 7.16-7.15 (m, 5H), 7.10-7.08 (m, 3H), 7.03-6.96 (m, 2H), 6.90-6.88 (m, 3H), 6.77 (s, 1H), 6.31 (s, 1H), 4.81-4.77 (m, 1H), 3.72-3.68 (m, 1H), 3.66 (s, 3H), 3.34-

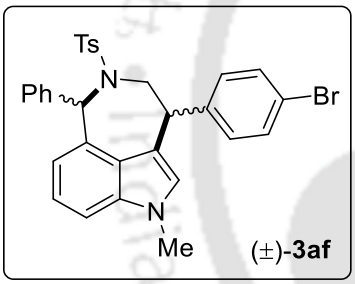
3.27 (m, 1H), 2.41 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.8, 142.1, 141.2, 138.9, 137.7, 136.3, 133.3, 130.2, 129.3, 129.1, 128.6, 128.3, 128.2, 127.6, 127.3, 126.6, 126.2, 126.0, 121.2, 119.1, 117.0, 108.2, 65.2, 49.6, 41.1, 32.9, 21.5, 19.6; FT-IR (KBr) 2982, 1732, 1373, 1241, 1045, 755 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{31}N_2O_2S$: 507.2101, found: 507.2104.



4-(3-Chlorophenyl)-6-methyl-1-phenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-**3ac**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.52; colorless solid; mp 161-162 °C; yield 62% (32 mg); mixture of diastereomers (2.2:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.69 (m, 0.81H), 7.31-7.29 (m, 3.29H), 7.20-7.10 (m, 11.48H), 7.06-7.04 (m, 0.61H), 7.00-6.98 (m, 1H), 6.93-6.83 (m, 4.50H), 6.71 (s, 0.41H), 6.67 (s, 1H), 6.36 (0.42H), 5.96 (s, 1H), 4.52-4.48 (m, 0.44H), 4.11-4.05 (m, 1H), 3.80-3.76 (m, 1H), 3.73-3.72 (m, 0.35H), 3.68 (s, 1H), 3.66-3.61 (m, 1H), 3.57 (s, 3H), 3.35-3.28 (m, 0.45H), 2.34 (s, 1H), 2.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.7, 143.1, 143.0, 142.0, 141.0, 140.2, 138.7, 137.7, 137.6, 136.9, 134.3, 133.2, 132.5, 129.94, 129.92, 129.4, 129.1, 128.9, 128.8, 128.74, 128.70, 128.5, 128.4, 128.1, 127.73, 127.71, 127.5, 127.3, 127.2, 127.0, 126.9, 126.7, 126.4, 126.2, 125.73, 125.70, 122.1, 121.4, 119.7, 119.2, 116.4, 116.2, 108.7, 108.3, 65.1, 63.5, 52.5, 50.3, 46.2, 42.9, 32.9, 32.7, 21.59, 21.53; FT-IR (KBr) 2926, 1733, 1343, 1256, 1090, 666, 593, 546 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{28}ClN_2O_2S$: 527.1555, found: 527.1563.

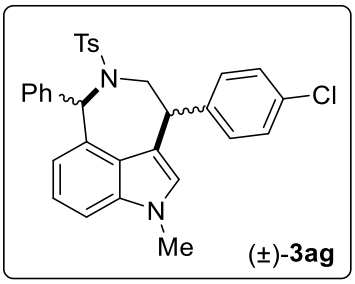


6-Methyl-1-phenyl-4-(*m*-tolyl)-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-**3ad**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.56; colorless solid; mp 171-172 °C; yield 65% (33 mg); mixture of diastereomers (2.5:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.32-7.29 (m, 1.29H), 7.24-7.21 (m, 2H), 7.18-7.16 (m, 5H), 7.14-7.09 (m, 3.68H), 7.06-7.03 (m, 1H), 7.01-7.00 (m, 0.70H), 6.98 (s, 1.17H), 6.95-6.93 (m, 1.11H), 6.91-6.86 (m, 3H), 6.84-6.82 (m, 1.16H), 6.77 (s, 0.40H), 6.73 (s, 1H), 6.67 (s, 0.39H), 6.38 (s, 1H), 5.93 (s, 0.38H), 4.50-4.46 (m, 1H), 4.17-4.10 (m, 0.41H), 3.79-3.74 (m, 1.43H), 3.67 (s, 3H), 3.63-3.59 (m, 0.40H), 3.54 (s, 1.20H), 3.38-3.32 (m, 1H), 2.33 (s, 3H), 2.29-2.27 (m, 5.24H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 142.8, 141.8, 141.1, 140.5, 140.3, 138.8, 138.2, 138.1, 137.69, 137.65, 136.9, 133.3, 132.5, 129.49, 129.44, 129.3, 129.1, 129.0, 128.6, 128.5, 128.4, 128.3, 128.07, 128.04, 127.7, 127.6, 127.5, 127.3, 126.7, 126.5, 126.1, 125.8, 125.69, 125.66, 121.9, 121.2, 119.6, 119.1, 117.2, 117.1, 108.6, 108.1, 65.1, 63.3, 52.9, 50.6, 46.3, 42.8, 32.9, 32.6, 21.56, 21.50; FT-IR (KBr) 2985, 1734, 1370, 1242, 1045, 750 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{31}N_2O_2S$: 507.2101, found: 507.2105.

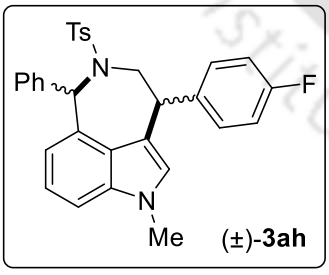


4-(4-Bromophenyl)-6-methyl-1-phenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-**3af**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.50; colorless solid; mp 174-175 °C; yield 75% (42 mg); mixture of diastereomers (2.1:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8 Hz, 2H), 7.38-7.36 (m, 2H), 7.35-7.32 (m, 1H), 7.30-7.28 (m, 1.51H), 7.22-7.19 (m, 1.50H), 7.18-7.10 (m, 8.57H), 7.05-7.02 (m, 1.94H), 7.00-6.98 (m, 0.52H), 6.87-6.83 (m, 5H), 6.70-6.69 (m, 1.38H), 6.34 (s, 1H), 5.97 (s, 0.47H), 4.52-4.48 (m, 1H), 4.11-4.05 (m, 0.51H), 3.82-3.77 (m, 0.51H), 3.75-3.70 (m, 1.10H), 3.67 (s, 3H), 3.64-3.60 (m, 0.52H), 3.56 (s, 1.49H), 3.32-3.25 (m, 1H), 2.33 (s, 3H), 2.27 (s, 1.50H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0, 142.7, 142.0, 140.9, 140.3, 140.2, 138.6, 137.7, 137.6, 137.1, 133.3, 132.5, 131.7, 130.44, 130.40, 129.4, 129.1, 128.9, 128.6, 128.5, 128.4, 128.1, 127.7, 127.6, 127.3, 126.6, 126.4, 126.2, 125.7, 122.1, 121.4, 121.0, 120.7, 119.7, 119.2, 116.6, 116.4, 108.7, 108.2, 65.0, 63.6, 52.5, 50.3, 45.9, 42.6, 32.9, 32.7, 21.58, 21.52; FT-IR (KBr) 2984, 1732,

1373, 1241, 1045, 748, 667 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{28}BrN_2O_2S$: 571.1049, found: 571.1043.

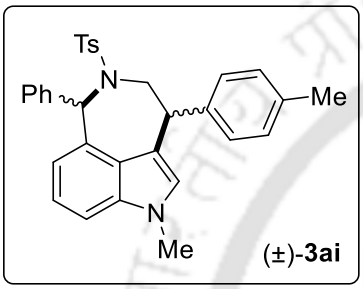


4-(4-Chlorophenyl)-6-methyl-1-phenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-3ag. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.51; colorless solid; mp 172-173 °C; yield 74% (39 mg); mixture of diastereomers (2:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.29-7.28 (m, 1.54H), 7.25-7.23 (m, 2H), 7.20-7.17 (m, 4.24H), 7.16-7.14 (m, 5H), 7.12-7.08 (m, 4H), 7.00-6.98 (m, 0.49H), 6.91-6.83 (m, 4.92H), 6.70-6.68 (m, 1.51H), 6.33 (s, 1H), 5.96 (s, 0.49H), 4.53-4.49 (m, 1H), 4.11-4.05 (m, 0.53H), 3.82-3.78 (m, 0.50H), 3.75-3.70 (m, 1H), 3.67 (s, 3H), 3.64-3.60 (m, 0.52H), 3.56 (s, 1.49H), 3.32-3.26 (m, 1H), 2.33 (s, 3H), 2.27 (s, 1.5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0, 142.2, 142.0, 141.0, 140.3, 139.6, 138.7, 137.7, 137.6, 137.1, 133.3, 132.9, 132.6, 132.5, 130.05, 130.01, 129.4, 129.1, 128.9, 128.7, 128.5, 128.4, 128.1, 127.7, 127.6, 127.3, 126.6, 126.4, 126.2, 125.7, 122.1, 121.4, 119.7, 119.2, 116.7, 116.5, 108.7, 108.2, 65.0, 63.6, 52.6, 50.4, 45.9, 42.5, 32.9, 32.7, 21.58, 21.51; FT-IR (KBr) 2925, 1733, 1340, 1255, 1090, 670, 593, 546 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{28}ClN_2O_2S$: 527.1555, found: 527.1552.

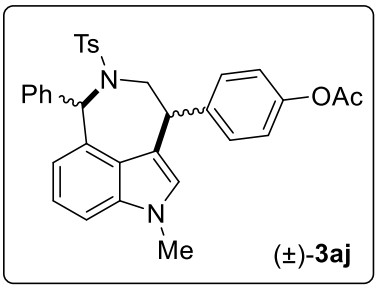


4-(4-Fluorophenyl)-6-methyl-1-phenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-3ah. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.48; colorless solid; mp 170-171 °C; yield 71% (36 mg); mixture of diastereomers (2.8:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.31-7.29 (m, 1.11H), 7.23-7.21 (m, 1.50H), 7.19-7.10 (m, 9.13H), 7.01-6.99 (m, 0.47H), 6.96-6.92 (m, 3.38H), 6.88-6.83 (m, 3.62H), 6.71 (s, 1H), 6.68 (s, 0.40H), 6.34 (s, 1H), 5.94 (s, 0.35H), 4.53-4.49 (m, 1H), 4.11-4.05 (m, 0.39H),

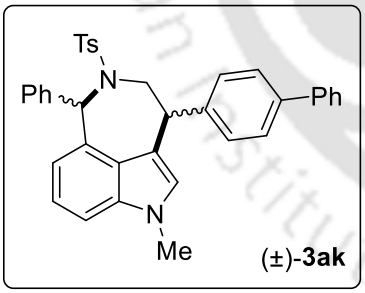
3.82-3.79 (m, 0.35H), 3.77-3.72 (m, 1H), 3.67 (s, 3H), 3.64-3.61 (m, 0.36H), 3.56 (s, 1H), 3.34-3.27 (m, 1H), 2.34 (s, 3H), 2.27 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 162.8 (d, $J_{C\text{-}F}$ = 243.6 Hz), 160.9, 142.9, 142.0, 141.0, 140.3, 139.4 (d, $J_{C\text{-}F}$ = 3.2 Hz), 138.7, 137.7, 137.6, 136.9, 136.64, 136.61, 133.3, 132.5, 130.19, 130.13, 130.1 (d, $J_{C\text{-}F}$ = 7.8 Hz), 129.4, 129.1, 128.9, 128.6, 128.46, 128.40, 128.0, 127.67, 127.62, 127.3, 126.6, 126.4, 126.1, 125.7, 122.0, 121.3, 119.6, 119.1, 117.0, 116.9, 115.5, 115.4 (d, $J_{C\text{-}F}$ = 21 Hz), 115.3, 108.7, 108.2, 65.0, 63.4, 52.9, 50.5, 45.7, 42.3, 32.9, 32.6, 21.5, 21.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ -115.3, -115.9; FT-IR (KBr) 2924, 1736, 1507, 1340, 1155, 744, 543 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{28}FN_2O_2S$: 511.1850, found: 511.1843.



6-Methyl-1-phenyl-4-(*p*-tolyl)-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-3ai. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.51; colorless solid; mp 179-180 °C; yield 72% (36 mg); mixture of diastereomers (2.1:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8 Hz, 2H), 7.30-7.29 (m, 1.46H), 7.22-7.20 (m, 2H), 7.17-7.13 (m, 4.91H), 7.12-7.07 (m, 3.34H), 7.05-7.04 (m, 3.28H), 7.02-6.98 (m, 0.90H), 6.89-6.87 (m, 3H), 6.85-6.80 (m, 1.35H), 6.72 (s, 1H) 6.66 (s, 0.42H), 6.37 (s, 1H), 5.93 (s, 0.46H), 4.49-4.45 (m, 1H), 4.14-4.07 (m, 0.50H), 3.75-3.70 (m, 1.56H), 3.66 (s, 3H), 3.62-3.59 (m, 0.56H), 3.53 (s, 1.31H), 3.35-3.28 (m, 1H), 2.33-2.31 (m, 3.48H), 2.30 (s, 3H), 2.26 (s, 1.22H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.8, 141.8, 141.1, 140.7, 140.3, 138.8, 137.7, 136.9, 136.5, 133.3, 132.6, 129.38, 129.34, 129.2, 129.1, 129.0, 128.6, 128.59, 128.55, 128.3, 127.6, 127.5, 127.3, 126.7, 126.6, 126.1, 125.8, 121.9, 121.2, 119.6, 119.1, 117.3, 108.6, 108.1, 65.1, 63.4, 53.0, 50.6, 45.9, 42.5, 32.9, 32.6, 21.57, 21.51, 21.2, 21.1; FT-IR (KBr) 2979, 1736, 1368, 1241, 1048, 751 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{31}N_2O_2S$: 507.2101, found: 507.2097.

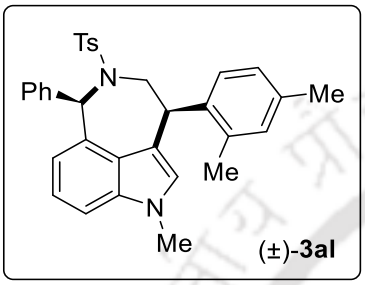


4-(6-Methyl-1-phenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indol-4-yl)phenyl acetate (±)-3aj. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.45; colorless solid; mp 169-170 °C; yield 69% (38 mg); mixture of diastereomers (2.1:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8 Hz, 2H), 7.33-7.29 (m, 1.51H), 7.23-7.11 (m, 12H), 7.01-6.95 (m, 4.36H), 6.88-6.82 (m, 4H), 6.71 (s, 1H) 6.67 (s, 0.45H), 6.41 (s, 1H), 5.96 (s, 0.46H), 4.56-4.52 (m, 1H), 4.13-4.06 (m, 0.48H), 3.81-3.72 (m, 1.49H), 3.67 (s, 3H), 3.64-3.62 (m, 0.49H), 3.55 (s, 1.44H), 3.34-3.27 (m, 1H), 2.34 (s, 3H), 2.29 (s, 1.44H), 2.27-2.26 (m, 4.48H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 169.6, 149.7, 149.5, 142.9, 141.9, 141.2, 141.0, 140.2, 133.3, 132.5, 129.66, 129.62, 129.4, 129.14, 129.11, 128.6, 128.44, 128.40, 128.0, 127.67, 127.61, 127.3, 126.7, 126.5, 126.2, 125.7, 122.0, 121.7, 121.6, 121.3, 119.6, 119.1, 108.7, 108.2, 65.0, 63.4, 52.8, 50.6, 45.9, 42.4, 32.9, 32.6, 21.57, 21.51, 21.29, 21.26; FT-IR (KBr) 2924, 2854, 1761, 1504, 1370, 1340, 1201, 1157, 748, 543 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{33}H_{31}N_2O_4S$: 551.1999, found: 551.1990.

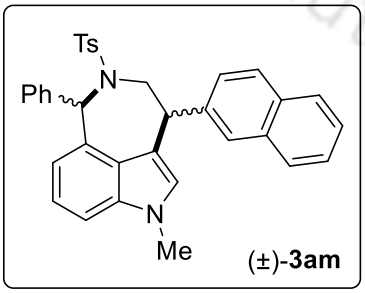


4-([1,1'-Biphenyl]-4-yl)-6-methyl-1-phenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-3ak. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.48; colorless solid; mp 173-174 °C; yield 77% (43 mg); mixture of diastereomers (3.3:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8 Hz, 2H), 7.57-7.53 (m, 2.68H), 7.48-7.46 (m, 2.50H), 7.42-7.38 (m, 2.34H), 7.33-7.30 (m, 2.31H), 7.24-7.21 (m, 4.02H), 7.18-7.14 (m, 4.85H), 7.12-7.10 (m, 2.20H), 7.07-7.05 (m, 0.68H), 7.01-6.99 (m, 0.32H), 6.91-6.87 (m, 3H), 6.83-6.81 (m, 0.66H), 6.73 (s, 1H), 6.69 (s, 0.33H), 6.43 (s, 1H), 6.01 (s, 0.30H), 4.59-4.55 (m, 1H), 4.20-4.14 (m, 0.32H), 3.85-3.77 (m, 1.33H), 3.70-3.67 (m, 3.33H), 3.54 (s, 1H), 3.41-3.34 (m, 1H), 2.33 (s,

3H), 2.24 (s, 0.91H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.9, 142.8, 141.8, 141.1, 140.9, 140.8, 140.3, 140.1, 139.9, 139.8, 138.8, 137.7, 137.6, 137.0, 133.3, 132.5, 129.4, 129.17, 129.13, 129.10, 129.0, 128.9, 128.8, 128.6, 128.4, 128.0, 127.64, 127.61, 127.4, 127.35, 127.32, 127.1, 126.6, 126.5, 126.2, 125.8, 122.0, 121.2, 119.6, 119.1, 117.0, 116.9, 108.7, 108.2, 65.1, 63.4, 52.9, 50.5, 46.1, 42.6, 32.9, 32.6, 21.5, 21.4; FT-IR (KBr) 2925, 1733, 1485, 1342, 1241, 1156, 1092, 757, 660, 548 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{37}H_{33}N_2O_2S$: 569.2257, found: 569.2261.

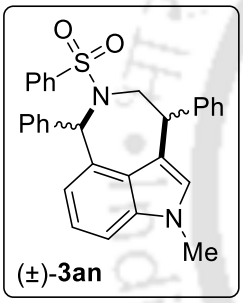


4-(2,4-Dimethylphenyl)-6-methyl-1-phenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-3al. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.48; colorless solid; mp 182-183 °C; yield 69% (36 mg); major diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.6 Hz, 2H), 7.16-7.14 (m, 4H), 7.09-7.07 (m, 2H), 6.98 (s, 1H), 6.90-6.84 (m, 5H), 6.77 (s, 1H), 6.33 (s, 1H), 4.77-4.73 (m, 1H), 3.73-3.68 (m, 1H), 3.66 (s, 3H), 3.31-3.24 (m, 1H), 2.38 (s, 3H), 2.32 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.8, 141.2, 139.1, 138.9, 136.18, 136.13, 133.3, 130.9, 129.3, 129.1, 128.69, 128.61, 128.3, 128.2, 127.8, 127.5, 127.3, 126.9, 126.7, 121.2, 119.0, 108.1, 65.1, 49.7, 40.7, 32.8, 21.5, 21.0, 19.5; FT-IR (KBr) 2923, 1735, 1451, 1239, 1156, 1091, 747, 657, 543 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{33}H_{33}N_2O_2S$: 521.2257, found: 521.2257.



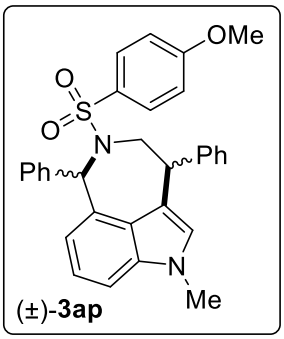
6-Methyl-4-(naphthalen-2-yl)-1-phenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-3am. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.46; colorless solid; mp 168-169 °C; yield 75% (40 mg); mixture of diastereomers (2.7:1 dr); ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.83-7.75 (m, 4H), 7.73-7.72 (m, 1.52H), 7.70-7.67 (m, 1.93H), 7.48-7.42 (m, 2.97H), 7.35-7.33 (m, 1.22H), 7.27-7.26 (m, 0.42H), 7.248-7.245 (m, 0.71H), 7.22-7.21 (m, 1.61H), 7.20-7.16 (m, 5.46H), 7.14-7.12 (m, 2H), 7.04-7.02 (m, 0.4H), 6.94-6.89 (m, 2.98H), 6.83-6.81 (m, 0.72H), 6.76 (s, 1H), 6.73 (s, 0.38H), 6.368-6.365 (m, 1H), 5.95-5.94 (m, 0.36H), 4.75-4.70 (m, 1H), 4.34-4.28 (m, 0.40H), 4.01-3.96 (m, 0.38H), 3.88-3.83 (m, 1H), 3.75-3.70 (m, 0.40H), 3.64 (s, 3H), 3.53 (s, 1.14H), 3.51-3.44 (m, 1H), 2.34 (s, 3H), 2.25 (s, 1.20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.9, 141.9, 141.1, 140.9, 140.3, 138.7, 138.3, 137.7, 137.6, 137.0, 133.5, 133.3, 132.7, 132.68, 132.61, 129.4, 129.2, 129.1, 128.7, 128.4, 128.3, 128.2, 128.1, 127.8, 127.79, 127.74, 127.67, 127.65, 127.4, 127.3, 127.2, 126.8, 126.7, 126.67, 126.61, 126.4, 126.2, 126.1, 125.9, 125.8, 125.7, 122.0, 121.3, 119.6, 119.1, 117.08, 117.00, 108.7, 108.2, 65.1, 63.5, 52.5, 50.3, 46.6, 43.1, 32.9, 32.6, 21.58, 21.51; FT-IR (KBr) 2923, 1733, 1456, 1341, 1241, 1153, 745, 660, 548 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{35}H_{31}N_2O_2S$: 543.2101, found: 543.2107.

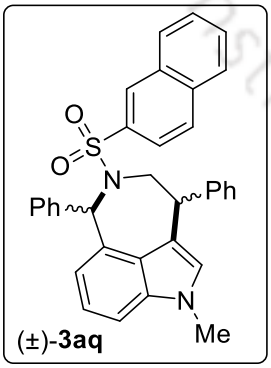


(±)-**3an**

6-Methyl-1,4-diphenyl-2-(phenylsulfonyl)-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-3an. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.49; colorless solid; mp 152-153 °C; yield 74% (35 mg); mixture of diastereomers (2.2:1 dr); ^1H NMR (400 MHz, $CDCl_3$) δ 7.84-7.82 (m, 2H), 7.44-7.39 (m, 1.11H), 7.33-7.27 (m, 5.19H), 7.25-7.19 (m, 5.88H), 7.18-7.10 (m, 6.67H), 7.05-6.98 (m, 2.37H), 6.90-6.87 (m, 3H), 6.76 (s, 1H), 6.70 (s, 0.47H), 6.356-6.353 (m, 1H), 5.916-5.913 (m, 0.45H), 4.52-4.47 (m, 1H), 4.17-4.10 (m, 0.48H), 3.82-3.75 (m, 1.48H), 3.69-3.67 (m, 0.36H), 3.65 (s, 3H), 3.52 (s, 1.42H), 3.40-3.33 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 141.7, 141.0, 140.5, 140.1, 139.7, 137.6, 133.1, 132.3, 132.2, 131.2, 129.1, 129.0, 128.8, 128.7, 128.69, 128.68, 128.65, 128.61, 128.4, 128.0, 127.8, 127.67, 127.64, 127.3, 127.2, 127.0, 126.7, 126.5, 126.2, 125.8, 121.9, 121.2, 119.6, 119.1, 117.0, 116.8, 108.8, 108.2, 65.1, 63.4, 53.0, 50.5, 46.3, 42.9, 32.9, 32.6; FT-IR (KBr) 3026, 1733, 1447, 1342, 1306, 1157, 1047, 745, 605 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{30}H_{27}N_2O_2S$: 479.1788, found: 479.1772.

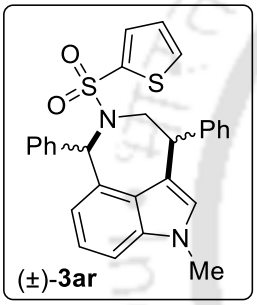


2-((4-Methoxyphenyl)sulfonyl)-6-methyl-1,4-diphenyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-3ap. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.45; colorless solid; mp 149-150 °C; yield 78% (39 mg); mixture of diastereomers (2.6:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.8 Hz, 2H), 7.35-7.27 (m, 2.44H), 7.25-7.19 (m, 5.23H), 7.18-7.11 (m, 6.94H), 7.02-6.99 (m, 1.15H), 6.94-6.92 (m, 2H), 6.88-6.86 (m, 1H), 6.78 (d, *J* = 9.2 Hz, 2H), 6.74 (s, 1H), 6.67 (s, 0.40H), 6.50-6.47 (m, 0.79H), 6.364-6.360 (m, 1H), 5.935-5.932 (m, 0.38H), 4.52-4.47 (m, 1H), 4.16-4.09 (m, 0.44H), 3.79-3.78 (m, 3.73H), 3.76-3.74 (m, 2.08H), 3.66 (s, 3H), 3.64-3.61 (m, 0.42H), 3.53 (s, 1.13H), 3.39-3.32 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 161.9, 143.7, 141.2, 140.6, 140.3, 137.7, 133.5, 133.2, 132.4, 131.7, 129.4, 129.1, 129.0, 128.7, 128.69, 128.66, 128.62, 128.5, 128.4, 128.0, 127.6, 127.5, 127.3, 126.9, 126.5, 126.1, 125.8, 122.0, 121.2, 119.6, 119.1, 117.12, 117.10, 113.9, 112.8, 108.7, 108.2, 65.0, 63.3, 55.6, 55.5, 52.9, 50.4, 46.2, 42.9, 32.9, 32.5; FT-IR (KBr) 2924, 2854, 1736, 1458, 1341, 1153, 1093, 557 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{29}N_2O_3S$: 509.1893, found: 509.1893.

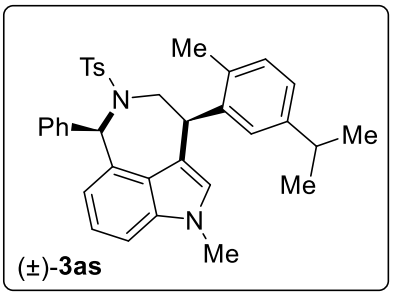


6-Methyl-2-(naphthalen-2-ylsulfonyl)-1,4-diphenyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-3aq. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.50; colorless solid; mp 155-156 °C; yield 71% (37 mg); mixture of diastereomers (2.5:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.90-7.88 (m, 1H), 7.86-7.83 (m, 2.19H), 7.81-7.79 (m, 1.21H),

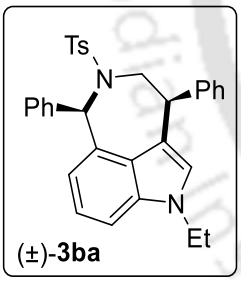
7.76-7.70 (m, 1H), 7.69-7.64 (m, 1.54H), 7.63-7.57 (m, 1.44H), 7.54-7.52 (m, 0.45H), 7.44-7.39 (m, 2.37H), 7.36-7.29 (m, 4.42H), 7.27-7.26 (m, 1.95H), 7.25-7.21 (m, 3.83H), 7.16-7.14 (m, 0.41H), 7.11-7.09 (m, 0.85H), 7.07-7.04 (m, 1.94H), 7.02-7.00 (m, 0.93H), 6.95 (s, 1H), 6.88 (s, 0.40H), 6.37-6.36 (m, 1H), 5.808-5.804 (m, 0.40H), 4.63-4.58 (m, 1H), 4.41-4.35 (m, 0.41H), 4.00-3.95 (m, 1H), 3.88-3.77 (m, 0.90H), 3.65 (s, 3H), 3.55-3.48 (m, 1H), 3.19 (s, 1.18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.7, 141.0, 140.3, 139.9, 138.5, 137.5, 137.3, 136.7, 134.5, 134.1, 133.0, 132.0, 131.7, 131.6, 129.4, 129.2, 129.1, 129.0, 128.9, 128.7, 128.68, 128.62, 128.59, 128.50, 128.49, 128.43, 128.2, 128.08, 128.04, 127.7, 127.6, 127.4, 127.39, 127.37, 127.33, 127.1, 126.9, 126.5, 126.4, 125.9, 125.84, 122.80, 122.5, 121.9, 121.2, 119.7, 119.1, 116.8, 116.6, 108.9, 108.2, 65.4, 63.6, 53.0, 50.6, 46.2, 43.1, 32.7, 32.0; FT-IR (KBr) 3027, 2935, 1735, 1493, 1451, 1339, 1154, 1131, 745, 701, 665, 545 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{34}H_{29}N_2O_2S$: 529.1944, found: 529.1947.



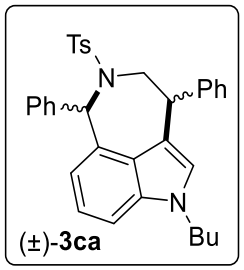
6-methyl-1,4-diphenyl-2-(thiophen-2-ylsulfonyl)-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-3ar. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.47; colorless solid; mp 149-150 ^{o}C; yield 72% (35 mg); mixture of diastereomers (2.1:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.48 (m, 1H), 7.38-7.36 (m, 1H), 7.32-7.28 (m, 1.78H), 7.28-7.24 (m, 3.64H), 7.23-7.20 (m, 4.50H), 7.18-7.12 (m, 6.21H), 7.06-7.01 (m, 1.49H), 6.92-6.90 (m, 2H), 6.87-6.85 (m, 2H), 6.76 (s, 1H), 6.73-6.72 (m, 0.49H), 6.69 (s, 0.49H), 6.61-6.59 (m, 0.48H), 6.399-6.396 (m, 1H), 5.977-5.974 (m, 0.47H), 4.68-4.63 (m, 1H), 4.23-4.17 (m, 0.47H), 3.82-3.78 (m, 1.48H), 3.73-3.69 (m, 0.50H), 3.66 (s, 3H), 3.54 (s, 1.50H), 3.41-3.34 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 142.7, 140.8, 140.4, 140.27, 140.23, 137.71, 137.70, 132.8, 131.89, 131.81, 131.3, 131.1, 130.3, 129.1, 128.77, 128.71, 128.6, 128.4, 127.8, 127.7, 127.6, 127.4, 127.05, 127.01, 126.5, 126.4, 126.3, 125.7, 121.9, 121.2, 119.7, 119.1, 117.08, 117.00, 109.0, 108.3, 65.3, 63.7, 53.4, 50.6, 46.2, 42.7, 32.9, 32.7; FT-IR (KBr) 3027, 2938, 1734, 1451, 1345, 1152, 1013, 744, 701, 607, 574 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{25}N_2O_2S_2$: 485.1352, found: 485.1351.



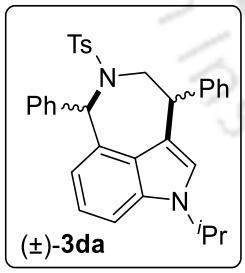
4-(5-Isopropyl-2-methylphenyl)-6-methyl-1-phenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-3as. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.50; colorless solid; mp 173-174 °C; yield 63% (34 mg); major diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.24-7.19 (m, 2H), 7.17-7.13 (m, 4H), 7.09-7.07 (m, 2H), 6.97-6.89 (m, 4H), 6.81-6.80 (m, 1H), 6.77 (s, 1H), 6.349-6.345 (m, 1H), 4.80-4.75 (m, 1H), 3.71-3.64 (m, 4H), 3.32-3.25 (m, 1H), 2.70-2.63 (m, 1H), 2.36-2.32 (m, 6H), 1.07-1.04 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.7, 142.8, 142.0, 141.2, 138.9, 137.7, 133.6, 133.5, 130.1, 129.3, 129.2, 128.6, 128.3, 127.6, 127.3, 126.5, 126.2, 124.3, 121.2, 119.0, 117.1, 108.1, 65.2, 49.6, 41.2, 33.6, 32.8, 24.1, 23.9, 21.5, 19.1; FT-IR (KBr) 2925, 1735, 1456, 1343, 1158, 1092, 747, 660, 549 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{35}H_{37}N_2O_2S$: 549.2570, found: 549.2576.



6-Ethyl-1,4-diphenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-3ba. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.52; colorless solid; mp 187-188 °C; yield 74% (37 mg); major diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8 Hz, 2H), 7.24-7.19 (m, 4H), 7.16-7.11 (m, 6H), 7.08-7.06 (m, 2H), 6.92-6.90 (m, 2H), 6.86-6.84 (m, 1H), 6.72 (s, 1H), 6.41 (s, 1H), 4.55-4.51 (m, 1H), 4.13-4.04 (m, 1H), 4.03-3.96 (m, 1H), 3.78-3.73 (m, 1H), 3.36-3.30 (m, 1H), 2.31 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 142.7, 141.1, 138.7, 136.6, 133.3, 129.28, 129.21, 128.7, 128.5, 128.3, 127.6, 127.38, 127.30, 126.9, 126.0, 121.0, 119.1, 117.1, 108.2, 65.2, 50.6, 46.3, 41.0, 21.5, 15.4; FT-IR (KBr) 2923, 1731, 1485, 1341, 1156, 1092, 663, 545 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{31}N_2O_2S$: 507.2101, found: 507.2106.

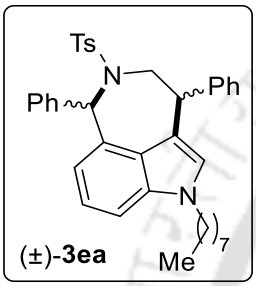


6-Butyl-1,4-diphenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-3ca. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.54; colorless solid; mp 201-202 °C; yield 76% (40 mg); mixture of diastereomers (2.7:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.66 (m, 2H), 7.33-7.27 (m, 1.45H), 7.25-7.19 (m, 6H), 7.15-7.12 (m, 7.61H), 7.05-7.03 (m, 2H), 6.99-6.92 (m, 3H), 6.85-6.81 (m, 1.70H), 6.74 (s, 1H), 6.69 (s, 0.39H), 6.38 (s, 1H), 5.96 (s, 0.37H), 4.53-4.49 (m, 1H), 4.11-4.00 (m, 1.41H), 3.93-3.84 (m, 1.36H), 3.83-3.81 (m, 0.37H), 3.78-3.73 (m, 1.36H), 3.66-3.61 (m, 0.39H), 3.36-3.29 (m, 1H), 2.29 (s, 3H), 2.24 (s, 1.18H), 1.71-1.60 (m, 2.77H), 1.25-1.21 (m, 2.79H), 0.94-0.88 (m, 4.13H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 142.7, 141.8, 141.1, 140.7, 140.4, 138.8, 136.99, 136.97, 136.93, 133.1, 132.7, 129.24, 129.20, 128.75, 128.70, 128.6, 128.5, 128.4, 128.3, 128.0, 127.6, 127.5, 127.34, 127.31, 126.9, 126.8, 126.5, 125.9, 125.0, 121.7, 121.0, 119.5, 119.0, 116.87, 116.83, 108.8, 108.3, 65.2, 63.3, 53.1, 50.6, 46.2, 46.1, 46.0, 42.9, 32.6, 32.2, 21.5, 20.2, 20.1, 13.87, 13.85; FT-IR (KBr) 2925, 1733, 1487, 1431, 1340, 1155, 1093, 1009, 665, 544 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{34}H_{35}N_2O_2S$: 535.2414, found: 535.2402.

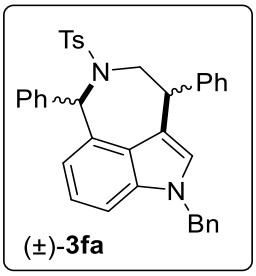


6-Isopropyl-1,4-diphenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-3da. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.51; colorless solid; mp 199-200 °C; yield 71% (37 mg); mixture of diastereomers (1.3:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.4 Hz, 2H), 7.38-7.30 (m, 2.82H), 7.29-7.26 (m, 3H), 7.25-7.23 (m, 4H), 7.21-7.19 (m, 1.33H), 7.17-7.14 (m, 6.74H), 7.13-7.10 (m, 2.13H), 7.05-7.03 (m, 2.14H), 7.01-6.97 (m, 1.44H), 6.96-6.93 (m, 2.61H), 6.86-6.84 (m, 1H), 6.82-6.80 (m, 1.13H), 6.73 (s, 1H), 6.70 (s, 0.74H), 6.508-6.505 (m, 1H), 6.05-6.04 (m, 0.72H), 4.63-4.58 (m, 1.16H), 4.57-4.53 (m, 1H),

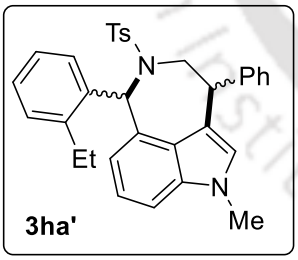
4.46-4.39 (m, 0.76H), 4.11-4.05 (m, 0.76H), 3.79-3.72 (m, 1.76H), 3.65-3.60 (m, 0.76H), 3.34-3.28 (m, 1H), 2.29 (s, 3H), 2.22 (s, 2.16H), 1.41 (d, J = 6.8 Hz, 3H), 1.36 (d, J = 6.4 Hz, 3H), 1.33-1.29 (m, 4.56H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.0, 142.6, 141.7, 141.1, 140.6, 140.3, 138.7, 136.9, 136.5, 133.1, 132.6, 129.2, 129.1, 128.79, 128.70, 128.68, 128.66, 128.5, 128.4, 128.3, 128.0, 127.6, 127.5, 127.35, 127.31, 126.88, 126.82, 126.7, 126.6, 126.0, 123.8, 121.5, 120.9, 120.8, 119.6, 119.1, 116.89, 116.81, 108.9, 108.2, 65.3, 63.3, 53.2, 50.8, 47.1, 46.9, 46.3, 43.1, 22.98, 22.97, 22.6, 22.5, 21.5, 21.4; FT-IR (KBr) 3066, 2977, 2929, 1734, 1372, 1287, 1242, 1157, 1092, 1046, 747, 701, 666, 544 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{33}H_{33}N_2O_2S$: 521.2257, found: 521.2256.



6-Octyl-1,4-diphenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-3ea. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.51; colorless solid; mp 207-208 ^{o}C; yield 78% (46 mg); mixture of diastereomers (2.7:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8 Hz, 2H), 7.34-7.28 (m, 1.41H), 7.24-7.20 (m, 5.40H), 7.16-7.14 (m, 7H), 7.12-7.10 (m, 1H), 7.07-7.05 (m, 2.12H), 6.99-6.97 (m, 1.18H), 6.93-6.91 (m, 2.15H), 6.86-6.82 (m, 1.88H), 6.74 (s, 1H), 6.69 (s, 0.42H), 6.39 (s, 1H), 5.97 (s, 0.36H), 4.55-4.51 (m, 1H), 4.12-4.06 (m, 0.60H), 4.03-3.89 (m, 2H), 3.88-3.81 (m, 0.86H), 3.79-3.74 (m, 1.70H), 3.67-3.62 (m, 0.42H), 3.36-3.29 (m, 1H), 2.31 (s, 3H), 2.24 (s, 1.15H), 1.75-1.70 (m, 2.15H), 1.67-1.62 (m, 0.84H), 1.31-1.26 (m, 13.80H), 0.88 (t, J = 6.4 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 142.7, 141.8, 141.1, 140.7, 140.4, 138.8, 136.97, 136.91, 133.2, 132.6, 129.2, 129.1, 128.76, 128.71, 128.66, 128.65, 128.5, 128.4, 128.3, 128.05, 128.02, 127.6, 127.5, 127.35, 127.30, 126.9, 126.8, 126.5, 125.9, 125.1, 121.7, 121.0, 119.5, 119.0, 116.85, 116.82, 108.8, 108.3, 65.2, 63.3, 53.1, 50.6, 46.4, 46.34, 46.30, 42.9, 31.8, 30.5, 30.1, 29.8, 29.35, 29.32, 29.2, 27.05, 27.01, 22.7, 21.5, 14.2; FT-IR (KBr) 2925, 2854, 1600, 1493, 1342, 1158, 1092, 743, 701, 665, 544 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{38}H_{43}N_2O_2S$: 591.3040, found: 591.3030.

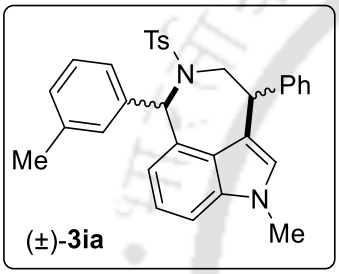


6-Benzyl-1,4-diphenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-3fa. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.48; colorless solid; mp 197-198 °C; yield 72% (41 mg); mixture of diastereomers (2.1:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8 Hz, 2H), 7.32-7.27 (m, 5.12H), 7.24-7.21 (m, 6.12H), 7.19-7.15 (m, 7H), 7.11-7.06 (m, 4.56H), 7.03-6.99 (m, 4.60H), 6.96-6.94 (m, 2.24H), 6.88-6.86 (m, 2H), 6.77 (s, 1H), 6.69 (s, 0.53H), 6.47 (s, 1H), 6.11 (s, 0.46H), 5.29-5.25 (m, 1H), 5.13-5.09 (m, 1H), 4.55-4.51 (m, 1H), 4.09 (t, *J* = 12 Hz, 0.48H), 3.84-3.76 (m, 1.45H), 3.69-3.64 (m, 0.48H), 3.39-3.33 (m, 1H), 2.31 (s, 3H), 2.26 (s, 1.51H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 142.8, 142.1, 141.1, 140.6, 140.5, 138.9, 137.5, 137.4, 137.3, 137.0, 133.3, 132.9, 129.3, 129.1, 128.8, 128.74, 128.71, 128.69, 128.67, 128.61, 128.5, 128.4, 127.9, 127.75, 127.70, 127.6, 127.5, 127.3, 126.99, 126.94, 126.7, 126.5, 126.1, 125.8, 122.1, 121.4, 119.8, 119.4, 117.75, 117.72, 109.2, 108.7, 65.1, 63.2, 53.1, 50.6, 50.1, 50.0, 46.2, 42.8, 21.6; FT-IR (KBr) 2924, 1735, 1451, 1339, 1155, 745, 698, 665, 544 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{37}H_{33}N_2O_2S$: 569.2257, found: 569.2253.

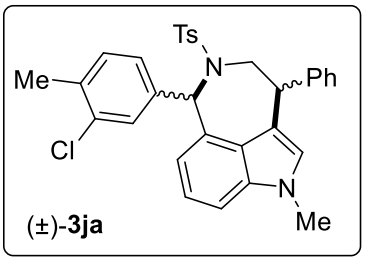


6-Methyl-1-(2-ethylphenyl)-4-phenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole 3ha'. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; colorless solid; mp 143-144 °C; yield 83% (43 mg); mixture of diastereomers (2:1 dr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8 Hz, 2H), 7.38 (d, *J* = 8 Hz, 0.51H), 7.32-7.27 (m, 1.67H), 7.25-7.23 (m, 2.40H), 7.21-7.20 (m, 1.64H), 7.19-7.15 (m, 2.67H), 7.13-7.10 (m, 4H), 7.07-7.02 (m, 2H), 7.01-6.99 (m, 2H), 6.97-6.90 (m, 2.36H), 6.85-6.84 (m, 1H), 6.78-6.75 (m, 2.48H), 6.68-6.63 (m, 2H), 6.22 (s, 1H), 5.77 (s, 0.48H), 4.53-4.49 (m, 1H), 4.18-4.12 (m, 0.53H), 4.02-3.99

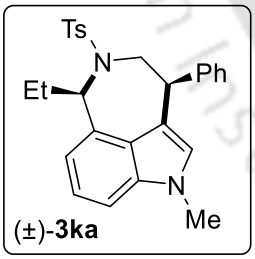
(m, 0.52H), 3.75-3.71 (m, 1H), 3.58 (s, 3H), 3.46 (s, 1.47H), 3.44-3.39 (m, 1H), 3.30-3.25 (m, 0.52H), 3.20-3.15 (m, 0.50H), 3.11-2.96 (m, 2.49H), 2.22 (s, 1.48H), 2.17 (s, 3H), 1.43 (t, J = 7.5 Hz, 1.50H), 1.34 (t, J = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4, 144.38, 144.31, 142.1, 141.2, 140.7, 137.9, 137.7, 137.5, 137.0, 136.8, 136.0, 134.6, 133.3, 131.3, 130.4, 129.5, 129.0, 128.9, 128.7, 128.6, 128.5, 128.3, 128.2, 127.6, 127.5, 127.36, 127.33, 126.8, 126.7, 126.3, 126.2, 125.4, 125.3, 122.1, 121.4, 119.3, 118.8, 117.0, 116.6, 108.3, 107.8, 63.2, 61.8, 52.5, 49.7, 44.5, 44.2, 32.7, 32.4, 25.0, 24.6, 21.5, 21.3, 15.8, 14.6; FT-IR (KBr) 2924, 1734, 1486, 1345, 1151, 1094, 669, 547 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{33}H_{33}N_2O_2S$: 521.2257, found: 521.2257; $[\alpha]_D^{25}$ = +32.86 (c = 0.07, $CHCl_3$); HPLC: *ee* for major diastereomer = 93% *ee* [YMC Chiral ART Cellulose-SC column, hexane/^{i}PrOH = 90:10, flow rate: 1 mL/min, λ= 254 nm, t_R = 13.93 min (major), 15.40 min (minor)].



6-Methyl-4-phenyl-1-(*m*-tolyl)-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-3ia. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.58; colorless solid; mp 140-141 °C; yield 79% (40 mg); mixture of diastereomers (1.3:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.4 Hz, 2H), 7.30-7.27 (m, 1.95H), 7.24-7.22 (m, 2.84H), 7.20-7.14 (m, 6.41H), 7.13-7.08 (m, 3.84H), 7.04-7.01 (m, 2.55H), 6.99-6.93 (m, 2.72H), 6.87-6.82 (m, 2.21H), 6.65-6.62 (m, 2.53H), 6.59-6.57 (m, 1H), 6.376-6.372 (m, 1H), 5.92-5.91 (m, 0.77H), 4.58-4.53 (m, 1H), 4.18-4.12 (m, 0.72H), 3.84-3.80 (m, 0.76H), 3.78-3.73 (m, 1H), 3.66 (s, 3H), 3.64-3.59 (m, 0.80H), 3.53 (s, 2.31H), 3.40-3.33 (m, 1H), 2.34 (s, 3H), 2.27-2.26 (m, 4.30H), 2.14(s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 142.8, 141.8, 141.0, 140.7, 140.1, 139.0, 138.3, 138.0, 137.7, 137.6, 137.0, 133.5, 132.7, 129.7, 129.4, 129.0, 128.7, 128.6, 128.59, 128.50, 128.4, 128.3, 128.1, 127.3, 126.9, 126.6, 126.3, 126.1, 125.8, 125.2, 121.9, 121.2, 119.6, 119.0, 117.1, 108.5, 108.1, 65.1, 63.3, 52.8, 50.7, 46.7, 43.0, 32.9, 32.6, 21.6, 21.56, 21.50, 21.4; FT-IR (KBr) 2924, 1729, 1484, 1342, 1159, 1096, 660, 543 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{31}N_2O_2S$: 507.2101, found: 507.2110.

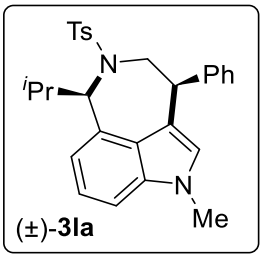


1-(3-Chloro-4-methylphenyl)-6-methyl-4-phenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-3ja. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.58; colorless solid; mp 144-145 °C; yield 72% (39 mg); mixture of diastereomers (1.5:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.30-7.27 (m, 2.93H), 7.24-7.21 (m, 2.41H), 7.19-7.11 (m, 8H), 7.08-7.02 (m, 2.14H), 7.01-6.95 (m, 2H), 6.85-6.83 (m, 2H), 6.66-6.65 (m, 2H), 6.61 (s, 1H), 6.58 (s, 0.62H), 6.385-6.381 (m, 1H), 5.95-5.94 (m, 0.64H), 4.56-4.51 (m, 1H), 4.19-4.12 (m, 0.64H), 3.87-3.83 (m, 0.64H), 3.81-3.76 (m, 1.64H), 3.67 (s, 3H), 3.54 (s, 1.94H), 3.35-3.28 (m, 1H), 2.36-2.35 (m, 4.86H), 2.27-2.25 (m, 4.91H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 143.2, 142.1, 140.7, 140.4, 139.8, 138.7, 137.7, 137.0, 136.8, 135.4 135.3, 134.7, 134.5, 132.8, 131.9, 131.1, 130.7, 129.5, 129.1, 128.7, 128.54, 128.51, 127.4, 127.2, 127.0, 126.6, 126.3, 125.7, 122.0, 121.3, 119.6, 119.0, 117.0, 108.8, 108.4, 64.5, 62.8, 52.8, 50.7, 46.7, 43.0, 32.9, 32.6, 21.6, 21.5, 19.8, 19.7; FT-IR (KBr) 2926, 1745, 1490, 1351, 1155, 1090, 745, 548 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{30}ClN_2O_2S$: 541.1711, found: 541.1715.

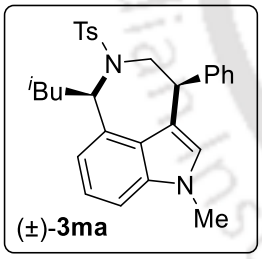


1-Ethyl-6-methyl-4-phenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-3ka. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.58; colorless solid; mp 182-183 °C; yield 75% (33 mg); major diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8 Hz, 2H), 7.36-7.28 (m, 5H), 7.15-7.10 (m, 4H), 6.90-6.88 (m, 1H), 6.338-6.334 (m, 1H), 5.28-5.24 (m, 1H), 4.54-4.50 (m, 1H), 4.02-3.97 (m, 1H), 3.62 (s, 3H), 3.59-3.52 (m, 1H), 2.32 (s, 3H), 1.92-1.78 (m, 2H), 0.75 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.7, 142.7, 138.8, 137.7, 137.4, 129.3, 128.8, 128.7, 127.2, 127.1, 124.0, 121.1, 117.4, 116.8, 107.7, 63.5,

49.2, 46.8, 32.8, 29.6, 21.5, 11.6; FT-IR (KBr) 2926, 1736, 1454, 1340, 1155, 1032, 749, 703, 657, 583 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{29}N_2O_2S$: 445.1944, found: 445.1950.

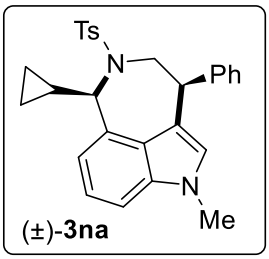


1-Isopropyl-6-methyl-4-phenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-3la. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.58; colorless solid; mp 183-184 °C; yield 63% (29 mg); major diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.4 Hz, 2H), 7.35-7.34 (m, 3H), 7.31-7.27 (m, 2H), 7.16-7.05 (m, 4H), 6.89-6.87 (m, 1H), 6.337-6.333 (m, 1H), 4.82 (d, *J* = 10 Hz, 1H), 4.50-4.45 (m, 1H), 4.04-3.99 (m, 1H), 3.64-3.57 (m, 4H), 2.30 (s, 3H), 2.10-2.06 (m, 1H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.77 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.7, 142.5, 138.6, 137.8, 135.0, 129.2, 128.8, 128.7, 127.3, 127.1, 124.6, 120.3, 119.3, 116.8, 108.1, 68.5, 49.8, 46.6, 32.8, 31.7, 21.56, 21.54, 20.9; FT-IR (KBr) 2928, 1456, 1341, 1302, 1150, 751, 699, 652, 543 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{31}N_2O_2S$: 459.2101, found: 459.2101.

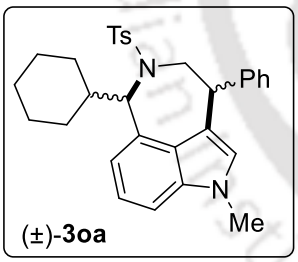


1-Isobutyl-6-methyl-4-phenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-3ma. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.58; colorless solid; mp 179-180 °C; yield 61% (29 mg); major diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.4 Hz, 2H), 7.36-7.28 (m, 5H), 7.16-7.10 (m, 2H), 7.07-7.05 (m, 2H), 6.87-6.85 (m, 1H), 6.306-6.302 (m, 1H), 5.47-5.43 (m, 1H), 4.50-4.45 (m, 1H), 4.01-3.96 (m, 1H), 3.66-3.62 (m, 1H), 3.60 (s, 3H), 2.30 (s, 3H), 1.85 (t, *J* = 10 Hz, 1H), 1.54-1.49 (m, 2H), 0.90-0.85 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.7, 142.6, 138.7, 137.7, 137.6, 129.2, 128.8, 128.7, 128.6, 127.4, 127.1, 124.2, 121.1, 117.3, 116.6, 107.6, 59.8, 49.3, 46.4, 46.0, 32.8, 24.7, 23.2, 21.9, 21.5; FT-

IR (KBr) 2936, 1457, 1339, 1305, 1150, 980, 751, 703, 657, 546 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{29}H_{33}N_2O_2S$: 473.2257, found: 473.2281.

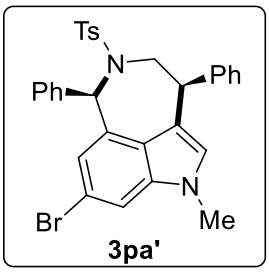


1-Cyclopropyl-6-methyl-4-phenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-3na. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.58; colorless solid; mp 177-178 °C; yield 69% (31 mg); major diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.37-7.27 (m, 5H), 7.18-7.12 (m, 4H), 6.90-6.88 (m, 1H), 6.365-6.361 (m, 1H), 4.91 (d, *J* = 7.2 Hz, 1H), 4.54-4.49 (m, 1H), 4.13-4.01 (m, 2H), 3.63 (s, 3H), 2.33 (s, 3H), 1.15-1.06 (m, 1H), 0.59-0.54 (m, 1H), 0.40-0.32 (m, 2H), 0.13-0.06 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 142.7, 138.9, 137.6, 134.9, 129.4, 128.9, 128.8, 128.7, 127.1, 127.0, 124.7, 120.9, 117.7, 117.1, 108.1, 65.8, 50.4, 47.3, 32.8, 21.5, 16.9, 6.5, 3.2; FT-IR (KBr) 2924, 1454, 1338, 1305, 1154, 1093, 981, 752, 703, 659, 548 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{29}N_2O_2S$: 457.1944, found: 457.1947.



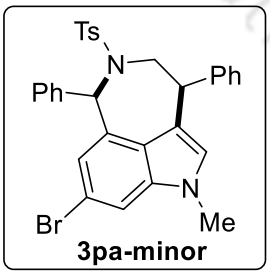
1-Cyclohexyl-6-methyl-4-phenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-3oa. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.58; colorless solid; mp 188-189 °C; yield 72% (36 mg); mixture of diastereomers (2.8:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.4 Hz, 2H), 7.40-7.27 (m, 6.72H), 7.16-7.03 (m, 5H), 6.85-6.79 (m, 1.80H), 6.337-6.333 (m, 1H), 5.926-5.922 (m, 0.35H), 5.03 (d, *J* = 11.2 Hz, 0.35H), 4.90 (d, *J* = 9.6 Hz, 1H), 4.63-4.58 (m, 0.36H), 4.46-4.41(m, 1H), 4.11-4.05 (m, 0.42H), 4.03-3.98 (m, 1H), 3.94-3.89 (m, 0.39H), 3.62 (s, 3H), 3.60-3.53 (m, 1H), 3.50 (s, 1H), 2.29 (s, 3H), 2.22 (s, 1H), 1.68-1.60 (m, 4.05H), 1.13-0.76 (m, 10.81H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 142.5, 138.7, 137.8, 134.5, 133.6, 129.1, 128.9, 128.8, 128.7, 128.6, 128.3, 127.5, 127.3, 127.1, 126.7,

124.7, 121.3, 120.3, 120.2, 119.5, 117.4, 116.7, 108.1, 108.0, 67.5, 67.0, 53.0, 49.8, 46.4, 43.4, 40.3, 32.8, 32.6, 31.9, 31.7, 31.4, 31.0, 29.8, 26.5, 26.3, 26.2, 21.5, 21.4; FT-IR (KBr) 2848, 1736, 1493, 1445, 1417, 1239, 1046, 747 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{35}N_2O_2S$: 499.2414, found: 499.2415.



3pa'

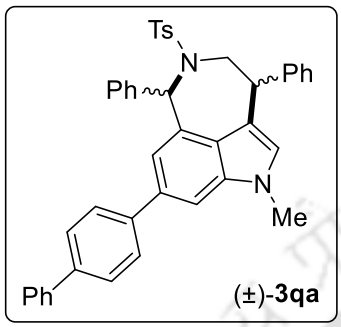
8-Bromo-6-methyl-1,4-diphenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole 3pa'. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.48; colorless solid; mp 170-171 °C; yield 56% (32 mg); major diastereomer; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8 Hz, 2H), 7.36 (s, 1H), 7.27 (s, 1H), 7.24-7.19 (m, 2H), 7.17-7.13 (m, 7H), 6.99 (s, 1H), 6.85-6.83 (m, 2H), 6.62 (s, 1H), 6.35 (s, 1H), 4.53-4.50 (m, 1H), 3.75-3.72 (m, 1H), 3.63 (s, 3H), 3.34-3.29 (m, 1H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3, 143.1, 140.3, 138.5, 138.4, 135.2, 129.7, 129.5, 129.1, 128.69, 128.64, 128.5, 127.8, 127.3, 127.1, 124.9, 121.8, 117.6, 114.7, 111.3, 64.6, 50.3, 46.4, 33.0, 21.6; FT-IR (KBr) 2924, 1735, 1457, 1346, 1154, 1092, 680, 550 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{28}BrN_2O_2S$: 571.1049, found: 571.1039; $[\alpha]_D^{25}$ = +15 (c = 0.02, $CHCl_3$); HPLC: *ee* for major diastereomer = >88% *ee* [YMC Chiral ART Cellulose-SC column, hexane/^{i}PrOH = 90:10, flow rate: 1 mL/min, λ= 254 nm, t_R = 12.54 min (major), 16.93 min (minor)].



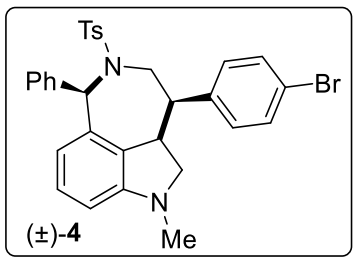
3pa-minor

8-Bromo-6-methyl-1,4-diphenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole 3pa. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.46; colorless solid; mp 170-171 °C; yield 28% (16 mg); minor diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.27 (m, 6H), 7.25-7.21 (m, 3H), 7.20-7.17 (m, 2H), 7.065-7.061 (m, 1H), 7.02-6.99 (m, 2H), 6.89 (d, *J* = 8 Hz, 2H), 6.54 (s, 1H), 5.934-5.930 (m, 1H), 4.22-4.16 (m, 1H), 3.74-3.69 (m, 1H), 3.64-

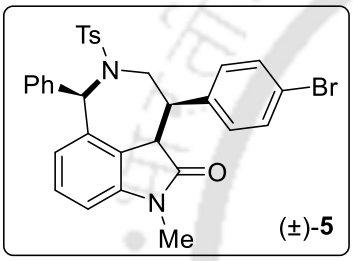
3.59 (m, 1H), 3.50 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.2, 140.2, 139.4, 138.3, 136.9, 134.2, 128.78, 128.72, 128.4, 127.9, 127.8, 127.5, 126.8, 126.7, 125.4, 122.6, 117.6, 115.2, 111.5, 62.7, 52.8, 42.9, 32.7, 21.5; FT-IR (KBr) 2926, 1735, 1459, 1347, 1154, 1092, 683, 549 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{28}BrN_2O_2S$: 571.1049, found: 571.1039.



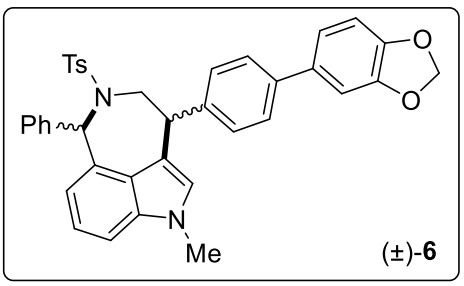
8-([1,1'-Biphenyl]-4-yl)-6-methyl-1,4-diphenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-3qa. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.51; colorless solid; mp 174-175 °C; yield 77% (49 mg); mixture of diastereomers (2.2:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.72 (m, 5H), 7.70-7.63 (m, 5H), 7.50-7.43 (m, 4H), 7.38-7.27 (m, 5.89H), 7.24-7.13 (m, 8.70H), 7.07-7.04 (m, 0.69H), 6.96-6.94 (m, 1.46H), 6.83-6.80 (m, 1.44H), 6.71 (s, 0.42H), 6.417-6.414 (m, 1H), 6.00-5.99 (m, 0.45H), 4.58-4.54 (m, 1H), 4.27-4.21 (m, 0.45H), 3.81-3.76 (m, 1.47H), 3.73 (s, 3H), 3.70-3.66 (m, 0.50H), 3.60 (s, 1.34H), 3.42-3.35 (m, 1H), 2.35 (s, 3H), 2.25 (s, 1.31H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 143.0, 141.9, 141.1, 140.98, 140.95, 140.8, 140.5, 140.0, 139.8, 139.7, 138.7, 138.3, 138.2, 137.0, 135.1, 134.1, 133.7, 132.8, 129.7, 129.4, 129.2, 128.97, 128.94, 128.69, 128.64, 128.4, 128.3, 128.1, 127.79, 127.71, 127.6, 127.5, 127.4, 127.18, 127.15, 127.0, 126.8, 126.6, 126.0, 125.4, 119.4, 118.6, 117.25, 117.23, 106.9, 106.5, 65.2, 63.4, 53.1, 50.6, 46.4, 42.9, 33.0, 32.7, 21.6, 21.5; FT-IR (KBr) 2984, 1733, 1462, 1418, 1240, 1045, 752 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{43}H_{37}N_2O_2S$: 645.2570, found: 645.2575.



4-(4-Bromophenyl)-6-methyl-1-phenyl-2-tosyl-2,3,4,4a,5,6-hexahydro-1H-azepino[5,4,3-cd]indole (±)-4. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.48; colorless solid; mp 165-166 °C; yield 85% (48 mg); major diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.24-7.21 (m, 5H), 7.16-7.12 (m, 1H), 6.89-6.87 (m, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 6.65 (d, *J* = 7.6 Hz, 1H), 6.49 (d, *J* = 7.6 Hz, 1H), 6.33 (s, 1H), 3.75-3.70 (m, 1H), 3.57-3.47 (m, 1H), 3.13-3.06 (m, 2H), 2.78-2.71 (m, 1H), 2.64 (s, 3H), 2.41 (s, 3H), 2.40-2.35 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2, 143.2, 140.2, 138.4, 137.7, 132.0, 129.6, 129.4, 128.9, 128.77, 128.70, 128.4, 128.2, 127.7, 127.4, 119.1, 107.4, 64.2, 61.5, 50.1, 49.0, 46.2, 35.9, 21.6; FT-IR (KBr) 2924, 1735, 1597, 1486 1339, 1156, 1008, 661, 601, 543 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{30}BrN_2O_2S$: 573.1206, found: 573.1205.



4-(4-Bromophenyl)-6-methyl-1-phenyl-2-tosyl-1,2,3,4,4a,6-hexahydro-5H-azepino[5,4,3-cd]indol-5-one (±)-5. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.41; colorless solid; mp 179-180 °C; yield 77% (45 mg); major diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.38 (m, 3H), 7.25-7.23 (m, 3H), 7.12-7.10 (m, 3H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.87-6.82 (m, 3H), 6.56 (s, 1H), 6.41 (d, *J* = 8.8 Hz, 2H), 4.37-4.32 (m, 1H), 3.67-3.62 (m, 2H), 3.44-3.41 (m, 1H), 3.01 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 144.8, 143.2, 138.6, 137.4, 136.7, 135.9, 131.2, 130.0, 129.7, 129.3, 129.0, 128.16, 128.11, 126.7, 126.2, 122.8, 121.2, 108.2, 64.4, 50.3, 49.2, 42.9, 26.4, 21.7; FT-IR (KBr) 2922, 2851, 1715, 1608, 1470, 1331, 1156, 1009, 600, 597, 541 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{28}BrN_2O_3S$: 587.0999, found: 587.1001.



4-(4-(benzo[d][1,3]dioxol-5-yl)phenyl)-6-methyl-1-phenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-6. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.49; colorless solid; mp 149-150 °C; yield 90% (55 mg); mixture of diastereomers (1.6:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8 Hz, 2.96H), 7.35-7.27 (m, 2H), 7.25-7.14 (m, 10.32H), 7.13-7.11 (m, 2.20H), 7.04-7.00 (m, 4.63H), 6.91-6.82 (m, 5.55H), 6.74 (s, 1H), 6.69 (s, 0.58H), 6.433-6.430 (m, 1H), 6.00 (s, 1.27H), 5.98 (s, 2H), 4.58-4.54 (m, 1H), 4.19-4.13 (m, 0.60H), 3.85-3.76 (m, 1.60H), 3.69-3.64 (m, 3.60H), 3.55 (s, 1.79H), 3.40-3.33 (m, 1H), 2.34 (s, 3H), 2.26 (s, 1.81H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.28, 148.23, 147.2, 147.1, 142.9, 142.4, 141.8, 141.1, 140.3, 139.8, 139.6, 139.4, 138.8, 137.7, 137.6, 137.0, 135.3, 135.2, 133.3, 132.6, 129.4, 129.17, 129.11, 129.08, 129.06, 128.6, 128.41, 128.40, 128.0, 127.64, 127.60, 127.3, 127.0, 126.6, 126.5, 126.2, 125.8, 122.0, 121.2, 120.5, 119.6, 119.1, 117.02, 117.00, 108.7, 108.6, 108.2, 107.63, 107.61, 101.29, 101.26, 65.1, 63.4, 52.9, 50.5, 46.0, 42.5, 32.9, 32.6, 21.58, 21.51; FT-IR (KBr) 2922, 1735, 1481, 1340, 1224, 1156, 1039, 808, 544 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{38}H_{33}N_2O_4S$: 613.2156, found: 613.2153.

Crystal Structure and Data of (±)-3aa

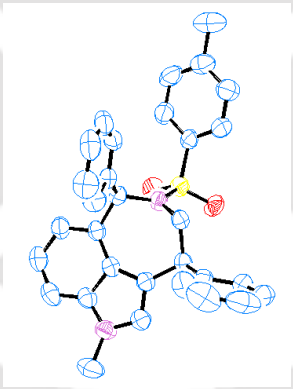


Figure S1. ORTEP diagram of 6-Methyl-1,4-diphenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-**3aa** with 50% ellipsoid (CCDC 2368687). H-Omitted for clarity.

Identification code	**(±)-3aa**
Empirical formula	'C31H28N2O2S'
Formula weight	492.61
Crystal habit, colour	block/Colorless
Temperature, *T*/K	294 K
Wavelength, λ/Å	0.71073
Crystal system	'monoclinic'
Space group	'C 2/c'

Unit cell dimensions	a = 28.290(4) Å b = 9.2132(14) Å c = 20.312(3) Å α = 90 β = 103.531(4) γ = 90
Volume, V/Å^3	5147.1(14)
Z	8
Calculated density, Mg·m^{-3}	1.271
Absorption coefficient, μ/mm^{-1}	0.157
F(000)	2080
θ range for data collection	2.24 to 22.28°
Limiting indices	-33 ≤ h ≤ 33, –10 ≤ k ≤ 10, –24 ≤ l ≤ 24
Reflection collected / unique	4536/2950
Completeness to θ	100%
Absorption correction	None
Max. and min. transmission	0.969 and 0.962
Refinement method	'SHELXL-2018/3 (Sheldrick, 2018)'
Data / restraints / parameters	4536/0/327
Goodness–of–fit on F^2	1.131
Final R indices [I>2sigma(I)]	R1 = 0.0570, wR2 = 0.1166
R indices (all data)	R1 = 0.1057, wR2 = 0.1526

Crystal Structure and Data of (±)-3pa-major

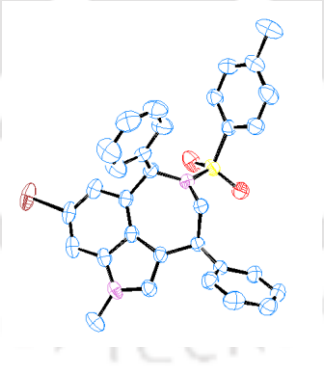


Figure S2. ORTEP diagram of 8-Bromo-6-methyl-1,4-diphenyl-2-tosyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indole (±)-**3pa-major** with 50% ellipsoid (CCDC 2368691). H-Omitted for clarity.

Identification code	**(±)-3pa-major**
Empirical formula	'C31H27BrN2O2S'
Formula weight	571.51
Crystal habit, colour	block/Colorless
Temperature, T/K	296 K

Wavelength, λ/Å	0.71073
Crystal system	'triclinic'
Space group	'P -1'
Unit cell dimensions	a = 8.3606(12) Å b = 10.4276(16) Å c = 15.974(2) Å α = 92.585(4) β = 105.246(4) γ = 95.304(4)
Volume, V/Å^3	1334.4(3)
Z	2
Calculated density, Mg·m^{-3}	1.422
Absorption coefficient, μ/mm^{-1}	1.650
F(000)	588
θ range for data collection	1.967 to 24.999°
Limiting indices	-9 ≤ h ≤ 9, –12 ≤ k ≤ 12, –18 ≤ l ≤ 18
Reflection collected / unique	4656/4039
Completeness to θ	99.2%
Absorption correction	Multi scan
Max. and min. transmission	0.7452 and 0.6324
Refinement method	'SHELXL-2018/3 (Sheldrick, 2018)'
Data / restraints / parameters	4656/0/336
Goodness–of–fit on F^2	0.763
Final R indices [I>2sigma(I)]	R1 = 0.0329, wR2 = 0.1025
R indices (all data)	R1 = 0.0403, wR2 = 0.1149

3.5 References

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S.; Yu, J.; Pivonka, D. E.; Li, S.; Thompson, C.; Zacco, A.; Elmore, C. S.; Schroeder, P.; Liu, J.; Hurley, C. A.; Ward, S.; Hunt, H. J.; Williams, K.; McLaughlin, J.; Hoesch, V.; Sydserff, S.; Maier, D.; Aharony, D. *ACS Med. Chem. Lett.* **2013**, *4*, 46.

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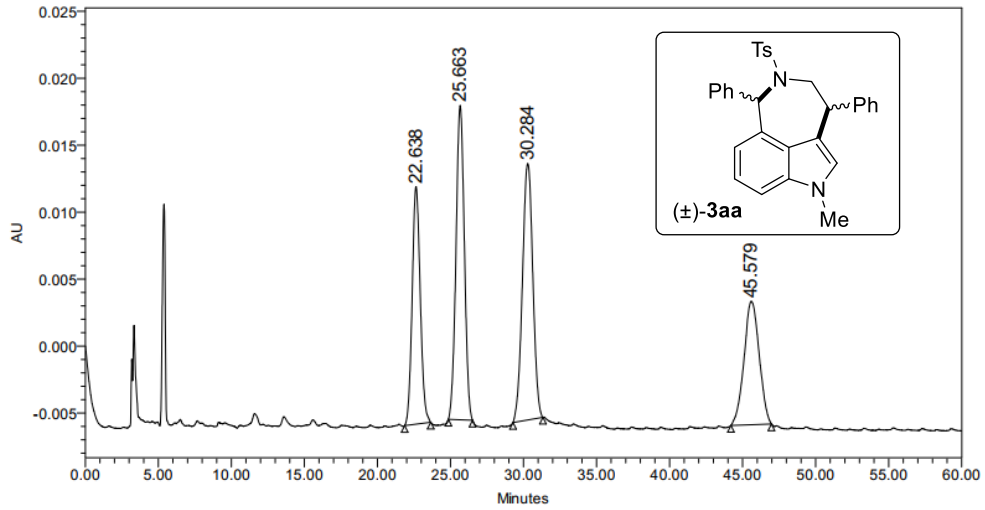
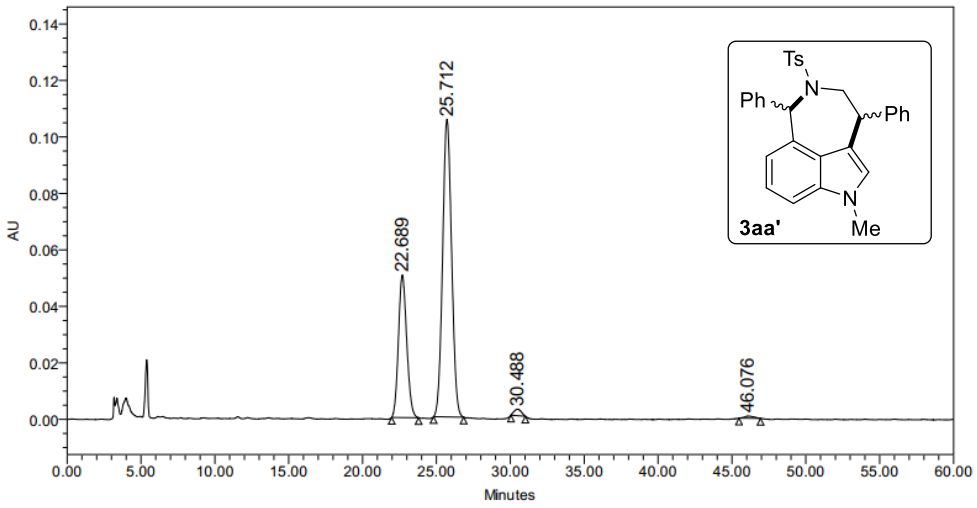
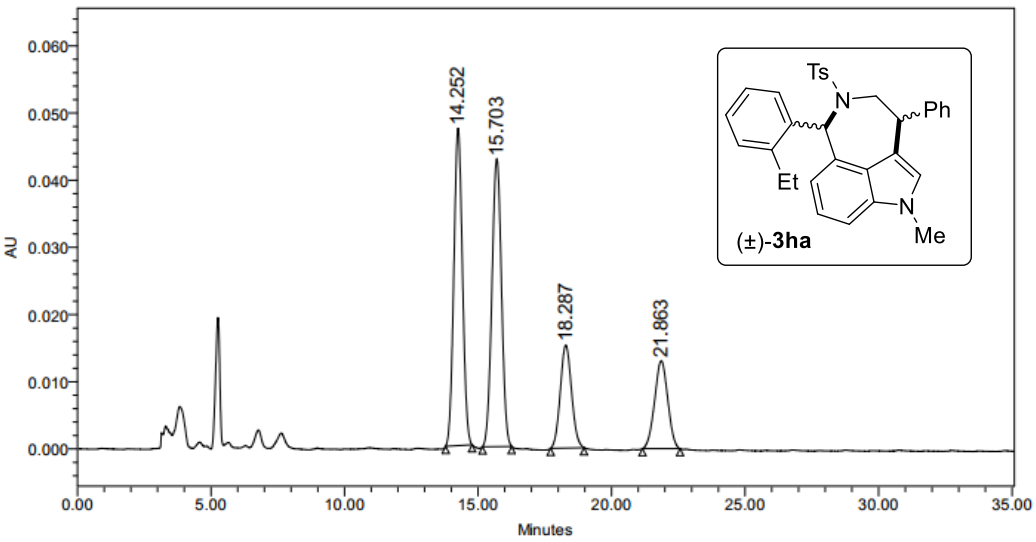
3.6 HPLC Chromatograms



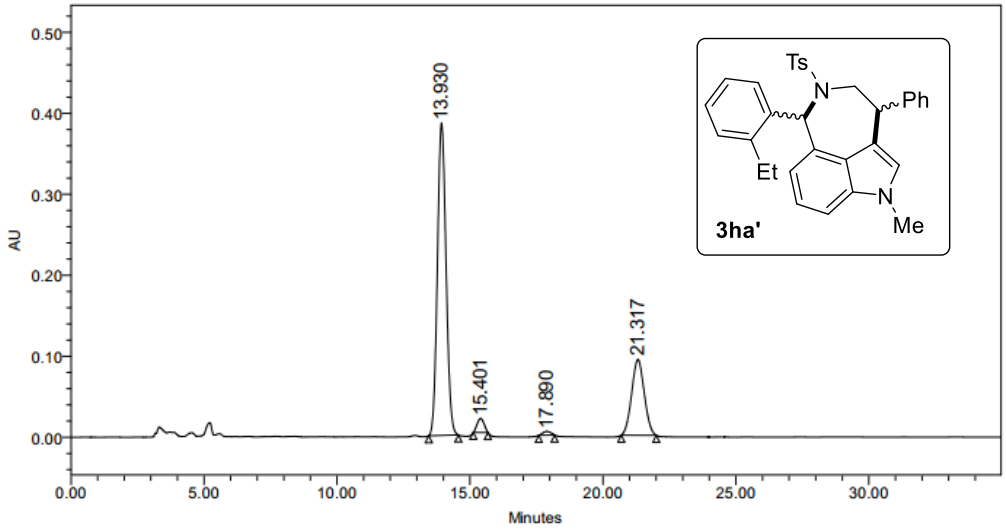
	RT	Area	% Area	Height
1	22.638	680784	21.13	17740
2	25.663	930497	28.88	23462
3	30.284	945526	29.35	19138
4	45.579	664697	20.63	9211



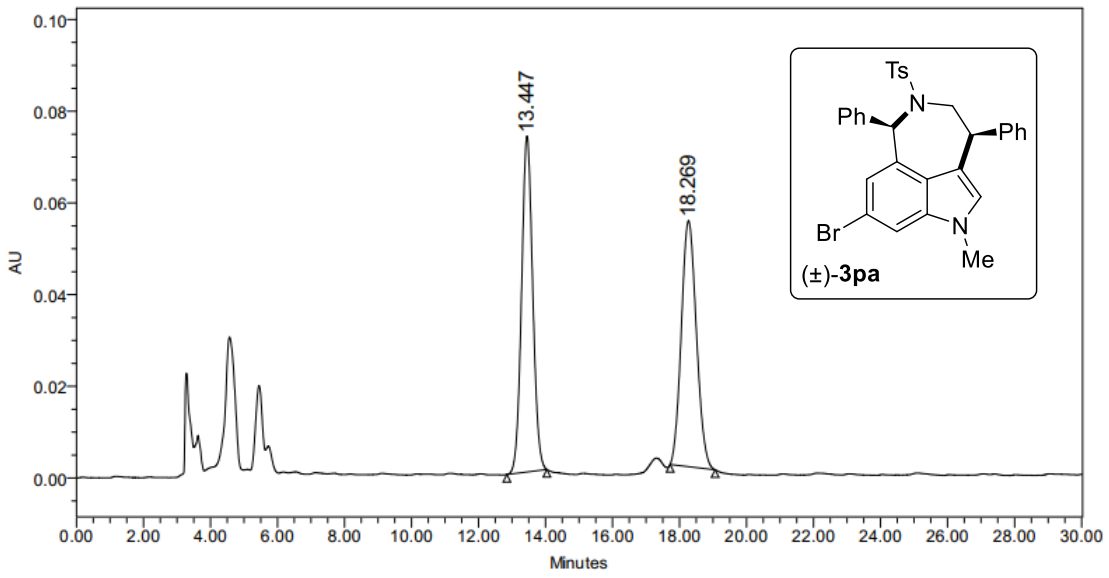
	RT	Area	% Area	Height
1	22.689	1966156	30.08	50431
2	25.712	4457591	68.21	105370
3	30.488	78877	1.21	2285
4	46.076	32900	0.50	750



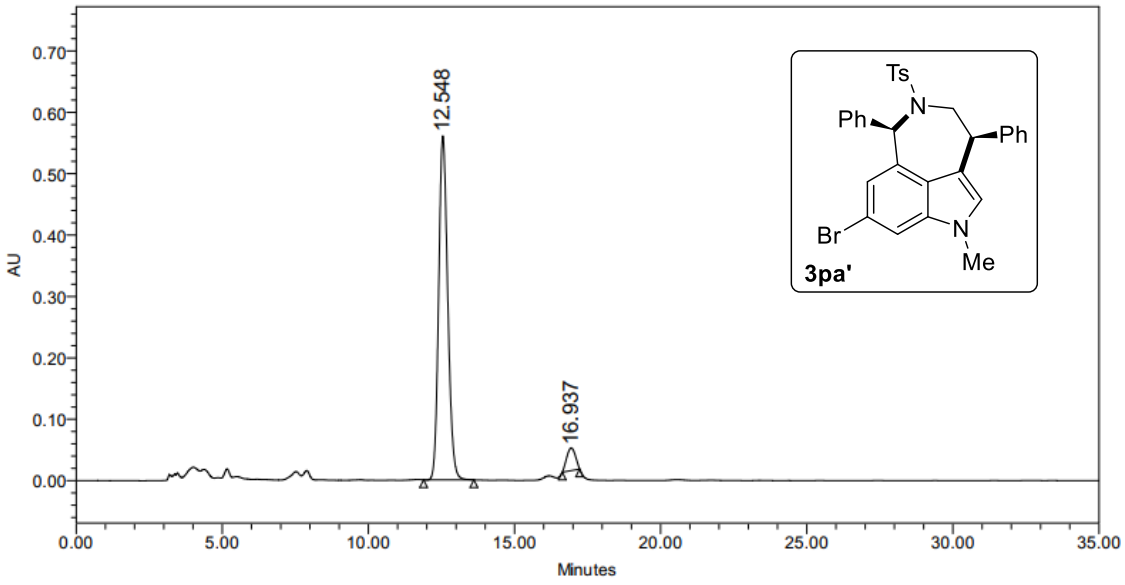
	RT	Area	% Area	Height
1	14.252	1056579	35.01	47244
2	15.703	1064087	35.26	42848
3	18.287	449734	14.90	15302
4	21.863	447413	14.83	13082



	RT	Area	% Area	Height
1	13.930	8675663	71.36	385831
2	15.401	314290	2.59	17291
3	17.890	96801	0.80	4670
4	21.317	3071005	25.26	93646

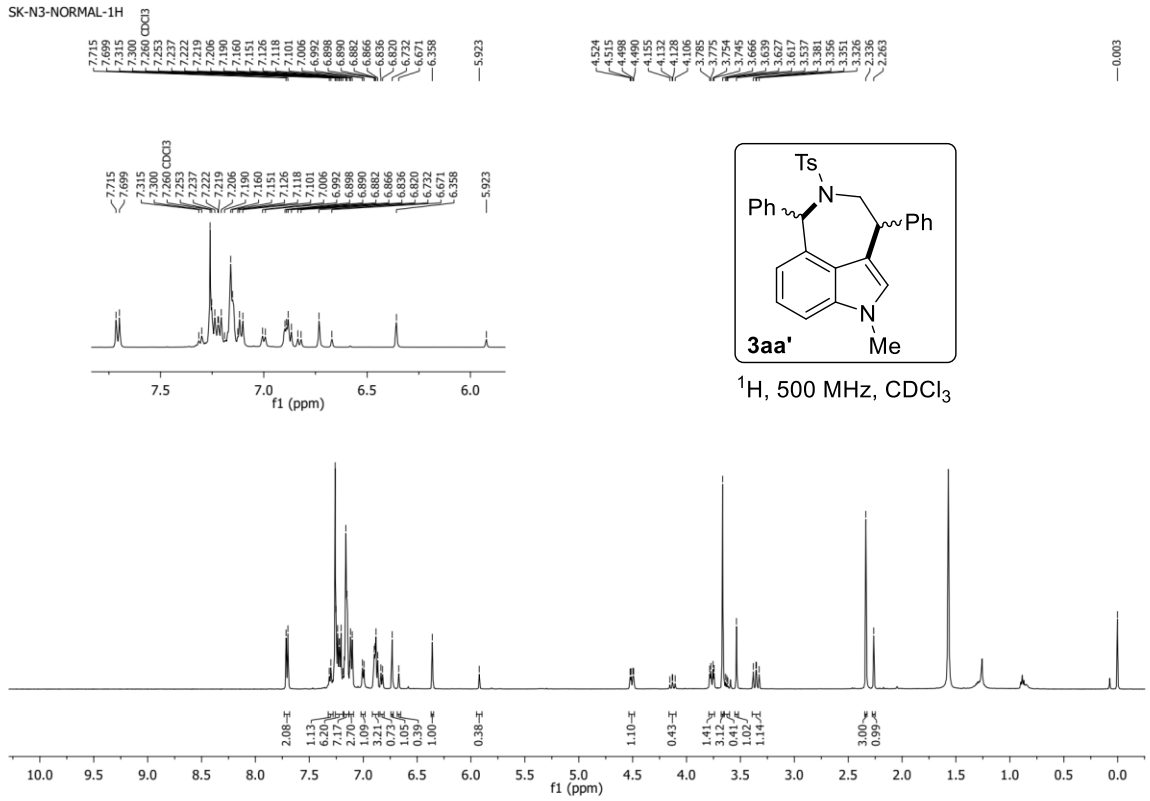


	RT	Area	% Area	Height
1	13.447	1688023	50.20	73267
2	18.269	1674750	49.80	53642

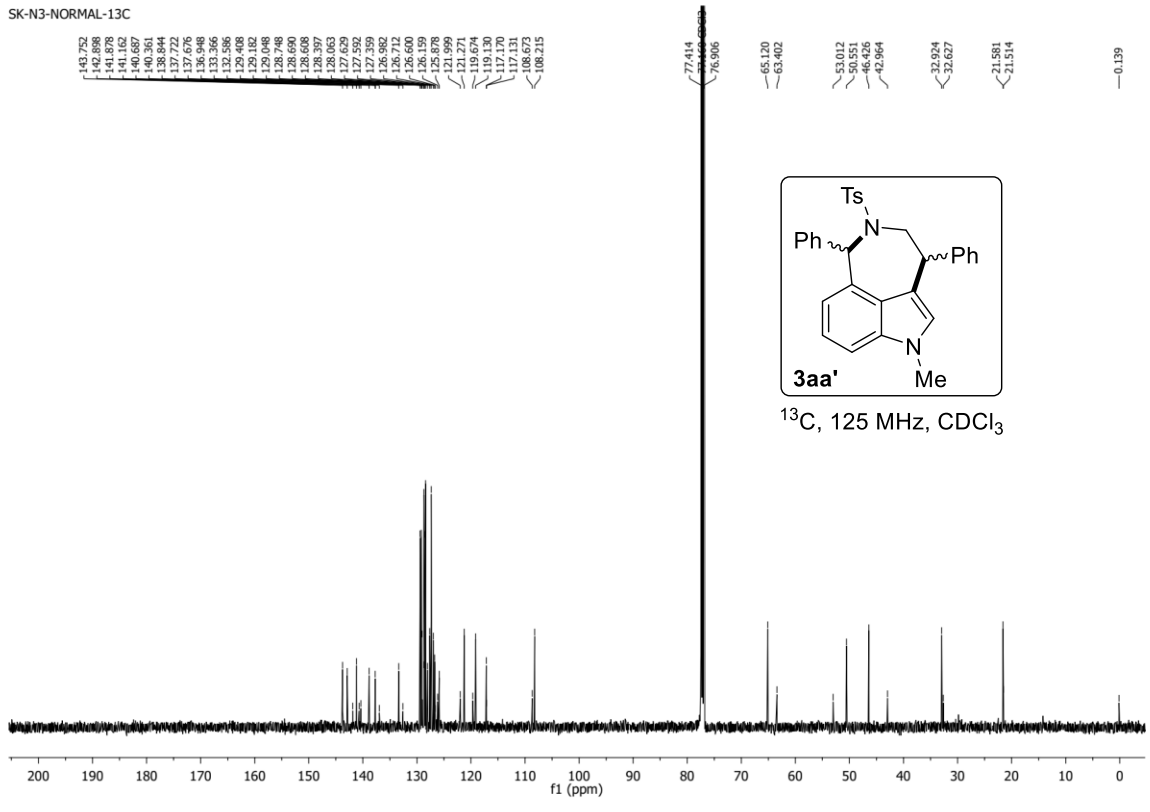


	RT	Area	% Area	Height
1	12.548	12074016	94.09	560171
2	16.937	758019	5.91	36971

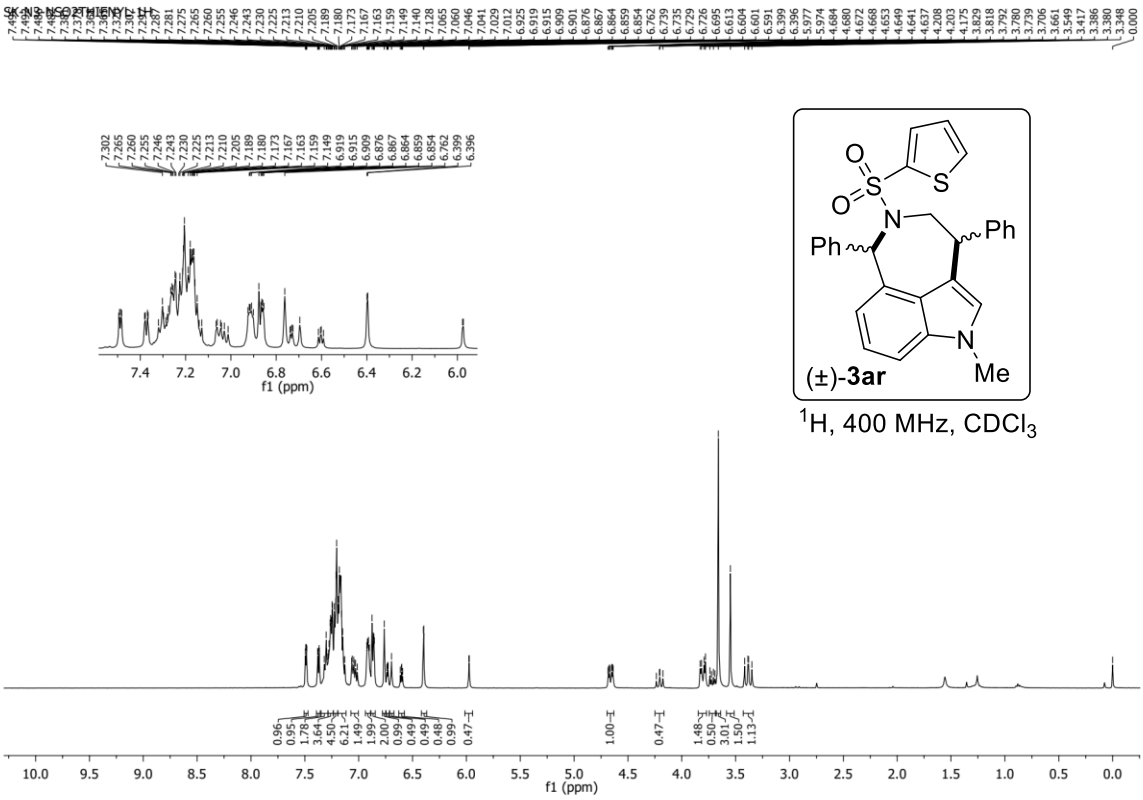
3.7 Selected NMR Spectra

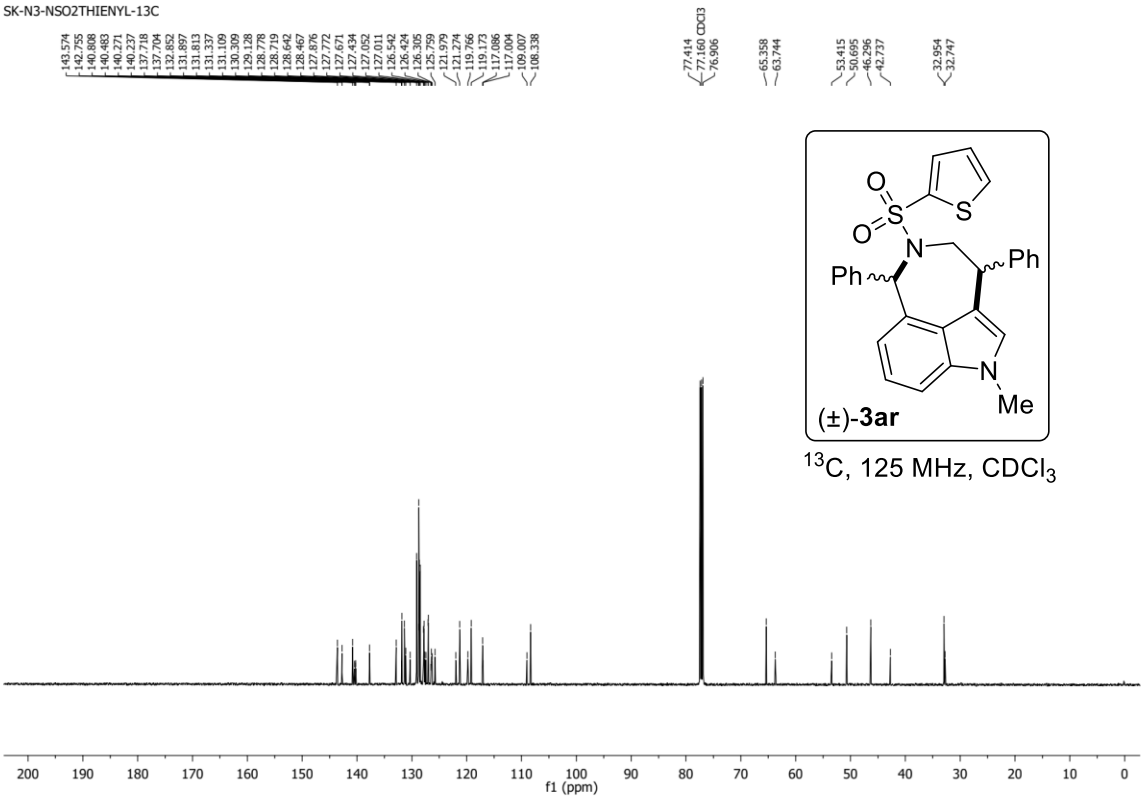


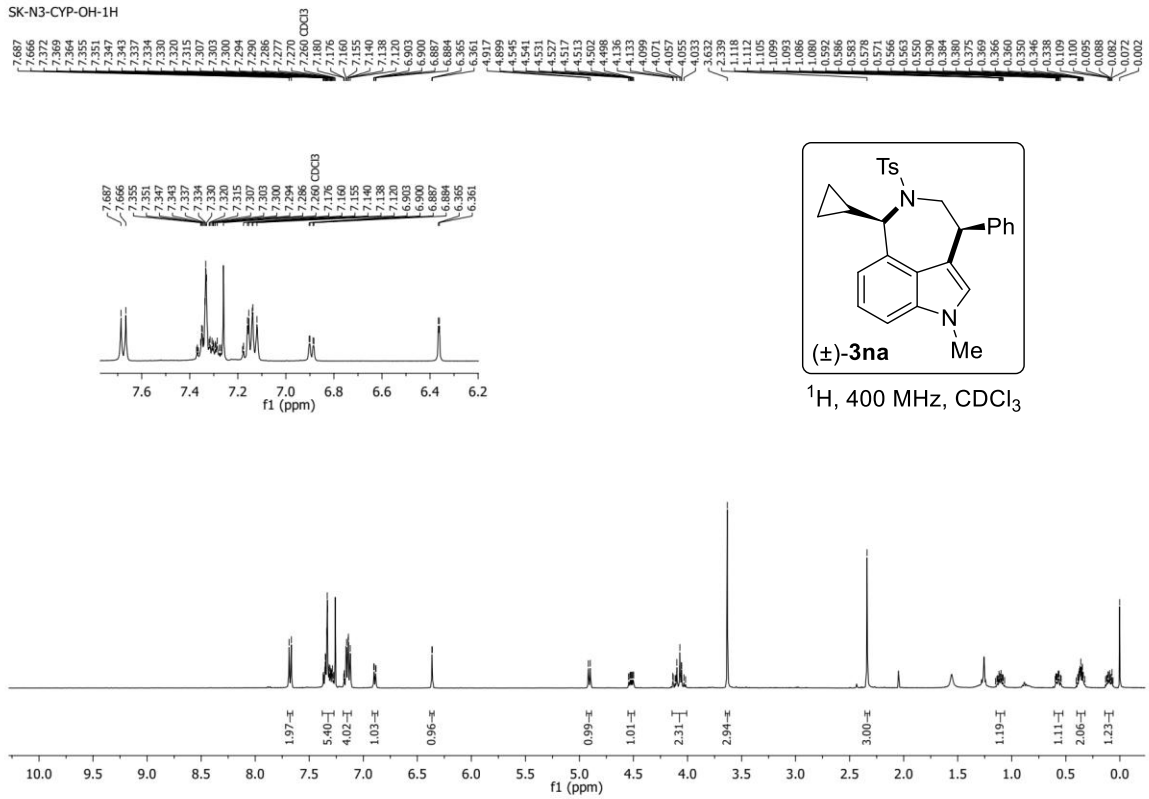
^{1}H, 500 MHz, $CDCl_3$



^{13}C, 125 MHz, $CDCl_3$







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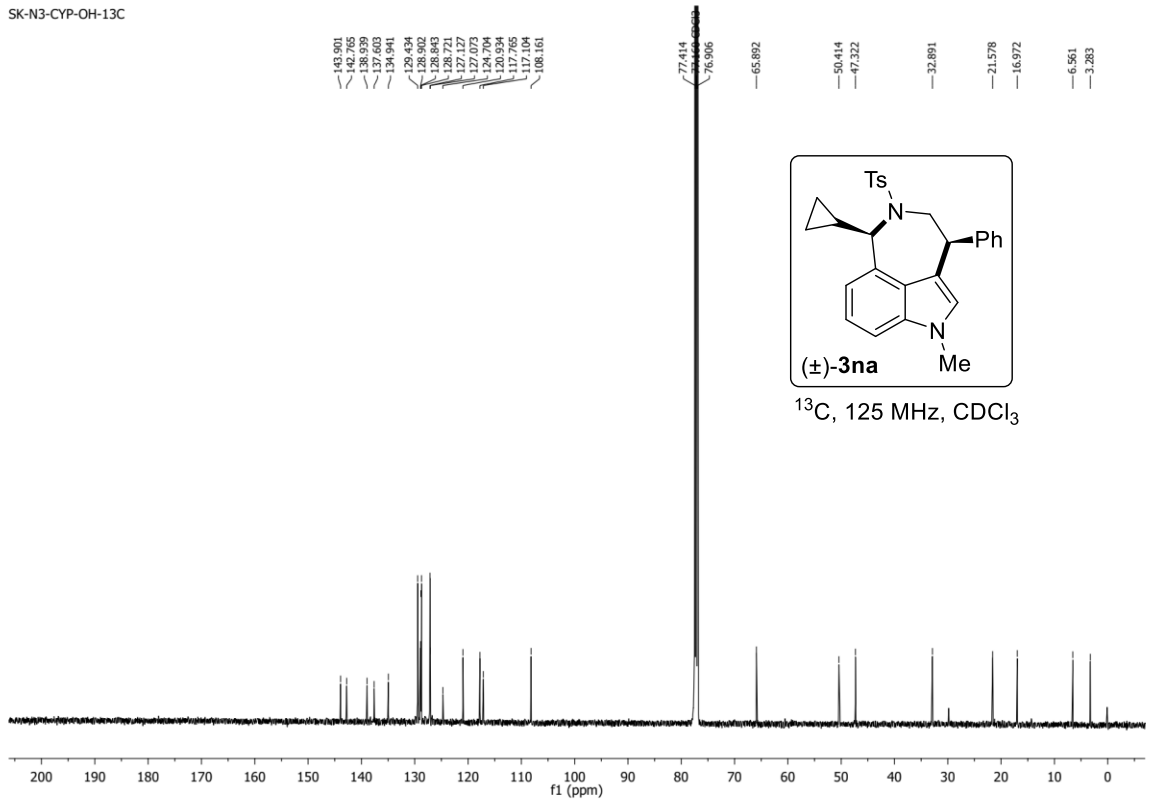
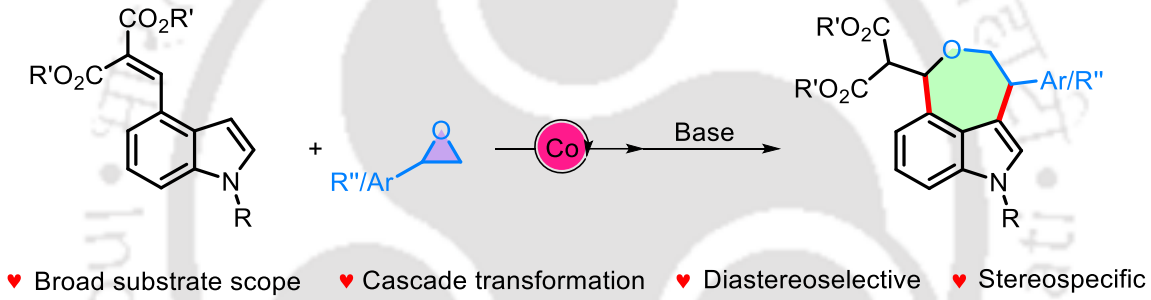


^{13}C, 125 MHz, $CDCl_3$

Chapter IV

Co(II)-Catalyzed Cascade (4+3)-Annulation of 4-Vinyl Indoles with Oxiranes: Stereospecific Access to Oxepinoindoles



♥ Broad substrate scope ♥ Cascade transformation ♥ Diastereoselective ♥ Stereospecific

Chem. Commun. **DOI**: 10.1039/D5CC06979C.

Co(II)-Catalyzed Cascade (4+3)-Annulation of 4-Vinyl Indoles with Oxiranes: Stereospecific Access to Oxepinoindoles

The distinctive architecture of medium-sized heterocyclic cores coupled with their diverse and compelling biological properties, has garnered sustained interest from the scientific community in the recent decades.[1] Contextually, the persistent identification of indole-fused seven-membered carbo- and heterocycles in skeletons of natural products and pharmaceuticals demands for stereoselective methodologies for their multifaceted synthesis.[2] Furthermore, owing to the biological interest and ubiquity of seven-membered cyclic ether moieties, the demand for harnessing versatile synthons[3] that can incorporate oxygen into the indole core could lead to generating distinctive indole-fused oxacyclic frameworks embedded in numerous alkaloids such as angustilodine and various anti-leishmanial and anti-tumoral agents (Figure 1).[4] However, difficulties in their synthesis mainly stem from the unfavourable entropic and enthalpic factors as well as significant transannular interactions that result competing reaction pathways favouring formation of smaller sized rings.[5] Therefore, notwithstanding continued efforts to articulate diverse strategic paradigms, there is a need for formulation of distinct methodologies that could lead to generation of diversified scaffolds in both atom- and step-economic manner. In this regard, oxiranes stand out as versatile three-atom synthons, which, owing to their intrinsic ring strain and wide accessibility can be explored for achieving miscellaneous oxacycles via C-C/C-O bond cleavage.[6] However their role as precursors for (4+3)-annulation remains underexplored. Moreover, in the recent decades, cobalt catalysis has emerged as a robust alternative to precious transition metal catalysts, owing to its earth abundance as well as economic and environmental advantages.[7] Thus, leveraging oxiranes for their functionality as dynamic 1,3-zwitterions for reaction with indoles embedded with alkylidene substitution at the C4 position could lead to generating oxepino cores. This chapter demonstrates an inexpensive cobalt-catalyzed cascade (4+3)-annulation of epoxides with 4-vinyl indoles to afford the seven-membered indole fused heterocyclic motifs in good yields and diastereoselectivity. Furthermore, using enantioenriched oxiranes, a series of optically active oxepino indoles could be obtained in up to >98% ee following the chirality transfer strategy.

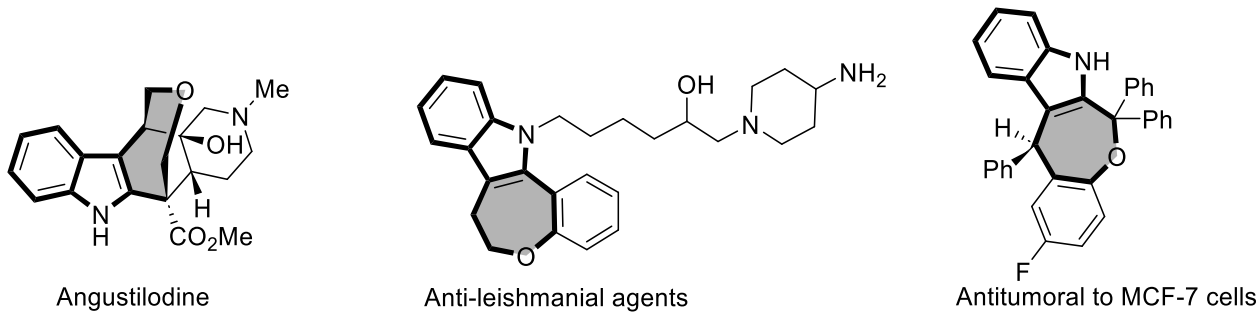
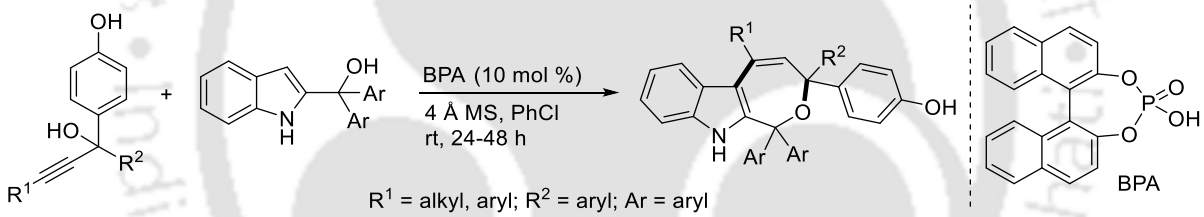


Figure 1. Pharmacologically Relevant Oxepinoindole Motifs

4.1 Literature

4.1.1 BPA-Catalyzed (3+4)-Annulation

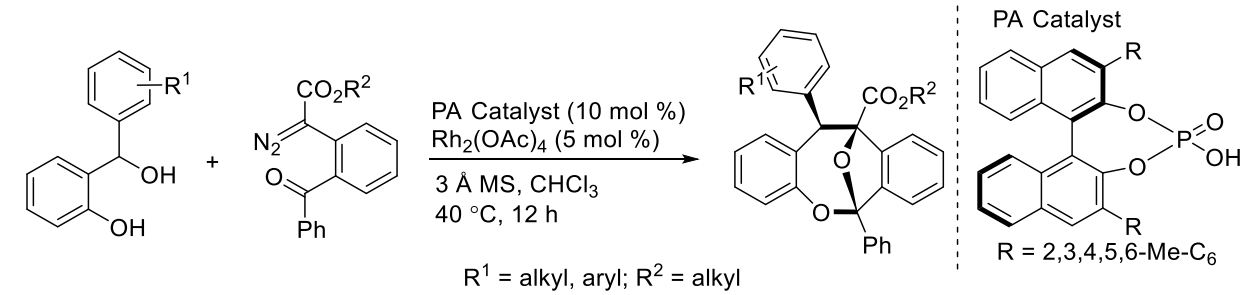
The Zhang group accomplished a Bronsted acid catalyzed (3+4)-annulation of propargylic *p*-quinone methides with 2-indolyl methanols (Scheme 1).[8] They demonstrated the utilization of 2-indolyl methanols as four-atom synthons under binaphthol derived phosphoric acid catalysis to afford structurally diverse polysubstituted indole fused oxepine scaffolds in high yields.



Scheme 1. (3+4)-Annulation of Propargylic *p*-Quinone Methides with 2-Indolylmethanols

4.1.2 (4+3)-Cycloannulation *via* Cooperative Catalysis

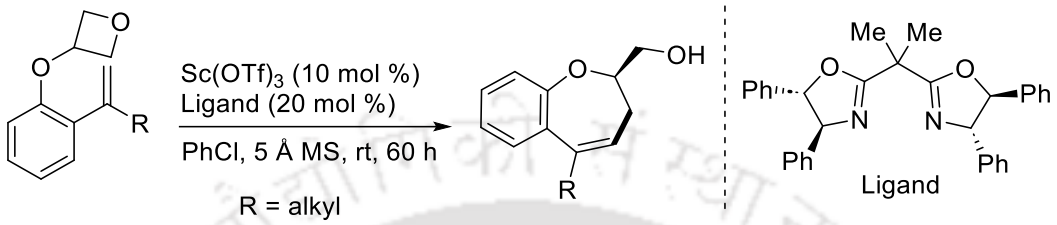
A highly diastereo- and enantioselective cooperative Rh/phosphoric acid catalytic strategy was developed for the (4+3)-cycloannulation of *o*-hydroxy benzhydryl alcohols with carbonyl ylides (Scheme 2).[9] A series of oxa-bridged heterocyclic motifs containing multiple stereogenic centers were obtained in high yields and stereoselectivity.



Scheme 2. (4+3)-Cycloannulation of *o*-Quinone Methides and Carbonyl Ylides

4.1.3 Sc-Catalyzed Oxetane Ring Opening

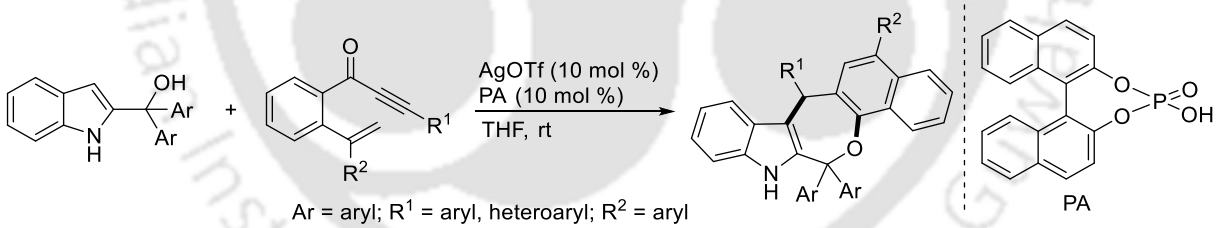
Sun and co-workers portrayed a Sc-catalyzed asymmetric ring-opening of oxetanes by carbon nucleophiles (Scheme 3).[10] A diverse array of oxetane tethered styrenes were subjected to cyclization under the standard conditions in presence of a chiral bisoxazoline ligand to afford benzo fused oxepine scaffolds in a highly efficient manner depicting good enantioselectivity.



Scheme 3. Sc-Catalyzed Enantioselective Dihydrobenzo[*b*]oxepine Synthesis

4.1.4 Cooperative Catalysis-Enabled (4+3)-Cycloaddition

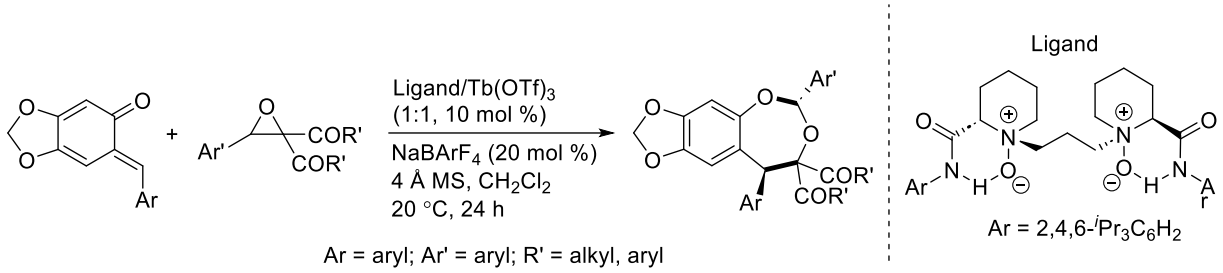
The Shi group demonstrated a Ag(I)-B-H co-catalyzed (4+3)-cycloaddition of 2-indolylmethanols with in-situ generated *o*-naphthoquinone methides (Scheme 4).[11] Under this cooperative strategy, diverse cyclohepta[*b*]indole frameworks were obtained in moderate to good yields. Using chiral phosphoric acid, the asymmetric version could be realized to deliver the chiral indole skeletons in 75% ee.



Scheme 4. (4+3)-Cycloaddition of 2-Indolyl methanols with *o*-NQMs

4.1.5 Asymmetric N, N′-dioxide/Tb^{III} Catalyzed (4+3)-Cycloaddition

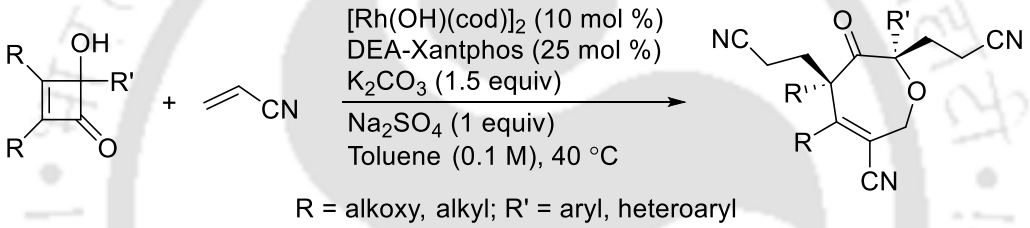
The Feng group demonstrated an asymmetric (4+3)-cycloaddition of *o*-QMs with donor-acceptor oxiranes using chiral N, N′-dioxide/Tb^{III} complex (Scheme 5).[12] Utilizing the chiral complex, the target dihydrobenzo[*d*][1,3]dioxepine scaffolds were obtained in excellent yields and good to excellent diastereo- and enantioselectivities.



Scheme 5. Asymmetric (4+3)-Cycloaddition of *o*-Quinone Methides with Oxiranes

4.1.6 Rh-Catalyzed Cascade C-C Bond Formation/Cleavage of Cyclobutenols

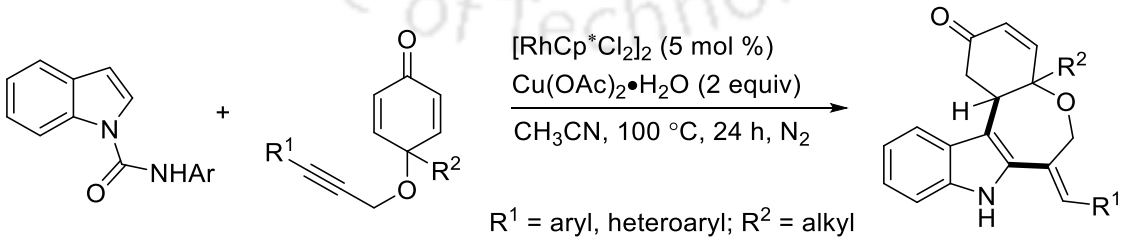
The Sarpong group demonstrated the skeletal remodelling of 4-hydroxy-2-cyclobutenones towards achieving substituted oxepane derivatives (Scheme 6).[13] The reaction proceeds *via* a Rh-catalyzed intermolecular and intramolecular conjugate addition, forming a fused bicycle and subsequent C-C bond cleavage leading to ring expansion.



Scheme 6. Seven-Membered Oxacycle Synthesis *via* Rh-Catalyzed Cascade C-C Bond Formation/Cleavage of Cyclobutenols

4.1.7 Rh-Catalyzed C-H Activation Initiated (5+2)-Annulation

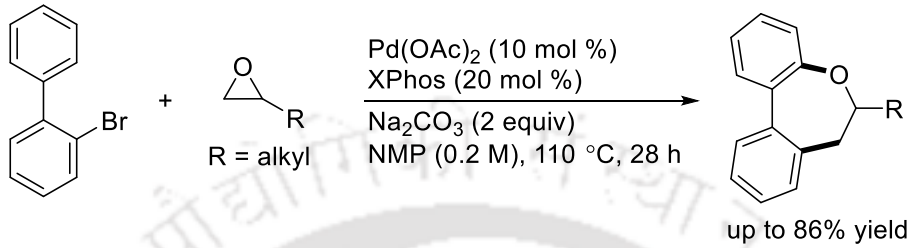
A Rh-catalyzed regioselective C2-alkenylation and intramolecular Friedel-Crafts alkylation relay was reported by the Li group (Scheme 7).[14] The reaction involves a diastereoselective (5+2)-annulation, affording indole-fused oxepines *via* indole 2,3-difunctionalizations.



Scheme 7. Seven-Membered Oxacycle Synthesis *via* Rh-Catalyzed C-H Activation Initiated Diastereoselective (5+2)-Annulation

4.1.8 Palladium-Catalyzed (4+3)-Annulation

The Cheng group developed a palladium catalyzed (4+3)-annulation of 2-bromobiphenyls and epoxides for the synthesis of functionalized dihydrodibenzo[*b*,*d*]oxepine derivatives (Scheme 8).[15] The reaction exhibits direct C-H/C-O bond activation followed by annulation utilizing readily available starting precursors offering broad substrate scope and scalability.



Scheme 8. Dihydrodibenzo[*b*,*d*]oxepines via Pd-Catalyzed (4+3)-Annulation

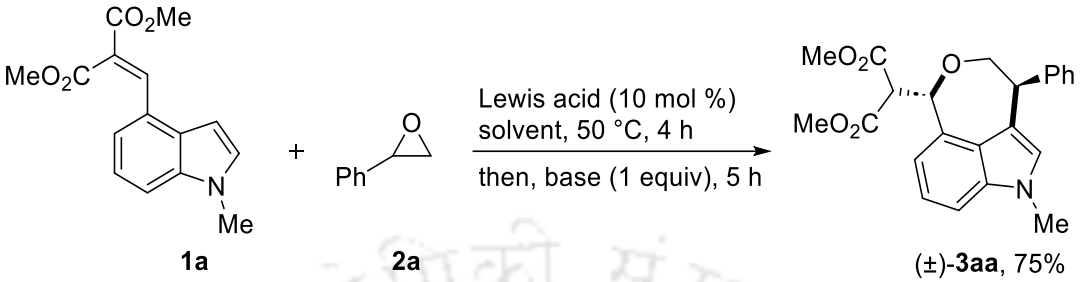
While considerable advancements have been made in the synthesis of the seven-membered oxacyclic frameworks, literature precedents described reveal that accessing tetrahydrooxepino[5,4,3-cd]indole scaffolds remain a significant synthetic challenge. In this context, the use of oxacyclopropane-mediated (4+3)-cyclization emerges as an efficient strategy for the construction of medium-sized rings with structural complexity. Accordingly, our work aims to focus on systematically exploring the reactivity of oxacyclopropanes in cycloaddition/tandem annulation processes, with the goal of developing methodologies for the diastereoselective synthesis of diverse indole-fused oxepine architectures.

4.2 Present Study

This chapter describes a cascade (4+3)-annulation of 4-vinyl indoles with oxiranes employing Co-catalysis to afford functionalized indole fused oxepine motifs. At the outset, we started our optimization studies by taking dimethyl 2-((1-methyl-1H-indol-4-yl)methylene)malonate **1a** and 2-phenyl oxirane **2a** as the model substrates (Table 1). Gratifyingly, in a series of Lewis acids screened, $Zn(OTf)_2$ could produce the desired product in up to 16%, while $Sc(OTf)_3$, $Ni(OTf)_2$, and $Cu(OTf)_2$ produced inferior outcomes (entries 1-4). Further screening with $FeCl_3$, $CoCl_2$, $CoCl_2•6H_2O$, $Co(OAc)_2•4H_2O$ and $Ni(ClO_4)_2•6H_2O$, revealed that with $Co(OAc)_2•4H_2O$, the yield of (±)-**3aa** increased significantly to 57% (entries 5-9). Amongst a series of bases surveyed, KO^{t}Bu, K_2CO_3, Na_2CO_3, Cs_2CO_3, NaOAc, DBU and DABCO, the former demonstrated the best outcome (entries 11-16). CH_2Cl_2 proved to be the solvent of choice over $(CH_2Cl)_2$, toluene, THF and CH_3CN that could result up to 60% yield (entries 17-

20). Subsequently, using 4 Å MS as additives led to improving the reactivity, yielding the annulated (±)-**3aa** in an increased yield of 75% (entry 10).

Table 1. Optimization of the Reaction Conditions.[a]

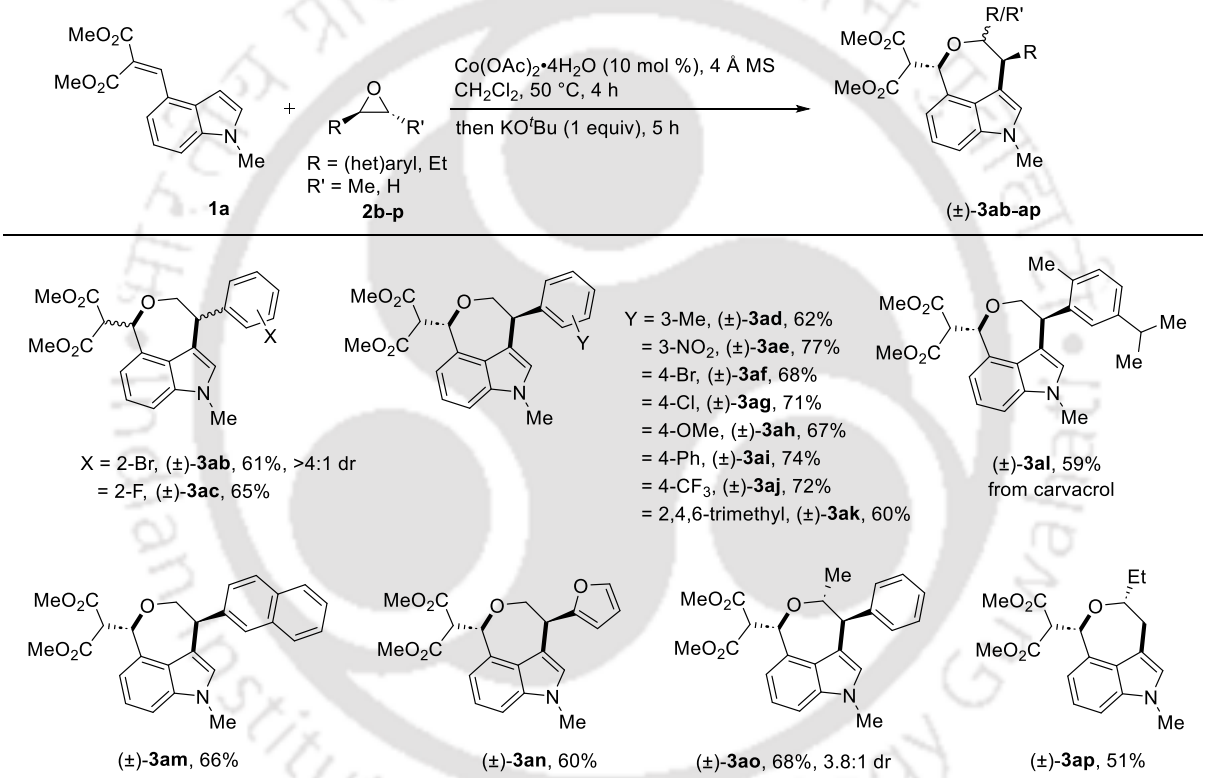


Entry	Lewis acid	Base	Solvent	Yield (%)[b]
1	$Sc(OTf)_3$	KO^{t}Bu	CH_2Cl_2	n.d.
2	$Ni(OTf)_2$	KO^{t}Bu	CH_2Cl_2	trace
3	$Zn(OTf)_2$	KO^{t}Bu	CH_2Cl_2	16
4	$Cu(OTf)_2$	KO^{t}Bu	CH_2Cl_2	trace
5	$FeCl_3$	KO^{t}Bu	CH_2Cl_2	trace
6	$CoCl_2$	KO^{t}Bu	CH_2Cl_2	23
7	$CoCl_2$•$6H_2O$	KO^{t}Bu	CH_2Cl_2	35
8	$Ni(ClO_4)_2$•$6H_2O$	KO^{t}Bu	CH_2Cl_2	15
9	$Co(OAc)_2$•$4H_2O$	KO^{t}Bu	CH_2Cl_2	57
[c]10	**$Co(OAc)_2$•$4H_2O$**	**KO^{t}Bu**	**CH_2Cl_2**	**75**
[c]11	$Co(OAc)_2$•$4H_2O$	K_2CO_3	CH_2Cl_2	61
[c]12	$Co(OAc)_2$•$4H_2O$	Na_2CO_3	CH_2Cl_2	55
[c]13	$Co(OAc)_2$•$4H_2O$	Cs_2CO_3	CH_2Cl_2	41
[c]14	$Co(OAc)_2$•$4H_2O$	NaOAc	CH_2Cl_2	trace
[c]15	$Co(OAc)_2$•$4H_2O$	DBU	CH_2Cl_2	n.d.
[c]16	$Co(OAc)_2$•$4H_2O$	DABCO	CH_2Cl_2	n.r.
[c]17	$Co(OAc)_2$•$4H_2O$	KO^{t}Bu	$(CH_2Cl)_2$	60

[c]18	$Co(OAc)_2•4H_2O$	KO^{t}Bu	toluene	n.d.
[c]19	$Co(OAc)_2•4H_2O$	KO^{t}Bu	THF	trace
[c]20	$Co(OAc)_2•4H_2O$	KO^{t}Bu	CH_3CN	45

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), Lewis acid (10 mol %), solvent (3 mL), 50 °C, 4 h, then, base (0.2 mmol), 5 h. [b]Isolated yield. [c]4 Å MS used. n.r.= no reaction. n.d.= not detected.

Table 2. Scope of Oxiranes[a,b]

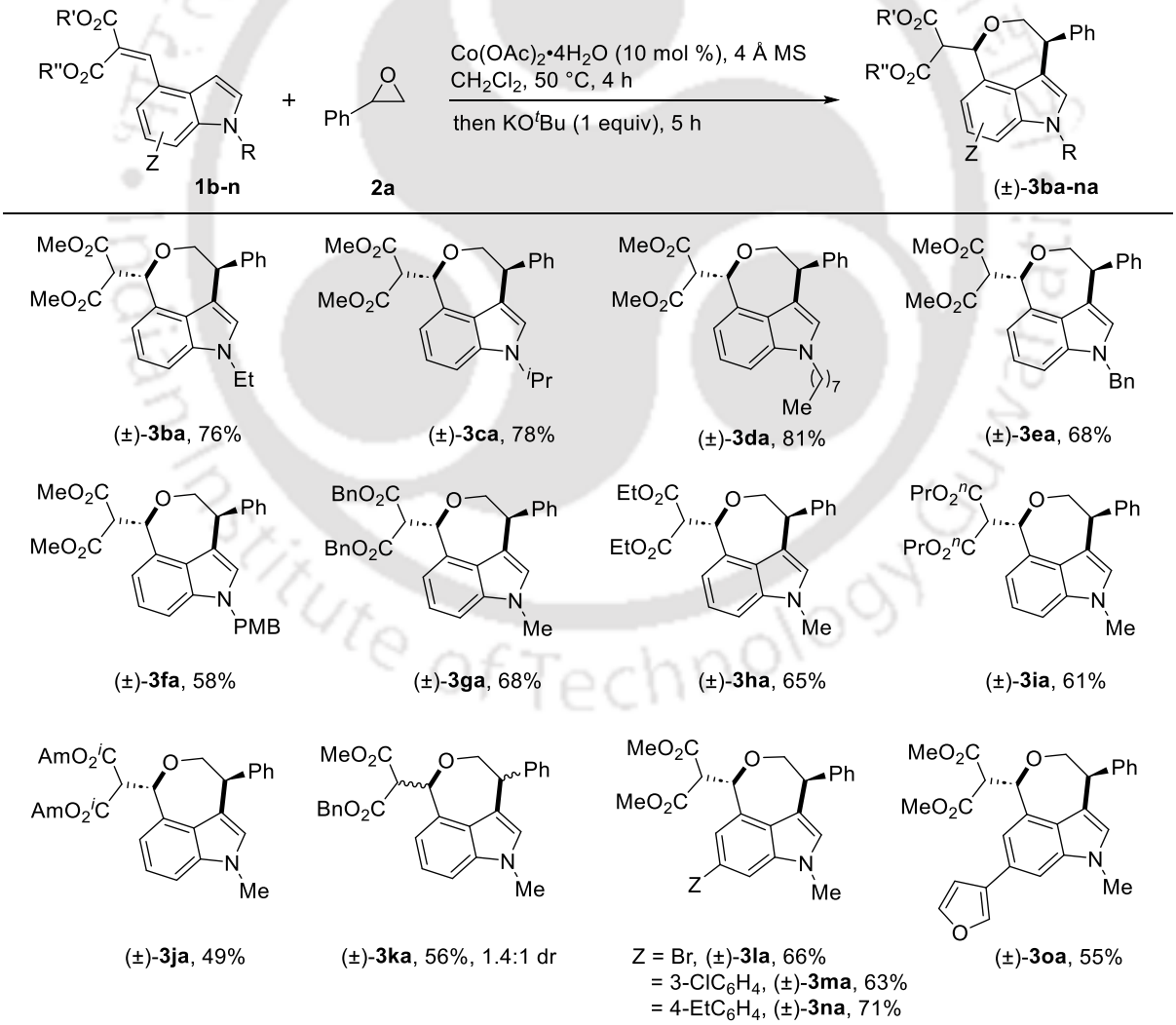


[a]Reaction conditions: **1a** (0.2 mmol), **2b-p** (0.24 mmol), $Co(OAc)_2•4H_2O$ (10 mol %), 4 Å MS (100 mg), CH_2Cl_2 (3 mL), 50 °C, 4 h; then, KO^{t}Bu (0.2 mmol), 5 h. [b]Isolated yield.

With the optimized reaction conditions in hand, we next moved forward towards evaluating our hypothesis with respect to a series of diversely substituted oxiranes **2b-p** with indolyl malonate **1a** as the standard substrate (Table 2). As illustrated, oxiranes bearing a series of diverse substitutions on the aryl ring were tolerated. Substitution at the *o*-position of the aryl ring with bromo **1b** and fluoro **1c** reacted efficiently to afford (±)-**3ab** and (±)-**3ac** in up to 65% yields. Moreover, substitution at the *m*-position with methyl **2d** and strong electron-

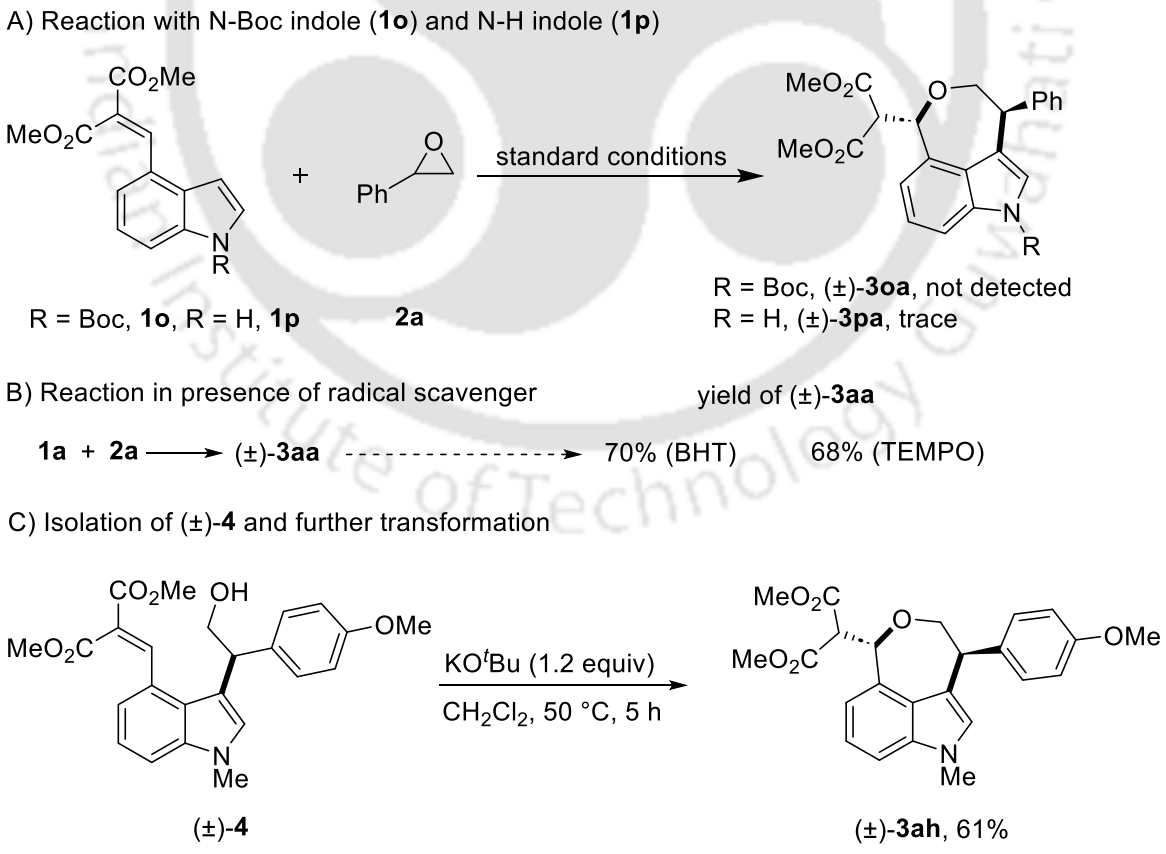
withdrawing nitro **2e** were amenable to deliver (±)-**3ad**-(±)-**3ae** as single diastereomers in 62% and 77% yields, respectively. Further, diverse substitution at the *p*-position of the aryl ring with bromo **2f**, chloro **2g**, methoxy **2h**, phenyl **2i** and electron-withdrawing trifluoromethyl **2j** were compatible in delivering the target heterocycles (±)-**3af**-(±)-**3aj** in 67-74% yields, while oxirane derived from trisubstituted **2k** produced (±)-**3ak** in 60% yield. Delightedly, carvacrol derived oxirane **2l** delivered **3al** in 59% yield. Oxiranes derived from 2-naphthyl **2m**, 2-furyl 2n and *β*-methyl **2o** afforded (±)-**3am**-(±)-**3ao** in up to 68% yields. Aliphatic 1,2-epoxybutane **2p** underwent nucleophilic ring-opening at the less sterically hindered methylene position to afford the regio- and diastereoselective annulated product (±)-**3ap** in 51% yield. The reduced yield of (±)-**3ap** may be due to the absence of a stabilizing aryl group and the decreased electrophilicity of the β-carbon of the oxirane.

Table 3. Scope of Indolylmalonates[a,b]



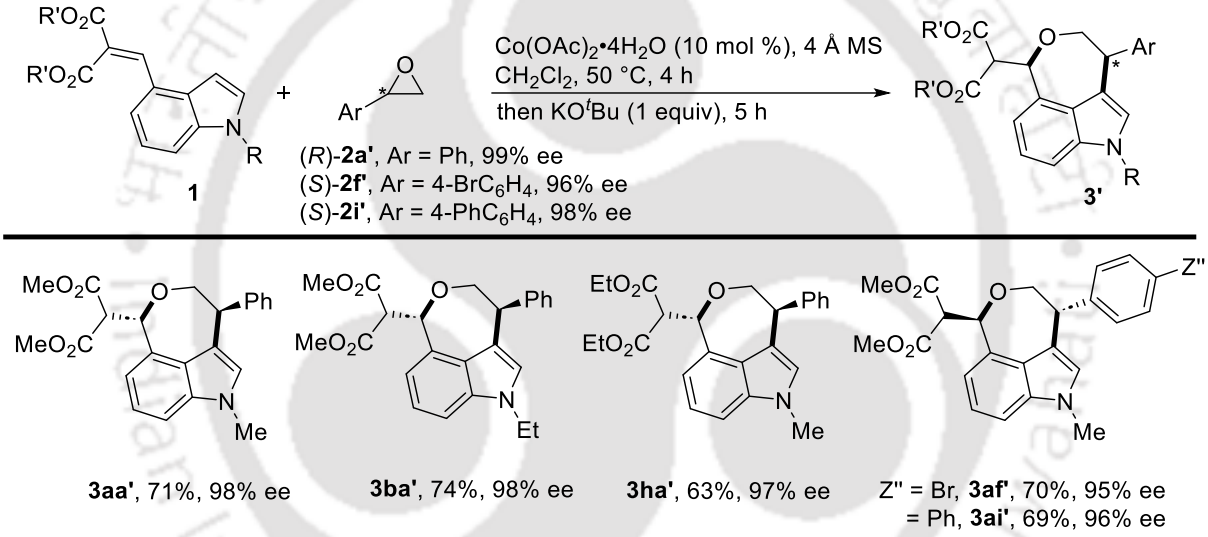
[a]Reaction conditions: **1b-o** (0.2 mmol), **2a** (0.24 mmol), $Co(OAc)_2$•$4H_2O$ (10 mol %), 4 Å MS (100 mg), CH_2Cl_2 (3 mL), 50 °C, 4 h; then, KO^{t}Bu (0.2 mmol), 5 h. [b]Isolated yield.

We next shifted our attention towards testing the generality of the protocol by screening functionally diverse indolyl malonates taking 2-phenyl oxirane **2a** as the representative substrate (Table 3). Indolyl malonates bearing diverse N-protecting groups such as ethyl **1b**, iso-propyl **1c**, long chain octyl **1d**, benzyl **1e** and PMB **1f** were amenable in affording the oxepinoindoles (±)-**3ba-fa** in up to 81% yields in a diastereoselective manner. Further substitution at the malonate center with numerous malonate esters such as dibenzyl **1g**, diethyl **1h** and dipropyl **1i** delivered (±)-**3ga-ia** in up to 68% yields. Delightedly, sterically encumbered di-isoamyl malonate ester **1j** and unsymmetrically substituted malonate ester **1k** were tolerated to give (±)-**3ja** and (±)-**3ka** in 49% and 56% yields, respectively. Substitution at the benzene core of the indole ring was well tolerated, delivering (±)-**3la-3na** in up to 71% yields. The reaction of a heteroaryl furyl substituted indole 1o, produced (±)-**3oa** in 55% yield. These outcomes highlight the potentiality of the described protocol in delivering electronically and functionally diverse oxepinoindoles in moderate to good yields.



Scheme 9. Mechanistic Investigations

To shed light into the reaction pathway, mechanistic experiments were performed (Scheme 9). Firstly, the reaction of N-Boc substituted indolyl malonate **1o** and NH indolyl malonate **1p** was carried out with **2a** (Scheme 9A). In the former case, no product formation was observed, indicating the reduced nucleophilicity of the pyrrole core in presence of an electron-withdrawing N-protecting group. Similarly, formation of a trace amount of product in the latter case can be owed to the possible coordination of the free NH with the catalyst, thereby inhibiting the reaction. Next, reaction in presence of radical scavengers BHT and TEMPO did not exhibit any significant reduction in the yield, thereby, effectively ruling out the involvement of radical intermediates (Scheme 9B). Further, isolation of the ring-opening intermediate (±)-**4** and subjecting to conditions of cyclization resulted (±)-**3ah** in 61% yield, thus confirming the involvement of a cascade pathway (Scheme 9C).

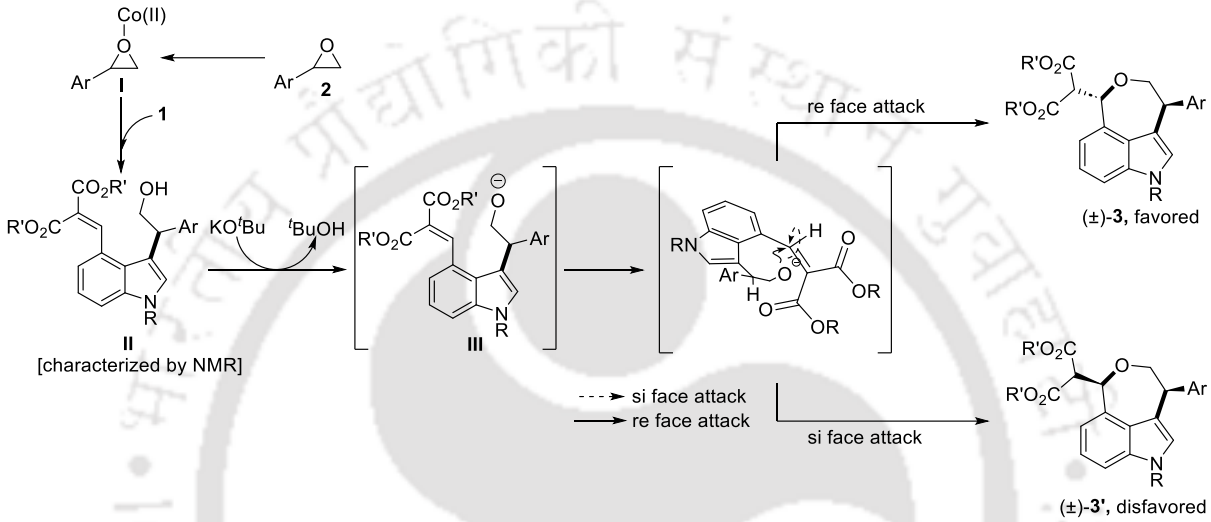


Scheme 10. Reaction with Enantiopure Oxiranes

The reaction of a set of substituted indolyl malonates was carried out with enantioenriched oxiranes (*R*)/(*S*)-**2′**. Indolyl malonate **1a** and N-ethyl substituted indolyl malonate **1b** reacted with (*R*)-**2a′** to deliver **3aa′** and **3ba′** in up to 74% yields and 98% ee. Diethyl malonate substituted indole **1h** delivered **3ha′** in 63% yield and 97% ee. Further, the reaction of indolyl malonate **1a** was performed with enantioenriched (*S*)-**2′**. Accordingly, (*S*)-**2f′** and (S)-**2i′** were amenable under the standard conditions to deliver **3af′** and **3ai′** in 95% ee and 96% ee respectively. These results corroborate the stereospecificity of the protocol in delivering enantioenriched products following a S_N2 reaction pathway.

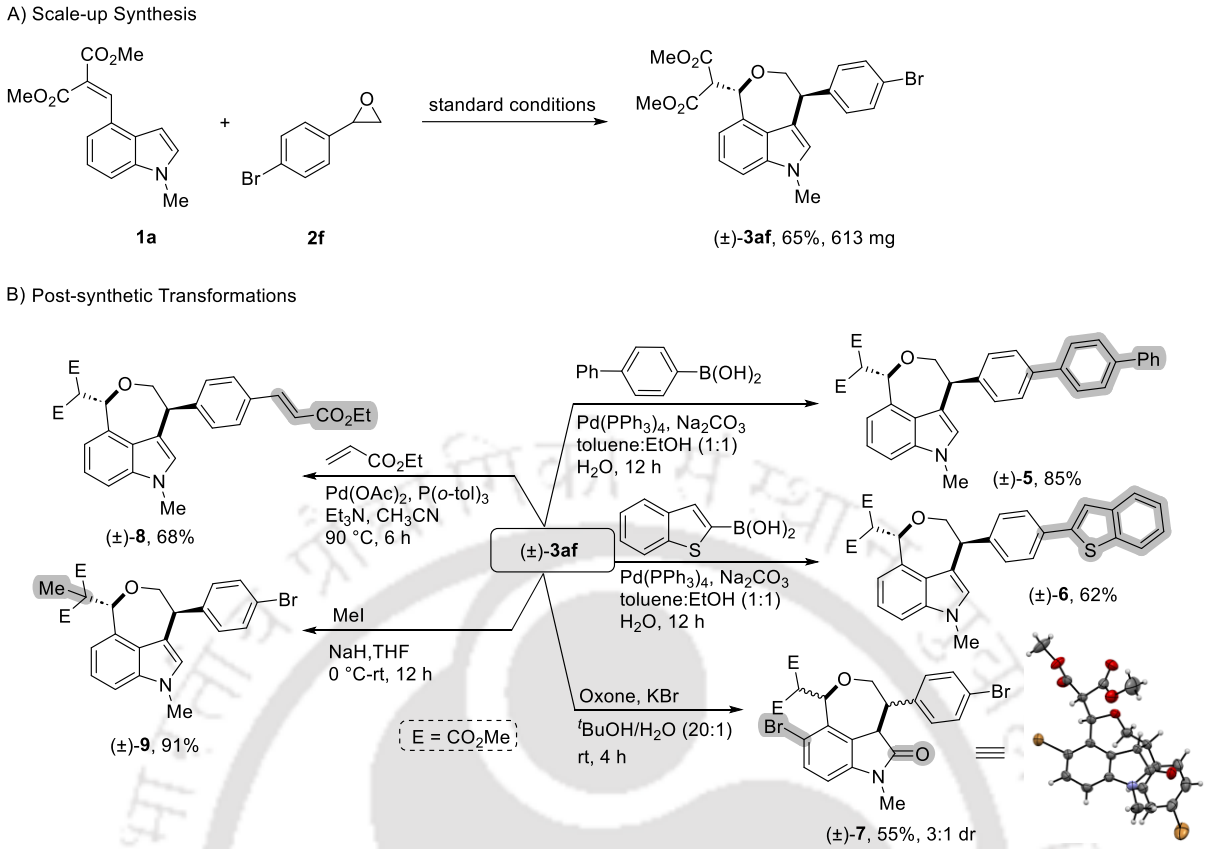
On the basis of these mechanistic studies and literature precedents,[16] a plausible mechanism is depicted in Scheme 11. In presence of the Lewis acid, initial coordination occurs with the

oxygen atom of the oxirane **2** to deliver the intermediate **I**. In presence of **1**, S_N2 attack occurs to deliver the Friedel-Crafts type ring-opening intermediate **II**. A sequential base-promoted deprotonation generates the transient intermediate **III**. The intermediate **III** can lead to an intramolecular oxa-Micheal addition on the tethered electrophilic alkylidene malonate to give (±)-**3**. The preferential formation of the major trans-isomer can be attributed to the selective oxa-Micheal addition of the oxirane to the re-face of the alkylidene malonate while an unfavorable si-face attack disfavored the formation of the minor cis-isomer (±)-**3′**.



Scheme 11. Plausible Mechanism

To showcase the practicality, scale-up synthesis was carried out by taking **1a** (2 mmol) and **2f** (2.4 mmol) as the model substrates (Scheme 12A). The reaction occurred to furnish (±)-**3af** in 65% yield (613 mg). Further, the annulated product was subjected to a series of post-synthetic transformations (Scheme 12B). A Pd-catalyzed Suzuki coupling in presence of [1,1'-biphenyl]-4-ylboronic acid and benzo[b]thiophen-2-ylboronic acid delivered (±)-**5** and (±)-**6** in 85% and 62% yields, respectively. In presence of Oxone and KBr, an oxidation of the indole occurred to give the oxindole along with concomitant bromination at the C5-position to give (±)-**7** in 55% yield and 3:1 dr. Moreover, using ethyl acrylate, a Pd-catalyzed Heck coupling could be achieved to afford (±)-**8** in 68% yield, while with MeI, alkylation occurred to give (±)-**9** in 91% yield.



Scheme 12. Post-Synthetic Transformations

In conclusion, a Co(II)-catalyzed cascade (4+3)-annulation of 4-alkylidene indole malonates with oxiranes was achieved to deliver indole fused oxepine motifs in moderate to good yields. The protocol follows mild reaction conditions, depicting broad substrate scope under inexpensive cobalt catalysis. With enantioenriched oxiranes, a stereospecific reaction pathway was followed, affording a series of optically active scaffolds in up to >98% ee.

4.3 Experimental Section

General Information. 1*H*-Indole-4-carbaldehyde, styrene, 1,2-epoxybutane, AD-mix-*α*, $Sc(OTf)_3$ (99%), $Ni(OTf)_2$ (96%), $Zn(OTf)_2$ (98%), $Cu(OTf)_2$ (98%), $FeCl_3$ (97%), $CoCl_2$ (97%), $CoCl_2•6H_2O$ (98%), $Co(OAc)_2•4H_2O$ (>98%), $Pd(PPh_3)_4$ (99%) and Oxone were purchased from Aldrich and used as received. (*R*)-Styrene oxide (>96%) was purchased from TCI and used as such. *m*-CPBA was purchased from SRL and used as such. KO^{t}Bu (98%) and DABCO (>98%) were purchased from Spectrochem and used as received. K_2CO_3, Na_2CO_3, Cs_2CO_3, NaOAc and DBU were purchased from Merck and used as received. The solvents were dried prior to use according to the standard procedure. SRL silica gel G/GF 254 plates were used for analytical TLC and SRL silica gel (100-200 mesh) was used for column

chromatography. NMR (^{1}H, ^{13}C and ^{19}F) 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 of (±)-**7** 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-2018/3* (Göttingen, Germany). HPLC analysis has been carried out using Chiralpak AD-H column utilizing *iso*-propanol and hexane as eluent. Optical rotation was determined using a Rudolph Autopol I Automatic Polarimeter at mentioned temperatures.

General Procedure for the Synthesis of (±)**-3aa-na**. Indolyl malonate **1** (0.2 mmol, 1 equiv), oxirane **2** (0.24 mmol, 1.2 equiv), $Co(OAc)_2$•$4H_2O$ (0.01 mmol, 0.1 equiv, 2.49 mg) and 4 Å molecular sieves (100 mg) were stirred in CH_2Cl_2 (3 mL) at 50 °C for 4 h in an oil bath under calcium chloride tube. Then, KO^{t}Bu (0.2 mmol, 1 equiv, 22 mg) was added and the resulting mixture was stirred at the same temperature for an additional 5 h. After completion, as monitored by TLC, the reaction mixture was allowed to cool to room temperature and diluted with CH_2Cl_2 (5 mL) and passed through a short pad of Celite using CH_2Cl_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 eluent to afford (±)-**3**.

General Procedure for the Enantiospecific Synthesis of 3aa′, **3af′**, **3ai′**, **3ba′** and **3ha′**. Indole **1** (0.2 mmol, 1 equiv), enantioenriched oxirane **2′** (0.24 mmol, 1.2 equiv), $Co(OAc)_2$•$4H_2O$ (0.01 mmol, 0.1 equiv, 2.49 mg) and 4 Å molecular sieves (100 mg) were stirred in CH_2Cl_2 (3 mL) at 50 °C for 4 h in an oil bath under calcium chloride tube. Then, KO^{t}Bu (0.2 mmol, 1 equiv, 22 mg) was added and the resulting mixture was stirred at the same temperature for an additional 5 h. The purification was performed as above presented general procedure. The enantiomeric excess was determined using chiral HPLC.

Procedure for Scale-up Synthesis of (±)**-3af**. Indolyl malonate **1a** (2 mmol, 1 equiv, 546 mg), oxirane **2f** (2.4 mmol, 1.2 equiv, 475 mg), $Co(OAc)_2$•$4H_2O$ (0.2 mmol, 0.10 equiv, 36 mg) and 4 Å molecular sieves (1 g) were stirred in CH_2Cl_2 (5 mL) at 50 °C for 4 h in an oil bath under calcium chloride tube. Then, KO^{t}Bu (2 mmol, 1 equiv, 224 mg) was added and the resulting

mixture was stirred at the same temperature for an additional 5 h. After completion, as monitored by TLC, the reaction mixture was allowed to cool to room temperature and diluted with CH_2Cl_2 (10 mL) and passed through a short pad of Celite using CH_2Cl_2 (20 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 to afford (±)**-3af**.

Synthesis of (±)**-5**.[17] To a solution of (±)**-3af** (0.1 mmol, 1 equiv, 47 mg) in toluene/EtOH (1:1, 3 mL), was added [1,1'-biphenyl]-4-ylboronic acid (0.1 mmol, 1 equiv, 19 mg), $Pd(PPh_3)_4$ (0.03 mmol, 0.03 equiv, 3 mg), Na_2CO_3 (0.1 mmol, 1 equiv, 11 mg) and H_2O (100 µL). The mixture was stirred at 100 °C for 12 h in an oil bath under a nitrogen atmosphere. After 12 h, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (10 mL) and washed with brine (1 X 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as eluent to give (±)**-5**.

Synthesis of (±)**-6**.[17] To a solution of (±)**-3af** (0.1 mmol, 1 equiv, 47 mg) in toluene/EtOH (1:1, 3 mL), was added the benzo[b]thiophen-2-ylboronic acid (0.1 mmol, 1 equiv, 17 mg), $Pd(PPh_3)_4$ (0.03 mmol, 0.03 equiv, 3 mg), Na_2CO_3 (0.1 mmol, 1 equiv, 11 mg) and H_2O (100 µL). The mixture was stirred at 100 °C for 12 h in an oil bath under a nitrogen atmosphere. After 12 h, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (10 mL) and washed with brine (1 X 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as eluent to give (±)**-6**.

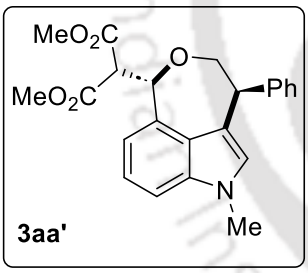
Synthesis of (±)**-7**.[18] To a solution of (±)**-3af** (0.1 mmol, 1 equiv, 47 mg) and KBr (0.1 mmol, 1 equiv, 12 mg) in $^tBuOH/H_2O$ (20:1) (2 mL) at room temperature, was added oxone (0.12 mmol, 1.2 equiv, 37 mg) and allowed to stir for 4 h under calcium chloride tube. After completion, as monitored by TLC, the reaction mixture was quenched with saturated aq. $Na_2S_2O_3$ (5 mL) and extracted with ethyl acetate (3 X 10 mL). The combined organic layers were washed with brine (5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as an eluent to afford (±)**-7**.

Synthesis of (±)**-8**.[19] To a solution of (±)**-3af** (0.1 mmol, 1 equiv, 47 mg) in CH_3CN (2 mL), was added ethyl acrylate (0.2 mmol, 2 equiv, 22 µL), Et_3N (0.5 mmol, 5 equiv, 70 µL), $Pd(OAc)_2$ (0.01 mmol, 0.1 equiv, 2.3 mg) and tri-*o*-tolylphosphine (0.02 mmol, 0.2 equiv, 6

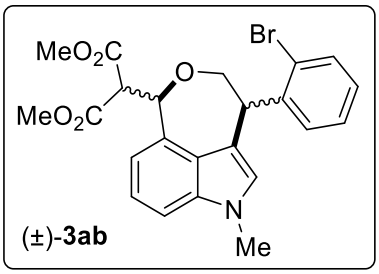
mg). The mixture was then allowed to stir at 90 °C for 6 h in an oil bath under nitrogen atmosphere. After completion, as monitored by TLC, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (5 mL) and passed through a short pad of celite using ethyl acetate (5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as eluent to give (±)-**8**.

Synthesis of (±)-**9**.[20] To a solution of NaH (60% dispersion in mineral oil, 0.15 mmol, 1.5 equiv, 6 mg) in THF (2 mL) at 0 ºC was added a solution of (±)-**3af** (0.1 mmol, 1 equiv, 47 mg) in THF (3 mL) under nitrogen atmosphere. The mixture was then allowed to stir at room temperature for 30 minutes. Then, MeI (0.2 mmol, 2 equiv, 28 mg) was added dropwise and the mixture was allowed to stir overnight at room temperature. After completion, as monitored by TLC, the reaction mixture was quenched with saturated aq. NH_4Cl (5 mL) and extracted with ethyl acetate (3 X 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as eluent to give (±)-**9**.

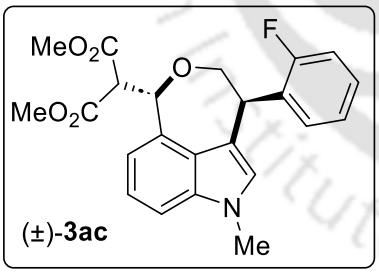
4.4 Characterization Data of the Products



Dimethyl 2-(6-methyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate 3aa′. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; yellow sticky liquid; yield 71% (55 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (m, 5H), 7.25-7.22 (m, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.479-6.475 (m, 1H), 5.62 (d, *J* = 6 Hz, 1H), 4.53-4.48 (m, 1H), 4.41-4.36 (m, 2H), 3.90-3.86 (m, 1H), 3.83 (s, 3H), 3.68 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 167.5, 142.1, 137.5, 134.8, 128.8, 128.7, 128.5, 127.0, 125.1, 121.3, 118.4, 114.4, 108.7, 82.9, 79.1, 57.6, 53.0, 52.5, 47.6, 32.9; FT-IR (KBr) 2950, 1736, 1454, 1300, 1246, 1155, 744, 702 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{24}NO_5$: 394.1649, found: 394.1651; $[\alpha]_D^{25}$ = +30 (c = 0.01, $CHCl_3$); HPLC: *ee* for major diastereomer = >98% *ee* [Chiralpak AD-H, hexane/^{i}PrOH = 80:20, flow rate: 1 mL/min, λ= 254 nm, t_R = 8.40 min (major), 10.73 min (minor)].

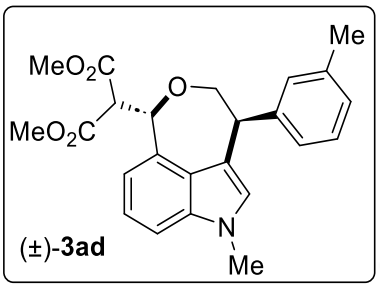


Dimethyl 2-(4-(2-bromophenyl)-6-methyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3ab**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.54; brown sticky liquid;; yield 61% (57 mg); mixture of diastereomers (4:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.59 (m, 1H), 7.54-7.52 (m, 0.26H), 7.25-7.19 (m, 2.16H), 7.18-7.15 (m, 3H), 7.12-7.07 (m, 1.25H), 7.03-6.99 (m, 0.28H), 6.81-6.79 (m, 0.28H), 6.78 (s, 0.25H), 6.77 (d, *J* = 7.2 Hz, 1H), 6.50-6.49 (m, 1H), 5.72 (d, *J* = 6 Hz, 0.25H), 5.64 (d, *J* = 6 Hz, 1H), 5.07-5.03 (m, 1H), 5.00-4.98 (m, 0.27H), 4.51-4.47 (m, 0.28H), 4.45-4.41 (m, 1H), 4.39 (d, *J* = 6 Hz, 1H), 4.35 (d, *J* = 5.6 Hz, 1H), 4.16-4.13 (m, 0.28H), 3.91-3.83 (m, 4H), 3.77 (s, 0.75H), 3.72 (s, 0.74H), 3.69 (s, 3H), 3.67 (s, 3H), 3.61 (s, 0.73H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.56, 168.50, 167.56, 167.50, 143.8, 137.5, 137.4, 134.8, 134.7, 132.3, 132.2, 128.4, 128.1, 127.87, 127.84, 127.6, 127.1, 125.9, 125.1, 124.7, 123.6, 121.4, 121.3, 117.2, 116.4, 114.9, 114.5, 108.8, 108.7, 83.1, 82.2, 74.9, 57.7, 57.6, 53.0, 52.8, 52.6, 52.5, 45.0, 32.9; FT-IR (KBr) 2924, 2853, 1736, 1435, 1244, 1155, 745 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{23}H_{22}BrNNaO_5$: 494.0574, found: 494.0564.

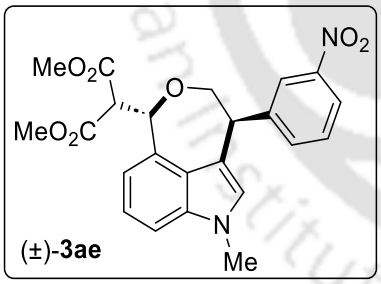


Dimethyl 2-(4-(2-fluorophenyl)-6-methyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3ac**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.51; yellow sticky liquid; yield 65% (53 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.20 (m, 3H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.09-7.04 (m, 2H), 6.77 (d, *J* = 7.2 Hz, 1H), 6.497-6.494 (m, 1H), 5.63 (d, *J* = 6 Hz, 1H), 4.85 (dd, *J* = 10.8, 4.4 Hz, 1H), 4.43-4.39 (m, 2H), 3.99-3.93 (m, 1H), 3.83 (s, 3H), 3.68 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 167.5, 162.3 (d, J_{C-F} = 245 Hz), 137.6, 134.7, 130.8 (d, J_{C-F} = 4.7 Hz), 128.8 (d, J_{C-F} = 14.3 Hz), 128.6 (d, J_{C-F} = 8.1 Hz), 127.8, 124.9, 124.2 (d, J_{C-F} = 3.5 Hz), 121.3, 117.2, 115.8 (d, J_{C-F} = 22.3 Hz), 114.5, 108.7,

82.9, 57.6, 53.0, 52.6, 40.6, 32.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -119.5; FT-IR (KBr) 2924, 1736, 1454, 1247, 1155, 748 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{23}H_{22}FNNaO_5$: 434.1374, found: 434.1363.

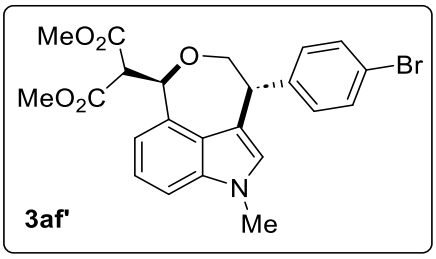


Dimethyl 2-(6-methyl-4-(m-tolyl)-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3ad**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.61; yellow sticky liquid; yield 62% (50 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.20 (m, 2H), 7.18-7.14 (m, 1H), 7.08-7.06 (m, 3H), 6.76 (d, *J* = 7.2 Hz, 1H), 6.487-6.483 (m, 1H), 5.61 (d, *J* = 5.6 Hz, 1H), 4.48-4.44 (m, 1H), 4.41-4.35 (m, 2H), 3.89-3.86 (m, 1H), 3.83 (s, 3H), 3.68 (s, 3H), 3.64 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 167.5, 142.1, 138.1, 137.5, 134.9, 129.6, 128.6, 128.4, 127.7, 126.0, 125.1, 121.2, 118.6, 114.4, 108.7, 82.9, 79.2, 57.7, 53.0, 52.5, 47.5, 32.9, 21.5; FT-IR (KBr) 2924, 2855, 1737, 1455, 1123, 747 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{24}H_{25}NNaO_5$: 430.1625, found: 430.1624.

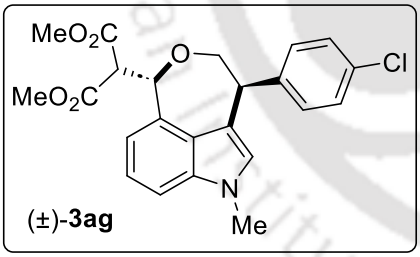


Dimethyl 2-(6-methyl-4-(3-nitrophenyl)-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3ae**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.48; yellow sticky liquid; yield 77% (67 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14-8.11 (m, 2H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.51-7.47 (m, 1H), 7.27-7.25 (m, 1H), 7.20 (t, *J* = 7.2 Hz, 1H), 6.80 (d, *J* = 7.2 Hz, 1H), 6.444-6.441 (m, 1H), 5.65 (d, *J* = 5.6 Hz, 1H), 4.67-4.62 (m, 1H), 4.41-4.37 (m, 2H), 3.90 (t, *J* = 11.6 Hz, 1H), 3.83 (s, 3H), 3.70 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 167.4, 148.6, 144.4, 137.6, 135.2, 134.5, 129.6, 128.3, 124.9, 123.7, 122.2, 121.7, 117.1, 114.8, 108.9, 82.9, 78.2, 57.5, 53.0, 52.5, 47.3, 33.0; FT-IR (KBr) 2924, 2853, 1734,

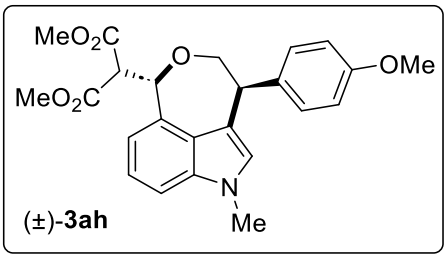
1525, 1455, 1346, 1245, 1081, 738 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{23}H_{22}N_2NaO_7$: 461.1319, found: 461.1317.



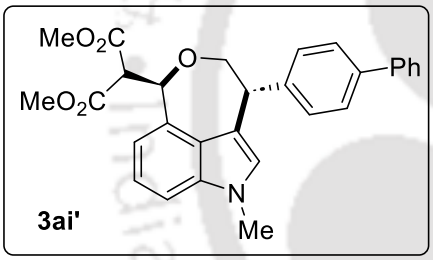
Dimethyl 2-(4-(4-bromophenyl)-6-methyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate 3af'. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.65; brown sticky liquid; yield 70% (65 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 2H), 7.24-7.22 (m, 1H), 7.19-7.14 (m, 3H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.459-6.455 (m, 1H), 5.61 (d, *J* = 5.6 Hz, 1H), 4.49-4.45 (m, 1H), 4.40-4.32 (m, 2H), 3.86-3.82 (m, 4H), 3.68 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 167.4, 141.2, 137.6, 134.7, 131.7, 130.6, 128.4, 125.0, 121.4, 120.8, 118.0, 114.6, 108.8, 82.9, 78.7, 57.6, 53.0, 52.5, 47.1, 32.9; FT-IR (KBr) 2925, 2855, 1736, 1455, 1299, 1155, 1010, 747 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{23}H_{22}BrNNaO_5$: 494.0574, found: 494.0546; $[\alpha]_D^{25}$ = -25 (c = 0.04, $CHCl_3$); HPLC: *ee* for major diastereomer = >96% *ee* [Chiralpak AD-H, hexane/^{i}PrOH = 90:10, flow rate: 1 mL/min, λ= 254 nm, t_R = 25.52 min (minor), 28.50 min (major)].



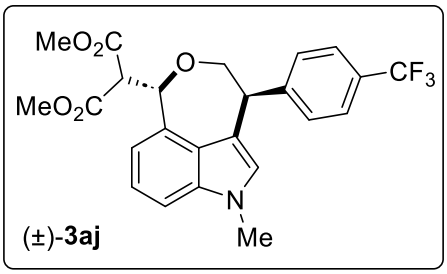
Dimethyl 2-(4-(4-chlorophenyl)-6-methyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3ag**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.62; brown sticky liquid; yield 71% (60 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.4 Hz, 2H), 7.25-7.15 (m, 4H), 6.77 (d, *J* = 7.2 Hz, 1H), 6.46-6.45 (m, 1H), 5.61 (d, *J* = 5.6 Hz, 1H), 4.51-4.47 (m, 1H), 4.40 (d, *J* = 5.6 Hz, 1H), 4.36 (dd, *J* = 11.6, 4.8 Hz, 1H), 3.86-3.80 (m, 4H), 3.68 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.5, 167.4, 140.7, 137.6, 134.7, 132.7, 130.2, 128.8, 128.4, 125.0, 121.4, 118.1, 114.5, 108.7, 82.9, 78.7, 57.6, 53.0, 52.5, 47.0, 32.9; FT-IR (KBr) 2951, 2863, 1734, 1488, 1298, 1155, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{23}H_{22}ClNNaO_5$: 450.1079, found: 450.1074.



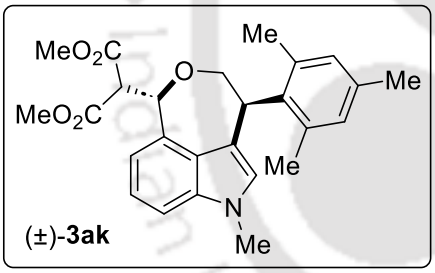
Dimethyl 2-(4-(4-methoxyphenyl)-6-methyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3ah**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; yellow sticky liquid; yield 67% (56 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.14 (m, 4H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 7.6 Hz, 1H), 6.487-6.483 (m, 1H), 5.60 (d, *J* = 5.6 Hz, 1H), 4.48-4.43 (m, 1H), 4.41 (d, *J* = 5.6 Hz, 1H), 4.35 (dd, *J* = 11.6, 4.8 Hz, 1H), 3.86-3.82 (m, 4H), 3.81 (s, 3H), 3.68 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 167.5, 158.5, 137.5, 134.8, 134.2, 129.8, 128.5, 125.0, 121.2, 118.8, 114.3, 113.9, 108.7, 82.8, 79.3, 57.6, 55.3, 53.0, 52.5, 46.8, 32.9; FT-IR (KBr) 2924, 2853, 1736, 1609, 1509, 1455, 1301, 1248, 748 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{24}H_{25}NNaO_6$: 446.1574, found: 446.1584.



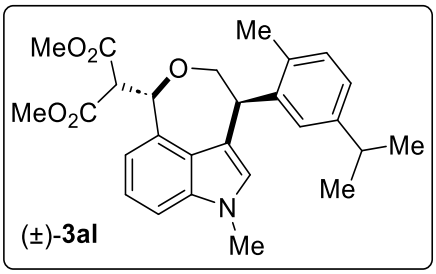
Dimethyl 2-(4-([1,1'-biphenyl]-4-yl)-6-methyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate 3ai′. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.63; colorless sticky liquid; yield 69% (64 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.5 Hz, 2H), 7.56 (d, *J* = 8 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.35 (d, *J* = 7.5 Hz, 3H), 7.24 (s, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 7 Hz, 1H), 6.54 (s, 1H), 5.64 (d, *J* = 5.5 Hz, 1H), 4.57-4.54 (m, 1H), 4.44-4.40 (m, 2H), 3.91 (t, *J* = 11.5 Hz, 1H), 3.84 (s, 3H), 3.70 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 167.5, 141.2, 141.0, 139.9, 137.6, 134.9, 129.3, 128.9, 128.6, 127.3, 127.1, 125.1, 121.3, 118.4, 114.5, 108.7, 82.9, 79.0, 57.7, 53.0, 52.5, 47.3, 32.9; FT-IR (KBr) 2923, 2852, 1737, 1301, 1340, 1156, 746 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{29}H_{27}NNaO_5$: 492.1781, found: 492.1777; $[\alpha]_D^{25}$ = -53.33 (c = 0.03, $CHCl_3$); HPLC: *ee* for major diastereomer = >95% *ee* [Chiralpak AD-H, hexane/^{i}PrOH = 90:10, flow rate: 1 mL/min, λ= 254 nm, t_R = 19.13 min (minor), 24.99 min (major)].



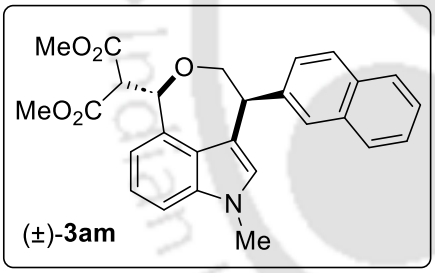
Dimethyl 2-(6-methyl-4-(4-(trifluoromethyl)phenyl)-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3aj**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.50; yellow sticky liquid; yield 72% (66 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8 Hz, 2H), 7.40 (d, *J* = 8 Hz, 2H), 7.24-7.13 (m, 2H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.446-6.443 (m, 1H), 5.63 (d, *J* = 5.2 Hz, 1H), 4.60-4.56 (m, 1H), 4.40-4.35 (m, 2H), 3.87 (t, *J* = 11.6 Hz, 1H), 3.83 (s, 3H), 3.69 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 167.4, 146.3, 137.6, 134.7, 129.3, 128.4, 127.6 (q, $J_{C\text{-}F}$ = 270 Hz), 125.6 (q, $J_{C\text{-}F}$ = 3.6 Hz), 125.0, 121.5, 117.6, 114.6, 108.8, 82.9, 78.5, 57.6, 53.0, 52.5, 47.5, 33.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ -62.3; FT-IR (KBr) 2927, 1735, 1485, 1325, 1241, 1046, 735 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{24}H_{22}F_3NNaO_5$: 484.1342, found: 484.1330.



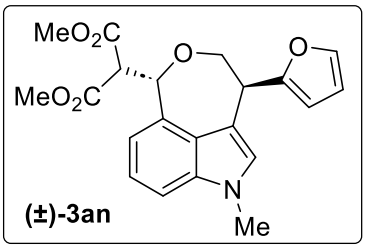
Dimethyl 2-(4-mesityl-6-methyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3ak**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.64; yellow sticky liquid; yield 60% (52 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.22 (m, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 6.91 (s, 1H), 6.78 (s, 1H), 6.74 (d, *J* = 7.2 Hz, 1H), 6.408-6.404 (m, 1H), 5.57 (d, *J* = 6 Hz, 1H), 4.97-4.93 (m, 1H), 4.42 (d, *J* = 6 Hz, 1H), 4.32 (dd, *J* = 12, 5.6 Hz, 1H), 4.12 (t, *J* = 11.6 Hz, 1H), 3.85 (s, 3H), 3.68 (s, 3H), 3.66 (s, 3H), 2.46 (s, 3H), 2.27 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 167.7, 137.8, 137.5, 137.4, 136.1, 135.0, 134.5, 131.0, 129.0, 126.8, 124.6, 121.2, 117.6, 114.1, 108.7, 83.4, 76.3, 57.6, 53.1, 52.6, 42.0, 32.8, 22.0, 21.5, 20.9; FT-IR (KBr) 2922, 1739, 1454, 1302, 1156, 744 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{26}H_{29}NNaO_5$: 458.1938, found: 458.1935.



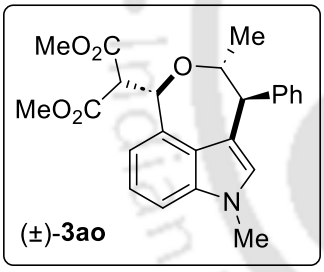
Dimethyl 2-(4-(5-isopropyl-2-methylphenyl)-6-methyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3al**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.62; orange sticky liquid; yield 59% (53 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.13 (m, 3H), 7.05-7.02 (m, 1H), 6.98 (s, 1H), 6.77 (d, *J* = 7.2 Hz, 1H), 6.427-6.423 (m, 1H), 5.61 (d, *J* = 5.6 Hz, 1H), 4.73-4.70 (m, 1H), 4.44 (d, *J* = 6 Hz, 1H), 4.38 (dd, *J* = 11.6, 4.8 Hz, 1H), 3.92 (t, *J* = 11.6 Hz, 1H), 3.85 (s, 3H), 3.67 (s, 3H), 3.66 (s, 3H), 2.39 (s, 3H), 2.80-2.73 (m, 1H), 1.17-1.14 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 167.6, 146.8, 140.0, 137.6, 134.9, 133.8, 130.4, 128.1, 125.1, 124.5, 121.2, 118.4, 114.2, 108.7, 83.1, 57.5, 53.0, 52.6, 33.8, 32.9, 24.2, 24.1; FT-IR (KBr) 2953, 2922, 2853, 1738, 1455, 1155, 747 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{27}H_{31}NNaO_5$: 472.2094, found: 472.2096.



Dimethyl 2-(6-methyl-4-(naphthalen-2-yl)-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3am**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.55; yellow sticky liquid; yield 66% (58 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.78 (m, 4H), 7.50-7.45 (m, 2H), 7.37-7.34 (m, 1H), 7.26-7.24 (m, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.47-6.46 (m, 1H), 5.66 (d, *J* = 5.6 Hz, 1H), 4.71-4.66 (m, 1H), 4.48-4.44 (m, 1H), 4.44-4.42 (m, 1H), 4.00 (t, *J* = 11.6 Hz, 1H), 3.84 (s, 3H), 3.664-3.662 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.6, 167.5, 139.5, 137.6, 134.9, 133.6, 132.7, 128.7, 128.2, 127.8, 127.7, 127.5, 127.1, 126.1, 125.7, 125.1, 121.3, 118.5, 114.5, 108.7, 83.0, 79.0, 57.7, 53.0, 52.5, 47.7, 32.9; FT-IR (KBr) 2922, 2851, 1737, 1454, 1247, 1129, 747 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{27}H_{25}NNaO_5$: 466.1625, found: 466.1608.

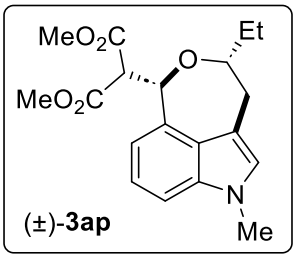


Dimethyl 2-(4-(furan-2-yl)-6-methyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3an**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.41; yellow sticky liquid; yield 60% (46 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.35 (m, 1H), 7.23-7.21 (m, 1H), 7.17-7.13 (m, 1H), 6.765-6.761 (m, 1H), 6.75-6.73 (m, 1H), 6.34-6.33 (m, 1H), 6.17 (d, *J* = 3.2 Hz, 1H), 5.60 (d, *J* = 5.6 Hz, 1H), 4.70-4.66 (m, 1H), 4.52-4.48 (m, 1H), 4.38 (d, *J* = 5.6 Hz, 1H), 3.96 (t, *J* = 11.6 Hz, 1H), 3.83 (s, 3H), 3.72 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 167.5, 154.9, 141.7, 137.7, 134.5, 127.8, 124.5, 121.4, 115.0, 114.5, 110.1, 108.8, 106.4, 82.8, 76.4, 57.7, 53.0, 52.5, 40.7, 33.0; FT-IR (KBr) 2922, 2851, 1736, 1456, 1155, 745 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{21}H_{21}NNaO_6$: 406.1261, found: 406.1269.

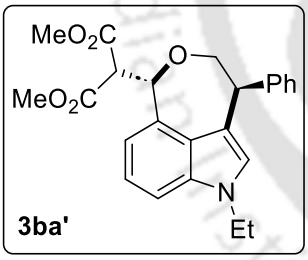


Dimethyl 2-(3,6-dimethyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3ao**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.57; yellow sticky liquid; yield 68% (55 mg); mixture of diastereomers (3.8:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.29 (m, 2.89H), 7.21-7.19 (m, 3.81H), 7.17-7.13 (m, 3.15H), 6.78 (s, 1H), 6.75 (d, *J* = 7.2 Hz, 1H), 6.70 (d, *J* = 7.2 Hz, 0.27H), 6.31 (s, 0.26H), 5.67 (d, *J* = 5.2 Hz, 1H), 4.44-4.40 (m, 1H), 4.38 (d, *J* = 5.2 Hz, 1H), 4.35 (d, *J* = 6.8 Hz, 0.32H), 4.21-4.20 (m, 1H), 4.069-4.062 (m, 0.35H), 3.87 (s, 0.79H), 3.81 (s, 3H), 3.68 (s, 0.80H), 3.67 (s, 3H), 3.64 (s, 0.80H), 3.62 (s, 3H), 1.07-1.06 (m, 3.84H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 168.7, 167.7, 167.6, 144.0, 143.7, 137.4, 137.3, 135.4, 135.3, 130.0, 129.2, 129.1, 128.5, 128.0, 127.6, 126.7, 126.0, 125.6, 125.1, 121.3, 121.1, 119.5, 118.6, 114.3, 114.0, 108.5, 108.4, 84.9, 82.1, 81.3, 58.3, 58.2, 54.0, 52.9, 52.7, 52.4, 52.3, 51.1, 32.8, 20.4, 20.2; FT-IR (KBr) 2951, 1732, 1453, 1434, 1320,

1245, 1155, 741, 703 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{24}H_{25}NNaO_5$: 430.1625, found: 430.1610.

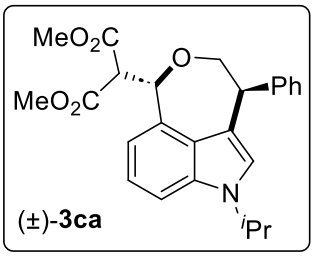


Dimethyl 2-(3-ethyl-6-methyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)-3ap. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.66; brown sticky liquid; yield 51% (35 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.4 Hz, 1H), 7.10 (t, *J* = 7.2 Hz, 1H), 6.85 (s, 1H), 6.65 (d, *J* = 7.2 Hz, 1H), 5.61 (d, *J* = 6.8 Hz, 1H), 4.29 (d, *J* = 6.8 Hz, 1H), 3.84 (s, 3H), 3.82-3.75 (m, 1H), 3.73 (s, 3H), 3.64 (s, 3H), 3.13-3.08 (m, 1H), 2.98-2.91 (m, 1H), 1.77-1.66 (m, 1H), 1.65-1.58 (m, 1H), 0.97 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 167.6, 137.6, 135.6, 126.2, 125.8, 121.3, 113.9, 113.0, 108.4, 84.7, 80.7, 58.3, 52.9, 52.4, 33.5, 32.8, 29.6, 10.3; FT-IR (KBr) 2950, 2922, 1738, 1455, 1434, 1321, 1155, 1065, 744 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{19}H_{23}NNaO_5$: 368.1468, found: 368.1459.

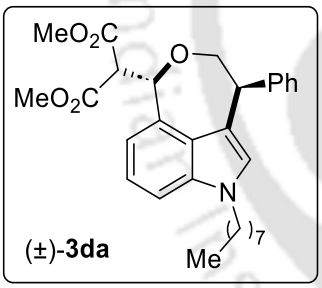


Dimethyl 2-(6-ethyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate 3ba′. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.46; yellow sticky liquid; yield 74% (60 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (m, 6H), 7.15 (t, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 7.2 Hz, 1H), 6.54-6.53 (m, 1H), 5.61 (d, *J* = 6 Hz, 1H), 4.52-4.48 (m, 1H), 4.41-4.36 (m, 2H), 4.09-4.03 (m, 2H), 3.89-3.83 (m, 4H), 3.65 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 167.5, 142.2, 136.6, 134.9, 129.0, 128.6, 126.9, 126.8, 125.3, 121.1, 118.5, 114.3, 108.8, 83.0, 79.2, 57.6, 53.0, 52.5, 47.8, 41.0, 15.5; FT-IR (KBr) 2951, 2873, 1736, 1435, 1155, 747, 702 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{24}H_{25}NNaO_5$: 430.1625, found: 430.1631; $[\alpha]_D^{25}$ = +20 (c = 0.02, $CHCl_3$); HPLC: *ee* for major diastereomer

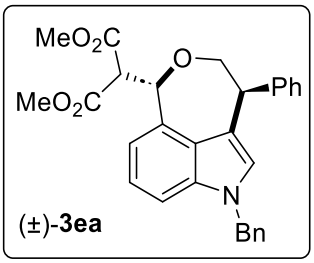
= >98% *ee* [Chiralpak AD-H, hexane/^{i}PrOH = 80:20, flow rate: 1 mL/min, λ= 254 nm, t_R = 6.53 min (major), 7.68 min (minor)].



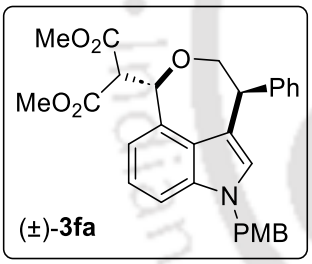
Dimethyl 2-(6-isopropyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3ca**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.48; yellow sticky liquid; yield 78% (65 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (m, 6H), 7.14 (t, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 7.6 Hz, 1H), 6.64-6.63 (m, 1H), 5.60 (d, *J* = 5.6 Hz, 1H), 4.65-4.58 (m, 1H), 4.53-4.48 (m, 1H), 4.40-4.34 (m, 2H), 3.87-3.81 (m, 4H), 3.66 (s, 3H), 1.44 (d, *J* = 6.8 Hz, 3H), 1.39 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 167.6, 142.2, 136.5, 134.9, 129.0, 128.6, 126.9, 125.3, 123.4, 120.9, 118.4, 114.4, 108.9, 83.0, 79.4, 57.6, 53.0, 52.5, 47.9, 47.0, 22.86, 22.82; FT-IR (KBr) 2925, 2853, 1737, 1434, 1192, 1129, 746, 701 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{25}H_{27}NNaO_5$: 444.1781, found: 444.1758.



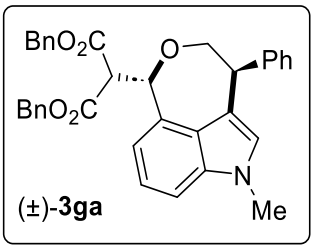
Dimethyl 2-(6-octyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3da**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.52; yellow sticky liquid; yield 81% (79 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.26 (m, 5H), 7.24 (s, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.517-6.513 (m, 1H), 5.60 (d, *J* = 5.6 Hz, 1H), 4.53-4.48 (m, 1H), 4.40-4.35 (m, 2H), 3.98 (t, *J* = 7.2 Hz, 2H), 3.88-3.83 (m, 4H), 3.65 (s, 3H), 1.25-1.22 (m, 12H), 0.86 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 167.5, 142.2, 136.8, 134.8, 129.0, 128.5, 127.6, 126.9, 125.2, 121.0, 118.2, 114.3, 108.9, 83.0, 79.3, 57.7, 53.0, 52.5, 47.7, 46.5, 31.8, 30.2, 29.29, 29.27, 27.1, 22.7, 14.2; FT-IR (KBr) 2927, 2855, 1738, 1435, 1258, 1125, 747, 701 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{30}H_{37}NNaO_5$: 514.2564, found: 514.2548.



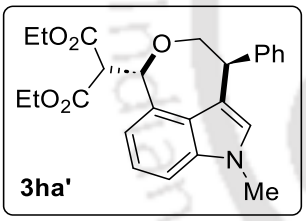
Dimethyl 2-(6-benzyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3ea**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.49; brown sticky liquid; yield 68% (63 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.26 (m, 6H), 7.24-7.22 (m, 2H), 7.19-7.17 (m, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.04-7.02 (m, 2H), 6.75 (d, *J* = 7.2 Hz, 1H), 6.599-6.595 (m, 1H), 5.62 (d, *J* = 5.6 Hz, 1H), 5.26-5.16 (m, 2H), 4.55-4.51 (m, 1H), 4.41-4.37 (m, 2H), 3.88 (t, *J* = 12 Hz, 1H), 3.83 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 167.5, 142.1, 137.5, 137.2, 134.9, 128.9, 128.8, 128.6, 128.1, 127.6, 127.0, 126.6, 125.5, 121.5, 119.1, 114.7, 109.3, 82.9, 79.2, 57.7, 53.0, 52.5, 50.2, 47.7; FT-IR (KBr) 2923, 2852, 1737, 1434, 1160, 735, 700 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{29}H_{28}NO_5$: 470.1962, found: 470.1948.



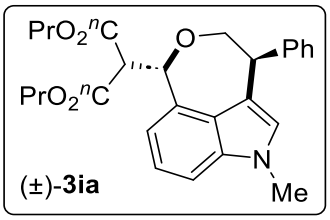
Dimethyl 2-(6-(4-methoxybenzyl)-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3fa**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.46; yellow sticky liquid; yield 58% (57 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.26 (m, 5H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.58-6.57 (m, 1H), 5.61 (d, *J* = 6 Hz, 1H), 5.19-5.09 (m, 2H), 4.54-4.50 (m, 1H), 4.40-4.36 (m, 2H), 3.90-3.86 (m, 1H), 3.83 (s, 3H), 3.75 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 167.5, 159.1, 142.1, 137.1, 134.9, 129.5, 128.9, 128.6, 128.09, 128.04, 127.0, 125.5, 121.4, 118.9, 114.6, 114.2, 109.3, 82.9, 79.2, 57.7, 55.4, 53.0, 52.5, 49.7, 47.7; FT-IR (KBr) 2926, 1736, 1513, 1434, 1248, 1175, 1031, 702 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{30}H_{29}NNaO_6$: 522.1887, found: 522.1889.



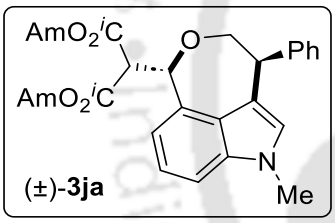
Dibenzyl 2-(6-methyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)-3ga. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.61; yellow sticky liquid; yield 68% (74 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.32 (m, 7H), 7.30-7.29 (m, 1H), 7.27-7.26 (m, 2H), 7.25-7.19 (m, 4H), 7.13-7.12 (m, 1H), 7.10-7.08 (m, 2H), 6.77 (d, *J* = 5.2 Hz, 1H), 6.477-6.474 (m, 1H), 5.68 (d, *J* = 3.6 Hz, 1H), 5.36-5.34 (m, 1H), 5.24-5.22 (m, 1H), 5.12-5.10 (m, 1H), 5.07-5.04 (m, 1H), 4.50 (d, *J* = 3.6 Hz, 1H), 4.48-4.45 (m, 1H), 4.26 (dd, *J* = 8, 3.2 Hz, 1H), 3.84 (t, *J* = 7.6 Hz, 1H), 3.70 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.9, 166.8, 142.3, 137.6, 135.7, 135.6, 134.9, 128.9, 128.68, 128.60, 128.47, 128.44, 128.42, 128.3, 128.1, 127.9, 126.9, 125.2, 121.3, 118.6, 114.7, 108.6, 82.6, 78.6, 67.5, 66.9, 58.1, 47.7, 32.9; FT-IR (KBr) 2925, 1733, 1454, 1122, 739, 698 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{35}H_{31}NNaO_5$: 568.2094, found: 568.2107.



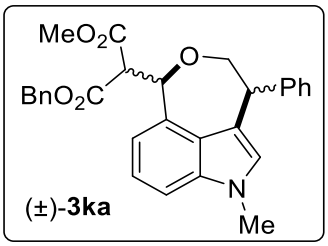
Diethyl 2-(6-methyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate 3ha′. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.58; yellow sticky liquid; yield 63% (53 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.27 (m, 5H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 7.5 Hz, 1H), 6.46 (s, 1H), 5.61 (d, *J* = 5.5 Hz, 1H), 4.53-4.49 (m, 1H), 4.39-4.32 (m, 3H), 4.28-4.22 (m, 1H), 4.19-4.12 (m, 1H), 4.11-4.05 (m, 1H), 3.87 (t, *J* = 11.5 Hz, 1H), 3.67 (s, 3H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.08 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 167.0, 142.3, 137.6, 135.2, 129.0, 128.6, 128.5, 126.9, 125.2, 121.2, 118.6, 114.5, 108.6, 82.9, 79.0, 61.8, 61.2, 58.0, 47.7, 32.9, 14.2, 14.1; FT-IR (KBr) 2925, 1732, 1454, 1300, 1155, 1123, 1095, 743, 702 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{25}H_{27}NNaO_5$: 444.1781, found: 444.1781; $[\alpha]_D^{25}$ = -20 (c = 0.01, $CHCl_3$); HPLC: *ee* for major diastereomer = >97% *ee* [Chiralpak AD-H, hexane/^{i}PrOH = 80:20, flow rate: 1 mL/min, λ= 254 nm, t_R = 7.78 min (major), 8.82 min (minor)].



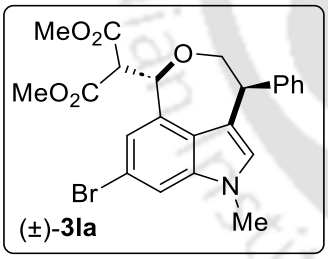
Dipropyl 2-(6-methyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3ia**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; yellow sticky liquid; yield 61% (54 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (m, 5H), 7.23-7.21 (m, 1H), 7.15 (t, *J* = 7.2 Hz, 1H), 6.79 (d, *J* = 7.2 Hz, 1H), 6.46-6.45 (m, 1H), 5.62 (d, *J* = 5.6 Hz, 1H), 4.52-4.48 (m, 1H), 4.37-4.34 (m, 2H), 4.28-4.22 (m, 1H), 4.19-4.13 (m, 1H), 4.07-3.96 (m, 2H), 3.87 (t, *J* = 11.6 Hz, 1H), 3.67 (s, 3H), 1.74-1.65 (m, 2H), 1.52-1.45 (m, 2H) 0.95 (t, *J* = 7.2 Hz, 3H), 0.76 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 167.1, 142.3, 137.6, 135.2, 129.0, 128.6, 128.4, 126.9, 125.2, 121.2, 118.6, 114.5, 108.5, 82.8, 79.0, 67.4, 66.8, 58.1, 47.7, 32.9, 22.0, 21.9, 10.4, 10.3; FT-IR (KBr) 2929, 2878, 1733, 1455, 1299, 1123, 744, 701 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{27}H_{31}NNaO_5$: 472.2094, found: 472.2092.



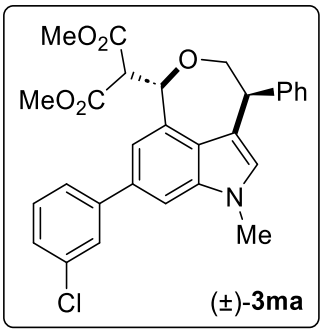
Diisopentyl 2-(6-methyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3ja**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.64; yellow sticky liquid; yield 49% (40 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (m, 5H), 7.22 (d, *J* = 8 Hz, 1H), 7.15 (t, *J* = 7.2 Hz, 1H), 6.79-6.77 (m, 1H), 6.45 (s, 1H), 5.61-5.60 (m, 1H), 4.51-4.47 (m, 1H), 4.38-4.19 (m, 4H), 4.11-4.00 (m, 2H), 3.86 (t, *J* = 11.6 Hz, 1H), 3.67 (s, 3H), 1.77-1.65 (m, 1H), 1.42-1.28 (m, 5H), 0.92-0.90 (m, 6H), 0.76-0.74 (m, 3H), 0.70-0.68 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 167.2, 142.3, 137.6, 135.1, 128.9, 128.6, 128.4, 126.9, 125.1, 121.2, 118.6, 114.5, 108.5, 82.7, 78.8, 64.5, 63.7, 58.1, 47.7, 37.2, 37.1, 32.9, 25.0, 24.5, 22.6, 22.5, 22.4, 22.2; FT-IR (KBr) 2956, 2925, 2868, 1734, 1454, 1156, 1121, 746, 701 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{40}NO_5$: 506.2901, found: 506.2908.



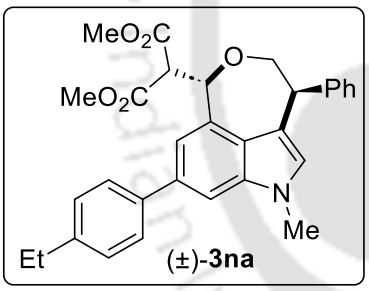
1-Benzyl 3-methyl 2-(6-methyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3ka**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.55; brown sticky liquid; yield 56% (52 mg); mixture of diastereomers (1.4:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.27 (m, 10.34H), 7.24-7.17 (m, 6.86H), 7.15-7.11 (m, 1.76H), 7.08-7.06 (m, 1.69H), 6.78 (d, *J* = 7.6 Hz, 0.72H), 6.72 (d, *J* = 7.2 Hz, 0.70H), 6.46 (s, 1.38H), 5.64 (dd, *J* = 10.8, 5.2 Hz, 1.63H), 5.35-5.32 (m, 0.72H), 5.24-5.20 (m, 0.70H), 5.12-5.03 (m, 2H), 4.51-4.41 (m, 3.39H), 4.33-4.28 (m, 1.70H), 3.88-3.82 (m, 1.71H), 3.81 (s, 3H), 3.68 (s, 2.12H), 3.67 (s, 2.13H), 3.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 167.9, 167.4, 166.9, 142.2, 142.1, 137.59, 137.54, 135.6, 135.4, 134.8, 128.97, 128.95, 128.68, 128.60, 128.5, 128.4, 128.3, 128.1, 127.9, 126.99, 126.97, 125.1, 125.0, 121.3, 121.2, 118.5, 118.4, 114.56, 114.50, 108.69, 108.65, 82.8, 82.7, 79.0, 78.8, 67.5, 66.9, 57.89, 57.83, 52.9, 52.5, 47.68, 47.64, 32.9, 29.8; FT-IR (KBr) 2923, 2853, 1734, 1454, 1300, 1153, 742, 700 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{29}H_{27}NNaO_5$: 492.1781, found: 492.1765.



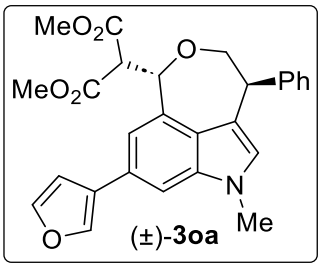
Dimethyl 2-(8-bromo-6-methyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3la**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.48; brown sticky liquid; yield 66% (62 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.34-7.26 (m, 3H), 7.25-7.23 (m, 2H), 6.87-6.86 (m, 1H), 6.448-6.444 (m, 1H), 5.57 (d, *J* = 5.6 Hz, 1H), 4.50-4.45 (m, 1H), 4.38-4.32 (m, 2H), 3.87-3.84 (m, 4H), 3.67 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 167.1, 141.7, 138.3, 136.4, 129.1, 128.8, 128.6, 127.1, 124.1, 118.9, 117.8, 114.6, 111.7, 82.2, 78.8, 57.4, 53.1, 52.6, 47.4, 33.0; FT-IR (KBr) 2950, 2865, 1733, 1454, 1434, 1243, 1128, 701 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{23}H_{22}BrNNaO_5$: 494.0574, found: 494.0557.



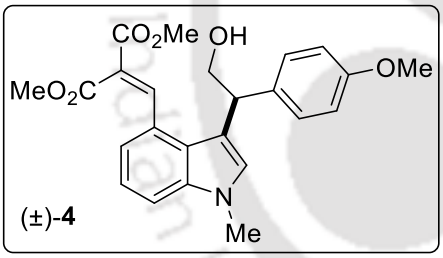
Dimethyl 2-(8-(3-chlorophenyl)-6-methyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)-**3ma**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.51; yellow sticky liquid; yield 63% (63 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.49-7.48 (m, 1H), 7.39-7.29 (m, 9H), 6.98 (s, 1H), 6.52 (s, 1H), 5.67-5.65 (m, 1H), 4.53-4.51 (m, 1H), 4.47-4.46 (m, 1H), 4.42-4.40 (m, 1H), 3.89 (t, *J* = 12 Hz, 1H), 3.84 (s, 3H), 3.73 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 167.5, 144.1, 141.9, 138.0, 135.3, 134.7, 133.3, 130.1, 129.5, 128.9, 128.6, 127.4, 127.1, 126.8, 125.5, 124.9, 118.6, 114.2, 107.3, 82.9, 79.1, 57.6, 53.0, 52.6, 47.5, 33.0; FT-IR (KBr) 2950, 1733, 1593, 1456, 1245, 1128, 786, 700 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{29}H_{26}ClNNaO_5$: 526.1392, found: 526.1368.



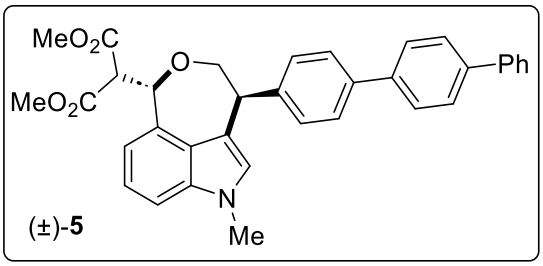
Dimethyl 2-(8-(4-ethylphenyl)-6-methyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)-**3na**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.53; yellow sticky liquid; yield 71% (70 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.40 (s, 1H), 7.35-7.27 (m, 7H), 7.02 (s, 1H), 6.499-6.495 (m, 1H), 5.67 (d, *J* = 5.6 Hz, 1H), 4.55-4.51 (m, 1H), 4.48 (d, *J* = 5.6 Hz, 1H), 4.42 (dd, *J* = 11.6, 4.8 Hz, 1H), 3.90 (t, *J* = 11.6 Hz, 1H), 3.84 (s, 3H), 3.71 (s, 3H), 3.66 (s, 3H), 2.74 (q, *J* = 7.6 Hz, 2H), 1.30 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 167.5, 143.0, 142.1, 139.6, 138.1, 135.0, 134.9, 129.0, 128.9, 128.6, 128.4, 127.3, 127.0, 124.3, 118.5, 114.4, 107.1, 83.0, 79.1, 57.7, 53.0, 52.5, 47.6, 32.9, 28.6, 15.7; FT-IR (KBr) 2928, 2870, 1735, 1455, 1245, 1127, 828, 702 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{31}H_{31}NNaO_5$: 520.2094, found: 520.2088.



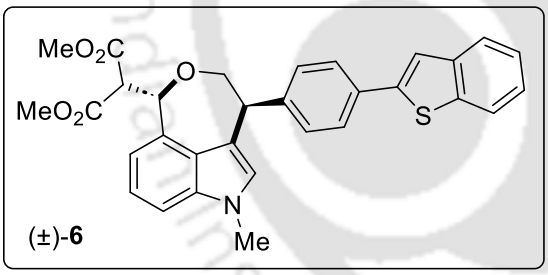
Dimethyl 2-(8-(furan-3-yl)-6-methyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3oa**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.43; yellow sticky liquid; yield 55% (50 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.70 (m, 1H), 7.49-7.48 (m, 1H), 7.33-7.28 (m, 6H), 6.92-6.91 (m, 1H), 6.72-6.71 (m, 1H), 6.47-6.46 (m, 1H), 5.62 (d, *J* = 5.5 Hz, 1H), 4.52-4.48 (m, 1H), 4.44-4.42 (m, 1H), 4.40-4.37 (m, 1H), 3.88 (t, *J* = 11.5 Hz, 1H), 3.83 (s, 3H), 3.70 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 167.5, 143.7, 142.0, 138.1, 138.0, 135.2, 128.9, 128.6, 127.4, 127.0, 125.8, 124.4, 118.7, 113.3, 109.3, 105.9, 82.8, 79.1, 57.7, 53.0, 52.6, 47.5, 33.0; FT-IR (KBr) 2923, 2854, 1737, 1452, 1435, 1159, 1131, 1021, 872, 702 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{25}NNaO_6$: 482.1574, found: 482.1580.



Dimethyl 2-((3-(2-hydroxy-1-(4-methoxyphenyl)ethyl)-1-methyl-1H-indol-4-yl)methylene)malonate (±)**-4**. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.30; brown sticky liquid; yield 85% (72 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.22-7.18 (m, 3H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 7.2 Hz, 1H), 6.85-6.83 (m, 2H), 4.53 (t, *J* = 6.4 Hz, 1H), 4.13-4.04 (m, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 3.76 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 164.5, 158.7, 144.0, 137.6, 133.6, 129.8, 128.3, 126.8, 126.3, 125.9, 121.7, 119.8, 115.1, 114.1, 111.5, 67.6, 55.3, 52.5, 52.4, 45.8, 33.1; FT-IR (KBr) 3395, 2930, 2851, 1736, 1609, 1509, 1455, 1301, 1248, 748 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{26}NO_6$: 424.1755, found: 424.1766.

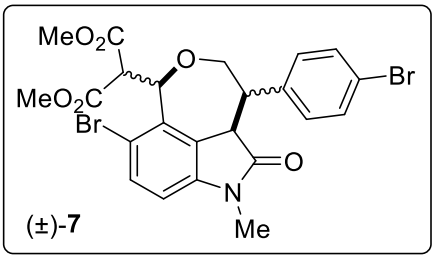


Dimethyl 2-(4-([1,1':4',1''-terphenyl]-4-yl)-6-methyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)-**5**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.45; brown sticky liquid; yield 85% (46 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 4H), 7.66 (d, *J* = 6.8 Hz, 2H), 7.61 (d, *J* = 8 Hz, 2H), 7.46 (t, *J* = 7.2 Hz, 2H), 7.38-7.36 (m, 3H), 7.26-7.24 (m, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 7.2 Hz, 1H), 6.567-6.564 (m, 1H), 5.65 (d, *J* = 6 Hz, 1H), 4.59-4.55 (m, 1H), 4.46-4.42 (m, 2H), 3.92 (t, *J* = 11.6 Hz, 1H), 3.84 (s, 3H), 3.70 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 167.5, 141.3, 140.8, 140.1, 139.8, 139.3, 137.6, 134.8, 129.4, 128.9, 128.6, 127.6, 127.4, 127.2, 127.1, 125.1, 121.3, 118.4, 114.5, 108.7, 82.9, 79.0, 57.7, 53.0, 52.5, 47.3, 32.9; FT-IR (KBr) 3028, 2949, 2867, 1734, 1483, 1243, 1155, 1126, 826, 765, 740 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{35}H_{31}NNaO_5$: 568.2094, found: 568.2082.

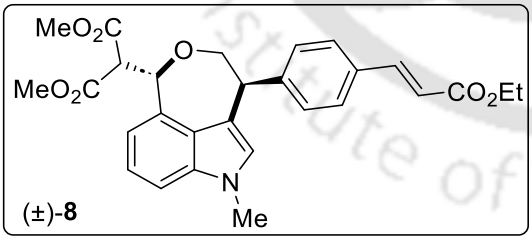


Dimethyl 2-(4-(4-(benzo[b]thiophen-2-yl)phenyl)-6-methyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)-**6**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.38; brown sticky liquid; yield 62% (32 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.82 (m, 1H), 7.78-7.76 (m, 1H), 7.68 (d, *J* = 8 Hz, 2H), 7.54 (s, 1H), 7.36-7.30 (m, 5H), 7.18 (t, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 7.2 Hz, 1H), 6.54-6.53 (m, 1H), 5.64 (d, *J* = 5.6 Hz, 1H), 4.57-4.53 (m, 1H), 4.43-4.39 (m, 2H), 3.93-3.86 (m, 1H), 3.84 (s, 3H), 3.70 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 167.5, 144.1, 142.4, 140.8, 139.5, 137.6, 134.8, 133.1, 129.5, 128.5, 126.7, 125.1, 124.6, 124.4, 123.6, 122.4, 121.4, 119.3, 118.1, 114.5, 108.8, 82.9, 78.8, 57.6, 53.0, 52.6, 47.4, 32.9; FT-IR (KBr) 2925, 2855, 1737, 1455, 1434,

1245, 1156, 746 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{28}NO_5S$: 526.1683, found: 526.1653.

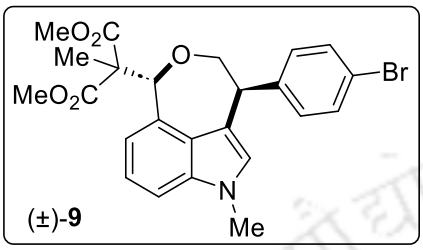


Dimethyl 2-(9-bromo-4-(4-bromophenyl)-6-methyl-5-oxo-1,3,4,4a,5,6-hexahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)-**7**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.30; colorless solid; mp 154-155 °C; yield 55% (31 mg); mixture of diastereomers (3:1 dr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.4 Hz, 1H), 7.30 (t, *J* = 8 Hz, 0.49H), 7.24-7.20 (m, 2.63H), 6.86 (d, *J* = 8 Hz, 0.35H), 6.71 (d, *J* = 7.6 Hz, 0.34H), 6.63 (d, *J* = 8 Hz, 1H), 6.57-6.53 (m, 2.46H), 5.57-5.56 (m, 1H), 5.53-5.51 (m, 0.32H), 4.57 (d, *J* = 8.8 Hz, 1H), 4.43-4.38 (m, 1.67H), 4.34 (d, *J* = 2.4 Hz, 1H), 4.07-4.00 (m, 1.36H), 3.84 (s, 3H), 3.72-3.71 (m, 2H), 3.63 (s, 3H), 3.52-3.46 (m, 1.34H), 2.90 (s, 1H), 2.87 (s, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 175.7, 167.8, 167.2, 166.97, 166.91, 145.1, 144.4, 137.5, 137.0, 135.1, 134.1, 133.6, 131.6, 131.5, 129.88, 129.80, 129.1, 127.2, 124.5, 121.7, 121.5, 119.9, 113.4, 109.1, 107.6, 82.4, 82.1, 72.7, 72.4, 55.3, 55.1, 53.1, 52.9, 52.8, 52.7, 46.9, 46.6, 45.9, 45.7, 29.8, 26.0; FT-IR (KBr) 2955, 2881, 1715, 1602, 1437, 1354, 1146, 1009, 1071, 809 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{22}Br_2NO_6$: 565.9808, found: 565.9805.



Dimethyl (E)-2-(4-(4-(3-ethoxy-3-oxoprop-1-en-1-yl)phenyl)-6-methyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)-**8**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.45; yellow sticky liquid; yield 68% (33 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 16 Hz, 1H), 7.49-7.47 (m, 2H), 7.30-7.28 (m, 2H), 7.25-7.15 (m, 2H), 6.78 (d, *J* = 7.2 Hz, 1H), 6.478-6.474 (m, 1H), 6.44 (d, *J* = 16 Hz, 1H), 5.62 (m, 1H), 4.55-4.51 (m, 1H), 4.40-4.35 (m, 2H), 4.29 (q, *J* = 7.2 Hz, 2H), 3.89-3.86 (m, 1H), 3.83 (s, 3H), 3.69 (s,

3H), 3.64 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 167.5, 167.2, 144.6, 144.4, 137.5, 134.7, 133.3, 129.5, 128.47, 128.41, 125.0, 121.4, 118.0, 117.9, 114.5, 108.8, 82.9, 78.7, 60.6, 57.6, 53.0, 52.6, 47.5, 32.9, 14.4; FT-IR (KBr) 2923, 2852, 1737, 1709, 1635, 1454, 1305, 1163, 1090, 1041, 743 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{28}H_{29}NNaO_7$: 514.1836, found: 541.1807.



Dimethyl 2-(4-(4-bromophenyl)-6-methyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)-2-methylmalonate (±)-**9**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; colorless sticky liquid; yield 91% (44 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 (d, J = 8.4 Hz, 2H), 7.24-7.23 (m, 1H), 7.16-7.13 (m, 3H), 6.67 (d, J = 7.8 Hz, 1H), 6.46 (s, 1H), 5.89 (s, 1H), 4.41-4.38 (m, 1H), 4.24 (dd, J = 11.4, 4.8 Hz, 1H), 3.86-3.82 (m, 4H), 3.78 (s, 3H), 3.68 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 170.4, 141.2, 137.7, 133.5, 131.7, 130.7, 128.6, 125.7, 121.2, 120.8, 118.0, 116.2, 108.5, 86.7, 78.6, 60.8, 53.1, 53.0, 47.1, 32.9, 14.6; FT-IR (KBr) 2925, 2855, 1736, 1455, 1299, 1155, 1010, 747 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{24}H_{24}BrNNaO_5$: 508.0730, found: 508.0725.

Crystal Structure and Data of (±)-**7**

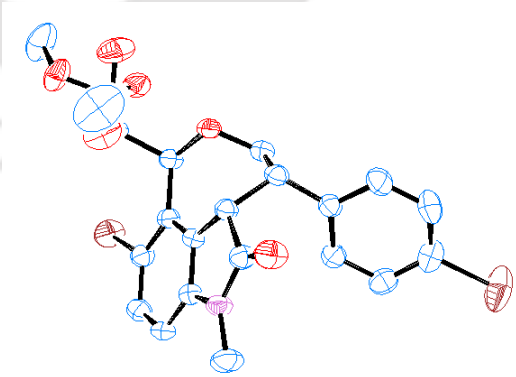


Figure S1. ORTEP diagram of dimethyl 2-(9-bromo-4-(4-bromophenyl)-6-methyl-5-oxo-1,3,4,4a,5,6-hexahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)-**7** with 50% ellipsoid (CCDC 2481146). H-Omitted for clarity.

Identification code	(±)-**7**

Empirical formula	'C23H21Br2NO6'
Formula weight	567.23
Crystal habit, colour	needle/Colorless
Temperature, *T*/K	296 K
Wavelength, λ/Å	0.71073
Crystal system	'monoclinic'
Space group	'P 21/c'
Unit cell dimensions	a = 10.123(5) Å b = 26.415(11) Å c = 8.733(4) Å α = 90 β = 103.709(1) γ = 90
Volume, *V*/Å^3	2268.8(18)
Z	4
Calculated density, Mg·m^{-3}	1.661
Absorption coefficient, μ/mm^{-1}	3.613
F(000)	1136
θ range for data collection	2.21 to 25.37°
Limiting indices	-12 ≤ h ≤ 12, –32 ≤ k ≤ 32, –10 ≤ l ≤ 10
Reflection collected / unique	4297/3524
Completeness to θ	99.7%
Absorption correction	None
Max. and min. transmission	0.865 and 0.714
Refinement method	'SHELXL-2018/3 (Sheldrick, 2015)'
Data / restraints / parameters	4297/0/292
Goodness–of–fit on F^2	1.093
Final *R* indices [*I*>2sigma(*I*)]	R1 = 0.0373, wR2 = 0.1105
R indices (all data)	R1 = 0.0496, wR2 = 0.1242

4.5 References

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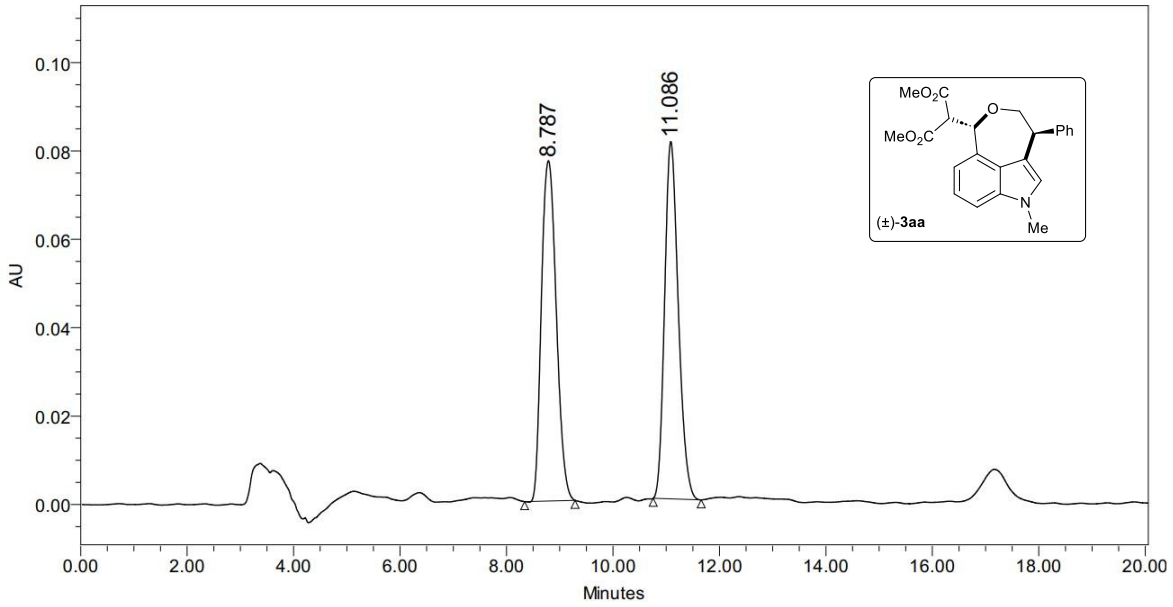
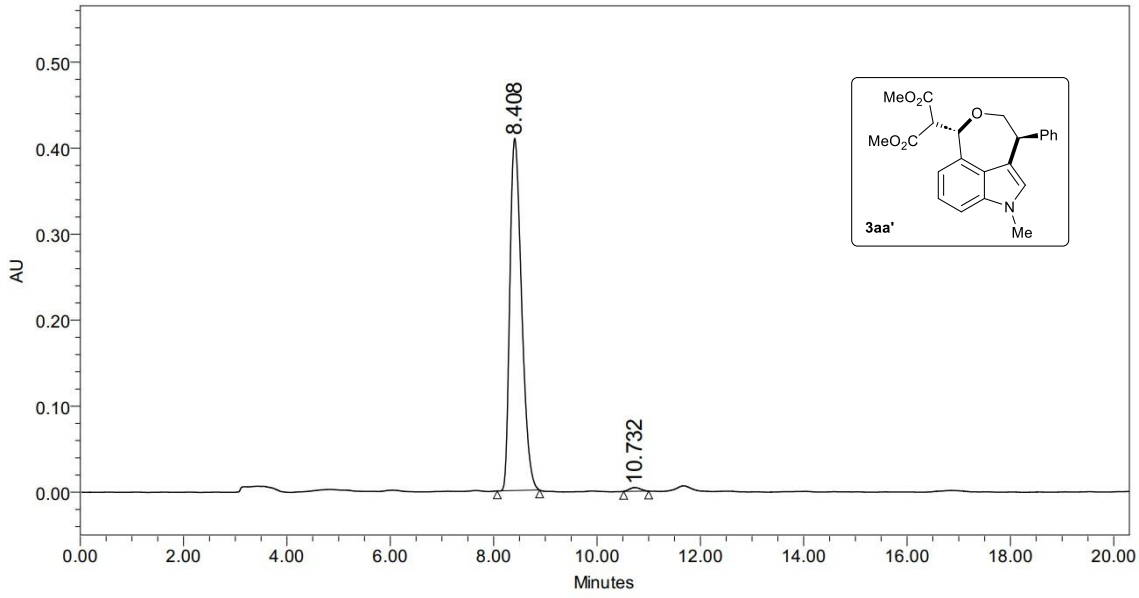
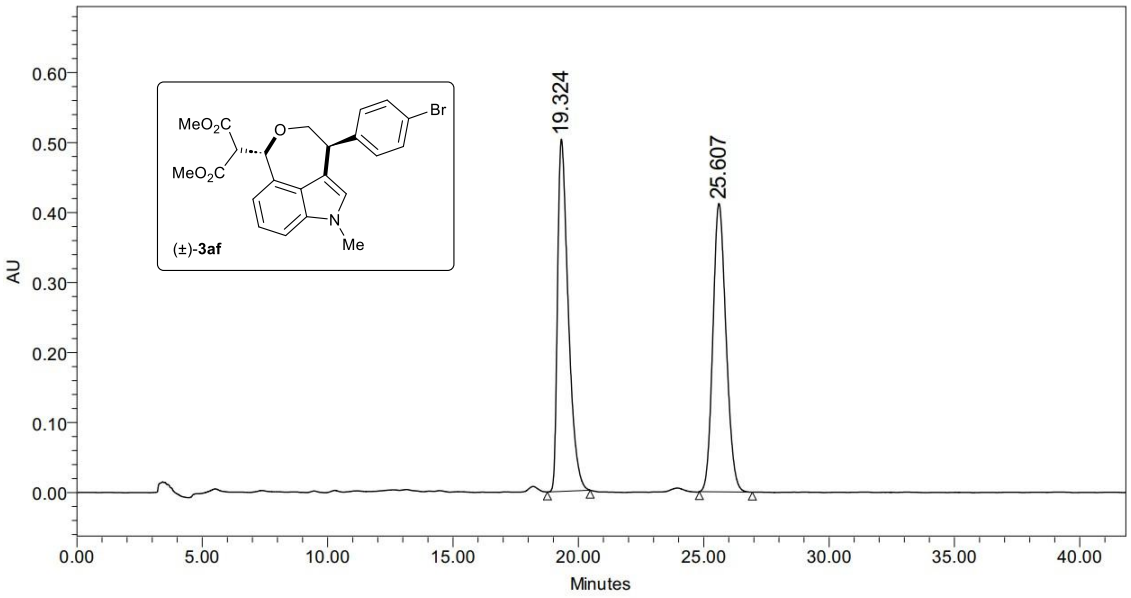
4.6 HPLC Chromatograms



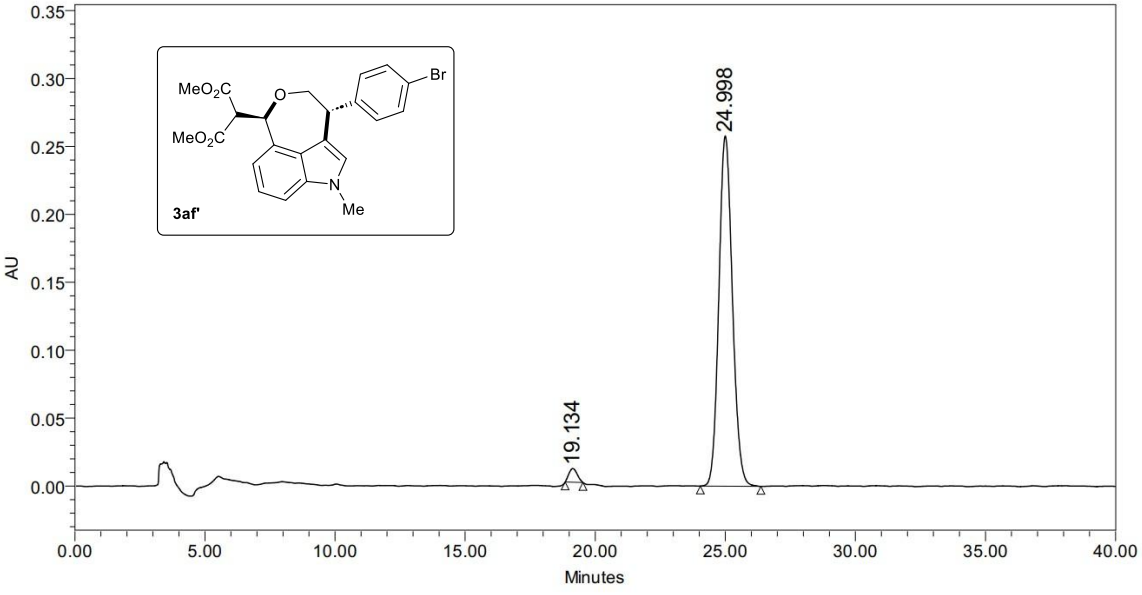
	RT	Area	% Area	Height
1	8.787	1496191	50.84	76986
2	11.086	1446870	49.16	80893



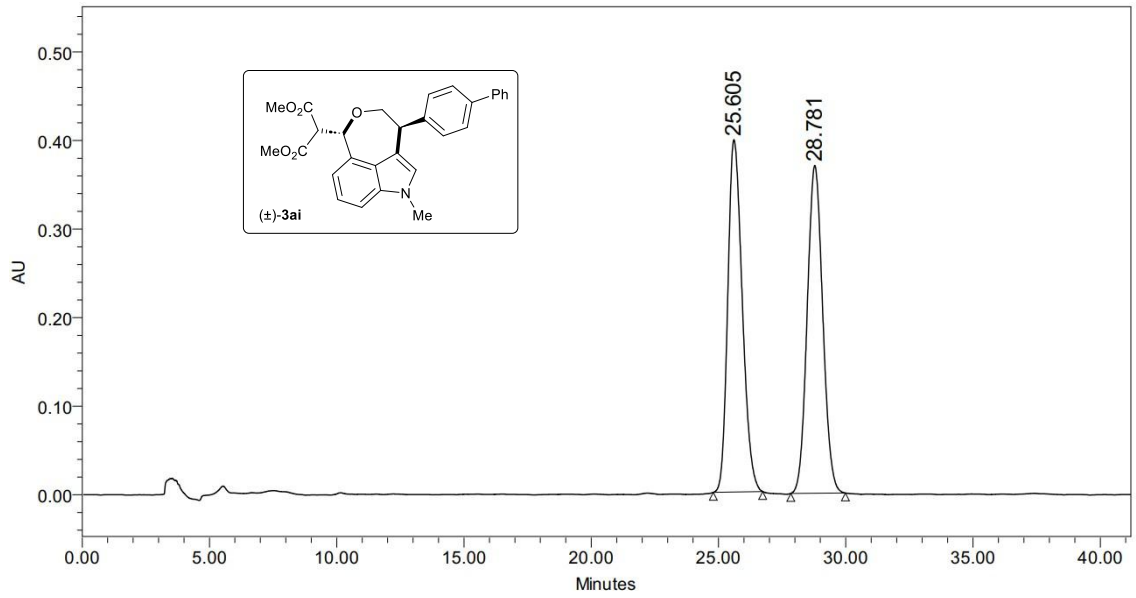
	RT	Area	% Area	Height
1	8.408	6467389	99.04	409449
2	10.732	62649	0.96	4240



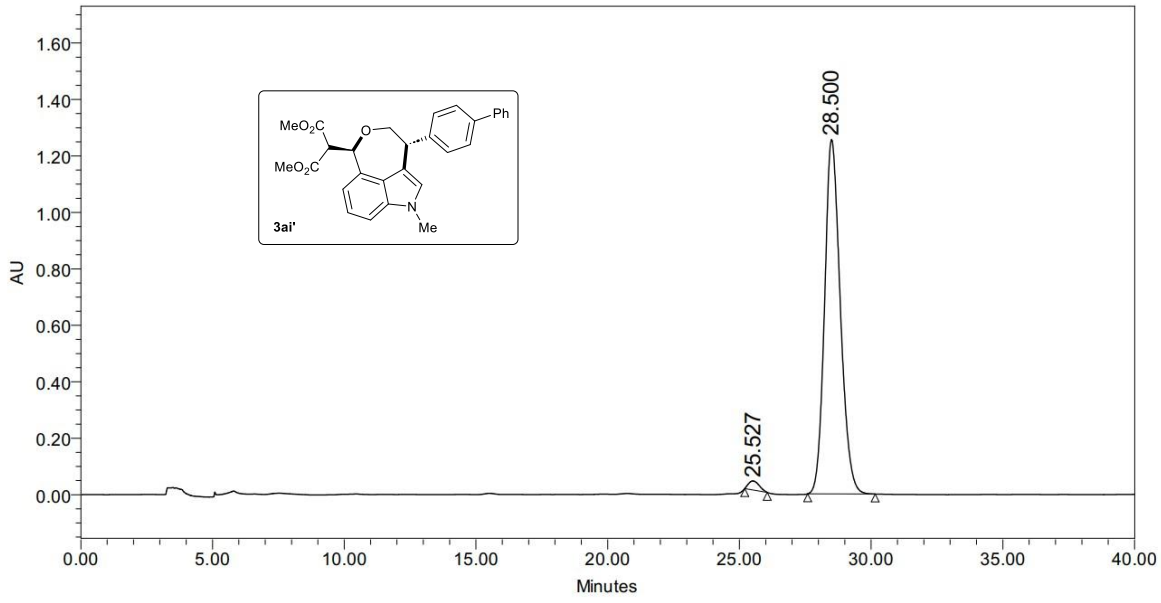
	RT	Area	% Area	Height
1	19.324	14967888	49.86	503346
2	25.607	15053667	50.14	412014



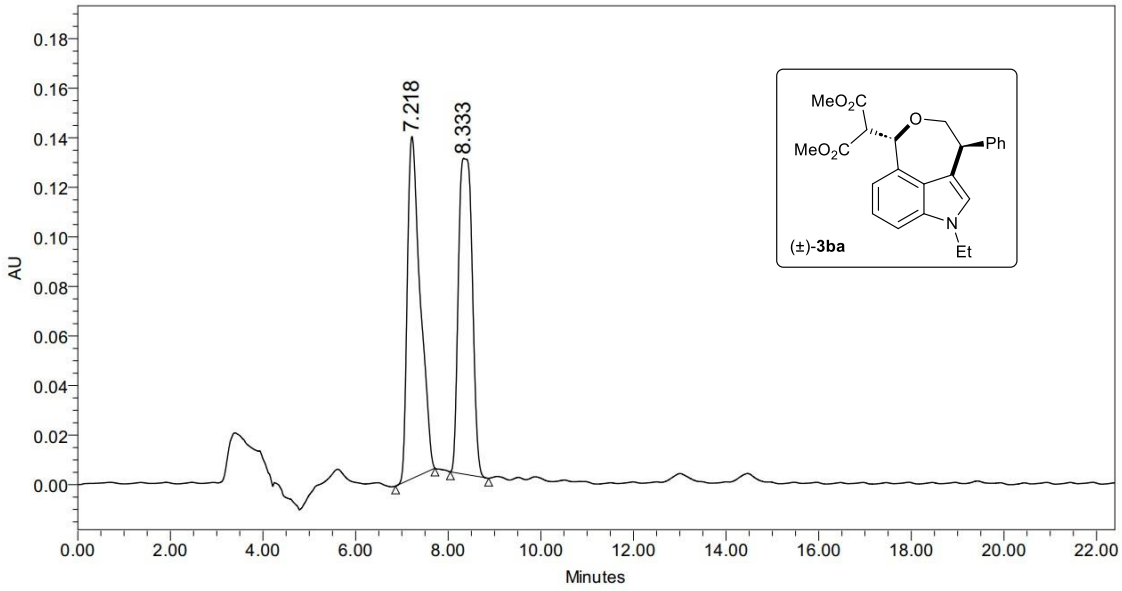
	RT	Area	% Area	Height
1	19.134	224855	2.35	10130
2	24.998	9332722	97.65	257824



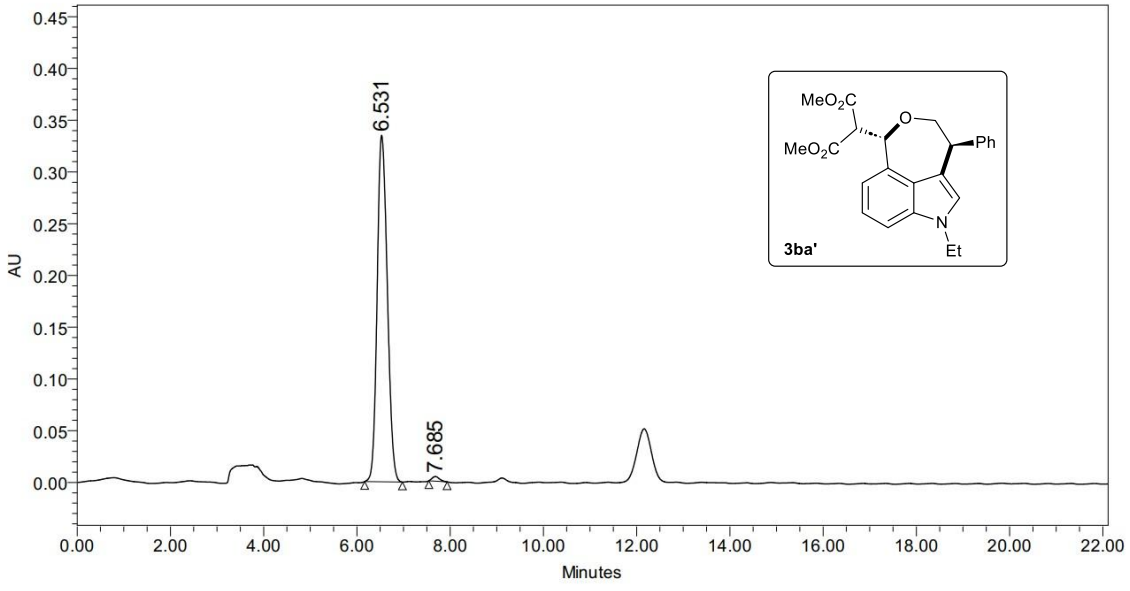
	RT	Area	% Area	Height
1	25.605	15703819	50.03	397811
2	28.781	15686928	49.97	370144



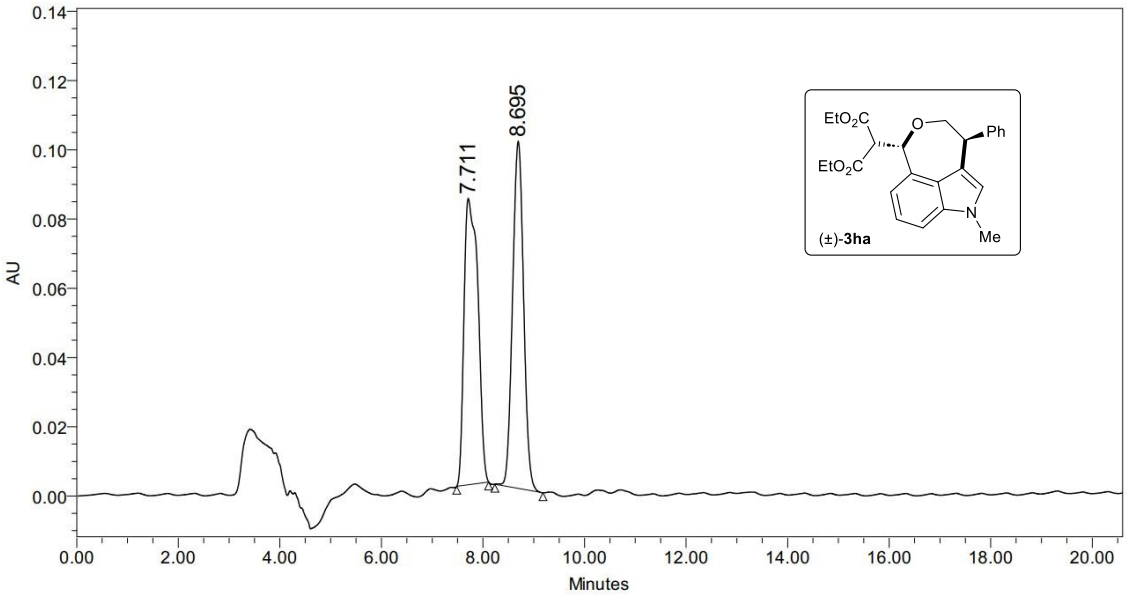
	RT	Area	% Area	Height
1	25.527	894491	1.68	31971
2	28.500	52196242	98.32	1255623



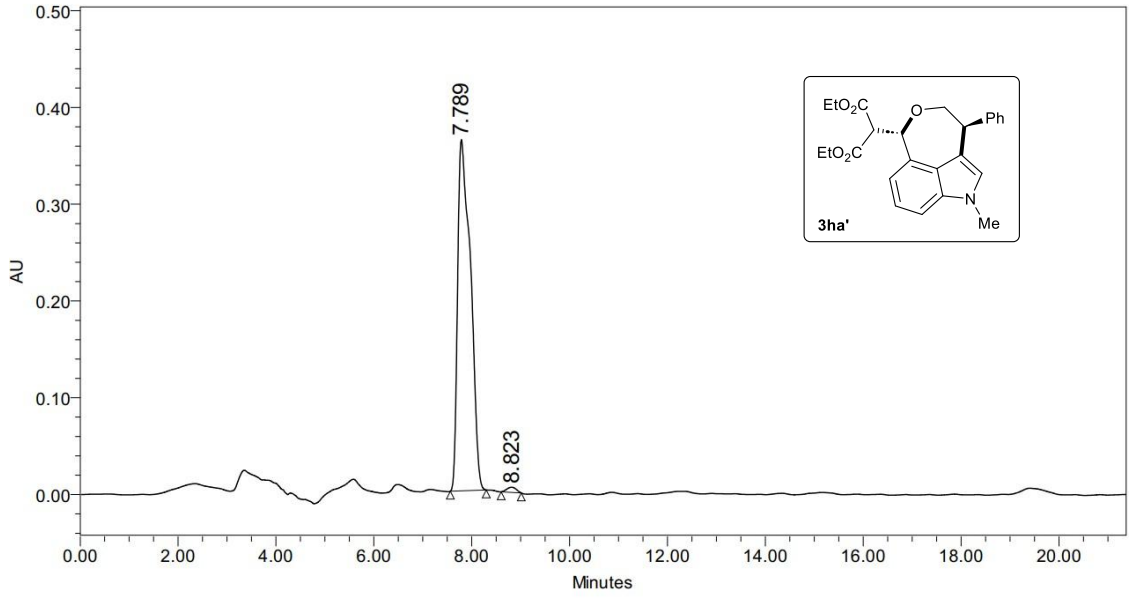
	RT	Area	% Area	Height
1	7.218	2663726	50.06	138058
2	8.333	2657424	49.94	127486



	RT	Area	% Area	Height
1	6.531	5063370	99.04	334813
2	7.685	49120	0.96	4501

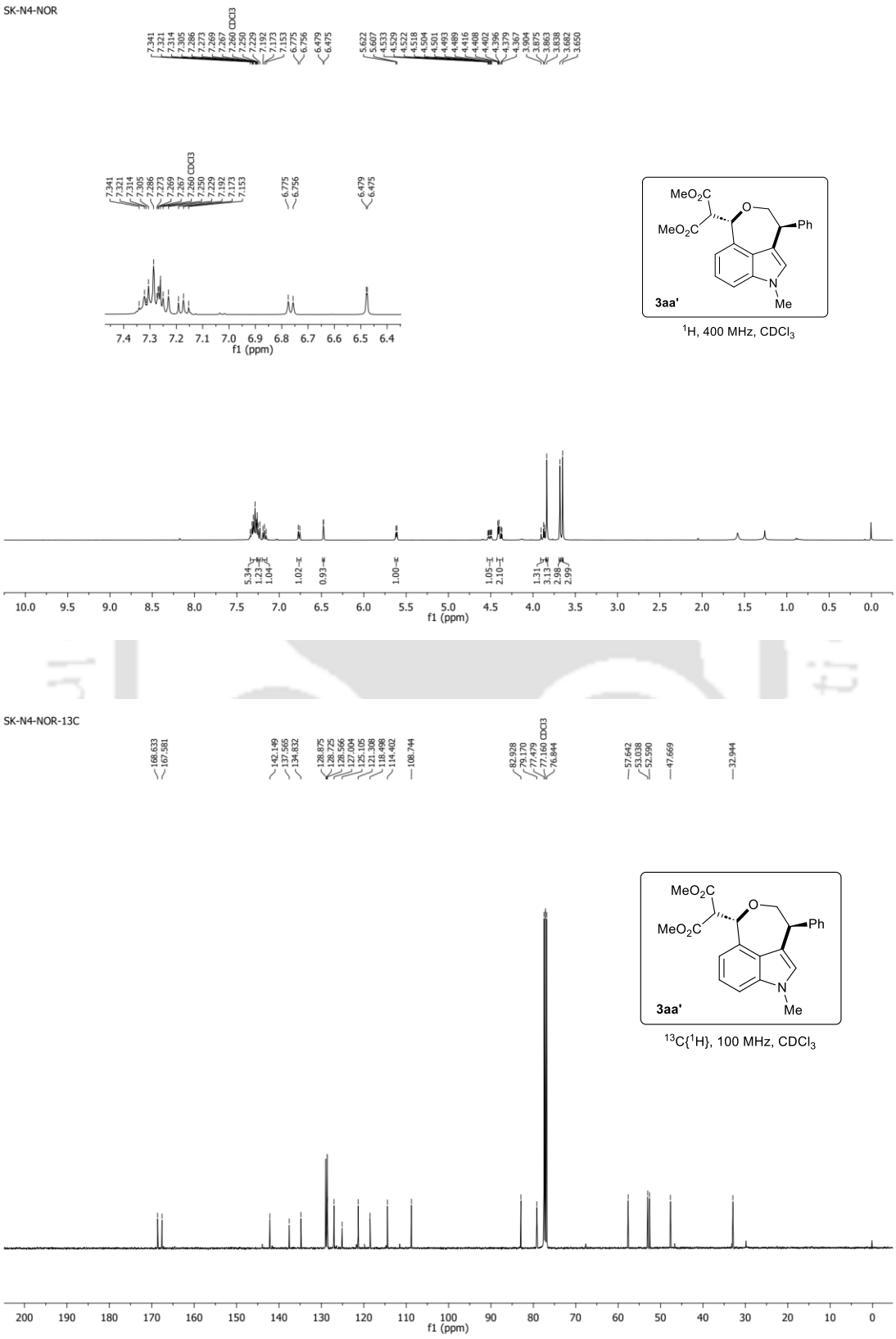


	RT	Area	% Area	Height
1	7.711	1562903	50.88	82705
2	8.695	1509014	49.12	100261

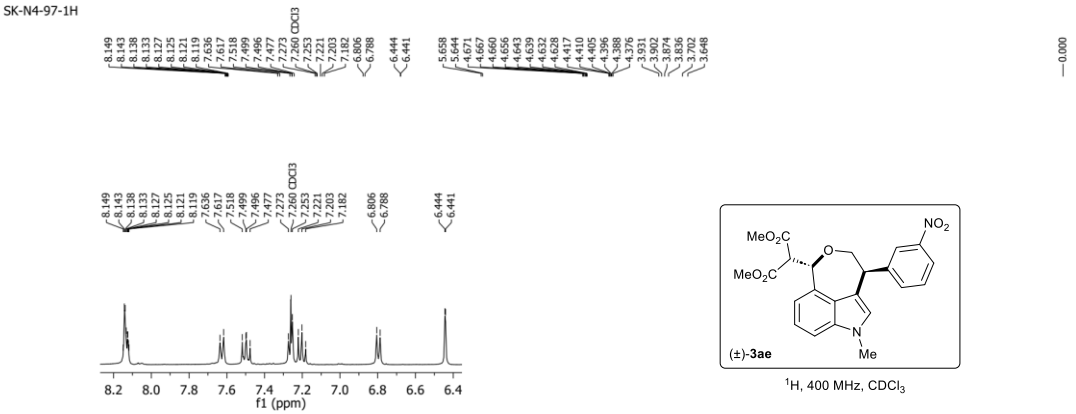


	RT	Area	% Area	Height
1	7.789	6621137	98.92	362813
2	8.823	72235	1.08	5396

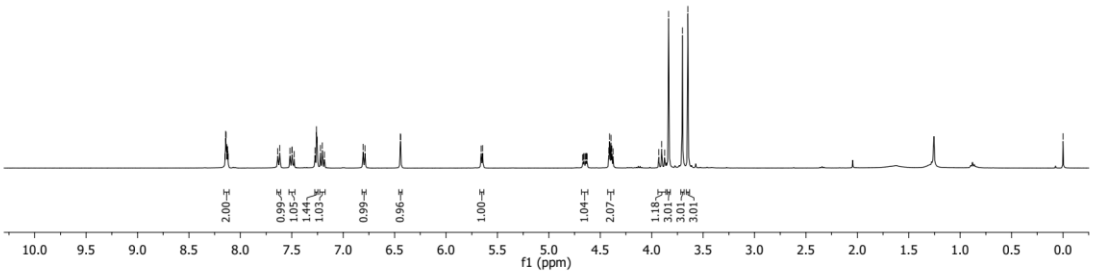
4.7 Selected NMR Spectra



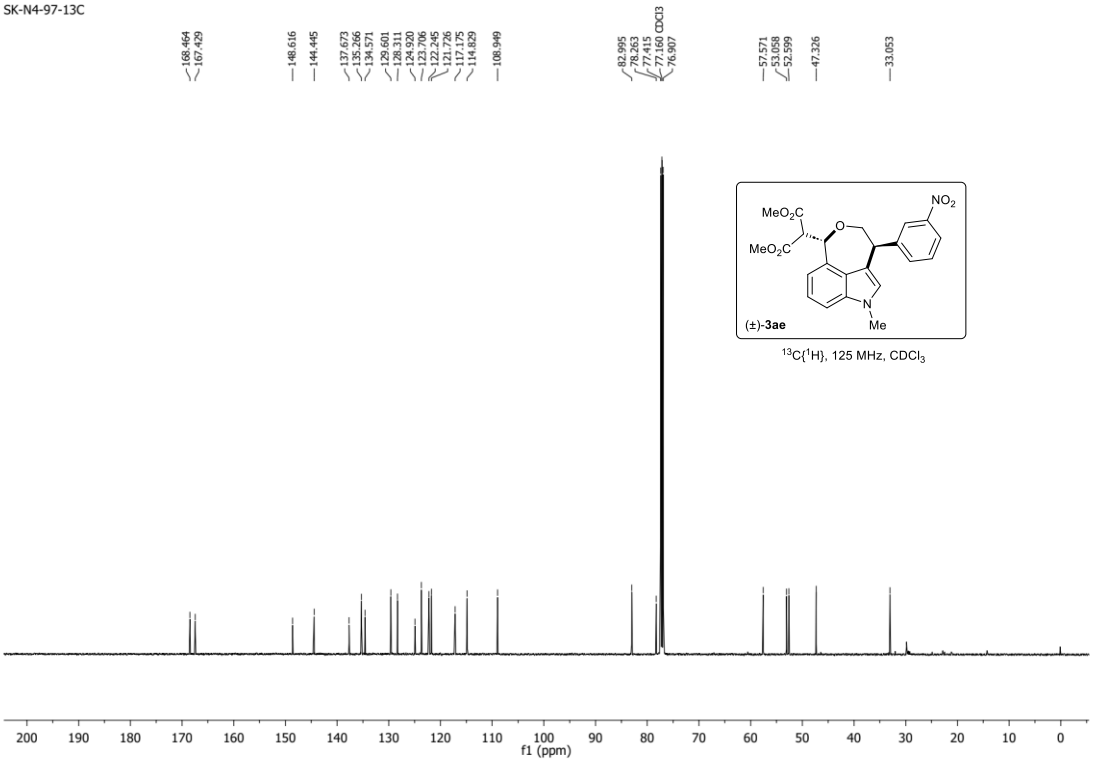
SK-N4-97-1H



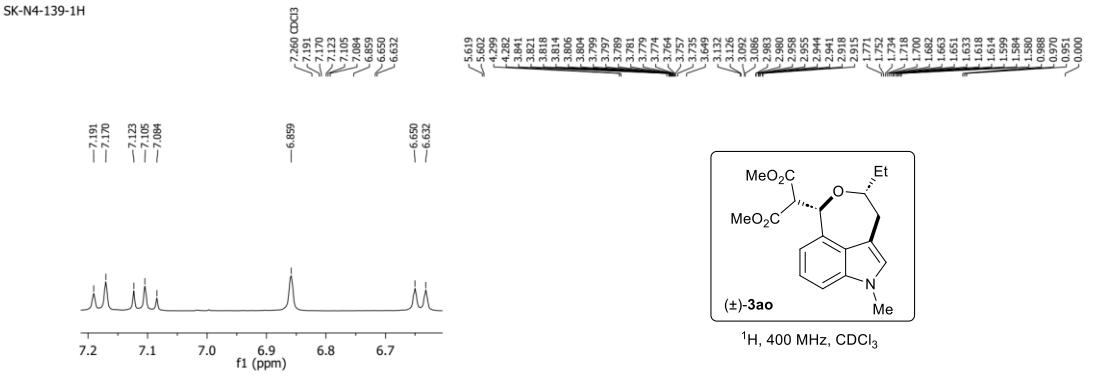
^{1}H, 400 MHz, $CDCl_3$

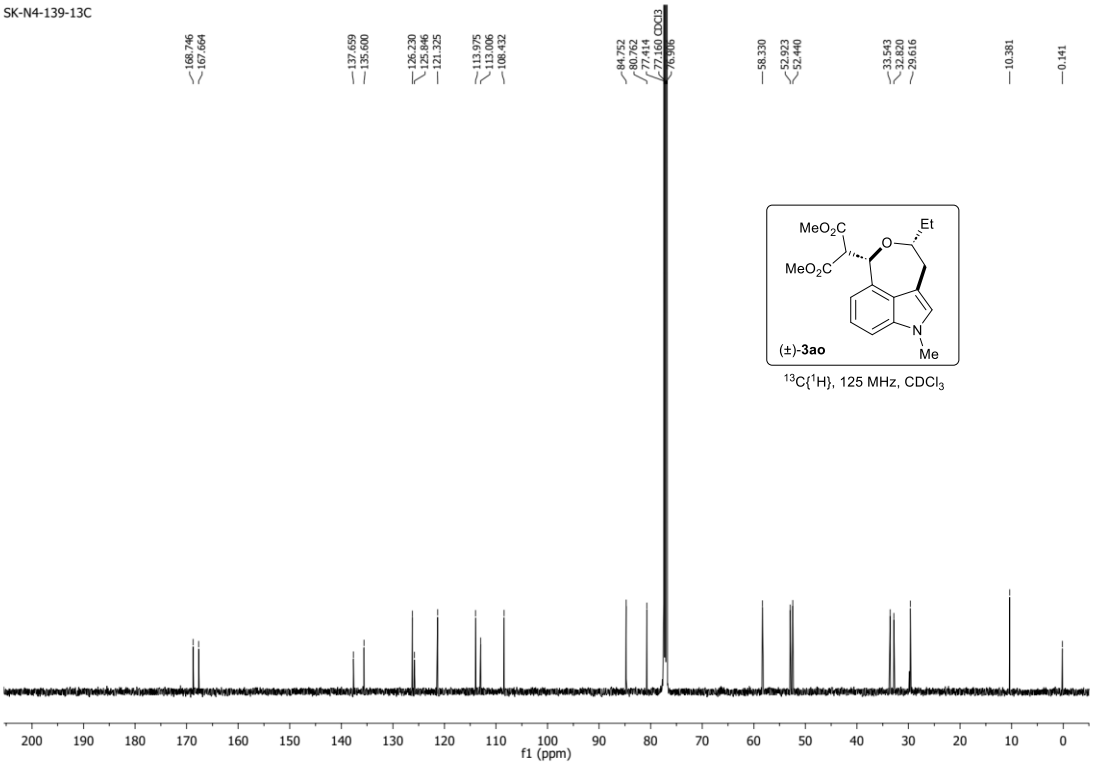


SK-N4-97-13C

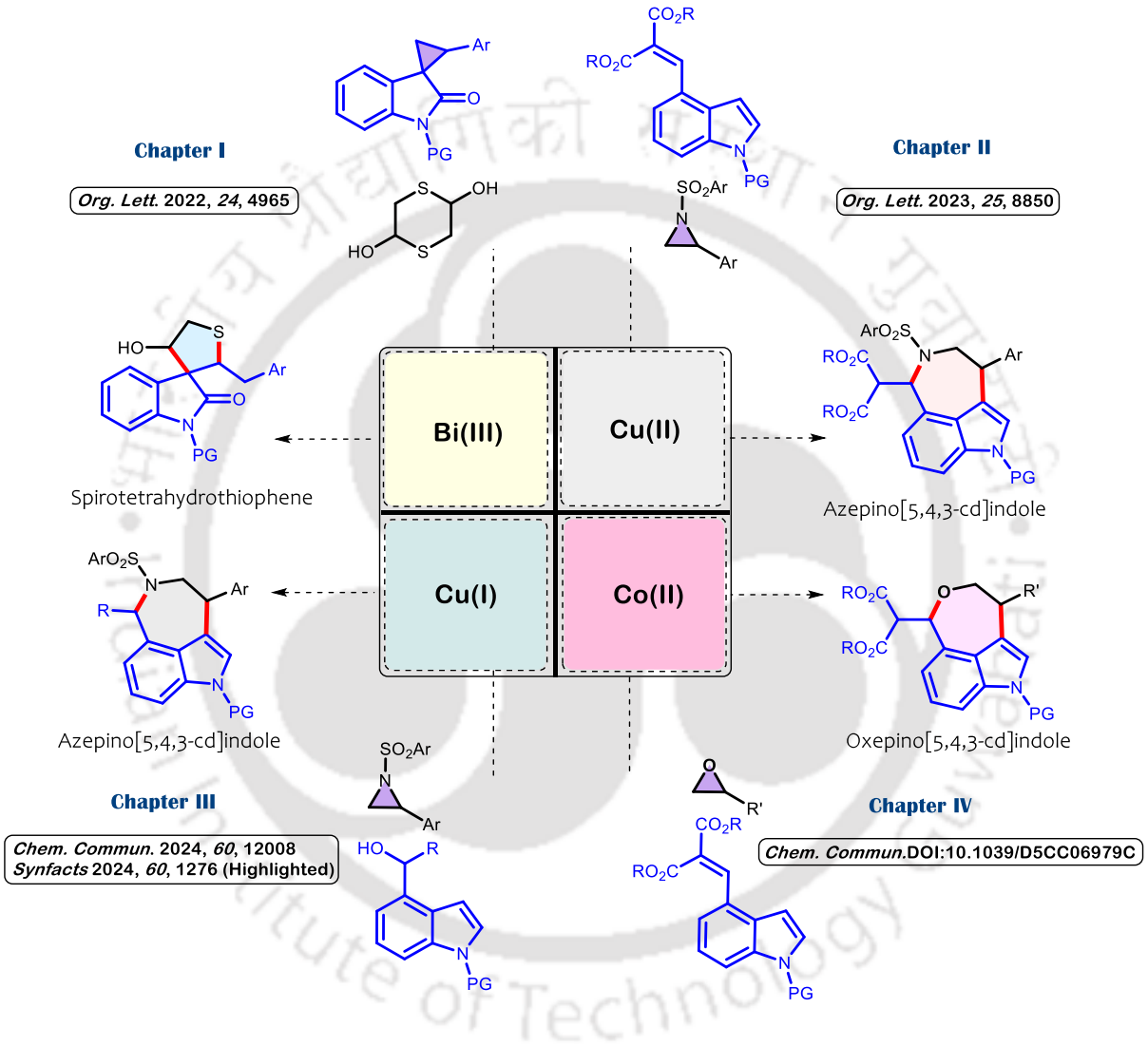


$^{13}C\{^1H\}$, 125 MHz, $CDCl_3$





Thesis Overview



Summary

Functionalized heterocycles serve as major building blocks in organic synthesis and are indispensable in modern organic chemistry due to their unparalleled versatility in both structure and reactivity. Thereby, research interest on the synthesis of these heterocyclic compounds has been rapidly increasing over the past decades owing to their extensive functional utility, enabling precise modulation of molecular behaviour and unlocking new pathways for therapeutic efficacy, reactivity and structural complexity. Incorporating functional groups into heterocyclic cores could lead to producing rings containing atoms like nitrogen, oxygen or sulphur, thus generating miscellaneous opportunities to fine-tune the physical, chemical and biological properties of these compounds. The thesis demonstrates how functionalized heterocycles not only serve as key intermediates in multistep synthesis, but also enable the rational design of compounds with tailored reactivity and selectivity. As synthetic methodologies continue to evolve towards greater efficiency, sustainability, and precision, the role of functionalized heterocycles will remain integral in advancing the frontiers of organic synthesis and its further real-world application.

Chapter I covers a Bi(III)-catalyzed formal (3+2)-cycloaddition of mono-activated spirocyclopropanes with inexpensive dithianediols as the sulphur surrogate. This chapter demonstrates the *de novo* utilization of spirocyclopropanes as 1,2-zwitterionic synthons rather than the well-established classical 1,3-zwitterion. Under the established methodology, a series of substituted spirotetrahydrothiophene moieties could be generated in a diastereoselective manner.

Chapter II describes a Cu(II)-catalyzed tandem (4+3)-annulation of 4-vinyl indoles with N-sulfonylated aziridines to afford functionalized azepinoindole scaffolds. A broad range of aziridines and indolyl malonates proved competent in delivering the desired fused nitrogen containing heterocycles. The described protocol allows for the one-pot construction of structurally diverse core skeletons inherent in numerous natural products and bio-active molecules. Further, in presence of a chiral ligand, the asymmetric version of the protocol succeeded efficiently to produce optically active scaffolds in up to 90% ee.

Chapter III focuses on a Cu(I)-catalyzed (4+3)-cycloaddition of 4-indolyl carbinols with N-sulfonylated aziridines to deliver privileged azepinoindole derivatives in moderate to good yields. Utilizing 4-indolyl alcohols as valuable alkylidene indoleninium ion precursors for dehydrative annulation with aziridines could lead to generation of structurally diverse bio-

relevant azepinoindole skeletons by suppressing the undesired Mannich (3+2)-cycloadduct. With enantioenriched aziridines, the reaction proceeded in a stereospecific manner affording optically active cores in up to >96% ee.

Chapter IV illustrates a Co(II)-catalyzed cascade (4+3)-annulation of 4-alkylidene indole malonates with oxiranes to deliver indole fused oxepine motifs in a diastereoselective manner. The protocol displayed broad substrate scope with respect to oxiranes and a series of substituted indolyl malonates. Moreover, with enantioenriched oxiranes, the protocol followed the chirality transfer, delivering optically active moieties in up to ≥95% ee. Diverse post-synthetic transformations, use of an inexpensive catalytic system and a stereospecific reaction pathway are the salient features.

List of Publications

Part of Thesis:

1. **Kar**, **S**.; Sarkar, T.; Maharana, P. K., Guha, A. K.; Punniyamurthy, T. Bi-Catalyzed 1,2-Reactivity of Spirocyclopropyl Oxindoles with Dithianediol: Access to Spiroheterocycles. *Org*. *Lett*. **2022**, *24*, 4965.
2. **Kar**, **S**.; Maharana**,** P. K.; Punniyamurthy, T.; Trivedi, V. Tandem (4 + 3)-Annulation of Aziridines: Stereoselective Access to Fused Azepinoindoles. *Org. Lett*. **2023**, *25*, 8850.
3. **Kar**, **S**.; Maharana, P. K.; Maity, S.; Trivedi, V.; Punniyamurthy, T. Copper-Catalyzed (4+3)-Cycloaddition of 4-Indolylcarbinols with Aziridines: Stereoselective Synthesis of Azepinoindoles. *Chem. Commun*. **2024**, *60*, 12008.
4. **Kar**, **S**.; Maharana, P. K.; Punniyamurthy, T. Cobalt-Catalysed (4+3)-Annulation of Oxiranes with 4-Vinyl Indoles: Stereospecific Access to Fused Oxepinoindoles. *Chem. Commun.* **DOI**: 10.1039/D5CC06979C.

Others:

1. Das, B. K.; Sarkar, T.; Maharana, P. K.; **Kar**, **S**.; Punniyamurthy, T. Cascade Zinc- and Silver Catalyzed Stereospecific C-O and C-N Bond Formations. *Eur*. *J. Org*. *Chem*. **2022**, *2022*, e202201237.
2. Sarkar, T.; **Kar**, **S**.; Maharana, P. K.; Shah, T. A.; Punniyamurthy, T. Transition Metal-catalyzed C-H Functionalization of Benzofused Azoles with Two or More Heteroatoms. Transition-Metal-Catalyzed C-H Functionalization of Heterocycles. Wiley March 25, 2023, pp 319-356.
3. Maharana, P. K.; Sarkar, T.; **Kar**, **S**.; Purkayastha, S. K.; Guha, A. K.; Punniyamurthy, T. Cobalt-Catalyzed Stereospecific C-N/C-O Bond Formation of Oxiranes with Diaziridines. *J. Org. Chem*. **2023**, *88*, 9447.
4. Shah, T. A.; Sarkar, T.; **Kar**, **S**.; Maharana, P. K.; Talukdar, K.; Punniyamurthy, T. Transition-Metal-Catalyzed Directed C-H Functionalization in/on Water. *Chem. Asian J.* **2024**, *19*, e202300815.
5. Samantaray, S.; Maharana, P. K.; **Kar**, **S**.; Saha, S.; Punniyamurthy, T. Redox-Neutral Zinc-Catalyzed Cascade [1,4]-H Shift/Annulation of Diaziridines with Donor-Acceptor Aziridines. *Chem. Commun*. **2024**, *60*, 3441.
6. Maharana, P. K.; Muthuraja, P.; **Kar**, **S**.; Tamilthendral, V.; Punniyamurthy, T. Cascade C-H Functionalization/Annulation of Arylamides with Maleimides: Access to Isoquinoline-1,3-diones. *Chem*. *Commun*. **2025**, *61*, 13449.

7. Muthuraja, P.; Maharana, P. K.; Tamilthendral, V.; **Kar**, **S**.; Punniyamurthy, T. Pd-Catalyzed Sequential Distal C-H Alkenylation and π-Allylic Amination of Arylacetic Acids using MBH Acetates: Access to Macrocyclic Lactams. *Chem*. *Sci*. **2026**, *17*, 346.
8. Swain, A.; Rout, L.; **Kar**, **S**.; Maharana, P. K.; Wang, Y.; Soddu, E.; Taillefer, M.; Ouali, A.; Punniyamurthy, T. *Chem*. *Asian*. *J*. **2026,** *21***,** e70471.

Conference Attended

1. **Subhradeep Kar**, Tanumay Sarkar, Prabhat Kumar Maharana, and Tharmalingam Punniyamurthy, "Bi-Catalyzed 1,2-Reactivity of Spirocyclopropyl Oxindoles with Dithianediol: Access to Spiroheterocycles." CRSI-NSC-28, IIT Guwahati, Guwahati, March 25-27th, 2022.
2. **Subhradeep Kar**, Tanumay Sarkar, Prabhat Kumar Maharana, and Tharmalingam Punniyamurthy, "Bi-Catalyzed 1,2-Reactivity of Spirocyclopropyl Oxindoles with Dithianediol: Access to Spiroheterocycles." FICS 2022, IIT Guwahati, Guwahati, December 2-4th, 2022. (**Best Oral Presentation Award**)
3. **Subhradeep Kar**, Tanumay Sarkar, Prabhat Kumar Maharana, and Tharmalingam Punniyamurthy, "Bi-Catalyzed 1,2-Reactivity of Spirocyclopropyl Oxindoles with Dithianediol: Access to Spiroheterocycles." ICETC-2023, Assam Don Bosco University, Guwahati, March 16-17th, 2023.
4. **Subhradeep Kar**, Tanumay Sarkar, Prabhat Kumar Maharana, and Tharmalingam Punniyamurthy, "Bi-Catalyzed 1,2-Reactivity of Spirocyclopropyl Oxindoles with Dithianediol: Access to Spiroheterocycles." RIC-2023, IIT Guwahati, Guwahati, May 14-16th, 2023. (**Best Poster Presentation Award**)
5. **Subhradeep Kar**, Prabhat Kumar Maharana, Tharmalingam Punniyamurthy and Vishal Trivedi, "Tandem (4+3)-Annulation of Aziridines: Stereoselective Access to Fused Azepinoindoles." CRSI-NSC-32, BITS Pilani, Pilani, February 2-4th, 2024. (**Best Poster Presentation Award**)
6. **Subhradeep Kar**, Prabhat Kumar Maharana, Tharmalingam Punniyamurthy and Vishal Trivedi, "Tandem (4+3)-Annulation of Aziridines: Stereoselective Access to Fused Azepinoindoles." XIX J-NOST 2024, IIT Gandhinagar, Gandhinagar, Gujarat, October 7-9th, 2024.
7. **Subhradeep Kar**, Prabhat Kumar Maharana, Swagata Maity, Vishal Trivedi and Tharmalingam Punniyamurthy, "Copper-Catalyzed (4+3)-Cycloaddition of 4-Indolylcarbinols with Aziridines: Stereoselective Synthesis of Azepinoindoles" SOS-2024, Berhampur University, Berhampur, Odisha, December 20-21st, 2024.
8. **Subhradeep Kar**, Prabhat Kumar Maharana, Swagata Maity, Vishal Trivedi and Tharmalingam Punniyamurthy, "Copper-Catalyzed (4+3)-Cycloaddition of 4-Indolylcarbinols with Aziridines: Stereoselective Synthesis of Azepinoindoles" FICS-2024, IIT Guwahati, Guwahati, December 2-4th, 2024. (**Best Poster Presentation Award**)