Development of Methods for the Direct Synthesis of C3-Functionalized Pyrroles

THESIS

Submitted in partial fulfillment of the requirements for the degree

of

DOCTOR OF PHILOSOPHY

by

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Under the Supervision of

Prof. Indresh Kumar

BIRLA INSTITUTE OF TECHNOLOGY AND SCIENCE

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2023

Dedicated To My Teachers

And

My Family

BIRLA INSTITUTE OF TECHNOLOGY AND SCIENCE
PILANI (RAJASTHAN)

CERTIFICATE

This is to certify that the thesis entitled **"Development of Methods for the Direct Synthesis of C3-Functionalized Pyrroles"** and submitted by **Mr. Amol Prakash Pawar** ID No. **2017PHXF0023P** for the award of the Ph.D. degree of the institute embodies his original work under my supervision.

Signature in full of the Supervisor:

Name: **Prof. Indresh Kumar**

Designation: **Associate Professor**

Date:

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Amol P. Pawar

ABSTRACT

The work discussed in this thesis entitled "**Development of Methods for the Direct Synthesis of C3-Functionalized Pyrroles"** provide a brief description of the development of the new method for synthesizing C3-substituted pyrroles form 1,4-dicarbonyls. The developed way is a multicomponent one-pot, domino/ cascade reaction sequence between succinaldehyde and amine and suitable electrophile using mild catalysis or catalyst-free conditions to access pyrroles.

The first chapter of the thesis described organocatalysis, in particular, amine catalysis, and its applications for developing various transformations, such as direct aldol reaction, Michael, and cascade reactions. In addition, discussions on the utilization of succinaldehyde for amine-catalyzed conversions to access various carbo-, and heterocyclic compounds have been briefly discussed. Moreover, a literature survey on the existing methods for synthesizing C3-substituted from the selective functionalization of pyrroles or directly from pyrrolidine is also disclosed.

The second chapter included the mild Lewis acid-catalyzed direct access to *β*-(C3)-functionalized pyrroles with succinaldehyde, isatin, and amine, followed by a Paal-Knorr reaction. The developed method has been applied to synthesize C3-substituted pyrroles in gram-scale synthesis.

The third chapter integrates novel synthetic methods to prepare a direct catalyst-free method for synthesizing *β*-functionalized pyrroles under open-flask conditions. With readily available and inexpensive starting materials such as reactive carbonyls and amines just before the Paal-Knorr reaction was a crucial parameter for developing C3-substituted pyrroles with moderate to good yields. This transformation was further probed computationally and well-supported with close energy profiles, and late-stage modifications on pyrroles were established.

The fourth chapter describes the first organocatalytic asymmetric synthesis of pyrroles having a chiral center at the C3-position. In this work, we have utilized the enamine generated from succinaldehyde and chiral amine catalyst for direct aldol reaction to develop the functionalized 1,4-dicarbonyl, which further reacts with a primary amine to furnish C3-substituted pyrroles asymmetrically. The practical utility of the developed protocol was also shown for the gram-scale synthesis of both enantiomers.

The fifth chapter describes a direct method to synthesize *β*-arylated/olefination pyrroles under open-flask catalyst-free conditions. In this method, a direct Michael reaction of *in-situ* generated enamine took place with alkene dienophile, afterword the Paal-Knorr with primary amine furnish C3-arylated/olefination pyrroles. The suitability of *α,β*–unsaturated 1,4-quinone units has been tested as a Michael acceptor under the developed conditions. Interestingly, C3-arylated pyrroles were obtained when benzoquinones were used as Michael acceptor, while C3-alkenylated pyrroles were obtained when naphthoquinone was employed under standard conditions.

The Sixth chapter summarizes the overall outcome of the Ph.D. thesis research work and the future scope of the work.

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LIST OF ABBREVIATIONS / SYMBOLS

Abbreviation/Symbol	Description
α	Alpha
[α]	Specific rotation
β	Beta
γ	Gamma
δ	Chemical shift
Δ	Heat
Å	Angstrom
Ac	Acetyl
Aq	Aqueous
ACN	Acetonitrile
Ar	Aryl
Bu	Butyl
t-BuOK	Potassium *tert*-butoxide
Calcd.	Calculated
°C	Degree centigrade
^{13}CNMR	Carbon-13 nuclear magnetic resonance
Cat.	Catalyst
CAN	Ceric ammonium nitrate
$CDCl_3$	Deuterated chloroform
Conc	Concentration
COSY	Correlation Spectroscopy (NMR)
d	Doublet
D-A	Donor-Acceptor
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
dd	Doublet of doublet
DDQ	2,3-Dichloro-5,6-Dicyanobenzoquinone
DMSO	Dimethysulphoxide
DMSO-d_6	Deuterated Dimethysulphoxide

LIST OF ABBREVIATIONS / SYMBOLS

DCE	Dichloroethane
DCM	Dichloromethane
DMA	*N*,*N*-Dimethylacetamide
DMAD	Dimethyl acetylene dicarboxylate
DMF	*N*,*N*-Dimethylformamide
ESI	Electron Spray Ionization (MS)
EtOAc	Ethyl acetate
Equiv	Equivalent
E	Electrophile
g	Gram
HRMS	High Resolution Mass Spectra
HSQC	Heteronuclear Single Quantum Correlation
IBX	2-Iodoxybenzoic acid
IR	Infrared
Hz	Hertz
hr	Hour
J	Coupling constant
Lit.	Literature
MS	Mass spectrometry
M.P	Melting point
m	Multiplet
mg	Milligram
MHz	Mega hertz
min	Minutes
mL	Milliliter
mmol	Millimole
MW	Microwave
N_2	Nitrogen gas
Nu	Nucleophile
^{1}HNMR	Proton Nuclear Magnetic Resonance

NOE	Nuclear Overhauser Effect (NMR)
NOESY	Nuclear Overhauser Effect Spectroscopy (NMR)
O_2	Oxygen gas
PEG	Polyethylene glycol
ppm	Parts per million
%	Percentage
p-TsOH	*p*-Toluenesulfonic acid
PMP	*p*-methoxyphenyl
rt	Room temperature
s	Singlet
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
$NaHCO_3$	Sodium hydrogencarbonate
$Na_2S_2O_3$	Sodium thiosulfate
t	Triplet
TBAB	Tetrabutylammonium bromide
Ts	Tosyl
Tert-	Tertiary
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
σ	Sigma

Chapter – 1

Amine Catalyzed Transformations of Succinaldehyde, and Synthesis of C3-Substituted Pyrrole

1.1 Introduction

The word "organocatalysis" is a combination of the words "organic" and "catalyst." It has been defined as increasing the rate of chemical reactions while adding a sub-stoichiometric mass of an organic compound. The field has received a great deal of attention in recent years because of both the novelty of the concept and, more importantly, the advantages of several organocatalytic reactions that meet the standards of well-known organic reactions.[1-2] The word organocatalysis was introduced in the scientific community by MacMillan in 2000 to describe the organic synthesis field.[3-4] Organocatalysis has several advantages due to its synthetic range and economic reasons. It has experienced remarkable growth in the emerging field of chemistry for two decades and developed as a third pillar next to metal and biocatalysts.[5-10] Recently, List and MacMillan groups were awarded the Nobel Prize 2021 for developing asymmetric organocatalysis. Most organocatalysts are air and moisture stable easy to handle even on a large scale compared to transition metals. In addition, organocatalysts are tolerant of several functional groups, thus, avoiding time-consuming and protecting group manipulations for such chemical transformations. Moreover, commonly the reactions are conducted under mild conditions and high concentrations, thus escaping the use of large amounts of solvents and minimizing waste.

In general, organocatalysts can be classified into two main categories, non-covalent, and covalent catalysis, depending on their modes of interaction with the substrate. In covalent catalysis, substrate activation occurs through the covalent bond formation between organocatalysts and substrates. In this category, amine catalysts and carbene catalysts have been involved. In non-covalent activations, substrates activation occurs through non-covalent interactions such as hydrogen bonds, e.g., thioureas and phosphoric acids, or ionic interactions (e.g., chiral phase transfer catalysts derived from cinchona alkaloids) between the substrate and the catalyst.[11-23] Among the various substrate activation modes, amine catalysis has been found to contribute significantly to the overall growth of organocatalysis through different asymmetric transformation/cascade/domino reactions.

1.2 Basic introduction to amine catalysis

The initial development of amine catalysis, which involves the enamine and iminium-ion activation of carbonyl compounds using a secondary amine catalyst, was shown by Barbas and MacMillan research groups at the beginning of this century. These two groups proposed the

formation of intermediates, like; Barbas-enamine and iminium-ion, when amine catalysts reacted with carbonyls such as aldehyde or ketone compounds.[23-24]

In this context, enamine **A** intermediates have been generated through the reaction of amine catalyst **1** with aldehyde **2**, which behaves as a nucleophile and can react with a series of electrophiles to furnish the α-substituted carbonyl **3**. This HOMO-raising phenomenon increases the electron density of the double bond of enamine **A** due to the conjugation of lone pairs of electrons from nitrogen (Figure 1.1(I)). The iminium ion LUMO-lowering phenomenon increases the electrophilicity of intermediate **B**, making it more reactive toward nucleophiles (Figure 1.1(II)).

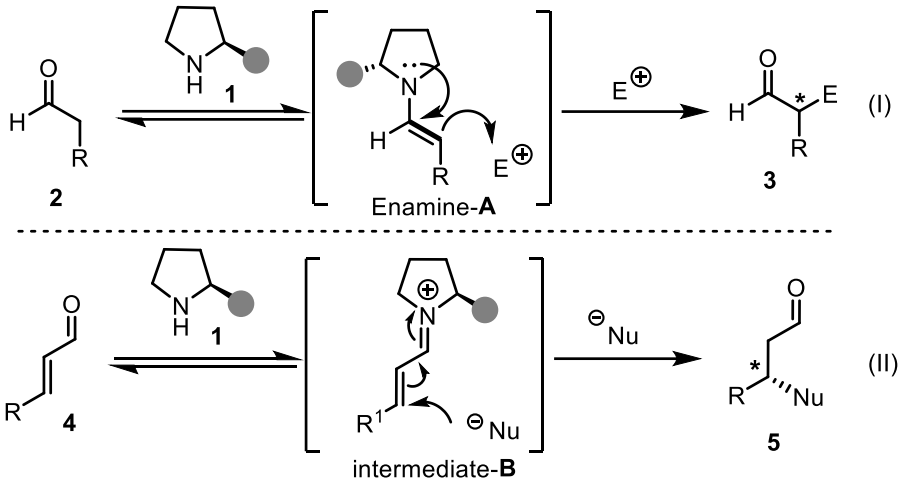
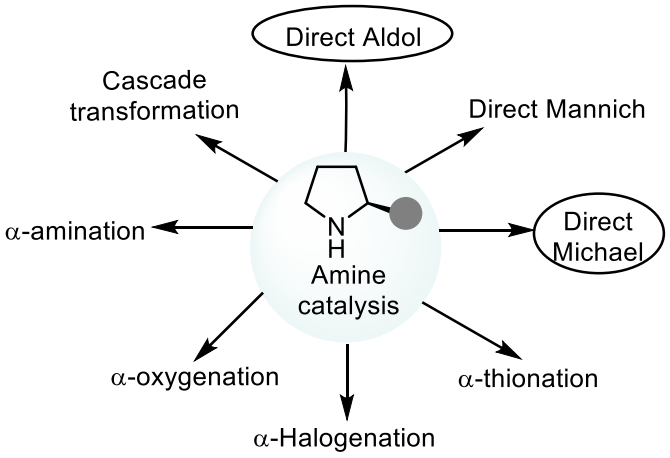


Figure 1.1 Covalent mode of activation of substrates via enamine intermediate.

In general, the concept of amine catalysis is flanked between enamine **A** and iminium-ion **B** intermediates. The idea of amine catalysis has been applied to several transformations (Scheme 1.1).

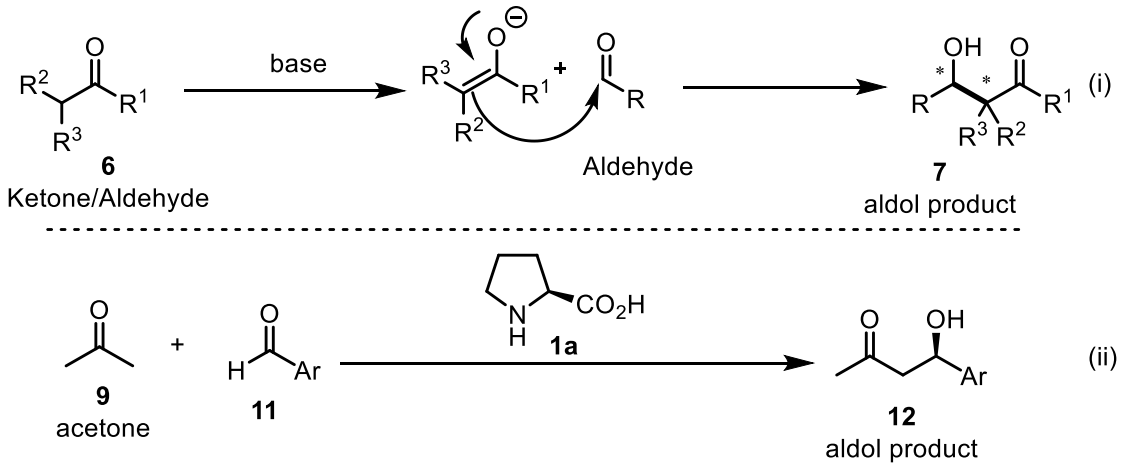


Scheme 1.1 Utilization of amine catalysis for various transformations.

Considering our research interest in the covalent mode of substrate activation, we focused on using in situ generated enamine intermediate and its applications in multiple changes, particularly direct aldol and Michael reactions.

1.2.1 Amine catalyzed direct aldol reaction

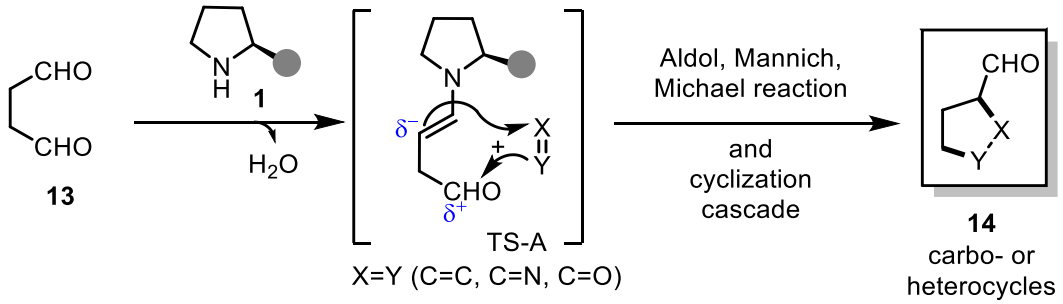
An aldol reaction mainly forms β-hydroxy carbonyl compounds from two carbonyl compounds through the assembly of a carbon–carbon bond, thereby one after making two new stereogenic centers to increase structural complexity (Scheme 1.2(i)).[25] β-hydroxy carbonyl units are found in various essential molecules from synthetically made or naturally occurring. The modern aldol reaction proceeds through active enolates in situ catalytic generations and attacks on carbonyl (aldehydes and ketones) compounds. A directed cross-aldol reaction of silyl enol ethers with carbonyl compounds, such as aldehydes and ketones, promoted by a Lewis acid, widely known as the Mukaiyama aldol reaction.[26] Although acids and bases are used for catalyzing aldolizations, the aldolase-like direct catalytic asymmetric aldol reaction remained an elusive challenge for a long time. The first direct aldol reaction using secondary Amine as organocatalysts via Barbas-enamine intermediate was established by Barbas and List to access a similar product. The reaction of aromatic aldehydes with excess acetone was found to proceed in the presence of a catalytic amount of (S)-proline in DMSO to provide the corresponding product with good yields and enantioselectivities (Scheme 1.2(ii)).[27]



Scheme 1.2 General representation of aldol reactions (i) and first direct aldol reaction (ii).

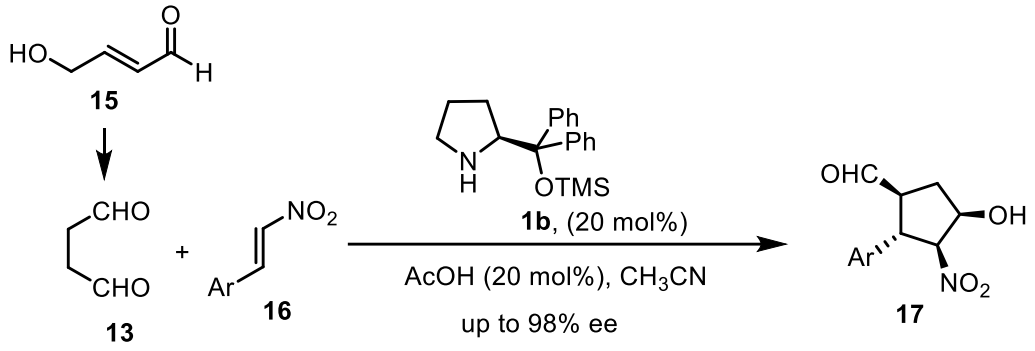
1.2.2 Succinaldehyde in amino-catalytic transformations

Organocatalytic domino/cascade reactions through amine-catalyzed activation of carbonyl compounds have become the ultra-modern transformations to design and develop an effective synthetic strategy. In this direction, linear dialdehydes such as glutaraldehyde, succinaldehyde, and other similar moieties have been proven as appropriate substrates for amine-catalyzed transformations. Apart from highly commercial availability with low cost and high reactivity, its unique structural features have the competency to efficiently perform the domino/cascade/tandem transformations for synthesizing valuable drug molecules and natural products. There are several transformations, such as Aldol/Mannich/Michael/Henry/Baylis-Hillman reaction, where linear dialdehydes have been utilized. In synthetic organic chemistry, linear dialdehydes have been recognized as essential substrates.[28] Linear dialdehydes and other higher homologated unsaturated or saturated dialdehydes undergo intramolecular and intermolecular transformation with various X=Y (C=C, C=N, C=O). In this direction, succinaldehyde **13**, a simple 1,4-dicarbonyl compound that acts like a 1,3-carbon donor-acceptor (D-A) precursor for amine-catalyzed transformations to access biologically functional scaffolds in asymmetric/non-asymmetric fashion according to the suitability as presented in (Scheme 1.3).[29] Succinaldehyde **13** is reasonably stable in an aqueous solution with a bitter smell. Besides this, a vast number of natural products and heterocyclic ring systems have also been synthesized successfully by succinaldehyde.[30]



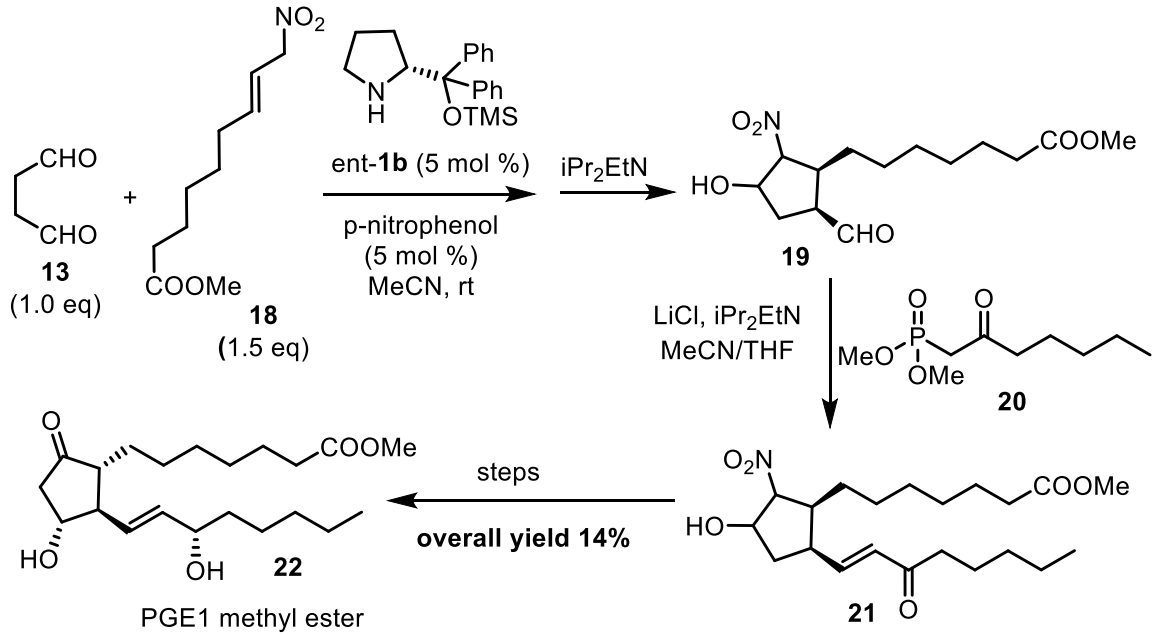
Scheme 1.3 Cyclopentane synthesis using secondary amine catalysis and succinaldehyde.

Several amine-catalyzed domino transformations of succinaldehyde **13** have been developed. In this direction, the initial [3+2] Michael-Henry reaction using organocatalytic cascade transformation was created by Hong and co-workers using nitro-alkenes **16** and succinaldehyde **13**, in situ generated from enal **15** masked dialdehyde, to furnished cyclopentane carboxaldehyde **17** with four successive stereocenters with remarkable enantioselectivity (Scheme 1.4).[31]



Scheme 1.4 Cyclopentane synthesis by amine catalyzed [3+2] Michael-Henry reaction.

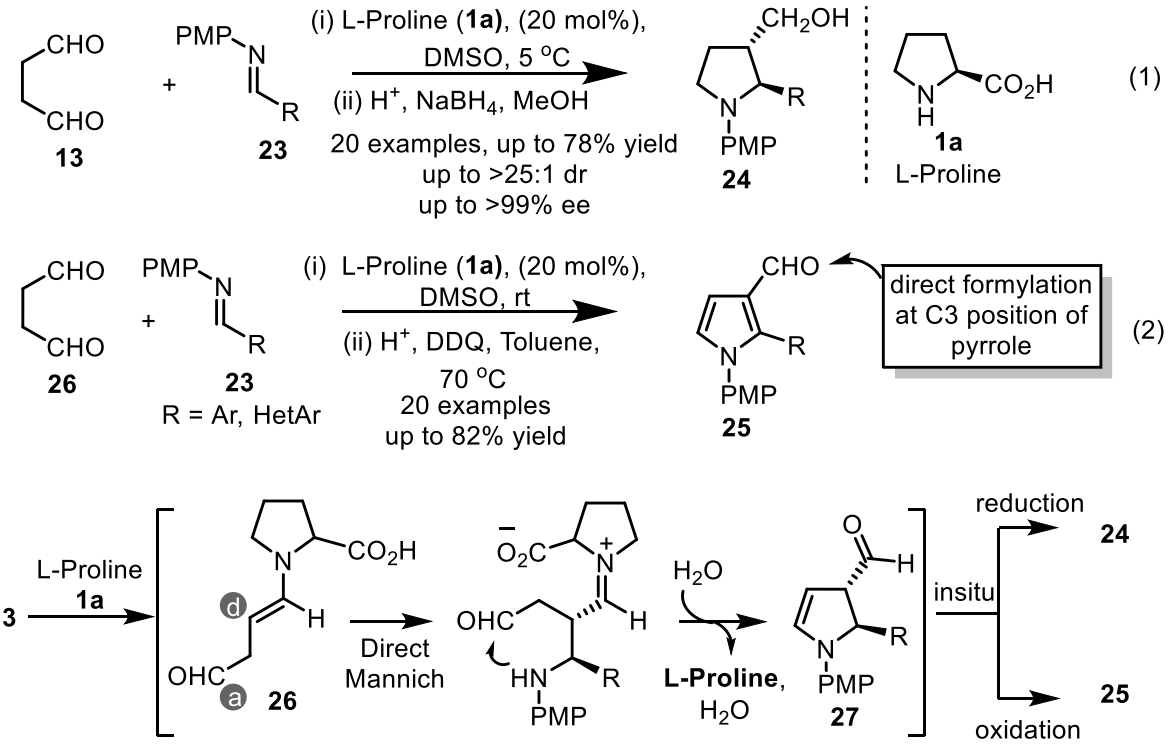
Hayashi and co-workers further explored the tremendous application of succinaldehyde by utilizing it in an amine-catalyzed domino reaction for the total asymmetric synthesis of prostaglandins.[32] This innovative approach proceeded through the following steps, *i.e.*, succinaldehyde **13** and nitroalkene **18** underwent direct Michael reaction catalyzed by diphenylprolinolsilyl ether ***ent*-1b** (5 mol%) followed by intramolecular [3+2] Henry reaction in the presence of *i*Pr_2EtN and subsequent Horner-Wadsworth-Emmons reaction in one pot. After additional transformation, PGE1 methyl ester **22** was afforded high yield and selectivity in a pot-economic fashion (Scheme 1.5).



Scheme 1.5 Total asymmetric synthesis of prostaglandins.

Kumar and co-workers utilized functional succinaldehyde **13** as a substrate in L-proline **1a** catalyzed organocatalytic cascade Mannich transformations to design the synthesis of nitrogen

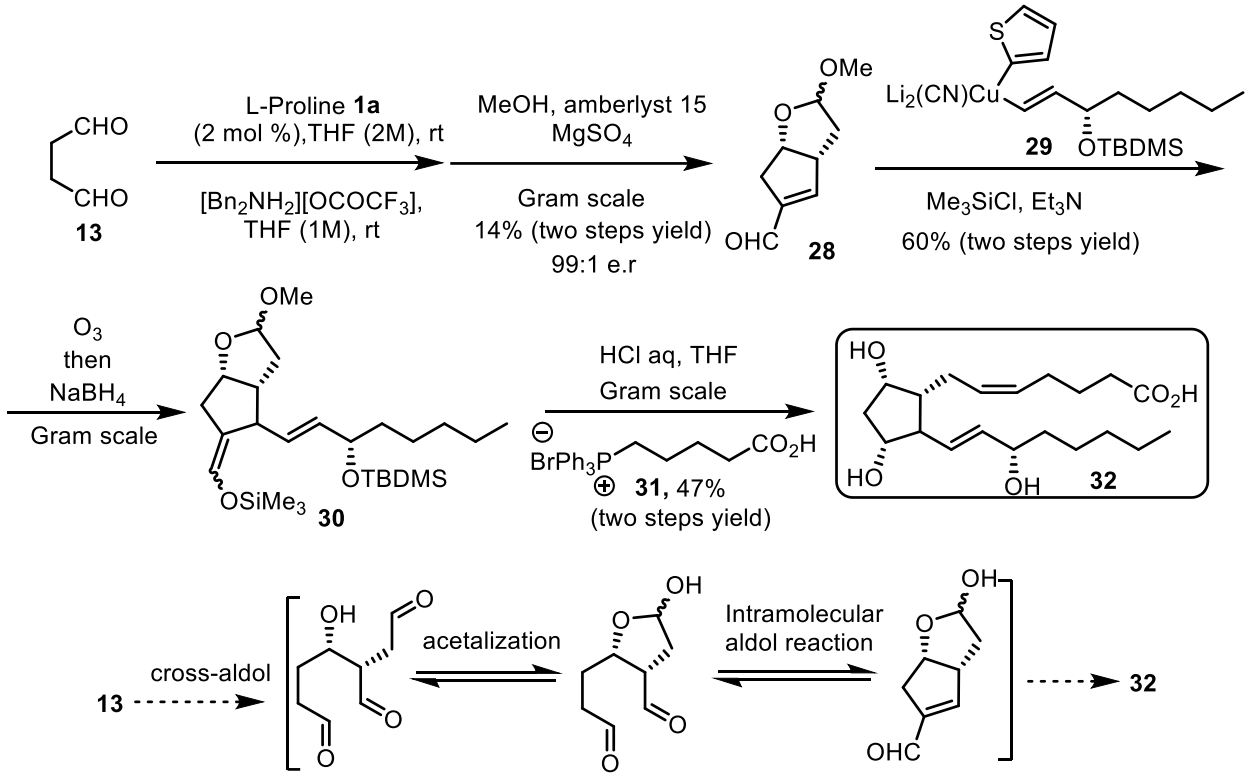
heterocycles. Initially, they developed a five-membered heterocycle, pyrrolidines **24,** with exceptionally good stereoselectivities and yield in a one-pot fashion (Scheme 1.6 (1)).[33] Followed by the first direct synthesis of substituted pyrrole-3-carboxaldehydes **25** in a two-step strategy was disclosed (Scheme 1.6 (2)).[34] These two [3+2] annulation transformations were identical up to intermediate **27**. Intermediate **27** reduced with $NaBH_4$ in, the presence of acid afforded *trans*-2,3-substituted pyrrolidine **24** with excellent enantioselectivities (up to >99% ee) and high yields. Intermediate **27** underwent oxidative aromatization by DDQ-furnished substituted pyrrole-3-carboxaldehyde **25** in good to high yields. Both [3+2] annulations proceeded through the L-proline **1a** catalyzed Mannich reaction between enamine **26** and imine **23**. Enamine **26** was in situ generated from succinaldehyde **13** and serves as a readily available 1,3-carbon donor-acceptor (D-A) precursor.



Scheme 1.6 Utilization of succinaldehyde in the synthesis of pyrrolidines and pyrroles.

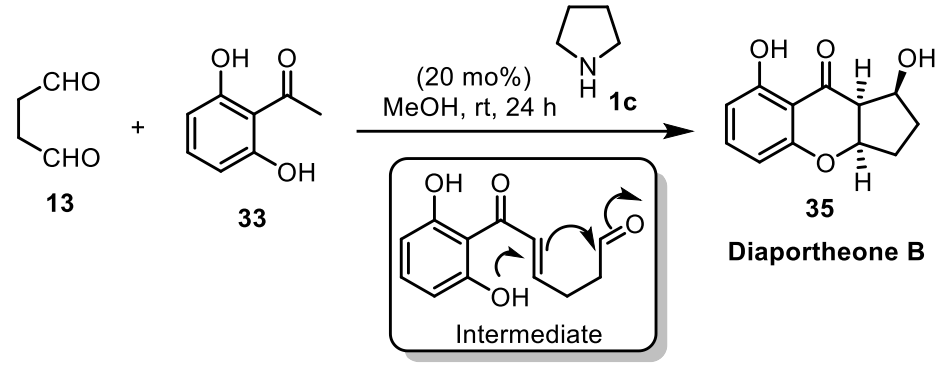
The first use of succinaldehyde **13** in amine catalyzed cascade reaction was explored by Agawam and co-workers for the stereocontrolled synthesis of prostaglandin PGF2α, **32.**[35] The first step was a one-step synthesis of functionalized bicyclic-enal **28** with an excellent enantiomeric excess (98%), produced by the direct cross-aldol reaction of succinaldehyde **13** followed by L-proline

1a catalyzed intramolecular aldol condensation. Most of the earlier methods for the Synthesis of PGF2α **32** were lengthy, time-consuming, and produced plenty of waste. In contrast, this method was very economical, completed in just six steps, and can be accessed in gram scale (Scheme 1.7).



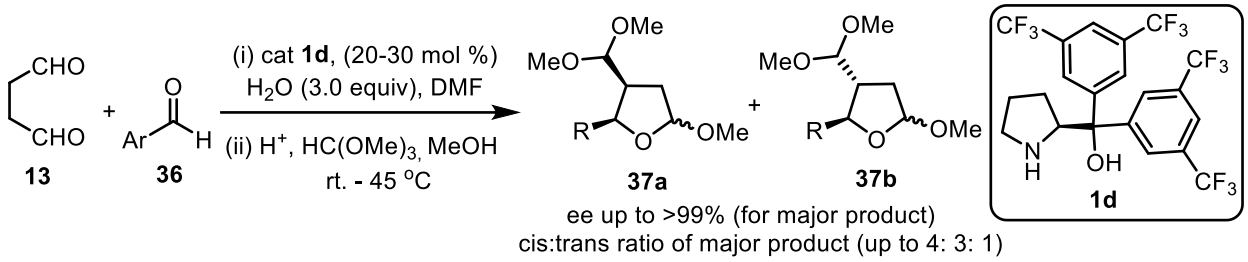
Scheme 1.7 Organocatalytic cascade strategy for Prostaglandins synthesis.

Reddy and co-workers have also discovered the captivating utility of succinaldehyde **13** for the amine-catalyzed synthesis of anti-TB agent Diaportheone B **35** (Scheme 1.8).[36] The overall transformations were catalyzed by pyrrolidine **1c**, involving condensation of 2,6-dihydroxy acetophenone **33** with succinaldehyde **13** to generate a very reactive intermediate, which subsequently underwent cyclization through domino fashion to furnished Diaportheone B **35**.



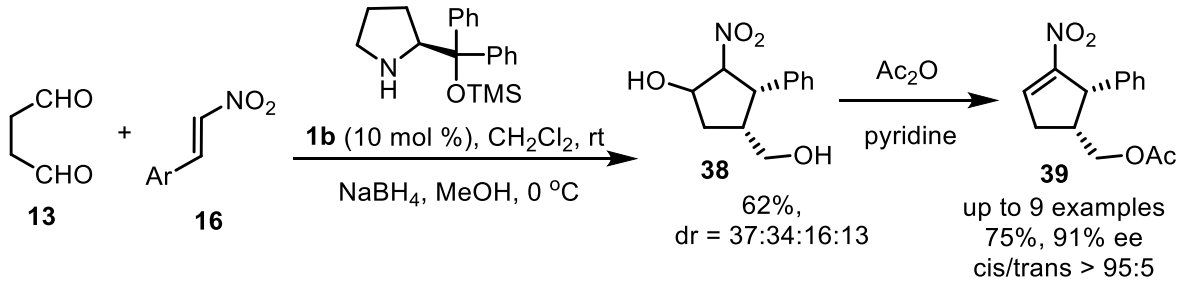
Scheme 1.8 Amine catalyzed cascade strategy for Diaportheone B synthesis.

A formal [3+2] cycloaddition domino approach of succinaldehyde **13** and other aromatic/ activated aldehydes **36** for the asymmetric synthesis of tetrahydrofurans **37a** and **37b** reported by Hayashi and co-workers (Scheme 1.9).[37] The overall transformation was a direct aldol reaction of succinaldehyde **13** with several aldehydes catalyzed by diarylprolinol **1d,** followed by an intramolecular cyclization that afforded good yields and high enantioselectivity.



Scheme 1.9 Formal [3+2] cycloaddition domino approach for the asymmetric synthesis of tetrahydrofurans.

The same group published an enantioselective domino Michael/Henry reaction introducing reacting partner succinaldehyde **13**, nitroalkenes **16** in the presence of diphenylprolinolsilyl ether **1b** as an organocatalyst to furnished *cis*-disubstituted cyclopentenes **39** with excellent diastereoselectivity and enantioselectivity (Scheme 1.10).[38]



Scheme 1.10 [3+2] cycloaddition for the synthesis of *cis*-disubstituted nitropentenes.

1.3 Importance and synthesis of C3-substituted pyrroles

Nitrogen-bearing heterocyclic compounds have gained significant attention in material chemistry, pharmaceutical chemistry, and synthetic organic chemistry. Pyrrole **40**, a simple five-member nitrogen aromatic heterocyclic system, was detected as a component of coal tar by F. F. Runge,[39] later in 1857. It was isolated from the pyrolysate of bone. The name pyrrole came from the Greek word Pyrrhus ("reddish, fiery") from the reaction applied to detect the red color it gives to wood when moistened with hydrochloric acid.[40]

Pyrroles are aromatic heterocyclic, nutty odor and colorless volatile liquid that readily darkens during air exposure and is generally purified by distillation before use.[41] The pKa of its conjugate base is –3.8, indicating that pyrrole is weakly basic and poorly acidic at the N-H position with a pKa of 17.5. Pyrrole is an electron-rich species containing 6π-electron and five *p*-orbitals and obeys Huckel's rule of aromaticity. Hence its reactivity is like aromatic compounds. Pyrrole usually undergoes electrophilic substitution at α-position (C2 or C5) due to the more significant number of resonating hybrid structures, with the highest degree of stability in the intermediate compared to electrophilic replacement at β-position (C3 or C4) (Figure 1.2). Pyrrole and its derivatives are five-membered heterocyclic systems, so it is present in several bioactive molecules and natural products and essential building blocks for numerous transformations in organic synthesis (Figure 1.2).[42]

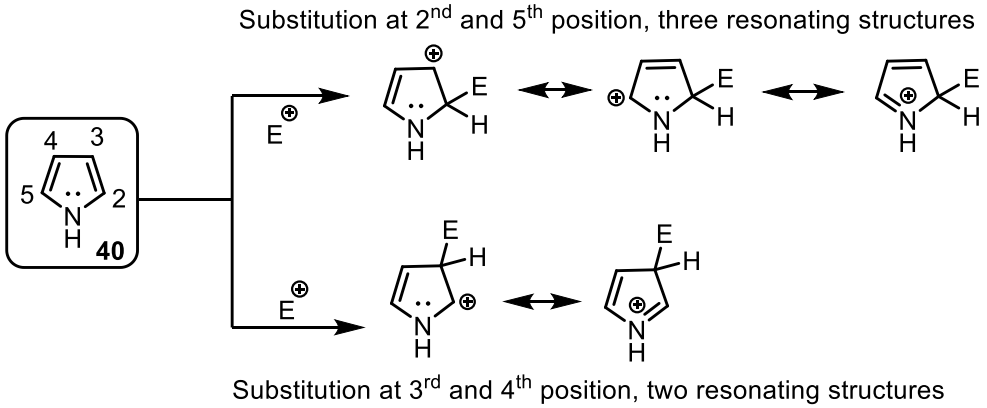


Figure 1.2 Electrophilic substitutions at α-and β-position of pyrrole.

The functionalized pyrrole derivatives have shown numerous applications in branches of science such as pharmacology, biology, agrochemicals, material sciences, dyes, Flavor-components, photographic chemicals, and functionalized materials.[43] Several naturally occurring molecules have pyrroles such as vitamin B_{12}, bile-pigment like bilirubin,

biliverdin, and porphyrinogens, porphyrins of heme, bacteriochlorin, chlorophyll, and chlorins. Besides, other secondary metabolites containing pyrrole are ryanodine, Makalu amine M, PQQ, rhazinilam, sceptrin, myrmicacin, lamellarin, and prodigious. Besides, medium-sized nitrogen heterocycles are privileged scaffolds in numerous natural and typical compounds,[44] in particular; pyrrole derivatives show diverse physiological activities. Such as a few reports on anti-tubercular,[45] anti-viral,[46,47] antibacterial,[48] anti-inflammatories.[49] BODIPY dyes are functionalized pyrrole derivatives with boron atoms that have been carried out in recent eras to explore their potential applications in materials, medical, and biological sciences, and BODIPY dyes are known to exhibit excellent photophysical properties, and its β-triazolyl BODIPYs derivatives are uses in Metal ions detection.[50]

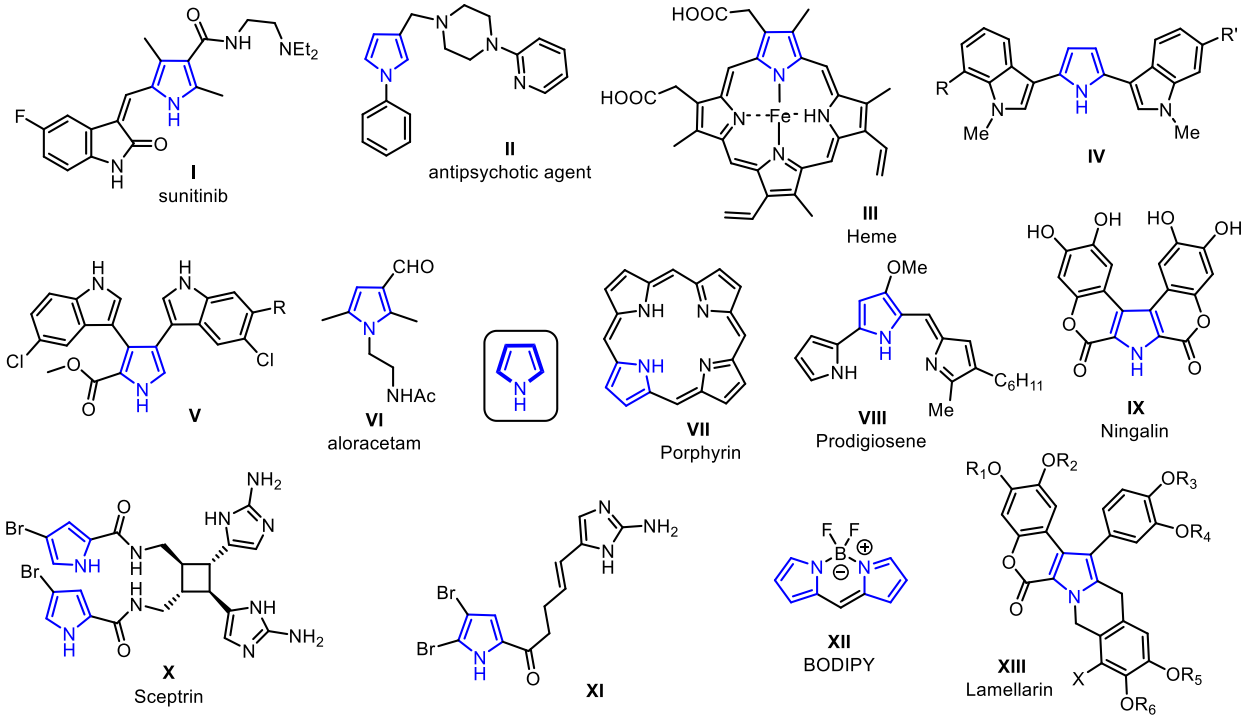
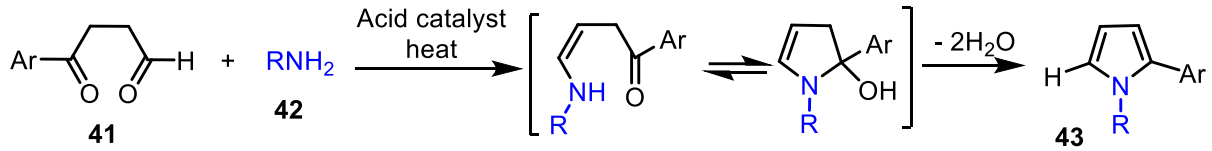


Figure 1.3 Selected bioactive pyrroles and related derivatives.

1.3.1 Multi-component reactions for the synthesis of pyrroles

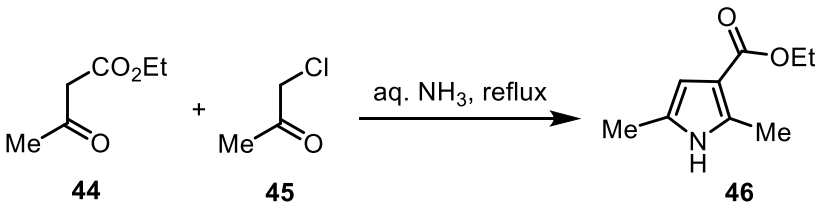
Due to the enormous importance of pyrrole, several methods have been developed for synthesizing this moiety, which include classical methods and several other multi-component reactions (MCRs).[51] The MCRs offer benefits over conventional multi-step syntheses and produce a significant route for modern synthetic chemistry.[52] The Paal-Knorr condensation is one of the classical methods for synthesizing pyrroles, where 1,4-dicarbonyl

unit **41** provides four carbon atoms of the ring and an amine compound **42** provides the nitrogen atom of the pyrrole (Scheme 1.11).[53] Nucleophilic addition of the amine **42** to the two carbonyl carbon atoms and the loss of the two moles of water afford the pyrrole **43**. This method provides a convenient way for synthesizing 1-substituted 2,5-dimethyl pyrroles **43** with alkyl or aryl substituents in both 2- and 5-positions.



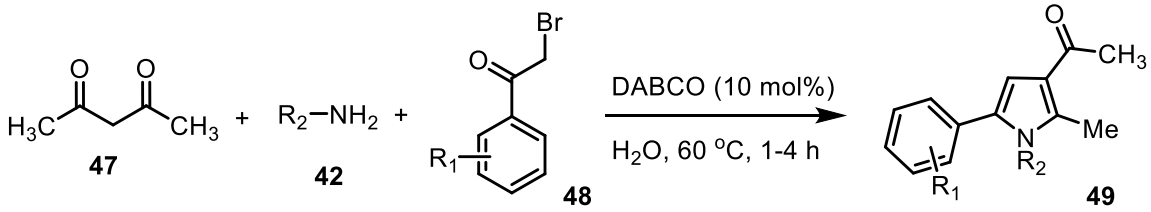
Scheme 1.11 Paal-Knorr condensation reaction.

In 1890, Hantzsch published a brief note reporting that the reaction between an equimolecular mixture of acetoacetic ester **44** and chloroacetone **45** under reflux in concentrated aqueous ammonia afforded a pyrrole derivative **46** (Scheme 1.12).[54]



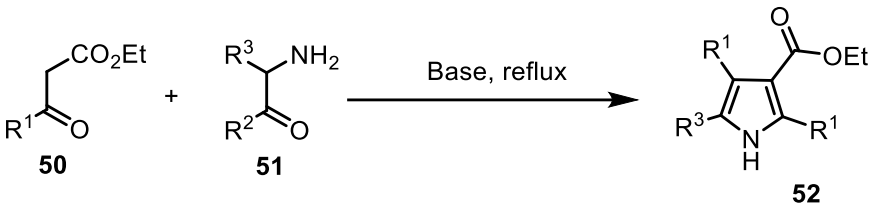
Scheme 1.12 The first multi-component pyrrole synthesis.

A base-catalyzed variation of the Hantzsch pyrrole **49** syntheses has been described by Meshram and co-workers using 1,4-diazabicyclo[2.2.2]octane (DABCO) as the catalyst and water as the reaction medium (Scheme 1.13).[55]



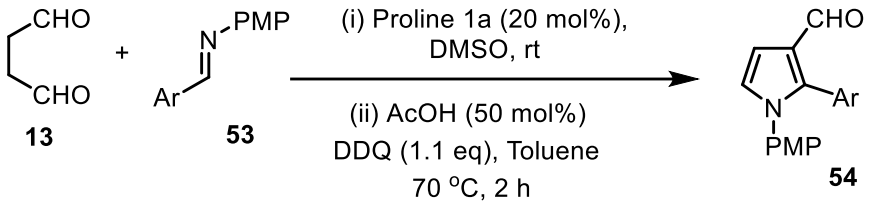
Scheme 1.13 Base-promoted Hantzsch pyrrole synthesis in water.

Knorr discovered the most widely applied ring closure reaction method, which involves the condensation of β-ketoester **50** with *α*-amino ketone **51** in the presence of a base to furnish pyrrole **52** (Scheme 1.14).[56]



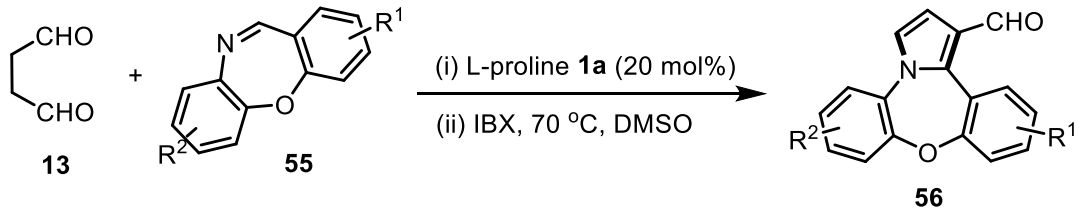
Scheme 1.14 Knorr pyrrole synthesis.

The synthesis of pyrrole from 1,4-dicarbonyls was the only report through Paal-Knorr reactions. Recently, Kumar and co-workers have placed significant efforts to develop an alternative method for synthesizing functionlized pyrrole from 1,4-dicrabonyls, imine under metal-free conditions. In this direction, firstly, they have utilized succinaldehyde **13** along with acyclic imine **53** as a suitable substrate for amine-catalyzed direct Mannich reaction/cyclization/aromatization sequence to access pyrrole-3-carboxaldehyde **54** in moderate to good yields (Scheme 1.15).[57]



Scheme 1.15 Synthesis of pyrrole-3-carboxaldehyde from succinaldehyde and imine.

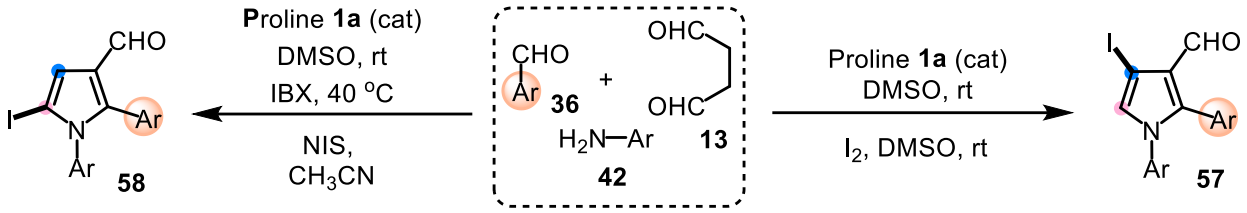
In 2019, the same group developed a protocol for synthesizing oxazepine-fused pyrroles **56** using succinaldehyde **13** and oxazepines **55** as cyclic imine through L-proline **1a** catalyzed direct Mannich/cyclization sequence, followed by IBX-mediated oxidative aromatization in the same pot (Scheme 1.16).[58]



Scheme 1.16 [3+2] cycloaddition for the synthesis of tetracyclic dibenzoxazepine-fused pyrroles.

Very recently, the multi-component synthesis of regioselective 4-iodo and 5-iodopyrrole-3-carbaldehyde **57/58** have been developed from succinaldehyde **13**, aromatic aldehyde **36**, and amines **42** as the common starting material by switching the reacting conditions. This site-

selective synthesis of 4-iodo-pyrrole-3-carboxaldehyde **57** was achieved through one-pot L-proline-catalyzed **1a** direct Mannich reaction-cyclization sequence between in situ generated imines and succinaldehyde **13**, followed by selective iodination and aromatization using molecular I_2. *N*-iodosuccinimide (NIS) mediated C5-iodination of in situ generated pyrrole was achieved to form 5-iodopyrrole-3-carbaldehyd **58** (Scheme 1.17). [59]



Scheme 1.17 Regioselective synthesis of 4-iodo and 5-iodopyrrole-3-carbaldehydes.

1.3.2 Literature reports accessing C3-functionalized pyrroles

In the previous section, we discussed some classical methods for synthesizing pyrrole. Besides, derivatization on pyrrole is another way to access functionalized units; however, it mainly occurs at the C2-position. Comparatively, access to C3-functionalized pyrrole is a challenging task that requires multi-step/indirect strategies and is being explored with limited scope. The existing protocols for C3-functionalized pyrrole can be strictly distributed in two ways: (i) directed functionalization on pyrrole (Path-I, Figure 1.4) and (ii) C3-functionalization-aromatization of *N*-substituted pyrrolidine (Path-II, Figure 1.4). The functionalization of pyrrole pre-derivative with either steric bulky groups [60] or electron-withdrawing groups [61] was required to administer the substitution at the C3-position (Figure 1.4).

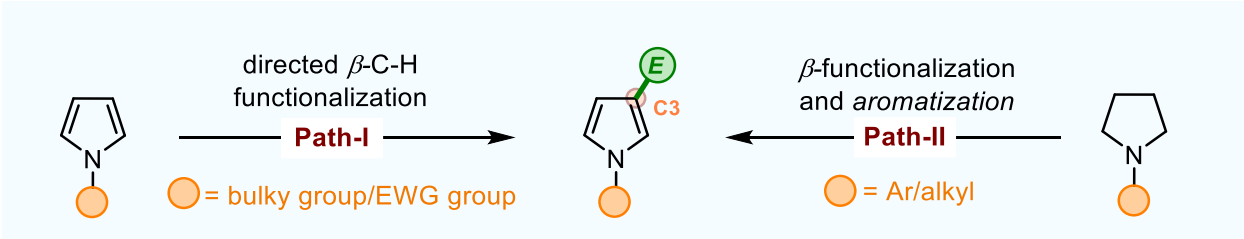


Figure 1.4 General access to C3-functionalized pyrroles.

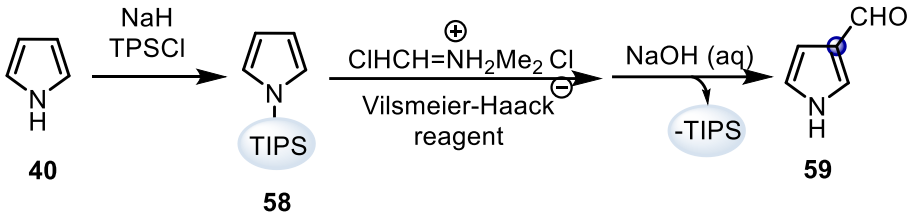
1.3.2.1 Path I Directed approach for the selective functionalization on preformed pyrroles

(A) Use of bulky group on pyrrole to access C3-substitution

Generally, the electrophilic aromatic substitution (S_EAr) reaction of pyrroles occurs mainly at the C2-position; however, the substitution can be directed to the C3-position by placing a

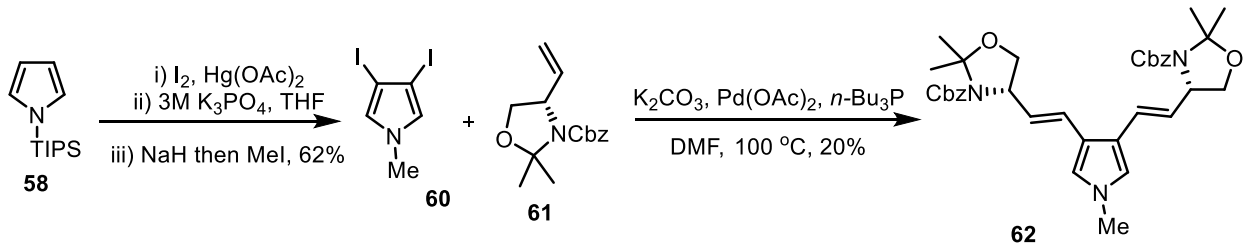
bulky group/electron-withdrawing group (EWG) on the pyrrole ring. For this purpose, ^{t}Bu, triphenylmethyl, tosyl, and tri-isopropylsilyl (TIPS) groups have been used as bulky substituents. *N*-tri-isopropylsilylpyrrole undergoes prime or selective kinetic electrophilic substitution at C3 and desilylation selective obtained C3-substituted pyrroles.

The initial report in this direction was to place -CHO group at the C3-position to access pyrrole-3-carboxaldehyde **59** by using the sterically bulky tri-isopropylsilyl group (TIPS) as protecting group on the nitrogen of pyrrole **58** followed by the Vilsmeier formylation and deprotection as a multi-step process (Scheme 1.18).[62]



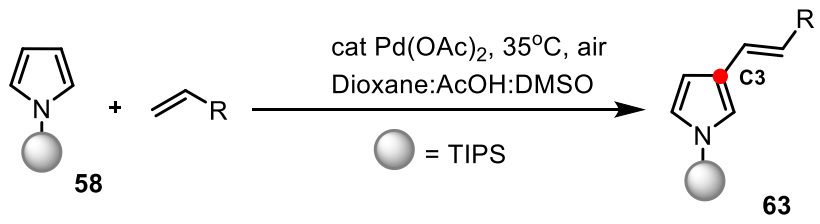
Scheme 1.18 Synthesis of 3-formyl pyrrole involving Vilsmeir-Haack reagent.

In 2002, Collier and co-workers developed a direct selective C3-iodination on *N*-TIPS pyrrole **58**, which was later utilized for synthesizing amino acid enclosing olefin **62** (Scheme 1.19).[63]



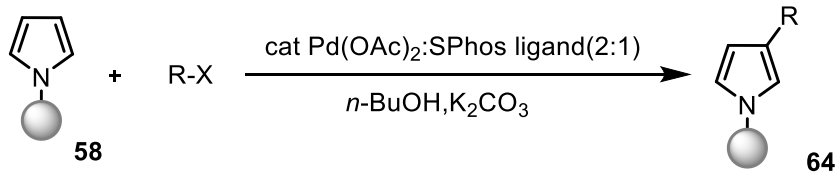
Scheme 1.19 Selective C3-halogenation on *N*-TIPS pyrrole.

In 2006, Gaunt and co-workers utilized bulky substituted pyrrole to synthesize Pd-catalyzed selective C-H bond functionalization at the C3-position of pyrrole to access C3-alkylated pyrroles **63** (Scheme 1.20).[64]



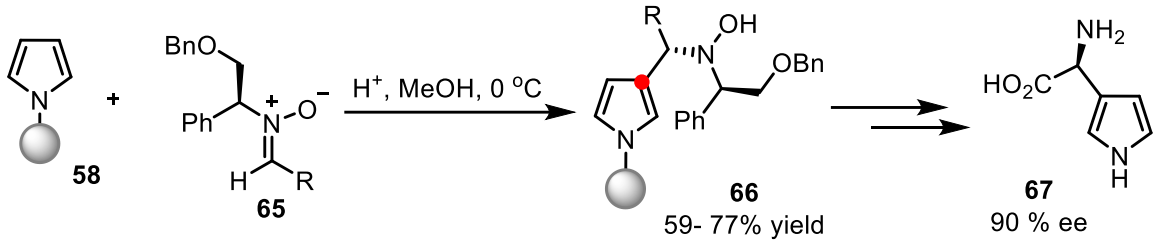
Scheme 1.20 Regioselective Pd-catalyzed C–H functionalization of pyrrole.

Later, Buchwald and Kelvin utilized the same technique for the Suzuki-Miyaura cross-coupling reaction of *N*-bulky group (TIPS) pyrrole **58** with aryl/heteroaryl halides to access C3-substituted pyrroles **64** (Scheme 1.21). [65]



Scheme 1.21 Suzuki-Miyaura coupling reaction for the synthesis of C3-substituted pyrroles.

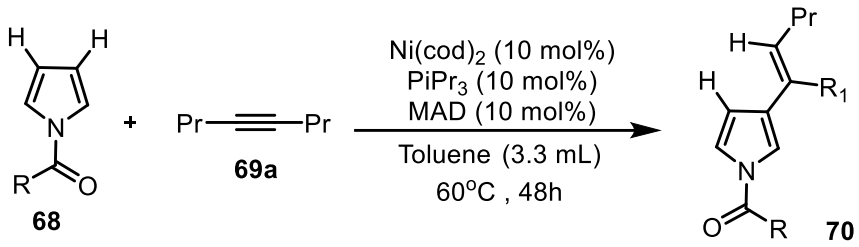
In 2008, Philouze and co-workers described the reaction of steric bulk *N*-TIPS pyrroles **58** with acyclic/cyclic nitrones-**65** as electrophile under acidic conditions lead to gives chiral C3-pyrrolic *N*-hydroxylamine **66** with good to excellent yields. The reaction between glyoxylate-centered chiral nitrones at the C-2 or the C-3 position of the pyrrole nucleus gave *N*-hydroxyamino esters in high yields as single diastereoisomer finally furnish chiral C3-substituted pyrrole **67** (Scheme 1.22).[66]



Scheme 1.22 Synthesis of C3-pyrrolic *N*-hydroxylamine from nitrones.

(B) Use of electron-withdrawing group on pyrrole

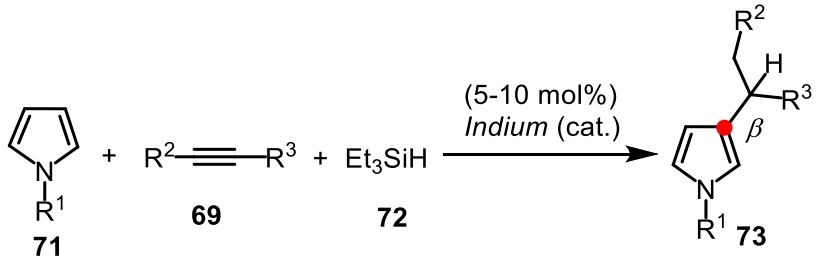
An electron-withdrawing group (EWG) has been placed on pyrrole to direct electrophile at the C3 position for S_EAr reaction. In this direction, Nakao and co-workers revealed nickel/aluminum co-operative catalyzed selective alkylation of *N*-EWG pyrrole **68** with unactivated internal alkynes **69** to furnish C3-substituted pyrrole **70** (Scheme 1.23).[67]



Scheme 1.23 Co-operative catalysis to achieve C3-substituted pyrroles.

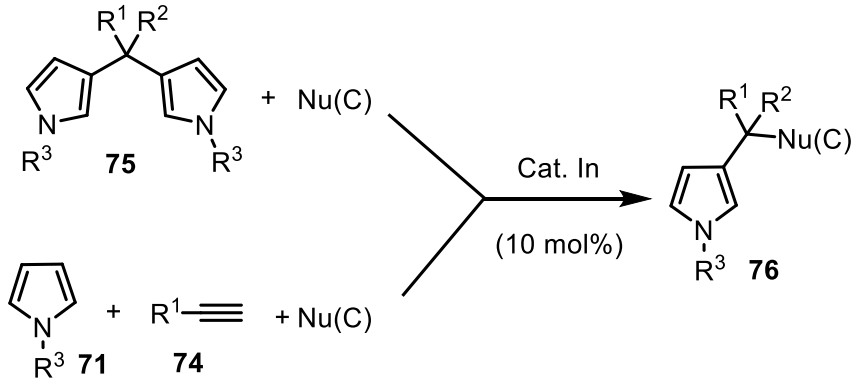
(C) Metal-catalyzed C3-derivatization on *N*-alkyl/*N*-H pyrrole

Tsuchimoto and co-workers have utilized the *N*-alkylated pyrrole extensively for the metal-catalyzed C3-functionalization of pyrrole. In this direction, the first report on $In(NTf_2)_3$ catalyzed, C3-alkylation of N-alkyl pyrrole **71** with alkyne **69** through hydride transfer to introduce alkyl groups onto a *β*-position of pyrroles **73** in a complete regioselective manner through lowering the catalyst loading (Scheme 1.24).[68]



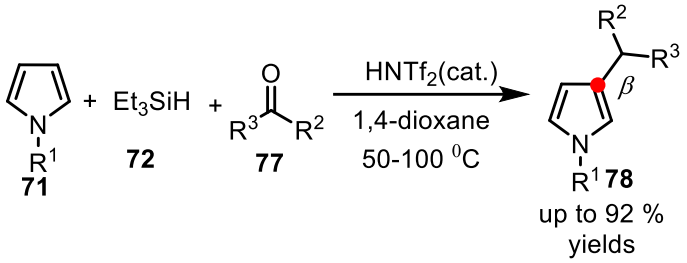
Scheme 1.24 Indium-catalyzed C-H functionalization at the C3-position of pyrrole.

The same group reported a promising method for preparing β-alkylpyrroles without contamination by α-alkylpyrroles using N-substituted pyrroles with carbonyl compounds and nucleophiles under indium catalysis. The selective β-alkylation is attributed to the selective elimination of an α-pyrrolyl group from the dipyrrolylalkane intermediates (Scheme 1.25).[69]



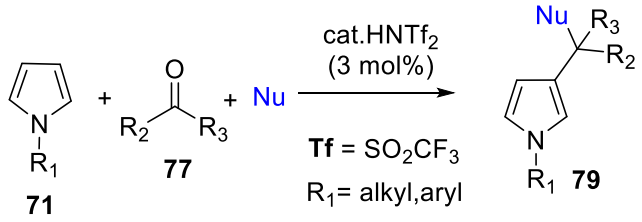
Scheme 1.25 Indium-catalyzed cleavage of *β,β′*-dipyrrolylalkanes into *β*- pyrrolyl.

In 2014, Tsuchimoto and co-workers developed a reductive *β*-alkylation of pyrroles with carbonyl compounds **77**, *N*-pyrrole **71,** and hydrosilanes **72** within sight of a Bronsted acid, trifluoromethane sulfonamide [$HN(SO_2CF_3)_2$] (Scheme 1.26). This metal-free protocol highlights lower catalyst loadings contrasted with the former indium variant and selective preparation of *β*-alkylpyrroles **78** (Scheme 1.26).[70]



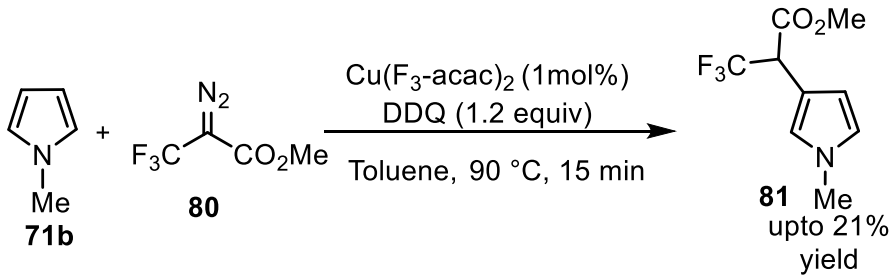
Scheme 1.26 Metal-free selective *β*-alkylation on pyrroles.

In the same year, they elongated their study to synthesize *β*-pyrrolyl nucleophilic tied alkanes **79** using $HNTf_2$ as a catalyst, regioselectively with pyrrole **71**; carbonyl compounds **77** and nucleophile along with hydrosilanes and Bronsted acid (Scheme 1.27).[71]



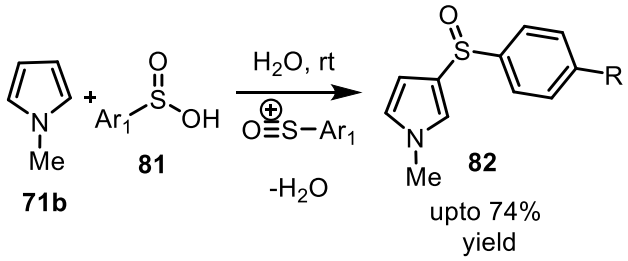
Scheme 1.27 Metal-free access of *β*- pyrrolylalkanes.

In 2015, Osipov and co-workers studied the metal-catalyzed CH-functionalization of pyrrole and its derivatives via the insertion of CF_3-carbene in situ generated from methyl 2-diazo-3,3,3-trifluoropropionate. Copper trifluoroacetonate allows the simultaneous introduction of the trifluoromethyl and carboxylate groups into the pyrrole ring (Scheme 1.28).[72]



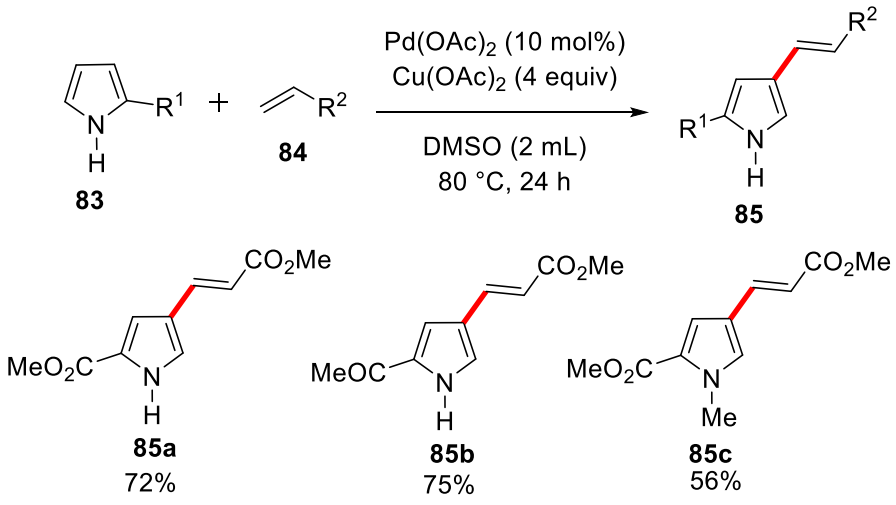
Scheme 1.28 Cu-catalyzed C-H functionalization on pyrrole.

Wang group developed an electrophilic sulfenylation of pyrroles **71b** reacted with aryl sulfonic acid **81** to synthesize C3-aryl sulfinyl pyrroles **82** in an aquatic medium, a simple operational protocol with moderate to good yields (Scheme 1.29).[73]



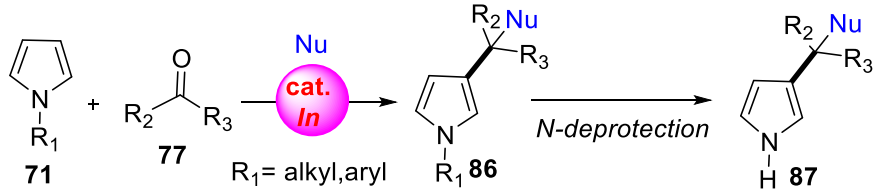
Scheme 1.29 Aqueous medium electrophilic sulfenylation on pyrrole.

In 2017, Laha and partners confirmed for the first time a regioselective C4 alkenylation of free-*NH*-pyrroles **85** with reactive alkenes **84**. A C2 substituent controlled the reaction on free *NH* or *N*-protected pyrroles for regioselective palladation (Scheme 1.30).[74]



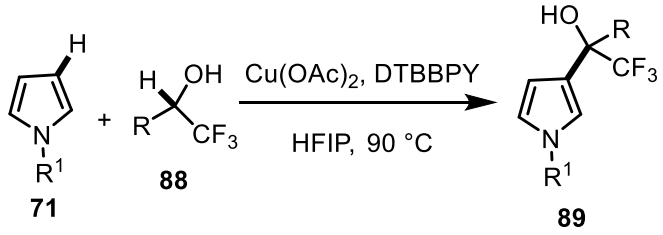
Scheme 1.30 Dual metal Pd (II) and Cu (II) catalyzed coupling reactions.

In 2017, Tsuchimoto *et al*. demonstrated the indium-catalyzed synthesis of *β*-alkylpyrroles **86** and **87** by a combination of *N*-substituted pyrroles **71**, carbonyl compounds **77**, and various nucleophiles. Dipyrrolylalkanes delivered *in situ* from the pyrrole, and carbonyl compounds are chief intermediates. The selective *β*-alkylation is achieved by the selective removal of the *α*-pyrrolyl group from the dipyrrolyl alkane intermediates, and the indium Lewis acid catalyst is irreplaceable for the advancement of both steps (Scheme 1.31).[75]



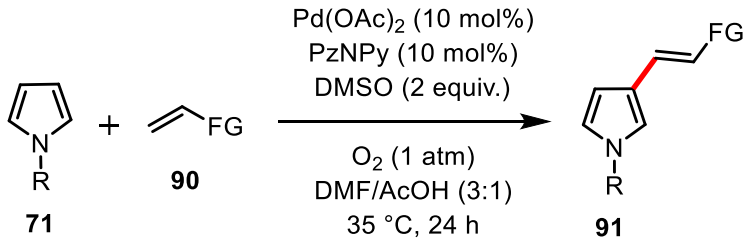
Scheme 1.31 Synthesis of *β*-alkylpyrroles from Indium catalyzed reaction.

In 2020, Jiang and co-workers developed a copper-catalyzed highly regioselective method for functionalizing pyrrole derivatives with fluoro alcohol **88** to construct various functional fluorine-containing building blocks. The reaction mechanism involved the fluoroalcohol oxidation step followed by an electronic addition reaction pathway (Scheme 1.32).[76]



Scheme 1.32 Cu-catalyzed direct C−C coupling reaction of aza-aromatic rings with fluoro alcohols.

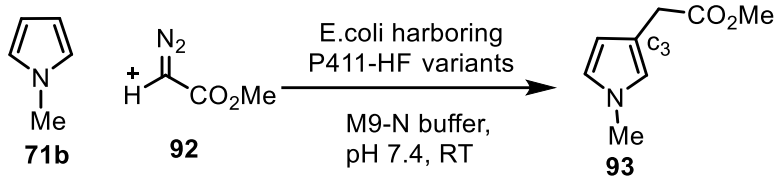
Joo and co-workers reported sterically controlled C–H alkenylations on *N*-substituted pyrrole **71** using $Pd(OAc)_2$ and pyrazolonaphthyridine [Pz(N)Py] as ligands, which led to steric demand for alkenylation **91** at the C3-substituted pyrroles. The steric demand and stable bidentate binding mode of the pyrazolonaphthyridine ligand were critical to the success of these sterically controlled alkenylations using oxygen as an oxidant to yield C3 substituted pyrroles **91** (Scheme 1.33).[77]



Scheme 1.33 Sterically controlled C–H alkenylation of pyrroles and thiophenes

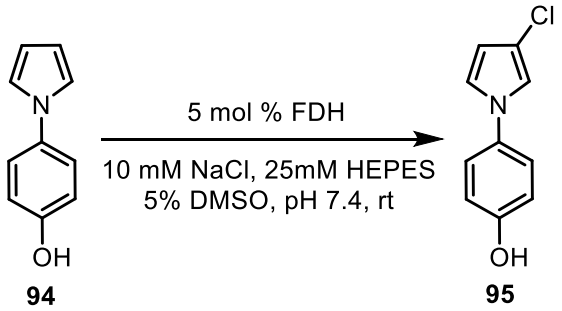
(D) Enzyme Catalyzed C3-selective pyrroles

The *C*3-alkylated product **93** was obtained through preparative-scale whole-cell enzymatic alkylation of 1-methylpyrrole **94b** with methyl 2-diazoacetate **92** using an enzymatic cytochrome P411 variant for carbene transfer to pyrrole (Scheme 1.34).[78]



Scheme 1.34 Cytochrome P411 enzyme catalyzed C3-alkylated product.

In 2017, J.C. Lewis and K.L. Tan. and co-workers described flavin-dependent halogenates (FDHs) enzyme unique scope and selective mono-chlorination of various aromatic and heteroaromatic **94**. A single halogenated product was obtained besides multiple electronically activated sites Scheme 1.35).[79]

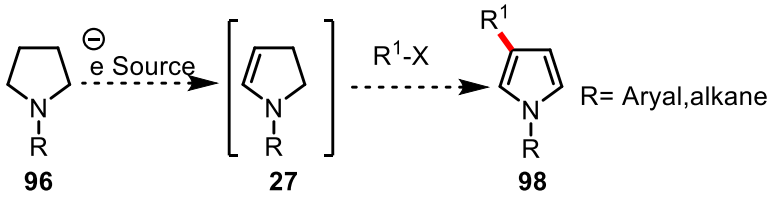


Scheme 1.35 Flavin-dependent halogenates enzyme catalyzed halogenation on pyrrole.

1.3.2.2 Path-II Synthesis of C3-pyrroles from saturated pyrrolidine ring

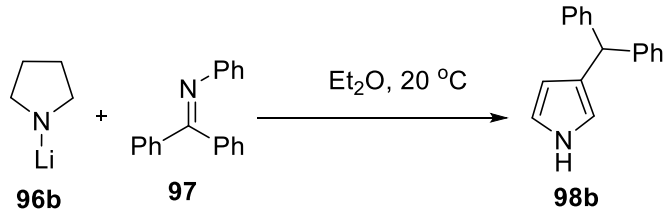
The current functionalization strategy of *N*-substituted pyrrolidine is quite interesting in accessing C3-functionalized pyrrole **98.** Recent reports are available in this direction. The *N*-

substituted tetrahydro pyrrolidine **97** on oxidation gives enamine **97**, which further reacts with aryl/alkyl halides, followed by aromatization furnishes C3 substituted pyrroles **98**. Path-II proceeds through various reaction conditions like free radical, conventional, electrochemical, and photolytic to synthesize *β*-substituted pyrroles/*β,β'*-di-substituted pyrroles (Scheme 1.36).



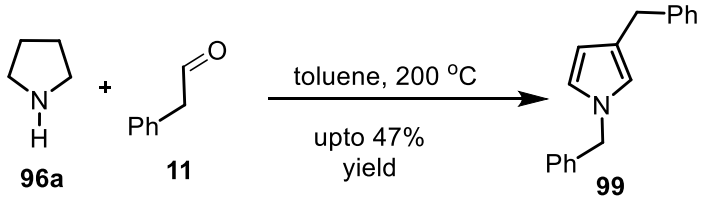
Scheme 1.36 Synthesis of *β*-substituted pyrroles from saturated pyrrolidine.

In 1971, Wittig reported non-directed *β*-C-H functionalization on pyrrolidine to obtain the saturated heterocycles/pyrrole **98b**. *N*-lithiated pyrrolidine **96b,** a charged anion, reacts with triphynylsubstitutent ketamine **97** to form C3 alkylated pyrrole (Scheme 1.37).[80]



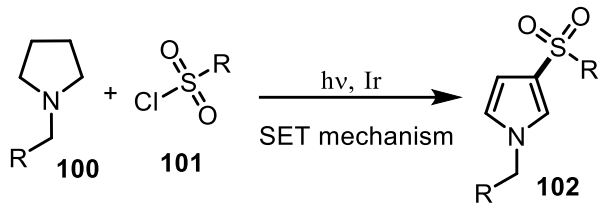
Scheme 1.37 C-H functionalization on pyrrolidine.

After fifty years, in 2009, Bogdal and co-workers extended the same work to achieve 1,3-disubstituted pyrroles by a microwave-assisted reaction of pyrrolidine **96a** and aldehydes **11** in toluene as well as in solvent-free conditions. Reactions get completed in a few minutes in the solvent-free condition but take a long time (up to 30 min) in toluene (Scheme 1.38).[81]



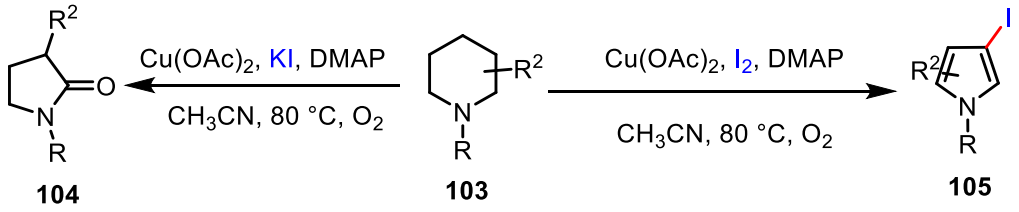
Scheme 1.38 Microwave-assisted *β*-fictionalization on pyrrole.

Rueping and co-workers developed a green and efficient route for synthesizing *β*-substituted pyrroles **102** from inactivated pyrrolidines **100** via an electron acceptor, oxidant-free dehydrogenative aromatization reaction. The mild reaction conditions make this approach an appealing and versatile strategy to functionalize/oxidize pyrrolidines by inserting alkyl/arylsulfonyl at the C3 position of pyrrole (Scheme 1.39).[82]



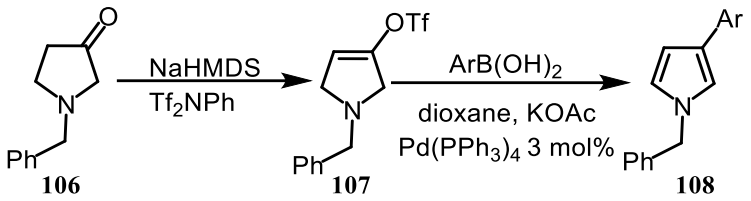
Scheme 1.39 Dehydrogenative aromatization and sulfonylation of pyrrolidines.

In 2019, the Fan group synthesized pyrrolidin-2-ones **104** and 3-iodopyrroles **105** *via* the cascade reactions of *N*-substituted piperidines **103**. Mechanistically, the formation of pyrrolidin-2-ones involves a domino process, including the *in-situ* construction of pyrrolidine-2-carbaldehyde followed by carboxylic acid formation, decarboxylation, and *ipso*-oxidation. On the other hand, 3-iodopyrroles are believed to be formed *via* the initial generation of pyrrolidine-2-carbaldehyde followed by carboxylic acid formation, decarboxylation, dehydrogenation, iodination, and aromatization (Scheme 1.40).[83]



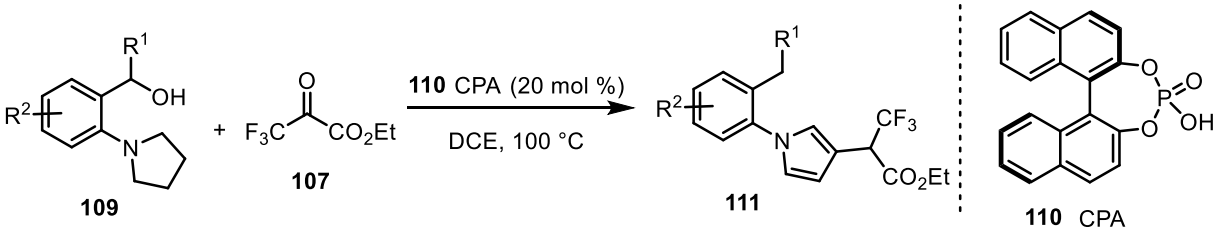
Scheme 1.40 Oxidative transformations on the piperidine.

In 2000, Choung and others developed an efficient method for synthesizing *β*-substituted pyrroles **108** from 1-Benzyalpyrrolidin-3-one **106** in tandem Suzuki dehydrogenation reaction. 1-Benzyalpyrrolidin-3-one **106** reacts with Tf_2NPh in the presence of a base to form Triflic-enolate **107**. It further coupled with aryl-boronic acid in the presence of $Pd(PPh_3)_4$ (3 mol%) as a catalyst in mild reaction conditions to access *β*-arylated pyrrole with moderate to good yield (Scheme 1.41). [84]



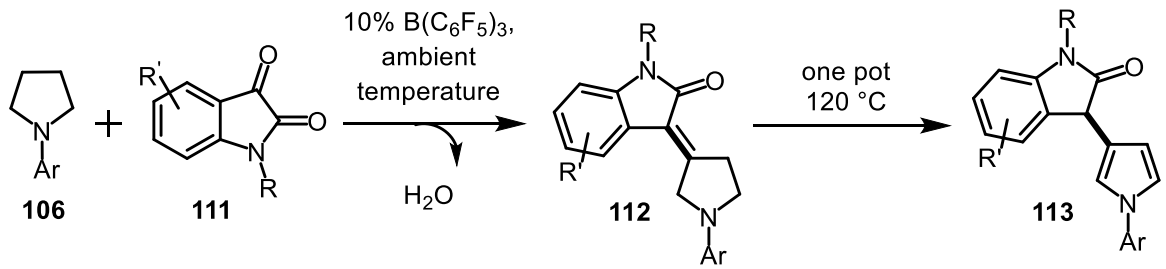
Scheme 1.41 Tandem Suzuki dehydrogenation reaction on 1-Benzyalpyrrolidin-3-one.

In 2020, Xiao's group developed a novel hydride transfer-initiated cascade *β*-functionalization/aromatization reaction on pyrrolidines to construct *β*-substituted pyrroles. A series of *β*-substituted *N*-aryl pyrroles **111** embedded with a trifluoromethyl group have been directly produced from *N*-aryl pyrrolidines **109** and ethyl 3,3,3-trifluoromethyl pyruvate **107**. This protocol represented an outstanding example of an organocatalytic dehydrogenative aromatization reaction (Scheme 1.42).[85]



Scheme 1.42 Functionalization of pyrrolidines *via* hydride transfer transfer-initiated cascade reaction.

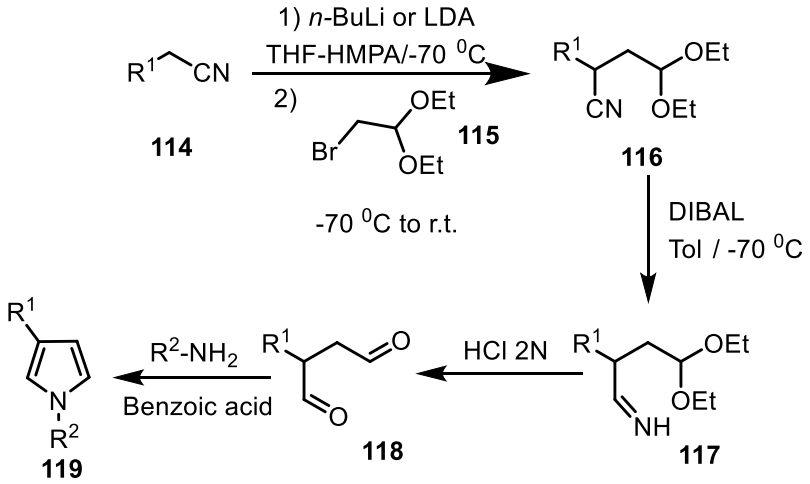
In 2020, Ma *et al.* reported the transition-metal- and oxidant-free straightforward process for *β*-(C−H) functionalization of pyrrolidine **106** to produce C3-substituted pyrroles **113**. Based on the unique catalytic ability of $B(C_6F_5)_3$ in hydrogen transfer, olefination between pyrrolidines **106** and isatins **111** through a borrowing hydrogen process was demonstrated, affording an array of C3-substituted pyrroles in good yields and high Z-selectivity at room temperature. (Scheme 1.43).[86]



Scheme 1.43 $B(C_6F_5)_3$ catalyzed synthesis of *β*-functionalized pyrroles

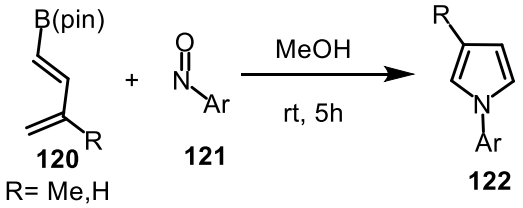
1.3.2.3 Miscellaneous examples as direct de novo synthesis

In 1996, Mendez and co-workers reported a convenient and versatile method for synthesizing monosubstituted succinaldehyde **118** and C3-substituted pyrroles from acetonitriles **114**. The reaction proceeds through multiple steps to obtain C3-substituted pyrroles (Scheme 1.44).[87]



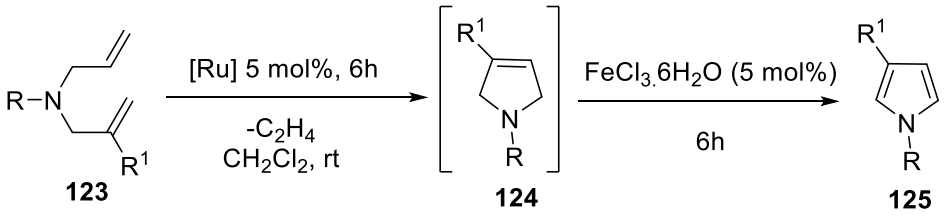
Scheme 1.44 *β*-functionalized pyrroles from substituted acetonitrile **114**.

In 2015, Whiting and group members proposed a new way to synthesize the regioisomeric and C3-substituted pyrrole **122** by a one-pot hetero-Diels-Alder reaction. *N*-aryl pyrroles resulted from [4+2] aza-Diels-Alder reaction between 1,3-phenylboronic esters **120** and nitrosoarenes **121** in good to excellent yields (Scheme 1.45).[88]



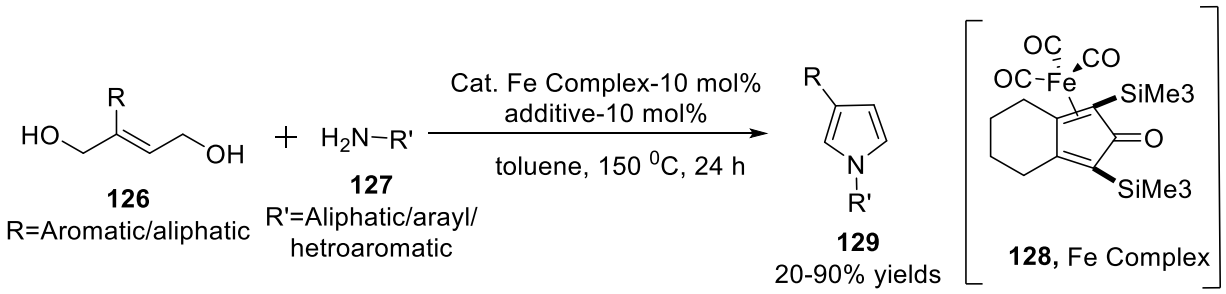
Scheme 1.45 aza-Diels-Alder reaction to synthesize *β*-substituted pyrrole.

In 2016, Samec and a co-worker mentioned a multi-step and pot-economic way to synthesize *β*-substituted pyrroles from amines and allylic alcohols, which includes Pd catalyzed synthesis of unsymmetrical diallylated amines **123** followed by Ru-catalyed ring-closing metathesis to form intermediate **124** and further Fe-catalyzed aromatization to give C3-substituted Pyrroles **125** (Scheme 1.46).[89]



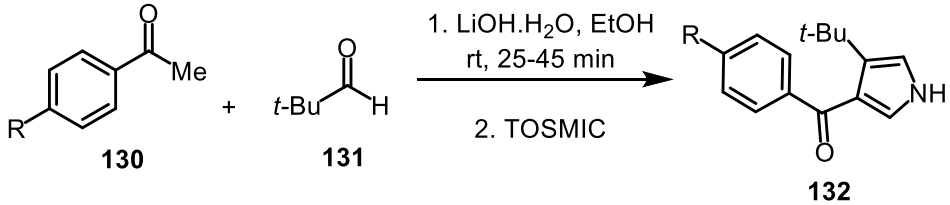
Scheme 1.46 Ru-catalyzed ring-closing metathesis followed by Fe-catalyzed aromatization to obtain *β*-substituted pyrroles.

In 2016, Sundaraju and co-workers invested access to C3- and *N*-substituted pyrrole **129** using (*E*)-2-phenylbut-2-ene-1,4-diol **126** and aliphatic, aromatic/heteroaromatic amine **127** as a model substrate along with the catalytic amount of [Fe]-catalyst and Me_3NO as an additive (Scheme 1.47)**.**[90]



Scheme 1.47 Iron-complex catalyzed selective *β*-substitution on pyrrole.

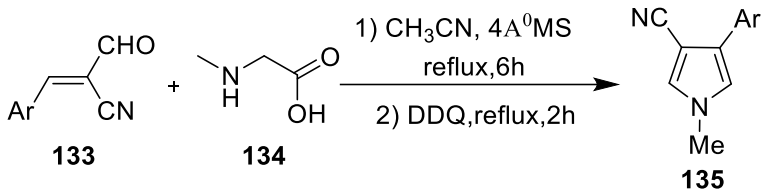
In 2018, Kaur and co-workers developed a one-pot synthesis of 3,4-disubstituted pyrrole **132** from acetophenone **130** and tri-methylacetaldehyde **131** using TOSMIC anion by lithium hydroxide in ethanol (Scheme 1.48).[91]



Scheme 1.48 Direct access of 3,4-disubstituted pyrroles.

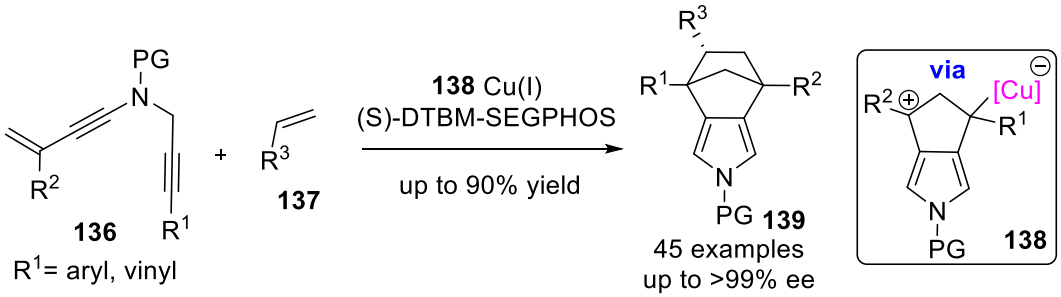
In 2018, Rao and co-workers developed simple oxidative cyclization to synthesize C3-substituted pyrroles **135** using mild reaction conditions. Azomethine ylides are *in-situ* generated

and undergo an intermolecular cycloaddition reaction to form pyrrole **135** in good yields (Scheme 1.49). [92]



Scheme 1.49 Oxidative cyclization for the synthesis of C3-substituted pyrroles.

Recently, Long and co-workers demonstrated the first asymmetric vinylic C–H functionalization through copper-catalyzed endocyclic cyclopentannulation of alkenyl diynes **136** with styrene **137** followed by formal [3 + 2] cycloaddition to access chiral pyrrole-fused bridged [2.2.1] skeletons **139** (Scheme 1.50).[93]



Scheme 1.50 Formal [3 + 2] cycloaddition to access chiral pyrrole-fused bridged [2.2.1] skeletons.

1.4 Conclusion

This Ph.D. thesis work aims to enhance the scope of the *de nova* approach to get pyrrole type reaction to synthesize tethered molecule with a C3-pyrrole motif followed by the Paal Knorr reaction. The synthesis of five-membered nitrogen heterocycles reveals their biological importance and presence in many natural products.

This chapter provides a brief introduction and history of the pyrrole-containing molecules synthesis method. In that multi-component one-pot, domino/cascade reaction could be a dominant route for synthesizing nitrogen-heterocyclic compounds asymmetrically and non-asymmetrically. Also, focus on involving succinaldehyde (1,4-dicarbonyl compound) with various amine sources followed by Paal Knorr reaction. The literature has disclosed the

applications of nitrogen-containing heterocycles in diverse scientific disciplines. Therefore, synthesizing fused heterocyclic libraries consisting of extremely precious five-membered scaffolds is highly demanding. In this direction, the strategy was developed commercially available inexpensive starting substrates such as succinaldehyde, various electrophiles with several *N*- Aromatic/heteroaromatic, aliphatic, and ammonium acetate as amine sources to produce pyrrole tethered with electrophiles regiospecifically and exhibited their biological activities. Besides this, metal-catalyzed, metal-free, and secondary amine organocatalysis is also an innovative part of the thesis that eliminates the use of hazardous and costly reagents in previous methods. This thesis work extensively utilized succinaldehyde via direct catalyst aldol reaction followed by Paal-Knorr reaction to furnish C3-substituted pyrrole in a non-asymmetric/asymmetric fashion.

1.5 References

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Chapter 2

Lewis-acid Catalyzed Synthesis of Pyrroles tethered with Oxindole at the C3-position

2.1 Introduction:

Nitrogen heterocycles are probably more in number among the entire heterocyclic scaffold present in nature. Pyrrole derivatives are essential for the progress of many branches of science, including biology, pharmacology, material sciences, agrochemicals, dyes, photographic chemicals, perfumes, and other organic compounds.[1-4] Pyrrole nucleus is widespread and is the critical structural fragment of many important bioactive molecules such as pentabromopseudodiline and pioluteorine, both isolated from bacterial sources prominent in marine natural products.[5] Ningalins and Lamellarins are a wide variety of anticancer drugs, antibiotics, and protease inhibitors,[6] showing multidrug resistance reversal activity against L1210 and HCT116 cell lines.[7] Nakamuric acid, axially chiral marinopyrroles, which showed good activity against methicillin-resistant staphylococcus aureus strains, the bacterial red pigment.[8] Prodigiosin, synthesized by bacteria belonging to the Serratia genus, has antibiotic properties.[9] Lamellarins K and L possess biological activities, which include cytotoxicity, HIV-1 integrase inhibition, and multidrug resistance reversal.[10] Storniamide family, isolated from various marine organisms (mollusks, ascidians, sponges) and containing 3,4-diarylpyrrole fragments showing potent activity as inhibitors of the multidrug resistance (MDR) phenomenon,[11] which can be considered as the main obstacle to successful anticancer chemotherapy. Besides the classic example of the tetrapyrrole nucleus of the porphyrins and hemoglobin, pyrrole substructures are present in many bioactive compounds. They have been proven to display a variety of physiological activities[12] including HIV fusion inhibitors,[13] anti-tubercular,[14] antibacterial,[15] antiviral,[16] anti-inflammatory,[17] and to inhibit cytokine-mediated diseases.[18] Additionally, they have been found to show potent inhibiting platelet aggregation[19] and hypertensive activities;[20] an excellent example for this case is atorvastatin calcium, the active material of a famous drug named “Atorvastatin” (produced by Pfizer drug company), this drug has cholesterol-lowering activity in blood. Tetra-aryl pyrroles were discovered to have great potential application in materials chemistry, showing the existence of semiconducting materials derived from hexa-(*N*-pirrolyl) benzene,[21] glucose sensors based on polypyrrole-latex materials[22] and polypyrrole materials for the detection and discrimination of volatile organic compounds.[23] Derivatives of the 4, 4-difluoro-4-boradipyrrin system (BODIPY) have strong absorption in the UV and emit very intense fluorescence. Nowadays, the compounds have many applications, including chemo sensors, laser manufacture, image diagnosis, etc.[24] Pyrrole is a basic unit in numerous natural

products, [25] pharmaceutical,[26] and functional materials.[27]

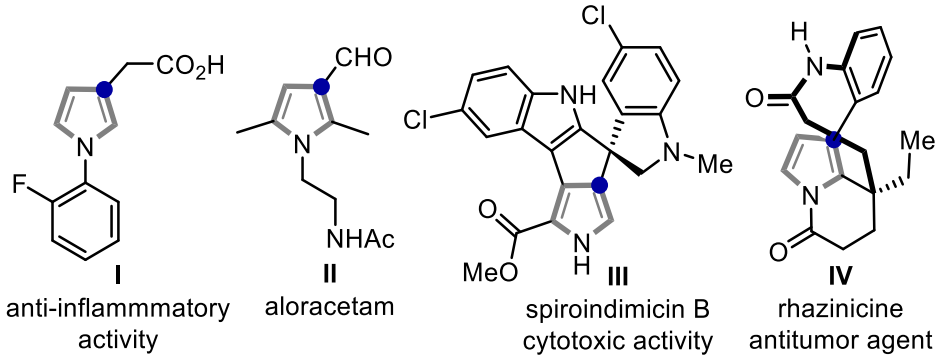
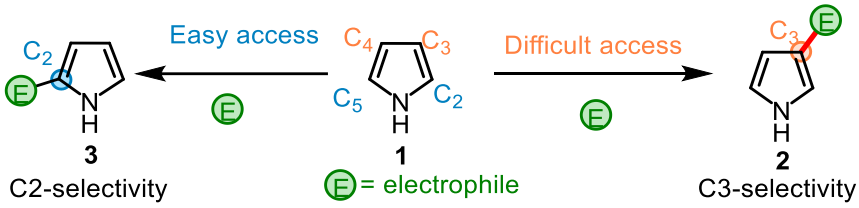


Figure 2.1 Representative examples of β-functionalized pyrroles-derived bioactive compounds.

Anti-inflammatory activity tolmetin; Aloracetam for treatment of Alzheimer's disease; Spiroindimicin B cytotoxic activity, Rhazinicine antitumor agent, Lamellarins and Ningalins are a large variety of antibiotics protease inhibitors and anticancer drugs. Several naturally manufactured molecules have pyrroles, such as vitamin B_{12}, Bile pigments like bilirubin, biliverdin, and porphyrinogens, porphyrins of heme, bacteriochlorins, chlorophyll, and chlorins.[28] Consequently, the synthesis of functionalized pyrrole is of continued interest, including metal-catalyzed reactions,[29] multicomponent reactions,[30] and classical techniques.[31]

2.2 Selective functionalization of pyrroles

Due to their intrinsic reactivity, pyrroles usually undergo electrophilic substitution at C2 or C5; several methods are reported in this direction. Bringing the substitution at the β-position (C3 or C4) appears difficult due to lower nucleophilicity (Scheme 2.1), and alternative strategies are developed in this direction.

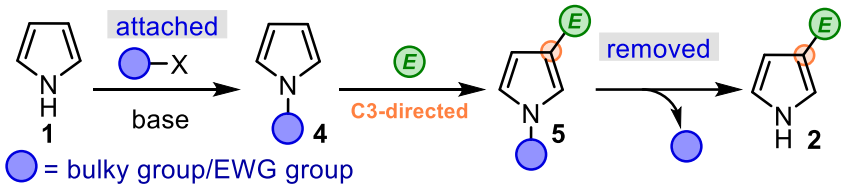


Scheme 2.1 Reactivity strategy of pyrrole for electrophilic substitution.

2.2.1 Approach for selective C3-functionalization of pyrroles

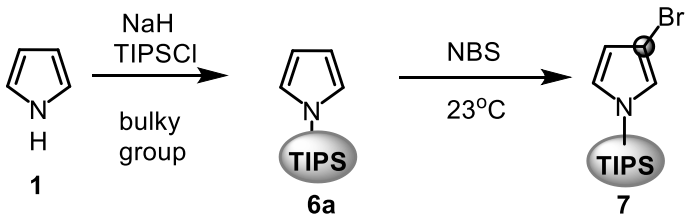
The selective functionalization on pyrrole at position C3 requires a well-designed strategy using pre-functionalized pyrrole either at the N-, or C-positions of pyrrole with the electronically bulky group or electron withdrawing group. The substitution pattern in pyrrole can be controlled by factors other than reaction conditions. The standard technique

is the introduction of (temporary) substituents, which can influence the direction of substitution either by electronic or steric effects. Several methods have been reported in this direction and discussed in Chapter **1** of the thesis. Notably, the selective access to C3-substituted pyrrole is often challenging to realize. The interest in the C3-functionalized pyrroles not only stems from their embedding in several natural products,[32] functional materials,[33] but also serve as suitable precursors to access other bioactive compounds.[34] Access to the C3-substituted pyrrole unit mainly relied on using functionalized pyrrole, either with the electron-withdrawing[35,36] or sterically bulky[37] groups to adjust incoming electrophile; however, the additional steps are required to remove the directing group (Scheme 2.2).



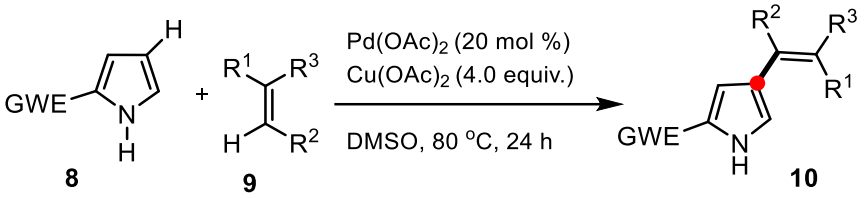
Scheme 2.2 Multistep synthesis of (C3)-functionalized pyrrole.

Additional approaches have been developed to access C3-functionalized pyrrole, including metal-catalyzed C-H functionalization,[38] C3-alkylation using *N*-alkyl pyrroles, [39] and others.[40] The use of sterically bulky triisopropyl silyl (TIPS) as protecting group on the nitrogen of pyrrole **1** was extensively explored by Muchowski and coworkers to bring various electrophiles at the C3-position of pyrrole. In this direction, N-bromosucclinamide (NBS) was used for the selective C3-bromination of *N*-TIPS pyrrole **7** (Scheme 2.3).[41] similar approaches were developed to bring other electrophiles to access C3-functionalized pyrrole by following the same strategy.[42-43]



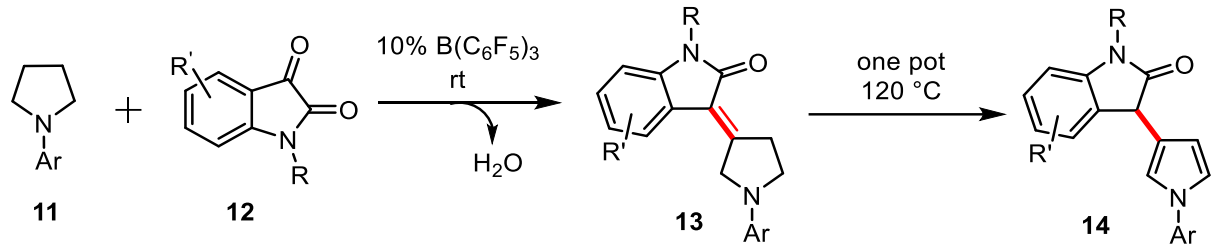
Scheme 2.3 Selective bromination on C3-pyrroles using *N*-bromosuccinimide.

In 2017, Laha and co-workers developed a regioselective metal-catalyzed oxidative C−H alkenylation of free (*N*H)-pyrroles **8**, decorated with C2-electron withdrawing group, with alkenes **9** to afford 4-alkenylated (*N*H)-pyrroles **10** in good to excellent yields (Scheme 2.4).[44]



Scheme 2.4 Oxidative C−H alkenylation on free NH-pyrrole.

Recently, Ma and coworkers reported a straightforward method for the transition metal-free and oxidant-free C−H functionalization of *N*-aryl pyrrolidine **11** with isatins **12** by exploiting the unique catalytic ability of $B(C_6F_5)_3$ in hydrogen transfer reaction to produce C3-substituted pyrroles **14** in good yields at room temperature (Scheme 2.5).[45]

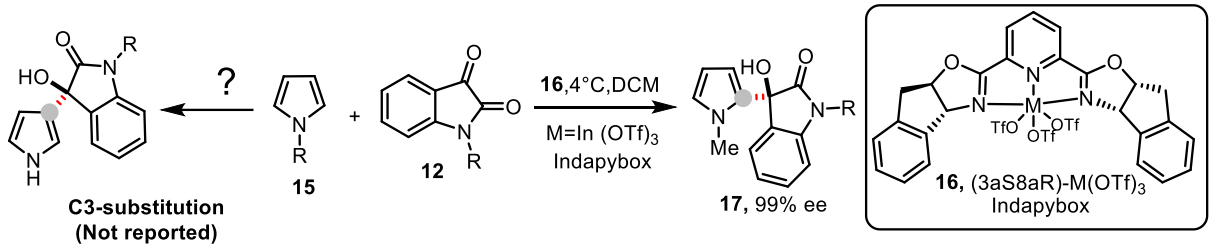


Scheme 2.5 $B(C_6F_5)_3$-Catalyzed *β*-Functionalization of Pyrrolidines.

2.2.2 Synthesis of chiral C2-hydroxyl-oxindol tethered pyrroles

The electrophilic attack on pyrrole without prior deprotonation occurs predominantly at the ring carbons rather than at the nitrogen. In general, an electrophilic attack at the *α*-position is kinetically preferred over the attack at the *β*-position. The asymmetric transformation of pyrrole through the S_EAr reaction also furnishes the product at the C2 position. In this context, asymmetric catalytic synthesis of C2-substituted pyrrole **17** (up to 99% ee) tethered with oxindole was recently developed by Fran and coworkers using chiral In(III)-catalyst **16** with complete regioselectivity (Scheme 2.6).[46] Whereas, the synthesis of a similar compound

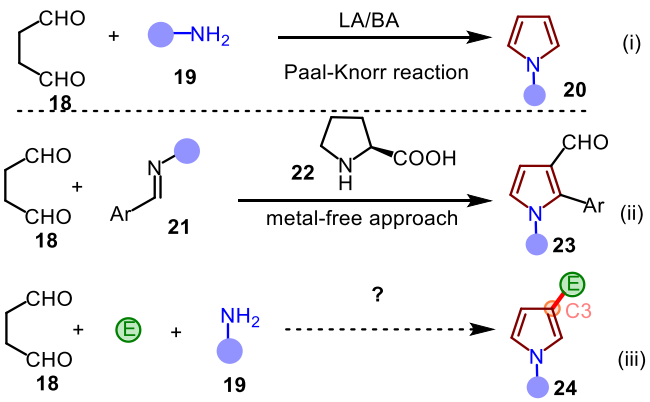
ethered at the C3-position is not reported, as far as we know. Thus, developing a method in this direction to access C3-substituted pyrrole tethered with oxindole is highly interesting.



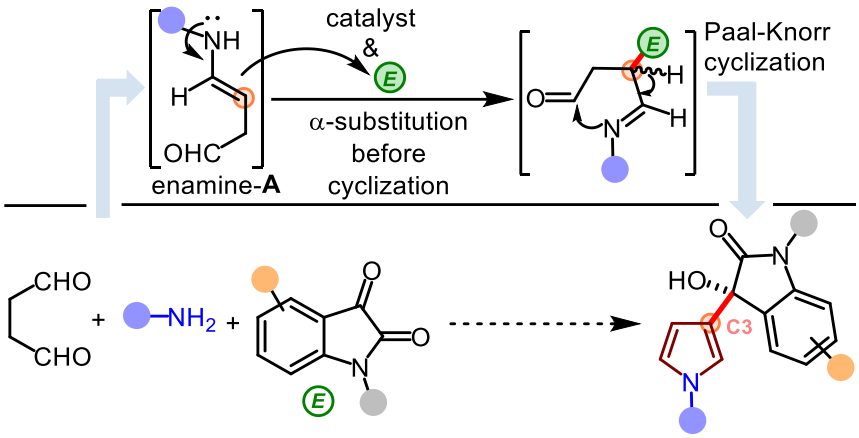
Scheme 2.6 In(III)-catalyzed synthesis of chiral C2-hydroxyl-oxindole pyrrole.

2.2.3 Our hypothesis of the present work

In the previous section, we have given a brief idea about the methods reported for synthesizing C3-substituted pyrrole, and the details of related methods have already been discussed in Chapter 1. Significant synthetic efforts have been directed to access C3-functionalized pyrrole from pre-functionalized pyrrole; however, the reported approaches have one or more drawbacks, such as requiring specially designed substrates, multistep processes with low yields, and harsh reaction conditions. Thus, developing a modular and straightforward pot-economic protocol to access strategically access readily substituted pyrrole from easily available materials till in high demand. For many reasons, Paal–Knorr reaction[47] is still the most convenient way to access pyrrole from 1,4-dicarbonyls under acidic conditions (Scheme 2.7(i)). Recently, our group devised a direct method for synthesizing functionalized pyrrole from succinaldehyde, and imine, an alternative to the Paal-Knorr reaction (Scheme 2.7(ii)).[48] Taking the idea from our previous work, we envision using suitable electrophiles along with succinaldehyde and amine so access C3-substituted pyrrole directly (Scheme 2.7(iii)).



Scheme 2.7 Our initial idea was to access C3-pyrrole directly from 1,4-dicarbonyls.



Scheme 2.8 Direct access to *β*-(C3)-functionalized pyrrole.

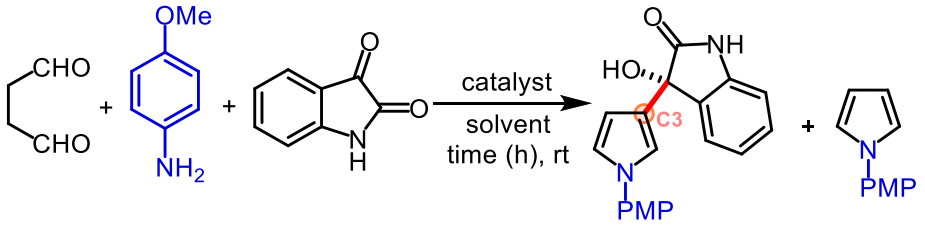
The present hypothesis could rely on the utilization of intermediate enamine-A, *in situ* generated through the condensation of succinaldehyde with an amine, with a suitable electrophile for the α-substitution,[49-50] before Paal-Knorr reaction, to furnish *β*-functionalized pyrrole (Scheme 2.8). Our previous efforts to functionalize pyrroles using 1, 4-dicarbonyls encouraged us to explore this idea. The pyrrole reaction on isatine was only known in the C2 position (Scheme 2.6), but the C3-hydroxyl-oxindole tethered pyrroles are not reported so far. We think of using isatin as a suitable electrophile, harvesting the reactivity of enamine before the Paal-Knorr cyclization reaction.

2.3 Results and discussion

Based on our hypothesis, we commenced the multicomponent investigation using aqueous succinaldehyde **18**, *p*-anisidine **19a**, and isatin **12a** as suitable electrophiles (Table 2.1). An initial attempt using TFA (10 mol%) in DMSO at room temperature delivered the desired product **24aa** with low yield (entry 1, Table 2.1). An improvement in the reaction yield (35%, entry 2, Table 2.1) and (47%, entry 3, Table 2.1) was observed using catalytic acetic acid and $Yb(OTf)_3$ in DMSO, respectively. Next, varying the solvents like Toluene, CH_3CN, THF, DMF, and CH_2Cl_2 failed to improve the reaction yields (entries 4-8, Table 1), increase in reaction time and catalyst 20 mol% furnished the product with low yield (entry 9, Table 2.1). Pleasingly, compound **24aa** was obtained with 81% yield in EtOH using $Yb(OTf)_3$ (10 mol%) (Entry 10, Table 2.1), also screened with different Lewis acids like $Zn(OTf)_3$, $Cu(OTf)_3$, $Sc(OTf)_3$,

$Bi(OTf)_3$, $BiCl_3$, $BiBr_3$, $YbCl_3.6H_2O$, $In(OTf)_3$, and $InCl_3$ lead to poor results between 48-68% yield (entry 11-19, Table 2.1). Variations in catalyst loading $Yb(OTf)_3$ (5 mol%) and also Yb $(OTf)_3$ (15 mol%) did not provide an improvement in yield. No desired product was observed without a catalyst (entry 22, Table 2.1); also, the bronsted acid like Acetic acid and *p*-Toluene sulphonic acid in EtOH did not improve yield 25 and 31%, respectively (entry 23-24, Table 2.1). The best result concerning the reaction yield was obtained in entry 10 (Table 2.1).

Table 2.1 Optimization of reaction conditions[a]



18 **19a** **12a** **24aa** **25a**

Entry	Solvent	Catalyst (mol%)	Time	Yield (%)[b& c]
1	DMSO	TFA (10)	10	20
2	DMSO	AcOH (10)	24	35
3	DMSO	$Yb(OTf)_3$ (10)	16	47
4	Toluene	$Yb(OTf)_3$ (10)	24	<10
5	CH_3CN	$Yb(OTf)_3$ (10)	20	35
6	THF	$Yb(OTf)_3$ (10)	14	42
7	DMF	$Yb(OTf)_3$ (10)	16	30
8	CH_2Cl_2	$Yb(OTf)_3$ (10)	16	45
9	THF	$Yb(OTf)_3$ (20)	24	38
10	**EtOH**	**$Yb(OTf)_3$ (10)**	**12**	**81**
11	EtOH	$Zn(OTf)_2$ (10)	18	48
12	EtOH	$Cu(OTf)_2$ (10)	18	42
13	EtOH	$Sc(OTf)_3$ (10)	16	62
14	EtOH	$Bi(OTf)_3$ (10)	16	45
15	EtOH	$BiCl_3$ (10)	16	49

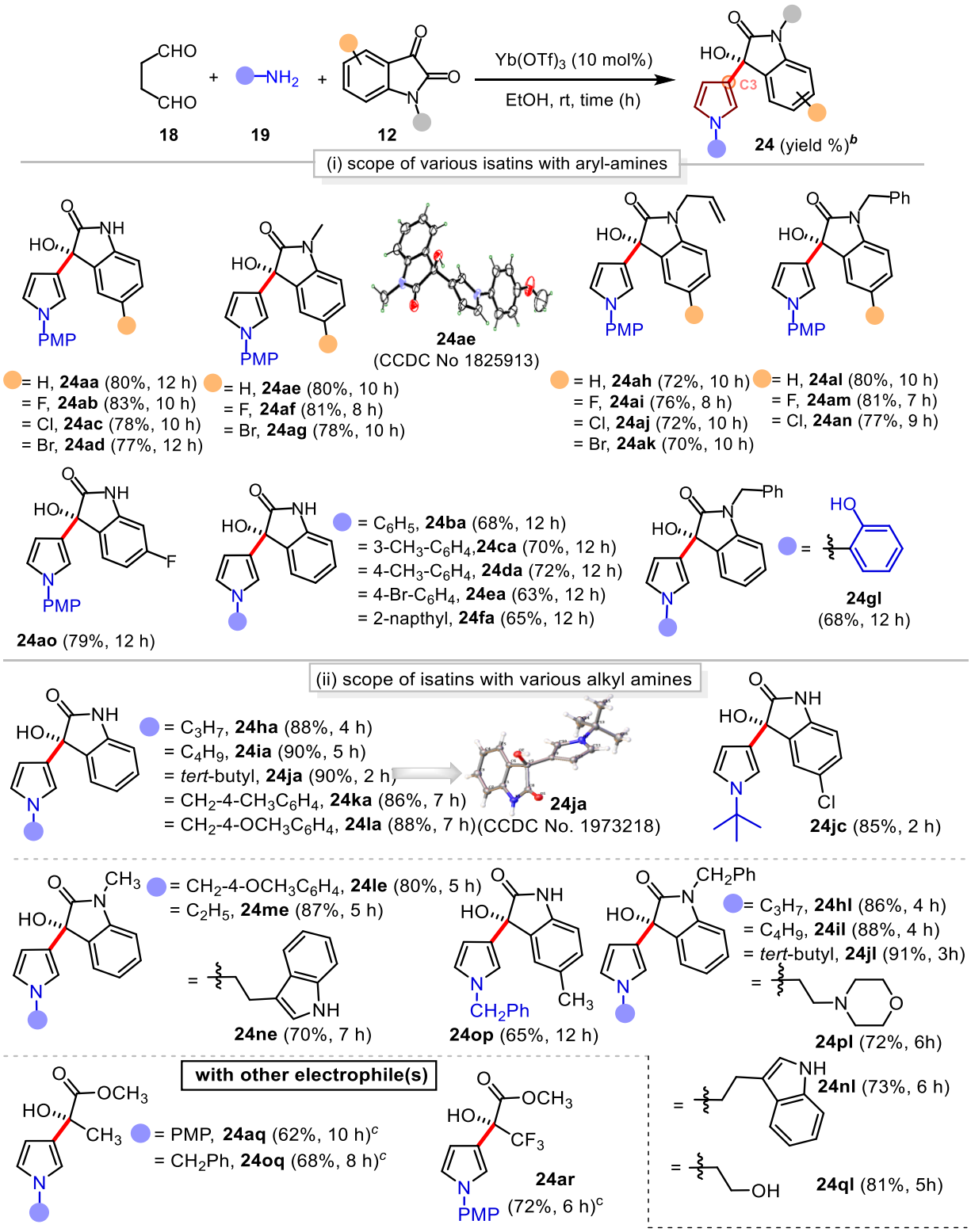
16	EtOH	$BiBr_3$ (10)	18	43
17	EtOH	$YbCl_3.6H_2O$ (10)	12	64
18	EtOH	In(OTf)3 (10)	16	50
19	EtOH	$InCl_3$ (10)	18	55
20	EtOH	$Yb(OTf)_3$ (5)	18	75
21	EtOH	$Yb(OTf)_3$ (15)	8	79
22	EtOH	No catalyst	24	Trace
23	EtOH	TFA (10)	24	26
24	EtOH	AcOH (10)	24	31

[a]Unless otherwise indicated, the reaction was carried out with succinaldehyde **18** (3.0 M sol, 0.6 mmol), *p*-anisidine **19a** (0.3 mmol), Isatin **12a** (0.3 mmol), Catalyst (10 mol %), Solvent (3.0 mL), rt.[b]Isolated yield of **24aa** refers to **12a** [c](≤10% of Paal-Knorr reaction *N*-PMP-pyrrole **25a** was also obtained).

With the optimal conditions in hand, we examine the scope of the reaction with various amines and isatins (Table 2.2). A broad range of electronically differentiated isatins **12a-12o** was used for reaction with aqueous succinaldehyde **18** and *p*-anisidine **19a** to furnish corresponding C3-pyrroles (**24aa-24ao**, 70-83% yields). Suitably substituted and alkyl-protected (Me, allyl, benzyl) isatins were well tolerated and potentially allowed for further functionalizations. Besides, other aromatic amines were employed successfully to furnish similar products **24ba**-**24fa** and **24gl** in good yields. Next, various alkylamines were examined with varying isatins; interestingly, alkylamines emerged as a better substrate than aryl-amines and took less time for reaction completion. A wide range of alkyl amines was successfully applied to furnish the corresponding pyrroles (**24ha**-**24ql**, Table 2.2) in excellent yields (up to 91%). Sterically bulky *tert*-butyl amine **19j** furnished products **24ja** (90% yield) and **24jm** (91% yield), while bio-relevant alkylamines (**22n** and **22o**) and unprotected polar functional amine (**22q**) gave related products **24ne, 24nl, 24pl,** and **24ql** respectively, in high yields. Notably, isatins protected with electron-withdrawing groups, such as Ts, Cbz, and Bz, failed to give the expected product, and corresponding imines condensed with primary amine were obtained, probably due to the high reactivity of isatin. The single-crystal X-ray analysis further confirmed the structure of **24ae** and **24ja**.[51]Besides, methyl

pyruvate **12q** and corresponding.

Table 2.2 Reaction scope with various primary amines **19** and substituted isatins **12**

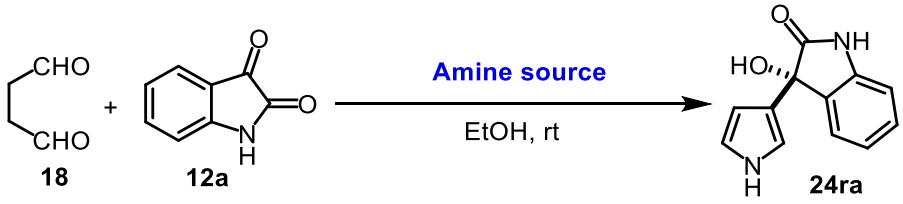


[a]Unless otherwise indicated, the reaction was carried out with succinaldehyde **18** (3.0 M sol, 0.6 mmol), amine **19** (0.3 mmol), isatin **12** (0.3 mmol), $Yb(OTf)_3$ (10 mol%), EtOH (3.0 mL), rt, 22-12 h. [b]Isolated yields of **24** refer to **12**. (≤10% of N-H/Ar/Alkyl-pyrrole **25** was also obtained in all the cases via the Paal-Knorr reaction).

Trifluoro-compound **12r** was also examined as a suitable electrophile with aryl/alkyl-amine and furnished corresponding *β*-substituted pyrroles **24aq** (68%), **24oq** (68%), and **24ar** (72%) under optimized conditions (Table 2.2).

Next, we get excited to explore the direct synthesis of the C3-substituted free-NH-pyrrole instead of aliphatic and aromatic amines; we screen the different ammonia sources. For this purpose, we examined NH_4OAc, aqueous ammonia, and NH_4Cl as amine sources and observed the respective product **24ra** formation (Table 2.3). Varying amounts of NH_4OAc, furnish products with 55%-71% yields (Table 2.3, entries 1-3). The generation of the product was not observed without a catalyst (Table 2.3, entry 4). Besides, other amine sources like aqueous ammonia and NH_4Cl did not furnish improved results (Table 2.3, entries 5-7). Thus, we prefer to perform the reaction with optimized conditions ((Table 2.3, entry 2). These preliminary results for the direct access to β-functionalized free NH-pyrrole are novel. They offer an opportunity to stitch other functionality at this position.

Table 2.3: Study for the reaction between succinaldehyde **18** and isatin **12a** with NH_4OAc as an amine source

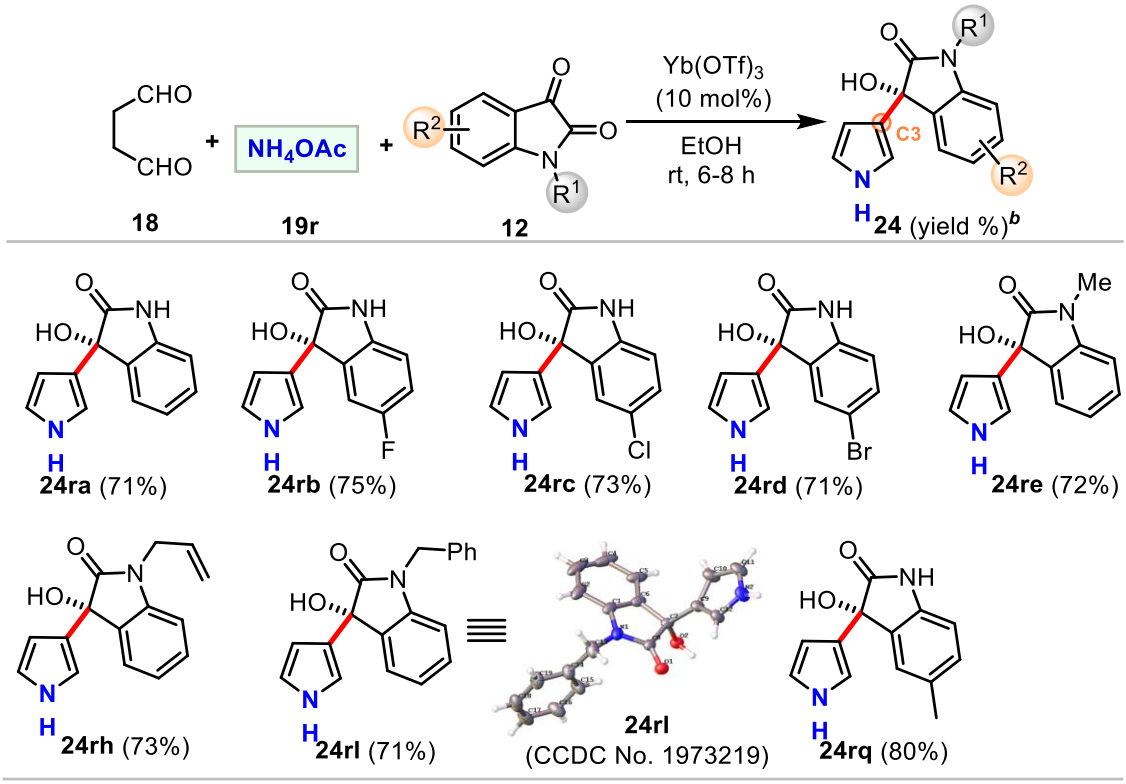


Entry	Amine source**19r-t**	Catalyst (10 mol%)	Time (h)	Yield **24aa** (%)
1	NH_4OAc (1.0 equiv.)	$Yb(OTf)_3$	18	55
2	**NH_4OAc (2.0 equiv.)**	**$Yb(OTf)_3$**	**12**	**71**
3	NH_4OAc (3.0 equiv.)	$Yb(OTf)_3$	10	71
4	NH_4OAc (2.0 equiv.)	No catalyst	24	35
5	Aq. NH_3 (3.0 equiv.)	$Yb(OTf)_3$	24	30

6	Aq. NH_3 (3.0 equiv.)	No catalyst	24	-
7	NH_4Cl (2.0 equiv.)	$Yb(OTf)_3$	12	-

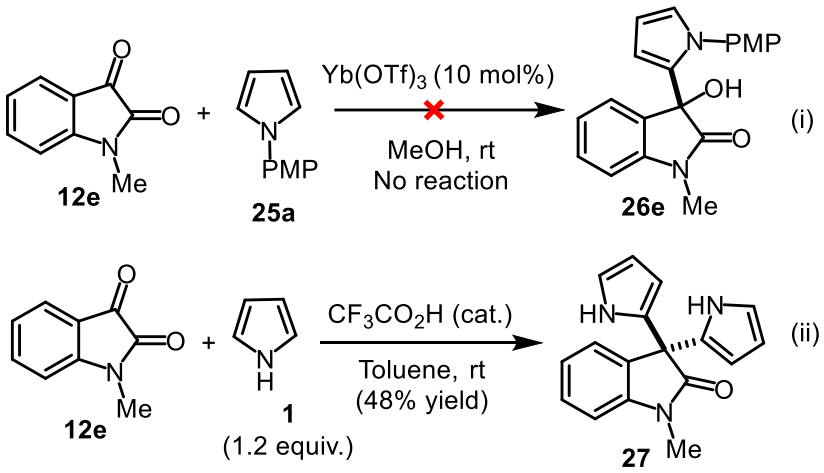
Pleasingly, NH_4OAc **19r** (2.0 equiv.) with aqueous succinaldehyde **18** and various isatin **12** furnished the corresponding free *N*-H pyrroles **24ra-24re**, **24rh**, **24rl**, and **24rq** in good to high yields (up to 80%) (Table 2.4). Different substituents (F, Cl, Br, CH_3) at the C5-position of the isatin and N-alkyl substitutions (Me, allyl, benzyl) were also examined to give similar products. The single-crystal X-ray analysis confirmed the structure of compound **24rl**.[51]These preliminary results for the direct access to β-functionalized free NH-pyrrole in a multicomponent fashion are novel and present an opportunity to stitch other functionality at this position in a simple way.

Table 2.4 Reaction scope of various isatin with NH_4OAc (**19r**)



[a]Unless otherwise indicated, the reaction was carried out with succinaldehyde **18** (3.0 M sol, 0.6 mmol), NH_4OAc **19r** (0.45 mmol), isatin **12** (0.3 mmol), $Yb(OTf)_3$ (10 mol%), EtOH (3.0 mL), rt, 4-8 h. [b]Isolated yields of **24** refer to **12**.

A separate set of model reactions between isatin and performed pyrroles were considered to find more information about the reaction pathway. The result between **12e** and N-PMP pyrrole **25a** under similar conditions failed to give C2-substituted pyrrole **26e** (Scheme 2.9(i)). At the same time, bis-pyrrole-indolin-2-one **27** was obtained as the first product for a reaction between **12a** and pyrrole **1** under acidic conditions (Scheme 2.9 (ii)). These two initial results verify the involvement of enamine intermediate in the developed protocol.

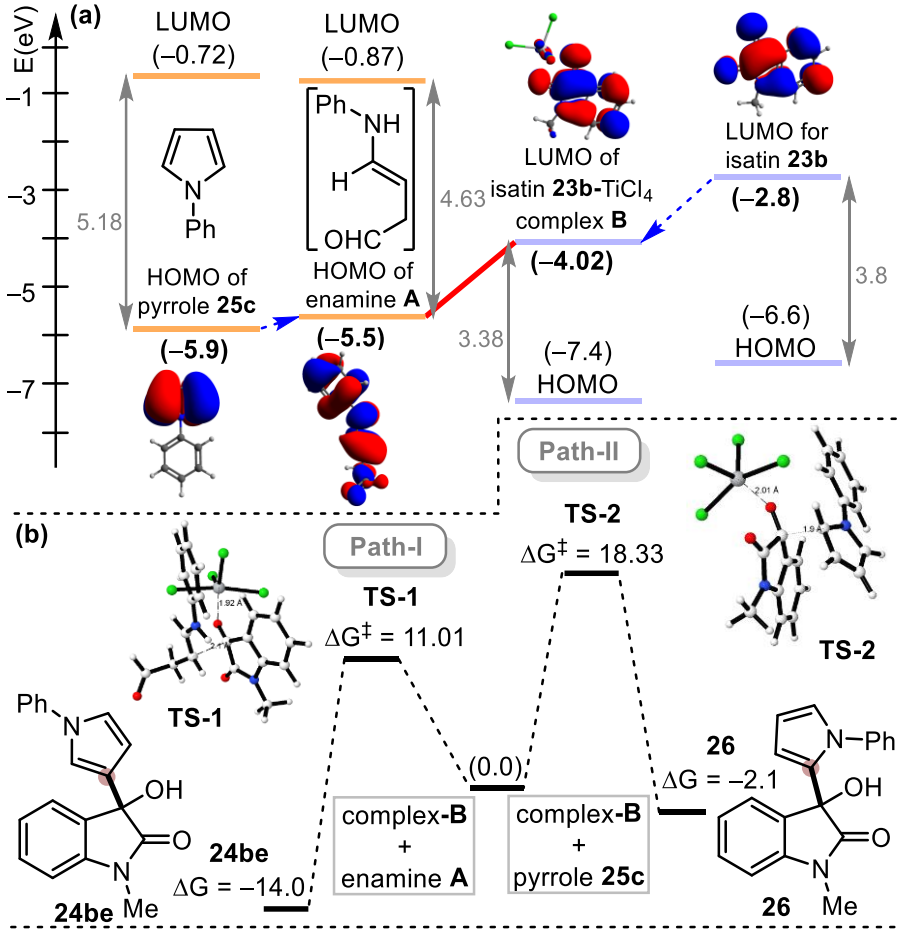


Scheme 2.9 Model reactions between isatin **12e** and preformed pyrroles **25a** and **1**.

2.3.1 Theoretical Calculations at the DFT Level

We performed density functional theory (DFT) calculations to gain more mechanistic insight and to investigate the origin of the observed experimental outcome (Scheme 2.10). For this purpose, we used B3LYP hybrid exchange-correlation functional [52] with a def2-TZVP basis set.[53]A correction for dispersion interaction is added using Grimme D3 with Becke-Johnson damping.[54]All the calculations, including geometry optimization and frequencies, were performed using ORCA 4.2 program in the gas phase, with RIJCOSX approximation for Coulomb and exchange integrals.[55] The reactivity of the preformed pyrrole **1c**, and in situ generated enamine-**A** was examined with activated isatin-$TiCl_4$ complex **B,** as shown in Scheme 2.5. The enamine-**A** displays an enhanced nucleophilicity over pyrrole **1c** because the HOMO of enamine-**A** (–5.5 eV) was higher by 0.4 eV than the HOMO of pyrrole **1c** (–5.9 eV). Similarly, the LUMO of isatin-complex-**B** (–4.02 eV) was found to be lowered by –1.22 eV, because of

Lewis acid activation, compared to LUMO (–2.8 eV) of isatin **12**, resulting in a greater electrophilicity.

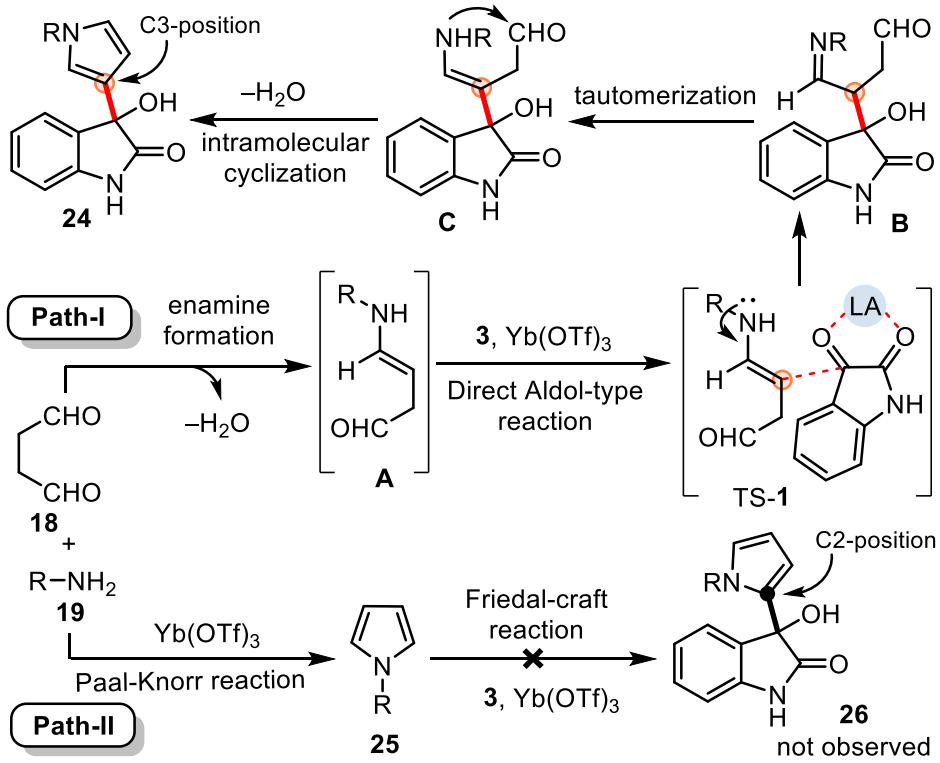


Scheme 2.10 (a) The HOMO and LUMO of pyrrole **25c**, enamine **A**, isatin **12b,** and isatin-complex **B**, (b) Transition State Geometries and Relative Activation Energies for the reaction for two possible mechanisms. (i) **TS-1** represents the direct synthesis of C-3 substituted pyrrole via the reaction between the intermediate enamine-**A** and isatin-complex **B** (Path-I), (ii) **TS-2** represents the access to C2-substituted pyrrole **26** through the Friedel-Craft reaction of pyrrole **25c** with isatin-complex **B**. Gibbs activation energies ($\Delta G^{\ddagger}$, kcal/mol) and Gibbs reaction energies (ΔG, kcal/mol) are shown.

Thus, expecting a superior interaction between enamine-**A** and activated complex-**B** as energy-gap is reduced to 1.48 eV, compared to the interaction between pyrrole **25c** and the same complex, where the energy gap is 1.88 eV (Scheme 2.10a). Next, the reactions of activated isatin

complex-**B** with enamine-**A** *via* TS-1 (Path-I) and pyrrole **25c** *via* TS-2 (Path-II) were examined. The Gibbs free energy (G) of reacting species was set to be 0.0 kcal/mol (Scheme 2.10b). The reaction of enamine-**A** with complex-**B** proceeds *via* TS-**1** ($\Delta G^{\ddagger}$ = 11.01 kcal/mol) to furnished *β*-(C3)-pyrrole **24be** (ΔG = –14.0 kcal/mol) after cyclization, while the Friedel-Craft reaction of pyrrole **25c** with isatin-complex-**B** *via* TS-**2** ($\Delta G^{\ddagger}$ = 18.33 kcal/mol) gave α-(C2)-pyrrole-**26** (ΔG = –2.1 kcal/mol). The more exergonic nature of path-I was attributed to the lower energy barrier of TS-**1** over TS-**2** by 7.32 kcal/mol and improved stability of **24be** over **26** by 11.9 kcal/mol. Hence, the DFT calculations validate the experimental outcome

2.3.2 Reaction mechanism, scale-up, and synthetic applications

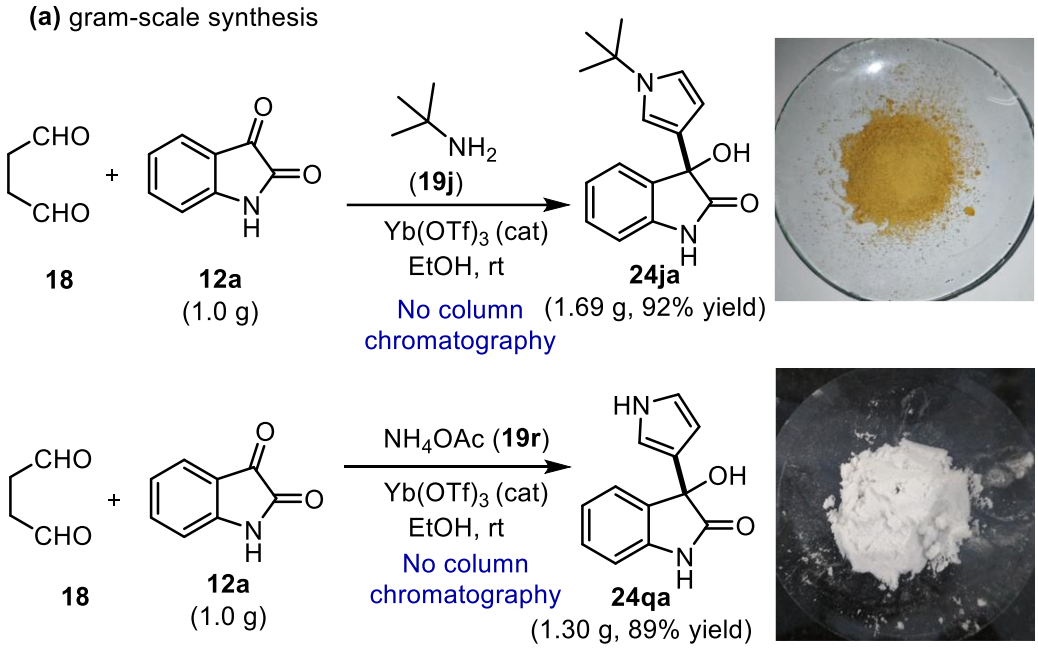


Scheme 2.11 The plausible reaction mechanism.

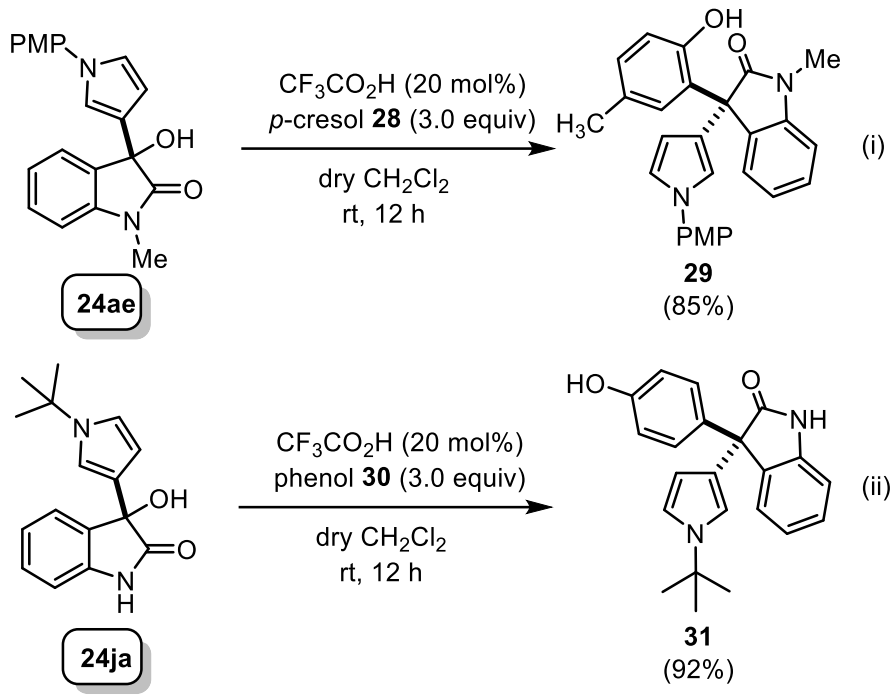
Based on theoretical study and experimental results, we proposed two possible pathways as plausible mechanisms that the reaction could follow (Scheme 2.11). In path-I, a direct aldol-type response between enamine-**A** and Lewis acid-activated isatin **12** *via* TS-1 resulted in intermediate-**B**. Following a tautomerization-cyclization sequence as an overall Paal-Knorr reaction, intermediate-**B** furnished the expected pyrrole **24**. While, in path-II pyrrole **25c**, in situ

generated through Paal-Knorr reaction succinaldehyde **18** and amine **19**, undertake a Friedel-craft response with Lewis acid activated isatin **12** to give α-(C2)-pyrrole-**26**, which was not observed in the response. The intermediates generated through path-I were detected by *in situ* HRMS study (Scheme 2.11), which further endorses the proposed mechanism. Thus, trapping enamine-**A** with suitable electrophiles is the key to success.

To showcase the synthetic utility of the method, a gram-scale reaction of isatin **12a** (1.0 g, 6.8 mmol) with succinaldehyde **18** (20.4 mmol**)** was carried out separately with *tert*-butyl amine **12j** and NH_4OAc **12r** under the optimized conditions to furnish the corresponding products **24ja** (1.69 g, 92% yield) and **24qa** (1.30 g, 89% yield), respectively, in improved outcomes through just filtration and washing with cold methanol (Scheme 2.12 (a)). Furthermore, the synthetic transformations of compounds **24ae** and **24ja** through Lewis-acid mediated Friedel-Craft reaction with *p*-cresol **28** and phenol **30** were performed to generate the corresponding all-carbon quaternary-center oxindole products **29** (85% yield) and **31** (78% yield), respectively (Scheme 2.12 (b)).



(b) Synthetic applications



Scheme 2.12 (a) Gram-scale preparation of **24ja** and **24qa** (b) Synthetic applications to access quaternary substituted oxindoles (**29** and **31**).

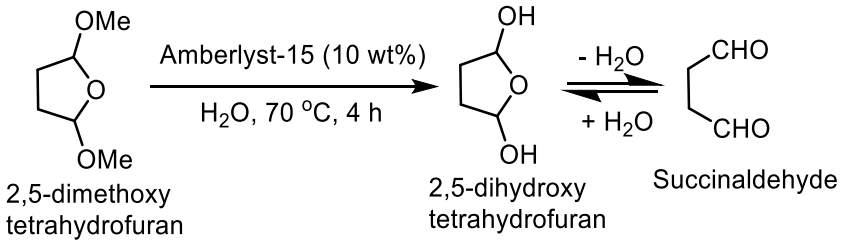
2.4 Conclusion

In summary, we have reported a straightforward and general method for directly synthesizing β-functionalized pyrroles under mild catalytic conditions. This new protocol highlights the simplicity of stitching together readily available starting materials such as aqueous succinaldehyde, amines, and isatin to access oxindole-tethered pyrroles at the *β*-position in a multicomponent fashion. The key to success lies in the utilization of *in situ* generated enamine-intermediate for α-substitution with isatin as an electrophile, before Paal-Knorr cyclization, without requiring complicated setups and tedious workarounds. The scope of this regiospecific reaction is quite comprehensive in terms of isatins and amines. DFT calculation further supported the reaction outcome. Given these promising results, this method is valuable for accessing other *β*-functionalized pyrroles. Efforts to exploit this reaction paradigm with a variety of electrophiles, as well as explore its asymmetric variants are underway in our laboratory.

2.5 General experimental methods

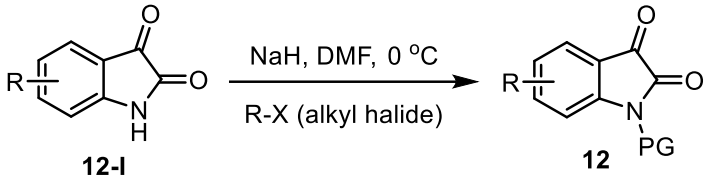
Unless otherwise stated, all commercially available compounds were used as received without further purification. All solvents employed in the reactions were distilled from appropriate drying agents. Starting materials; aqueous succinaldehyde **18** (3M sol) was prepared using the reported procedure; isatin was used as recurred or protected with alkyl halides following the reported protocol. The reactions under the standard conditions were monitored by thin-layer chromatography (TLC) on Merck silica gel 60 F254 pre-coated plates (0.25 mm). Column chromatographic purification was performed on silica gel (100–200 mesh) using a mixture of hexane/EtOAc. Chemical yields refer to pure, isolated substances. ^{1}H spectra were recorded on a BRUKER-AV400 (400 MHz) in $CDCl_3$or DMSO-D6 solution, and spectral data were reported in ppm relative to tetramethylsilane (TMS) as an internal standard. ^{13}C-NMR spectra were recorded on a BRUKER-AV400 (101 MHz) in $CDCl_3$or DMSO-D6 solution with complete proton decoupling. High-resolution mass spectra were recorded on Agilent 6545 Q-TOF LC/MS. HPLC Chromatogram was recorded on of Waters (PDA detector), and EZ determined melting points– Melt Automated Melting Point Apparatus and are uncorrected.

2.5.1 Preparation of aqueous succinaldehyde 18 solution[56] To a stirred solution of 2,5-dimethoxy tetrahydrofuran (5.0 g, 37.9 mmol) in H_2O (12.5 mL) was added Amberlyst-15 (10 wt.%), and further heated at 70 ^{o}C for 4 h in an open flask and allow the MeOH evaporate. The resulting solution was cooled to room temperature and used directly after filtration.



2.5.2 Preparation of *N*-Alkyl isatin 12.[57]To a stirred solution of substituted isatin **12-I** (3.0 mmol, 1.0 equiv.) in DMF (15.0 mL) at 0 °C, was added NaH (60% dispersion in mineral oil, 140 mg, 3.5 mmol, 1.17 equiv.) in one portion and stirred for 5 minutes. Alkyl halide (Methyl Iodide, allyl bromide, or benzyl bromide, 1.2 equiv.) was added at 0 ^{o}C, and continued to be stirred at room temperature. TLC monitored the progress of the reaction. The reaction mixture was then poured into saturated aqueous NH_4Cl and extracted with ethyl acetate. The combined

organic portions were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated to give *N*-alkyl isatin (*N*-Methyl isatin, *N*-allyl isatin, *N*-benzyl isatin) high yields.



12-I **12**

2.5.3 General procedure for the reaction between succinaldehyde, aryl/alkyl amines, and isatins To a stirred solution of isatin **23** (other electrophiles) (0.3 mmol, 1.0 equiv.) and $Yb(OTf)_3$ (0.03 mmol, 0.1 equiv.) in EtOH (3.0 mL) in a round bottom flask was added succinaldehyde **18** (3M aqueous sol., 0.6 mmol, 2.0 equiv.), aryl/alkyl amine **19** (0.3 mmol, 1.0 equiv.) at room temperature. The combined reaction mixture was stirred for 2-12 h at the same temperature, and TLC monitored the reaction's progress. Upon completion, the solvent was removed under reduced pressure. The reaction mass was stirred between $NaHCO_3$ (3.0 mL, 10% aqueous sol.) and ethyl acetate (4.0 mL) for five minutes, and the organic layer was separated. The aqueous layer was again extracted with ethyl acetate (1 × 4 mL), and combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude mass was passed through a small pad of silica gel column by eluting with petroleum ether/EtOAc to get corresponding pyrrole **24** (up to 91% yields).

2.5.4 Procedure for the reaction between succinaldehyde, NH_4OAc, and isatins

To a stirred solution of isatin **23** (0.3 mmol, 1.0 equiv.) and Yb(OTf), $_3$ (0.03 mmol, 0.1 equiv.) in EtOH (3.0 mL) in a round bottom flask was added succinaldehyde **18** (3M aqueous sol., 0.6 mmol, 2.0 equiv.) and NH_4OAc **19r** (43 mg, 0.6 mmol, 2.0 equiv.) at room temperature The combined reaction mixture was stirred for 12 h at the same temperature and progress of the reaction was monitored by TLC. Upon completion, the solvent was removed under reduced pressure. The reaction was stirred between brine (3.0 mL) and ethyl acetate (4.0 mL) for five minutes, and the organic layer was separated. The aqueous layer was again extracted with ethyl acetate (1 × 4 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude mass was passed through a small pad of silica gel column by eluting with petroleum ether/EtOAc (1:1) to get corresponding pyrroles **24** (up to 87% yields).

2.5.5 Procedure for the gram-scale synthesis of 24ja

To a stirred solution of isatin **12a** (1.0 g, 6.8 mmol, 1.0 equiv.) and $Yb(OTf)_3$ (421 mg, 0.68 mmol, 0.1 equiv.) in EtOH (45.0 mL) in a round bottom flask was added succinaldehyde **18** (3 M aqueous sol., 4.5 mL, 13.6 mmol, 2.0 equiv.) and *tert*-butyl amine **19j** (0.5 g, 6.8 mmol, 1.0 equiv.) at room temperature, and further stirred for 4 h. The progress of the reaction was monitored by TLC and observed through the formation of solid material, which was initially transparent. The reaction mixture was cooled in an ice-water bath, filtered, and washed with cold EtOH to obtain the brownish-yellow solid compound **24ja** (1.69 g, 92 % yield) with >95% purity. The purity of the compound was checked with the HPLC using the C-18 column (CH_3CN: H_2O (90:10), flow rate 1.0 ml/min).

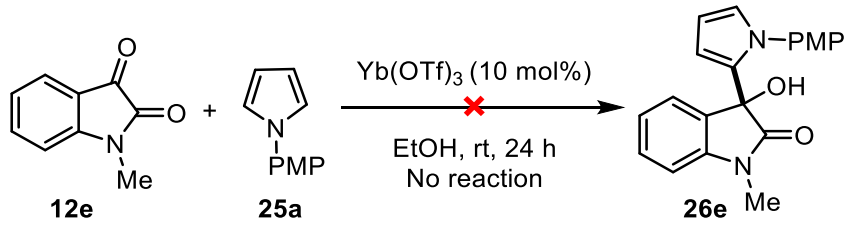
2.5.6 Procedure for the gram-scale synthesis of 24ra

To a stirred solution of isatin **12a** (1.0 g, 6.8 mmol, 1.0 equiv.) and $Yb(OTf)_3$ (421 mg, 0.68 mmol, 0.1 equiv.) in EtOH (45.0 mL) was added succinaldehyde **18** (3 M aqueous sol., 4.5 mL, 13.6 mmol, 2.0 equiv.) and ammonium acetate (NH_4OAc) **19r** (0.967 g, 13.6 mmol, 2.0 equiv.), and further stirred for 8 h. TLC monitored the progress of the reaction. The total reaction mass was poured into the crushed ice to get a solid precipitate filtered and washed with cold EtOH to obtain the gray-solid compounds **24ra** (1.30 g, 89% yield) with >95% purity. The purity of the compound was checked with the HPLC using the C-18 column (CH_3CN: H_2O (90:10), flow rate 1.0 ml/min).

2.5.7 Control experiments

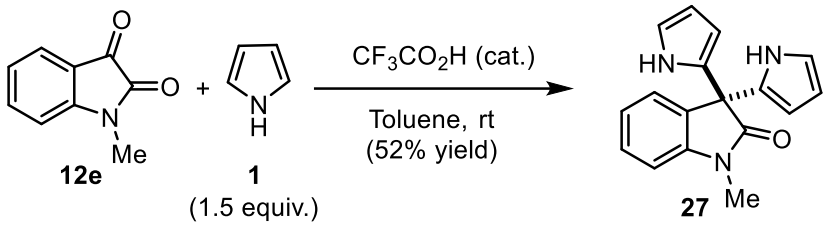
A) The model reaction between isatin 23e and preformed pyrrole 25a

To a stirred solution of *N*-methylisatin **12e** (48 mg, 0.3 mmol, 1.0 equiv.) and *N*-PMP-pyrrole **25a** (78 mg, 0.45 mmol, 1.5 equiv.) in EtOH (3.0 mL) was added $Yb(OTf)_3$ (0.03 mmol, 10 mol%) at room temperature. We did not observe any reaction between them even after 24 h.



B) Model reaction between isatin 12e and pyrrole 1

To a stirred solution of *N*-methyl isatin **12e** (48 mg, 0.3 mmol, 1.0 equiv.) and pyrrole **1** (30 mg, 0.45 mmol, 1.5 equiv.) in Toluene (1.5 mL) was added CF_3CO_2H (10 mol %) at 0 °C and further stirred at room temperature. The progress of the reaction was monitored by TLC and quenched by mixing with saturated $NaHCO_3$ (2.0 mL, 10% aqueous sol.) and ethyl acetate (3.0 mL) for five minutes, and the organic layer was separated. The aqueous layer was then extracted with ethyl acetate (1 × 3.0 mL), and the combined organic layers were washed with brine once, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mass was purified through a silica gel column by eluting with hexane: ethyl acetate (3:2) to give bis-pyrrole **27** as the solid white product (43 mg, 52% yields).



2.5.8 Synthesis applications of the developed methodology

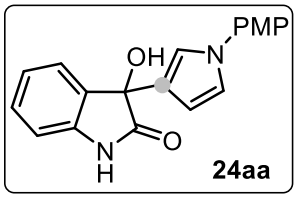
A) Preparation of quaternary oxindole tethered pyrrole 29 To a stirred solution of **24ae** (100 mg, 0.3 mmol, 1.0 equiv.) and *p*-cresol **28** (97 mg, 0.9 mmol, 3.0 equiv.) in dry CH_2Cl_2 (3.0 mL) was added trifluoroacetic acid (20 mol%) at room temperature and further stirred for 12 h. TLC monitored the progress of the reaction. Once completed, the reaction was mixed with $NaHCO_3$ (3.0 mL, 10% aqueous sol.) and CH_2Cl_2 (3.0 mL) for five minutes, and the organic layer was separated. The organic layer was washed with brine once, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mass was purified by passing through a small pad of silica gel column by eluting with hexane: ethyl acetate (3:2) to give quaternary oxindole **29** as the solid white product (108 mg, 85% yields).

B) Preparation of quaternary oxindole tethered pyrrole 31 To a stirred solution of **24ae** (200 mg, 0.75 mmol, 1.0 equiv.) and phenol **30** (208 mg, 2.25 mmol, 3.0 equiv.) in dry CH_2Cl_2 (7.0 mL) was added trifluoroacetic acid (20 mol%) at room temperature and further stirred for 12 h. TLC monitored the progress of the reaction. Once completed, the reaction was mixed with $NaHCO_3$ (10% aqueous solution, 6.0 mL) and CH_2Cl_2 (5.0 mL) for five minutes, and the organic

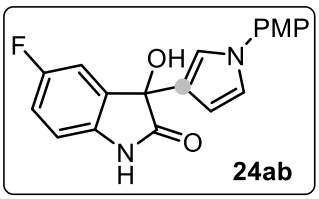
layer was separated. The organic layer was washed with brine once, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mass was purified by passing through a small pad of silica gel column by eluting with hexane: ethyl acetate (3:2) to give quaternary oxindole-tethered pyrrole **31** as a solid white product (236 mg, 92% yields).

2.6 Characterization data

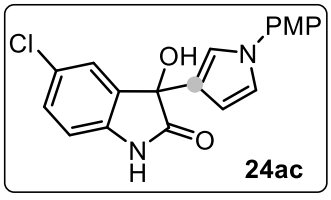
3-hydroxy-3-(1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)indolin-2-one (24aa). Purification with petroleum ether/EtOAc(3/2) as eluent; Yellow solid (77 mg, 80% yield, mp = 122-124 °C.**^{1}H NMR (400 MHz, DMSO-d_6)** δ 10.25 (s, 1H), 7.38 (d, *J* = 8.0 Hz, 3H), 7.22 (t, *J* = 7.7 Hz, 1H), 7.16 (s, 1H), 6.98 (q, *J* = 8.5 Hz, 4H), 6.84 (d, *J* = 7.7 Hz, 1H), 6.24 (d, *J* = 9.0 Hz, 2H), 3.76 (s, 3H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)** δ 179.1, 157.5, 141.9, 133.9, 133.8, 129.3, 126.5, 125.1, 122.1, 121.4 (2C), 120.0, 117.6, 115.2 (2C), 110.0, 109.6, 74.1, 55.8. **IR (KBr)/cm^{-1}**3232, 2932, 1713,1612, 1520, 1466, 1396, 1342, 1242, 1196. **HRMS (ESI)** *m*/*z*: [M + H]$^+$Calcd for $C_{19}H_{17}N_2O_3$ 321.1239; Found 321.1244.



5-fluoro-3-hydroxy-3-(1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)indolin-2-one (24ab). Purification with petroleum ether/EtOAc(3/2) as eluent; Brown solid (84 mg, 83% yield, mp = 128-130 °C). **^{1}H NMR (400 MHz, DMSO-d_6)** δ 10.27 (s, 1H), 7.41 (d, *J* = 9.0 Hz, 2H), 7.24 (dd, *J* = 8.2, 2.7 Hz, 1H), 7.19 – 7.16 (m, 1H), 7.06 (ddd, *J* = 9.6, 8.6, 2.7 Hz, 1H), 7.01 – 6.96 (m, 3H), 6.83 (dd, *J* = 8.5, 4.3 Hz, 1H), 6.37 (s, 1H), 6.25 (dd, *J* = 2.9, 1.7 Hz, 1H), 3.77 (s, 3H). **^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6)** δ 178.5, 158.1 (d, *J* = 237.1 Hz), 157.1, 137.5, 135.1 (d, *J* = 7.4 Hz), 133.3, 125.4, 121.0 (2C), 119.6, 117.2, 115.0 (d, *J* = 23.2 Hz), 114.7 (2C), 112.3 (d, *J* = 24.2 Hz), 110.3 (d, *J* = 7.7 Hz), 109.0, 73.9, 55.3. **IR (KBr)/cm^{-1}**3425,2924, 1713,1636, 1589, 1474, 1358, 1257, 1196. **HRMS (ESI)** *m*/*z*: [M + H]$^+$Calcd for $C_{19}H_{16}FN_2O_3$ 339.1145; Found 339.1148.

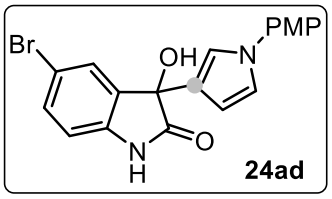


5-chloro-3-hydroxy-3-(1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)indolin-2-one (24ac). Purification with petroleum ether/EtOAc(3/2) as eluent; White solid (82 mg, 78% yield, mp = 120-122 °C). **^{1}H NMR (400 MHz, DMSO-d_6)** δ 10.40 (s, 1H), 7.42 (d, *J* = 9.0 Hz, 2H), 7.38 (d, *J* = 2.2 Hz, 1H), 7.28 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.18 (t, *J* = 2.6 Hz, 1H), 7.02 – 6.97



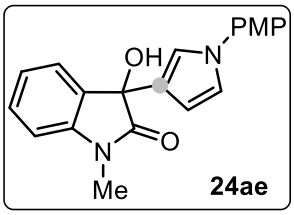
(m, 3H), 6.86 (d, *J* = 8.3 Hz, 1H), 6.40 (s, 1H), 6.23 (dd, *J* = 3.0, 1.7 Hz, 1H), 3.77 (s, 3H). **^{13}C{^{1}H} NMR (101 MHz, DMSO-*d*$_6$)** δ 178.7, 157.6, 140.8, 136.0, 133.7, 129.1, 126.2, 125.8, 125.1, 121.5 (2C), 120.2, 117.7, 115.2 (2C), 111.6, 109.4, 74.2, 55.8. **IR (KBr)/cm^{-1}**3348,2924, 1720, 1666, 1520, 1466, 1342, 1242, 1180. **HRMS (ESI)** *m*/*z*: [M + H]$^{+}$Calcd for $C_{19}H_{16}ClN_2O_3$ 355.0849; Found 355.0855.

5-bromo-3-hydroxy-3-(1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)indolin-2-one (24ad).



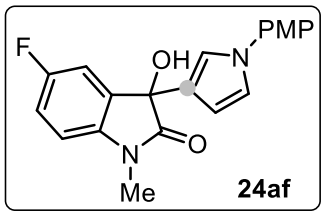
Purification with petroleum ether/EtOAc(3/2) as eluent; Brown solid (92 mg, 77% yield, mp = 115-117 ^{o}C**). ^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 10.41 (s, 1H), 7.48 (d, *J* = 1.9 Hz, 1H), 7.41 (td, *J* = 5.8, 5.2, 2.9 Hz, 3H), 7.18 (t, *J* = 2.6 Hz, 1H), 7.00 (d, *J* = 9.0 Hz, 3H), 6.81 (d, *J* = 8.2 Hz, 1H), 6.40 (s, 1H), 6.23 – 6.20 (m, 1H), 3.77 (s, 3H). **^{13}C{^{1}H} NMR (101 MHz, DMSO-*d*$_6$)** δ 178.1, 157.1, 140.7, 135.9, 133.3, 131.5, 127.3, 125.3, 121.0 (2C), 119.7, 117.1, 114.7 (2C), 113.4, 111.7, 108.9, 73.8, 55.4. **IR (KBr)/cm^{-1}**3430,2947, 1720,1612, 1512, 1466, 1319, 1242, 1196. **HRMS (ESI)** *m*/*z*: [M + H]$^{+}$Calcd for $C_{19}H_{15}BrN_2O_3$ 399.0344; Found 399.0350.

3-hydroxy-3-(1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)-1-methylindolin-2-one (24ae).



Purification with petroleum ether/EtOAc(4/1) as eluent; White solid (80 mg, 80% yield, mp = 138-140 ^{o}C). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.59 (dd, *J* = 7.3, 1.3 Hz, 1H), 7.36 (td, *J* = 7.7, 1.3 Hz, 1H), 7.25 (d, *J* = 8.9 Hz, 2H), 7.16 (td, *J* = 7.6, 1.0 Hz, 1H), 6.99 (t, *J* = 2.1 Hz, 1H), 6.95 (t, *J* = 2.6 Hz, 1H), 6.91 (d, *J* = 8.9 Hz, 2H), 6.88 (d, *J* = 7.8 Hz, 1H), 6.52 (dd, *J* = 3.0, 1.8 Hz, 1H), 3.83 (s, 3H), 3.39 (s, 1H), 3.23 (s, 3H).**^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$)** δ 177.6, 157.7, 143.0, 133.8, 131.1, 129.4, 124.5, 124.3, 123.1, 122.1 (2C), 120.6, 118.6, 114.5 (2C), 108.6, 108.5, 74.0, 55.4, 26.3. **IR (KBr)/cm^{-1}**3394,2924, 1713,1597, 1514, 1350, 1265, 1203, 1080. **HRMS (ESI)***m*/*z*: [M + H]$^{+}$Calcd for $C_{20}H_{19}N_2O_3$ 335.1395; Found 335.1401.

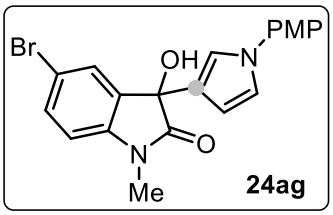
5-fluoro-3-hydroxy-3-(1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)-1-methylindolin-2-one (24af).



Purification with petroleum ether/EtOAc(4/1 as eluent; Red solid (86 mg, 81% yield, mp = 166-168 ^{o}C). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.34 (dd, *J* = 7.7, 2.6 Hz, 1H), 7.25 (d, *J* = 8.9 Hz, 2H), 7.06 (ddd, *J* = 9.2, 8.5, 2.6 Hz, 1H), 6.99 (t, *J* = 2.0 Hz, 1H), 6.96 (dd, *J* = 3.0, 2.3

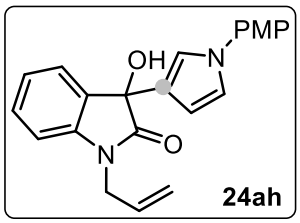
Hz, 1H), 6.93 (d, *J* = 9.0 Hz, 2H), 6.80 (dd, *J* = 8.5, 4.0 Hz, 1H), 6.49 (dd, *J* = 3.0, 1.8 Hz, 1H), 3.84 (s, 3H), 3.23 (s, 3H).**^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$)** δ 177.3, 159.8 (d, *J* = 241.6 Hz), 158.0, 139.1, 133.8, 132.6 (d, *J* = 7.6 Hz), 123.9, 122.3 (2C), 121.0, 118.7, 115.7 (d, *J* = 23.5 Hz), 114.6 (2C), 112.8 (d, *J* = 24.9 Hz), 109.1 (d, *J* = 8.0 Hz), 108.4, 74.1, 55.5, 26.5. **IR (KBr)/cm^{-1}**3417,2926, 1713,1628, 1566, 1512, 1360, 1257, 1103, 1049. **HRMS (ESI)** *m*/*z*: [M + H]$^+$Calcd for $C_{20}H_{18}FN_2O_3$ 353.1301; Found 353.1305.

5-bromo-3-hydroxy-3-(1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)-1-methylindolin-2-one (24ag).



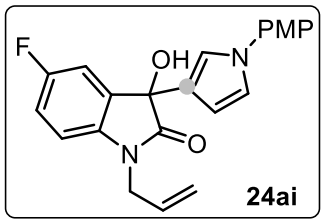
Purification with petroleum ether/EtOAc(4/1) as eluent; Light brown solid (96 mg, 78% yield, mp = 191-194 ^{o}C). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.67 (d, *J* = 1.7 Hz, 1H), 7.46 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.24 (d, *J* = 8.9 Hz, 2H), 6.98 – 6.95 (m, 1H), 6.95 – 6.93 (m, 1H), 6.91 (d, *J* = 8.9 Hz, 2H), 6.73 (d, *J* = 8.3 Hz, 1H), 6.46 (dd, *J* = 2.9, 1.9 Hz, 1H), 3.81 (s, 3H), 3.20 (s, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$)** δ 177.0, 158.0, 142.3, 133.8, 133.0, 132.3, 127.8, 123.8, 122.4 (2C), 121.0, 118.7, 115.8, 114.6 (2C), 110.0, 108.4, 74.0, 55.5, 26.5. **IR (KBr)/cm^{-1}**3387,2916, 1713,1651, 1605, 1512, 1350, 1250, 1188, 1049. **HRMS (ESI)** *m*/*z*: [M + H]$^+$Calcd for $C_{20}H_{18}BrN_2O_3$ 413.0501; Found 413.0506.

1-allyl-3-hydroxy-3-(1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)indolin-2-one (24ah). Purification



with petroleum ether/EtOAc(4/1) as eluent; Colorless semi-solid (78 mg, 72% yield). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 7.45 (dd, *J* = 7.3, 1.3 Hz, 1H), 7.39 (d, *J* = 9.0 Hz, 2H), 7.30 (td, *J* = 7.7, 1.3 Hz, 1H), 7.17 (t, *J* = 2.6 Hz, 1H), 7.07 (tt, *J* = 7.5, 1.2 Hz, 1H), 7.02 – 6.94 (m, 4H), 6.39 (s, 1H), 6.21 (dd, *J* = 3.0, 1.7 Hz, 1H), 5.86 (ddt, *J* = 17.1, 10.2, 4.9 Hz, 1H), 4.38 – 4.22 (m, 2H), 3.77 (s, 3H).**^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$)** δ 177.2, 157.8, 142.3, 133.9, 131.1 (2C), 129.4, 124.6, 124.5, 123.0, 122.2 (2C), 120.8, 118.6, 117.5 , 114.5 (2C), 109.4, 108.5, 74.0, 55.5, 42.4. **IR (KBr)/cm^{-1}**3414,2924, 1733,1625, 1532, 1358, 1188, 1049. **HRMS (ESI)** *m*/*z*: [M + H]$^+$Calcd for $C_{22}H_{21}N_2O_3$361.1552; Found 361.1558.

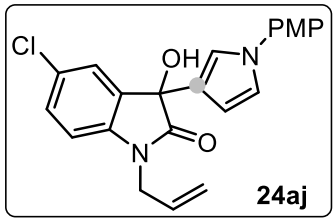
1-allyl-5-fluoro-3-hydroxy-3-(1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)indolin-2-one (24ai).



Purification with petroleum ether/EtOAc(4/1) as eluent; Yellow semi-solid (86 mg, 76% yield). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.33 (dd, *J* = 7.7, 2.6 Hz, 1H), 7.25 (d, *J* = 8.5 Hz, 2H), 7.01 (dp, *J* = 6.4,

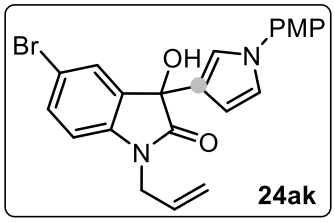
3.9, 3.2 Hz, 2H), 6.97 – 6.87 (m, 3H), 6.79 (dd, *J* = 8.6, 4.1 Hz, 1H), 6.51 – 6.41 (m, 1H), 5.83 (ddd, *J* = 15.9, 10.6, 5.2 Hz, 1H), 5.32 – 5.13 (m, 2H), 4.41 (dd, *J* = 16.5, 5.2 Hz, 1H), 4.27 (dd, *J* = 16.5, 5.3 Hz, 1H), 3.83 (s, 3H), 3.64 (s, 1H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)** δ 177.1, 159.4 (d, *J* = 241.6 Hz), 157.9, 138.2, 133.8, 132.8 (d, *J* = 7.9 Hz), 131.0, 124.1, 122.3 (2C), 120.9, 118.5, 117.7, 115.5 (d, *J* = 23.5 Hz), 114.6 (2C), 112.8 (d, *J* = 24.8 Hz), 110.1 (d, *J* = 7.9 Hz), 108.4, 74.2, 55.5, 42.5. **IR (KBr)/cm^{-1}**3425,2932, 1723,1635, 1504, 1360, 1257, 1180. **HRMS (ESI)** *m*/*z*: $[M + H]^+$Calcd for $C_{22}H_{19}FN_2O_3$ 379.1458; Found 379.1463.

1-allyl-5-chloro-3-hydroxy-3-(1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)indolin-2-one (24aj).



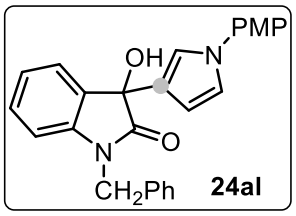
Purification with petroleum ether/EtOAc(4/1) as eluent; Brown semi-solid (85 mg, 72% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.57 (d, *J* = 2.2 Hz, 1H), 7.28 (td, *J* = 8.8, 8.3, 2.2 Hz, 3H), 7.00 (d, *J* = 2.2 Hz, 1H), 6.97 (t, *J* = 2.7 Hz, 1H), 6.95 (d, *J* = 6.9 Hz, 2H), 6.80 (d, *J* = 8.3 Hz, 1H), 6.48 (t, *J* = 2.4 Hz, 1H), 5.85 (ddt, *J* = 17.1, 10.3, 5.2 Hz, 1H), 5.26 (s, 1H), 5.23 (d, *J* = 5.6 Hz, 1H), 4.43 (dd, *J* = 16.4, 5.3 Hz, 1H), 4.29 (dd, *J* = 16.4, 5.1 Hz, 1H), 3.85 (s, 3H), 3.32 (s, 1H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)** δ 176.8, 158.0, 140.9, 133.9, 132.8, 130.9, 129.3, 128.5, 125.2, 124.0, 122.4 (2C), 121.1, 118.6, 117.8, 114.7 (2C), 110.5, 108.3, 74.1, 55.6, 42.5. **IR (KBr)/cm^{-1}**3435,2924, 1713,1615, 1514, 1435, 1348, 1250, 1180. **HRMS (ESI)** *m*/*z*: $[M + H]^+$Calcd for $C_{22}H_{20}ClN_2O_3$ 395.1162; Found 395.1157.

1-allyl-5-bromo-3-hydroxy-3-(1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)indolin-2-one (24ak).



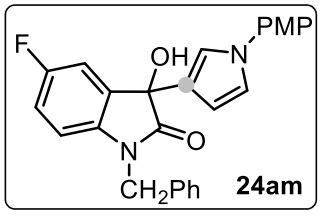
Purification with petroleum ether/EtOAc(4/1) as eluent; Brown solid (92 mg, 70% yield, mp = 188-191 ^{o}C). **^{1}H NMR (400 MHz, DMSO-d_6)** δ 7.57 (d, *J* = 2.1 Hz, 1H), 7.49 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.42 (d, *J* = 9.0 Hz, 2H), 7.19 (t, *J* = 2.6 Hz, 1H), 7.04 (t, *J* = 2.0 Hz, 1H), 7.00 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.56 (s, 1H), 6.22 (dd, *J* = 2.9, 1.8 Hz, 1H), 5.90 – 5.79 (m, 1H), 5.18 (t, *J* = 1.7 Hz, 1H), 5.15 (dq, *J* = 7.1, 1.6 Hz, 1H), 4.38 – 4.22 (m, 2H), 3.77 (s, 3H). **^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6)** δ 176.5, 157.6, 141.6, 135.7, 133.7, 132.1, 132.0, 127.6, 125.6, 121.5 (2C), 120.3, 117.7, 117.3, 115.2, 114.7 (2C), 111.7, 109.3, 74.0, 55.8, 41.9. **IR (KBr)/cm^{-1}**3410,2924, 1713,1605, 1522, 1350, 1265, 1180, 1057. **HRMS (ESI)** *m*/*z*: $[M + H]^+$Calcd for $C_{22}H_{20}BrN_2O_3$ 439.0657; Found 439.0662.

1-benzyl-3-hydroxy-3-(1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)indolin-2-one (24al).



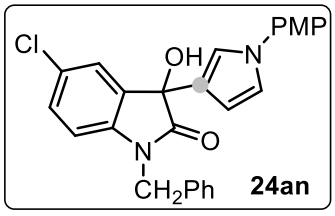
Purification with petroleum ether/EtOAc(4/1) as eluent; Brown solid (98 mg, 80% yield, mp = 114-116 ^{o}C). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.59 – 7.54 (m, 1H), 7.34 – 7.27 (m, 5H), 7.24 (d, *J* = 6.8 Hz, 2H), 7.23 – 7.19 (m, 1H), 7.09 (td, *J* = 7.6, 0.9 Hz, 1H), 7.00 (t, *J* = 2.0 Hz, 1H), 6.98 – 6.95 (m, 1H), 6.91 (d, *J* = 9.0 Hz, 2H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.51 (dd, *J* = 2.9, 1.8 Hz, 1H), 4.99 (d, *J* = 15.8 Hz, 1H), 4.87 (d, *J* = 15.8 Hz, 1H), 3.82 (s, 3H), 3.20 (s, 1H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$)** δ177.5, 157.7, 142.3, 135.5, 133.9, 131.1, 129.5, 128.8 (2C), 127.6, 127.1 (2C), 124.6, 124.5, 123.2, 122.3 (2C), 120.9, 118.6, 114.6 (2C), 109.6, 108.5, 74.1, 55.5, 43.8. **IR (KBr)/cm^{-1}**3425,2932, 1713, 1605, 1512, 1358, 1296, 1050. **HRMS (ESI)** *m*/*z*: [M + H]$^{+}$Calcd for $C_{26}H_{23}N_2O_3$411.1708; Found 411.1714.

1-benzyl-5-fluoro-3-hydroxy-3-(1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)indolin-2-one (24am).



Purification with petroleum ether/EtOAc(4/1) as eluent; Dark brown solid (104 mg, 81% yield, mp = 128-130 ^{o}C). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.37 – 7.28 (m, 8H), 7.05 (t, *J* = 2.1 Hz, 1H), 7.01 (dd, *J* = 3.0, 2.3 Hz, 1H), 6.98 – 6.91 (m, 3H), 6.67 (dd, *J* = 8.6, 4.0 Hz, 1H), 6.52 (dd, *J* = 3.0, 1.8 Hz, 1H), 5.02 (d, *J* = 15.8 Hz, 1H), 4.89 (d, *J* = 15.8 Hz, 1H), 3.86 (s, 4H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$)** δ 177.4, 159.4 (d, *J* = 241.9 Hz), 158.0, 138.1, 135.2, 133.8, 128.8 (2C), 128.7 (d, *J* = 17.7 Hz), 127.7, 127.1 (2C), 124.1, 122.3 (2C), 121.1, 118.5, 115.6 (d, *J* = 23.5 Hz), 114.6 (2C), 112.7 (d, *J* = 24.7 Hz), 110.3 (d, *J* = 8.0 Hz), 108.3, 74.3, 55.5, 44.0. **HRMS (ESI)** *m*/*z*: [M + H]$^{+}$Calcd for $C_{26}H_{22}FN_2O_3$ 429.1614; Found 429.1618.

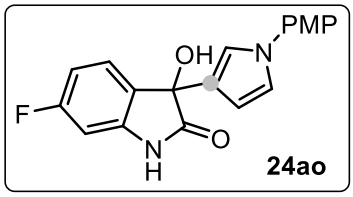
1-benzyl-5-chloro-3-hydroxy-3-(1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)indolin-2-one (24an).



Purification with petroleum ether/EtOAc(4/1) as eluent; Red solid (102 mg, 77% yield, mp = 148-150 ^{o}C). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 7.48 (d, *J* = 2.3 Hz, 1H), 7.42 (d, *J* = 8.9 Hz, 2H), 7.35 – 7.28 (m, 5H), 7.21 (t, *J* = 2.6 Hz, 1H), 7.06 (t, *J* = 2.1 Hz, 1H), 7.01 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.65 (s, 1H), 6.28 – 6.22 (m, 1H), 4.91 (s, 2H), 3.78 (s, 3H).**^{13}C{^{1}H} NMR (101 MHz, DMSO-*d*$_6$)** δ 176.1, 157.6, 141.1, 136.6, 135.4, 133.7, 129.1 (3C), 127.9, 127.6 (2C), 127.2, 125.6, 125.0, 121.5 (2C), 120.4, 117.7, 115.2 (2C), 111.2, 109.3,

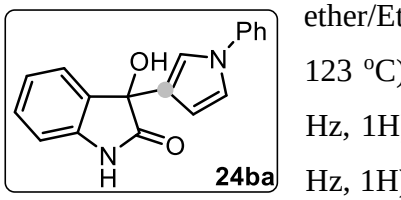
74.1, 55.9, 43.1. **IR (KBr)/cm^{-1}**3425,2924, 1713,1605, 1504, 1342, 1250, 1180. **HRMS (ESI)** *m*/*z*: [M + H]$^+$Calcd for $C_{26}H_{21}ClN_2O_3$ 445.1319; Found 445.1325.

6-fluoro-3-hydroxy-3-(1-(4-methoxyphenyl)-1H-pyrrol-3-yl)indolin-2-one (24ao).

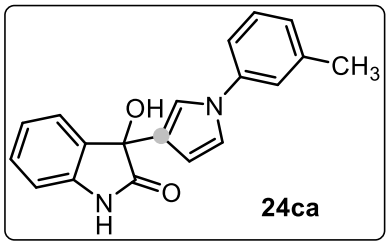


Purification with petroleum ether/EtOAc(4/1) as eluent; brown solid (80 mg, 79% yield, mp = 200-202 ^{o}C). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 10.27 (s, 1H), 7.46 – 7.36 (m, 2H), 7.23 (dd, *J* = 8.2, 2.7 Hz, 1H), 7.17 (t, *J* = 2.6 Hz, 1H), 7.05 (td, *J* = 9.1, 2.8 Hz, 1H), 7.01 – 6.95 (m, 3H), 6.82 (dd, *J* = 8.4, 4.3 Hz, 1H), 6.36 (s, 1H), 6.28 – 6.20 (m, 1H), 3.76 (s, 3H).**^{13}C{^{1}H} NMR (101 MHz, DMSO-*d*$_6$)** δ 179.0, 158.5 (d, *J* = 236.9 Hz), 157.6, 138.0, 135.6 (d, *J* = 7.3 Hz), 133.8, 125.9, 121.5 (2C), 120.1, 117.7, 115.5 (d, *J* = 23.4 Hz), 115.2 (2C), 112.8 (d, *J* = 24.2 Hz), 110.8 (d, *J* = 7.8 Hz), 109.5, 74.4, 55.8. **IR (KBr)/cm^{-1}**3425,2924, 1720, 1504, 1350, 1250, 1180. **HRMS (ESI)** *m*/*z*: [M + H]$^+$Calcd for $C_{19}H_{16}FN_2O_3$ 339.1139; Found 339.1143.

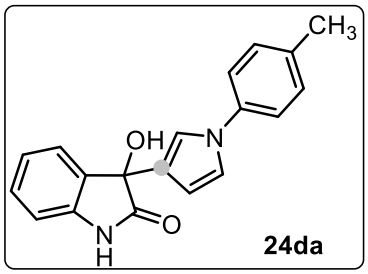
3-hydroxy-3-(1-phenyl-1*H*-pyrrol-3-yl)indolin-2-one (24ba). Purification with petroleum ether/EtOAc(3/2) as eluent; Yellow solid (59 mg, 68% yield, mp = 121-123 ^{o}C). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.06 (s, 1H), 7.53 (d, *J* = 7.3 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.32 – 7.22 (m, 4H), 7.11 (t, *J* = 7.4 Hz, 1H), 7.04 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.51 (s, 1H), 3.32 (s, 1H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$)** δ 179.3, 140.3, 140.2, 131.5, 129.6, 129.5 (2C), 126.0, 125.0, 124.8, 123.2, 120.6 (2C), 120.5, 118.3, 110.3, 109.0, 74.4; **IR (KBr)/cm^{-1}**3433,2932, 1713,1605, 1497, 1350. HRMS (ESI) *m*/*z*: [M + H]$^+$Calcd for $C_{18}H_{15}N_2O_2$ 291.1133; Found 291.1139.



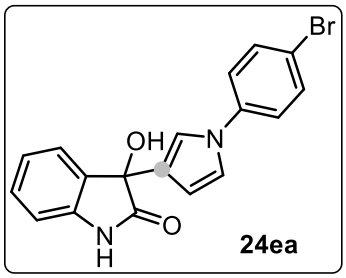
3-hydroxy-3-(1-(m-tolyl)-1*H*-pyrrol-3-yl)indolin-2-one (24ca). Purification with petroleum ether/EtOAc(3/2) as eluent; Brown solid (64 mg, 70% yield, mp = 183-186 ^{o}C). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.86 (s, 1H), 7.56 (d, *J* = 6.5 Hz, 1H), 7.39 – 7.29 (m, 2H), 7.13 (d, *J* = 7.9 Hz, 3H), 7.05 (d, *J* = 6.9 Hz, 3H), 6.92 (d, *J* = 6.8 Hz, 1H), 6.52 (s, 1H), 3.27 (s, 1H), 2.39 (s, 3H). **^{13}C{1H} NMR (101 MHz, CDCl$_3$)** δ 179.1, 140.2, 140.1, 139.6, 131.5, 129.6, 129.3, 126.8, 125.1, 124.6, 123.2, 121.4, 120.6, 118.3, 117.8, 110.2, 108.8, 74.3, 21.4. **IR (KBr)/cm^{-1}** 3435, 2930, 1717, 1607, 1495, 1352. **HRMS (ESI)** *m*/*z*: [M + H]$^+$Calcd for $C_{19}H_{17}N_2O_2$ 305.1290; Found 305.1288.



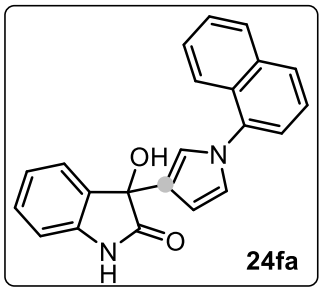
3-hydroxy-3-(1-(p-tolyl)-1*H*-pyrrol-3-yl)indolin-2-one (24da). Purification with petroleum ether/EtOAc(3/2) as eluent; Brown solid (65 mg, 72% yield, mp = 189-192 °C).**^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.22 (s, 1H), 7.53 (d, *J* = 7.4 Hz, 1H), 7.30 – 7.23 (m, 2H), 7.17 (d, *J* = 2.3 Hz, 4H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.00 (dt, *J* = 13.2, 2.3 Hz, 2H), 6.90 (d, *J* = 7.7 Hz, 1H), 6.53 – 6.44 (m, 1H), 3.36 (s, 1H), 2.34 (s, 3H). **^{13}C{1H} NMR (101 MHz, CDCl$_3$)** δ 179.3, 140.2, 138.0, 135.8, 131.5, 130.0 (2C), 129.6, 125.0, 124.5, 123.1, 120.6 (3C), 118.4, 110.3, 108.7, 72.9, 20.8. **IR (KBr)/cm^{-1}** 3433, 2932, 1713, 1605, 1497, 1350, 1255, 1140. **HRMS (ESI)** *m*/*z*: [M + H]$^+$Calcd for $C_{19}H_{17}N_2O_2$ 305.1290; Found 305.1294.



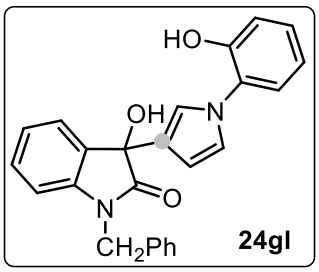
3-(1-(4-bromophenyl)-1*H*-pyrrol-3-yl)-3-hydroxyindolin-2-one (24ea). Purification with petroleum ether/EtOAc(3/2) as eluent; Yellow solid (70 mg, 63% yield, mp = 132-136 °C). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 10.26 (s, 1H), 7.59 (d, *J* = 8.9 Hz, 2H), 7.48 (d, *J* = 8.9 Hz, 2H), 7.36 (dt, *J* = 7.4, 0.9 Hz, 1H), 7.32 – 7.28 (m, 1H), 7.22 (td, *J* = 7.7, 1.3 Hz, 1H), 7.08 – 7.04 (m, 1H), 6.99 (td, *J* = 7.5, 1.1 Hz, 1H), 6.87 – 6.79 (m, 1H), 6.28 (s, 1H), 6.26 (dd, *J* = 3.0, 1.7 Hz, 1H). **^{13}C{1H} NMR (101 MHz, CDCl$_3$)** δ 183.6, 146.7, 144.1, 138.4, 137.7 (2C), 134.1, 132.3, 129.9, 126.9, 126.4 (2C), 124.6, 122.7, 122.0, 115.2, 114.8, 78.8. **IR (KBr)/cm^{-1}**3410,2924, 1720,1605, 1481, 1342, 1196, 1057. **HRMS (ESI)** *m*/*z*: [M + H]$^+$Calcd for $C_{18}H_{14}BrN_2O_2$ 369.0238; Found 369.0242.



3-hydroxy-3-(1-(naphthalen-2-yl)-1*H*-pyrrol-3-yl)indolin-2-one (24fa). Purification with petroleum ether/EtOAc(3/2) as eluent; Brown solid (66 mg, 65% yield, mp = 144-146 °C). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 10.26 (s, 1H), 8.02 (dd, *J* = 21.9, 7.9 Hz, 2H), 7.65 (d, *J* = 7.7 Hz, 1H), 7.58 (qd, *J* = 7.8, 6.4, 2.2 Hz, 3H), 7.45 (dd, *J* = 13.7, 7.5 Hz, 2H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.05 (q, *J* = 2.2 Hz, 1H), 7.00 (t, *J* = 7.7 Hz, 1H), 6.84 (dd, *J* = 11.7, 4.8 Hz, 2H), 6.40–6.34 (m, 1H), 6.30 (d, *J* = 1.8 Hz, 1H). **^{13}C{1H} NMR (101 MHz, DMSO-*d*$_6$)** δ 179.1, 141.9, 137.6, 134.3, 133.9, 129.3, 129.1, 128.8, 128.3, 127.7, 127.1, 126.1, 125.7, 125.2, 123.9, 123.6, 122.8, 122.1, 121.6, 110.1, 109.0 74.0. **IR (KBr)/cm^{-1}**3410,2924, 1720,1605, 1481, 1342, 1196, 1057. **HRMS (ESI)** *m*/*z*: [M + H]$^+$Calcd for $C_{22}H_{17}N_2O_2$ 341.1290; Found 341.1294.

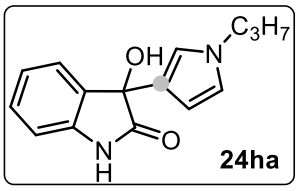


1-Benzyl-3-hydroxy-3-(1-(2-hydroxyphenyl)-1*H*-pyrrol-3-yl)indolin-2-one (24gl).

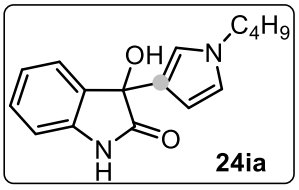


Purification with petroleum ether/EtOAc(7/3) as eluent; Brown solid (81 mg, 68% yield, mp =179-182 ºC).**^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.55 (d, *J* = 7.2 Hz, 1H), 7.28 (m, 5H), 7.19 (t, *J* = 7.8 Hz, 2H), 7.14 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.93 (t, *J* = 1.8 Hz, 1H), 6.90 (t, *J* = 7.6 Hz, 1H), 6.82 (t, *J* = 2.5 Hz, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 6.52 – 6.48 (m, 1H), 5.01 – 4.81 (m, 2H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$)** δ 177.9, 150.3, 142.1, 135.4, 131.2, 129.4, 128.8 (3C), 127.9, 127.6, 127.1 (2C), 126.4, 124.7, 124.5, 123.3, 123.0, 120.8, 120.6, 117.2, 109.7, 108.6, 74.3, 43.9. **HRMS (ESI)** *m/z*: [M + H]$^+$Calcd for $C_{25}H_{21}N_2O_3$ 397.1551; Found 397.1557.

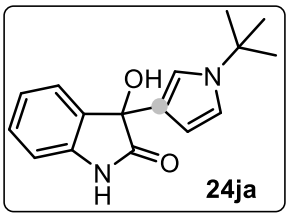
3-hydroxy-3-(1-propyl-1*H*-pyrrol-3-yl)indolin-2-one (24ha). Purification with petroleum ether/EtOAc(7/3) as eluent; Brown solid (68 mg, 88% yield, mp = 153-156 °C). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 10.14 (s, 1H), 7.32 (d, *J* = 7.2 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 6.97 (t, *J* = 7.2 Hz, 1H), 6.80 (d, *J* = 7.7 Hz, 1H), 6.64 (t, *J* = 2.4 Hz, 1H), 6.50 (t, *J* = 1.9 Hz, 1H), 6.05 (s, 1H), 6.04–6.01 (m, 1H), 3.72 (t, *J* = 7.1 Hz, 2H), 1.62 (h, *J* = 7.3 Hz, 2H), 0.79 (t, *J* = 7.4 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, DMSO-*d*$_6$)** δ179.4, 141.8, 134.3, 129.0, 125.0, 123.7, 121.9, 121.1, 119.5, 109.9, 107.4, 74.1, 50.8, 24.8, 11.5. **HRMS (ESI)** *m/z*: [M + H]$^+$Calcd for $C_{15}H_{17}N_2O_2$ 257.1290; Found: 557.1279.



3-(1-butyl-1*H*-pyrrol-3-yl)-3-hydroxyindolin-2-one (24ia). Purification with petroleum ether/EtOAc(7/3) as eluent; Brown solid (73 mg, 90% yield, mp = 162-165 °C). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 10.13 (s, 1H), 7.31 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.19 (td, *J* = 7.7, 1.3 Hz, 1H), 6.97 (td, *J* = 7.5, 1.1 Hz, 1H), 6.80 (d, *J* = 7.7 Hz, 1H), 6.64 (t, *J* = 2.5 Hz, 1H), 6.50 (t, *J* = 2.0 Hz, 1H), 6.03 (s, 1H), 6.02 (dd, *J* = 2.7, 1.8 Hz, 1H), 3.76 (t, *J* = 7.2 Hz, 2H), 1.63–1.55 (m, 2H), 1.24 – 1.17 (m, 2H), 0.85 (t, *J* = 7.4 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, DMSO-*d*$_6$)** δ178.9, 141.3, 133.8, 128.5, 124.5, 123.2, 121.4, 120.6, 119.0, 109.4, 106.9, 73.6, 48.4, 33.1, 19.3, 13.5. **HRMS (ESI)** *m/z*: [M + H]$^+$Calcd for $C_{16}H_{19}N_2O_2$ 271.1446; Found: 271.1442.

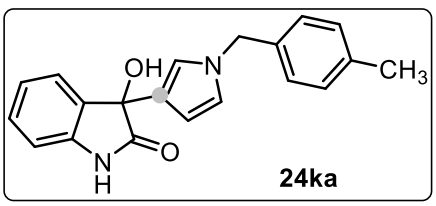


3-(1-(tert-butyl)-1*H*-pyrrol-3-yl)-3-hydroxyindolin-2-one (24ja). Purification with petroleum ether/EtOAc(7/3) as eluent; Brownish solid (73 mg, 90% yield, mp = 178–181 °C).**^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.31 (s, 1H), 7.48 (d, *J* = 7.3 Hz, 1H), 7.18 (td, *J* = 8.7, 7.7, 1.0 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.88 – 6.82 (m, 2H), 6.74 (t, *J* = 2.7 Hz, 1H), 6.28 (dd, *J* = 2.8, 1.9 Hz, 1H), 4.15 (s, 1H), 1.41 (s, 9H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)** δ 180.8, 140.4, 132.1, 129.0, 124.6, 122.7, 121.5 118.3, 116.7, 110.6, 106.4, 74.8, 54.9, 30.5 (3C). **HRMS (ESI)** *m/z*: [M + H]$^+$Calcd for $C_{16}H_{19}N_2O_2$ 271.1446; Found: 271.1449.



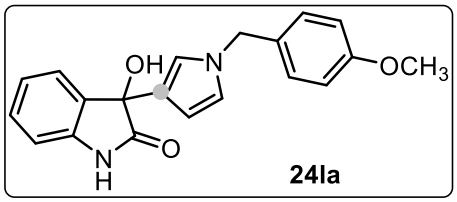
24ja

3-hydroxy-3-(1-(4-methylbenzyl)-1*H*-pyrrol-3-yl)indolin-2-one(24ka). Purification with petroleum ether/EtOAc(7/3) as eluent; Pale yellow solid (82 mg, 86% yield, mp = 157-160 °C). **^{1}H NMR (400 MHz, DMSO-d_6)** δ 10.16 (s, 1H), 7.30 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.18 (td, *J* = 7.7, 1.3 Hz, 1H), 7.14 – 7.08 (m, 4H), 6.96 (td, *J* = 7.5, 1.0 Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.71 (t, *J* = 2.5 Hz, 1H), 6.57 (t, *J* = 2.0 Hz, 1H), 6.08 (s, 1H), 6.04 (dd, *J* = 2.8, 1.7 Hz, 1H), 4.94 (s, 2H), 2.26 (s, 3H). **^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6)** δ 178.9, 141.4, 136.7, 135.6, 133.8, 129.0 (2C), 128.6, 127.6 (2C), 124.5, 123.7, 121.5, 121.0, 119.2, 109.4, 107.3, 73.6, 52.0, 20.7. **HRMS (ESI**) *m/z*: [M + H]$^+$Calcd for $C_{20}H_{19}N_2O_2$ 319.1446; Found: 319.1453.



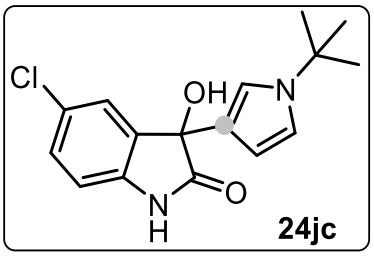
24ka

3-hydroxy-3-(1-(4-methoxybenzyl)-1*H*-pyrrol-3-yl)indolin-2-one (24la). Purification with petroleum ether/EtOAc(7/3) as eluent; Pale yellow solid (88 mg, 88% yield, mp =157-160 °C).**^{1}H NMR (400 MHz, DMSO-d_6)** δ 10.12 (s, 1H), 7.30 (d, *J* = 7.2 Hz, 1H), 7.21–7.14 (m, 3H), 6.98 – 6.93 (m, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 7.7 Hz, 1H), 6.70 (t, *J* = 2.5 Hz, 1H), 6.57 (t, *J* = 1.9 Hz, 1H), 6.05 (s, 1H), 6.03 (dd, *J* = 2.6, 1.8 Hz, 1H), 4.91 (s, 2H), 3.72 (s, 3H). **^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6)** δ 178.8, 158.7, 141.3, 133.8, 130.5, 129.0 (2C), 128.5, 124.5, 123.7, 121.5, 120.8, 119.1, 113.9 (2C), 109.4, 107.3, 73.6, 55.1, 51.7. **HRMS (ESI)** *m/z*: [M + H]$^+$Calcd for $C_{20}H_{19}N_2O_3$ 335.1395; Found: 335.1387.

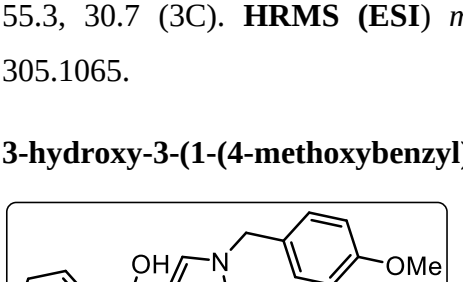


24la

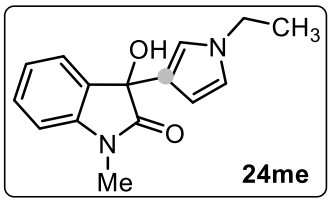
3-(1-(tert-butyl)-1*H*-pyrrol-3-yl)-5-chloro-3-hydroxyindolin-2-one (24jc). Purification with petroleum ether/EtOAc(7/3) as eluent; Brown solid (77 mg, 85% yield, mp = 191–194 °C). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.21 (s, 1H), 7.48 (d, *J* = 2.1 Hz, 1H), 7.22 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.85 (t, *J* = 2.1 Hz, 1H), 6.82 – 6.77 (m, 2H), 6.26 (dd, *J* = 2.9, 1.9 Hz, 1H), 3.27 (s, 1H), 1.47 (s, 9H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)** δ 179.2, 138.6, 133.5, 129.2, 128.3, 125.5, 121.0, 118.9, 116.7, 111.2, 106.2, 74.6, 55.3, 30.7 (3C). **HRMS (ESI**) *m/z*: [M + H]$^+$Calcd for $C_{16}H_{18}ClN_2O_2$ 305.1057; Found: 305.1065.



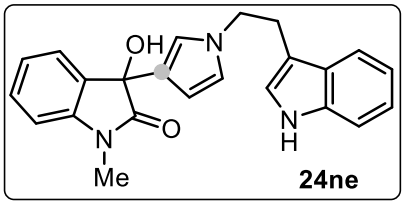
3-hydroxy-3-(1-(4-methoxybenzyl)-1*H*-pyrrol-3-yl)-1-methylindolin-2-one (24le). Purification with petroleum ether/EtOAc(4/1) as eluent; Brown solid (83 mg, 80% yield, mp = 136-139 °C). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.54 – 7.50 (m, 1H), 7.31 (td, *J* = 7.7, 1.2 Hz, 1H), 7.13 – 7.08 (m, 1H), 7.05 (d, *J* = 8.7 Hz, 2H), 6.85 – 6.80 (m, 3H), 6.71 (t, *J* = 2.0 Hz, 1H), 6.57 (t, *J* = 2.5 Hz, 1H), 6.32 (dd, *J* = 2.8, 1.8 Hz, 1H), 4.87 (s, 2H), 3.77 (s, 3H), 3.16 (s, 3H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)** δ 177.6, 159.1, 143.1, 131.3, 129.3, 129.2, 128.7 (2C), 124.4, 122.8 (2C), 121.6, 120.1, 114.0 (2C), 108.3, 107.3, 73.9, 55.2, 52.9, 26.2. **HRMS (ESI**) *m/z*: [M + H]$^+$Calcd for $C_{21}H_{21}N_2O_3$ 349.1552; Found: 349.1558.



3-(1-ethyl-1*H*-pyrrol-3-yl)-3-hydroxy-1-methylindolin-2-one (24me). Purification with petroleum ether/EtOAc(4/1) as eluent; White solid (67 mg, 87% yield, mp = 123-126 °C). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.54 (ddd, *J* = 7.3, 1.3, 0.6 Hz, 1H), 7.32 (td, *J* = 7.8, 1.3 Hz, 1H), 7.11 (td, *J* = 7.6, 1.0 Hz, 1H), 6.83 (dt, *J* = 7.7, 0.8 Hz, 1H), 6.68 (t, *J* = 2.0 Hz, 1H), 6.60 (t, *J* = 2.5 Hz, 1H), 6.31 (dd, *J* = 2.8, 1.8 Hz, 1H), 3.83 (q, *J* = 7.3 Hz, 2H), 3.23 (s, 1H), 3.18 (s, 3H), 1.36 (t, *J* = 7.3 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)** δ 177.7, 143.2, 131.3, 129.3, 124.4, 122.9, 122.3, 120.8, 119.2, 108.3, 106.9, 74.0, 44.3, 26.3, 16.3. **HRMS (ESI**) *m/z*: [M + H]$^+$Calcd for $C_{15}H_{17}N_2O_2$ 257.1290; Found: 257.1287.

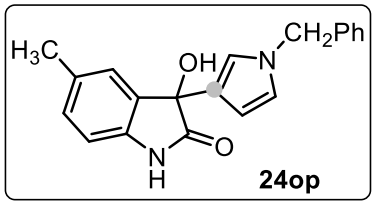


3-(1-(2-(1H-indol-3-yl)ethyl)-1*H*-pyrrol-3-yl)-3-hydroxy-1-methylindolin-2-one (24ne).

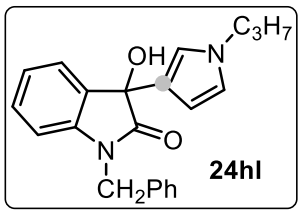


Purification with petroleum ether/EtOAc(3/2) as eluent; White solid (78 mg, 70% yield, mp = 144-147°C). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.48 (d, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 8.3 Hz, 2H), 7.12 (td, *J* = 7.3, 2.9 Hz, 2H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.77 – 6.74 (m, 1H), 6.59 (d, *J* = 2.2 Hz, 2H), 6.32 (t, *J* = 2.2 Hz, 1H), 4.06 (t, *J* = 7.0 Hz, 2H), 3.31 (s, 1H), 3.20 (s, 3H), 3.16 (t, *J* = 7.2 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 177.7, 143.1, 136.1, 131.4, 129.3, 127.1, 124.5, 122.9, 122.4, 122.3, 121.9, 121.5, 119.9, 119.3, 118.2, 112.0, 111.3, 108.4, 106.9, 74.1, 50.4, 27.6, 26.3. **HRMS (ESI)** *m/z*: $[M + H]^+$Calcd for $C_{23}H_{22}N_3O_2$ 372.1712; Found: 372.1717.

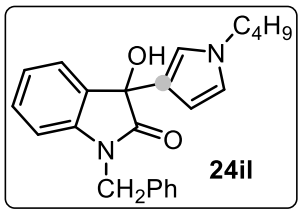
3-(1-benzyl-1H-pyrrol-3-yl)-3-hydroxy-5-methylindolin-2-one (24op) Purification with petroleum ether/EtOAc(3/2) as eluent; White solid (62 mg, 65% yield, mp = 197-200 °C). **^{1}H NMR (400 MHz, DMSO-d_6)** δ 10.02 (s, 1H), 7.32 (dd, *J* = 8.0, 6.4 Hz, 2H), 7.29 – 7.23 (m, 1H), 7.22 – 7.16 (m, 2H), 7.11 (d, *J* = 1.8 Hz, 1H), 6.98 (dd, *J* = 7.9, 1.8 Hz, 1H), 6.71 (t, *J* = 2.6 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 6.62 (d, *J* = 2.1 Hz, 1H), 6.02 (t, *J* = 2.3 Hz, 1H), 6.00 (s, 1H), 5.01 (s, 2H), 2.25 (s, 3H). **^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6)** δ 179.8, 139.7, 139.6, 134.8, 131.1, 129.6, 129.4 (2C), 128.3 (3C), 126.1, 124.8, 121.9, 120.2, 110.0, 108.2, 74.6, 53.1, 21.6. **HRMS (ESI)** *m/z*: $[M + H]^+$Calcd for $C_{20}H_{19}N_2O_2$ 319.1441; Found: 319.1447.



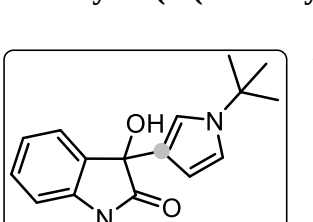
1-benzyl-3-hydroxy-3-(1-propyl-1*H*-pyrrol-3-yl)indolin-2-one (24hl). Purification with petroleum ether/EtOAc(7/3) as eluent; White solid (89 mg, 86% yield, mp = 231–235 °C). **^{1}H NMR (400 MHz, DMSO-d_6)** δ 7.42 (d, *J* = 6.7 Hz, 1H), 7.30 (d, *J* = 4.2 Hz, 4H), 7.25 (dt, *J* = 9.1, 4.5 Hz, 1H), 7.19 (td, *J* = 7.7, 1.1 Hz, 1H), 7.03 (t, *J* = 7.3 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.68 (t, *J* = 2.4 Hz, 1H), 6.56 (t, *J* = 1.9 Hz, 1H), 6.31 (s, 1H), 6.11 – 6.06 (m, 1H), 4.87 (q, *J* = 15.8 Hz, 2H), 3.74 (t, *J* = 7.1 Hz, 2H), 1.63 (h, *J* = 7.3 Hz, 2H), 0.79 (t, *J* = 7.4 Hz, 3H).**^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6)** δ 177.8, 142.2, 136.9, 133.8, 129.0 (3C), 127.8, 127.6 (2C), 124.8, 123.5, 122.8, 121.3, 119.6, 109.4, 107.3, 74.0, 50.8, 42.9, 24.8, 11.5. **HRMS (ESI)** *m/z*: $[M + H]^+$Calcd for $C_{22}H_{23}N_2O_2$ 347.1759; Found: 347.1767.



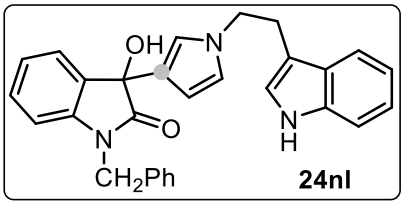
1-benzyl-3-(1-butyl-1*H*-pyrrol-3-yl)-3-hydroxyindolin-2-one (24il).Purification with petroleum ether/EtOAc(4/1) as eluent; Pale yellow solid, 95 mg, 88% yield, mp = 242-246 °C). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 7.46 – 7.41 (m, 1H), 7.31 (d, *J* = 4.4 Hz, 3H), 7.28 – 7.22 (m, 1H), 7.20 (td, *J* = 7.7, 1.2 Hz, 1H), 7.07 – 7.01 (m, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.68 (t, *J* = 2.5 Hz, 1H), 6.58 (t, *J* = 2.0 Hz, 1H), 6.32 (s, 1H), 6.10 (dd, *J* = 2.6, 1.8 Hz, 1H), 4.99 – 4.76 (m, 2H), 3.78 (t, *J* = 7.1 Hz, 2H), 1.64 – 1.55 (m, 2H), 1.21 (dq, *J* = 14.6, 7.3 Hz, 2H), 0.86 (t, *J* = 7.4 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, DMSO-*d*$_6$)** δ 177.3, 141.7, 136.5, 133.3, 128.5 (3C), 127.3, 127.1 (2C), 124.3, 123.0, 122.3, 120.8, 119.1, 108.9, 106.9, 73.5, 48.4, 42.4, 33.1, 19.3, 13.5. **HRMS (ESI**) *m/z*: $[M + H]^+$Calcd for $C_{23}H_{25}N_2O_2$ 361.1916; Found: 361.1924.



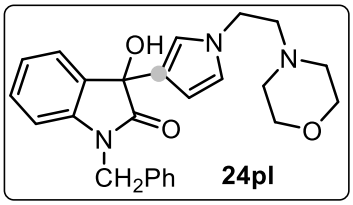
1-benzyl-3-(1-(*tert*-butyl)-1*H*-pyrrol-3-yl)-3-hydroxyindolin-2-one (24jl). Purification with petroleum ether/EtOAc(4/1) as eluent; White solid (98 mg, 91% yield, mp =174-176 °C). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.59 (d, *J* = 7.2 Hz, 1H), 7.29 (q, *J* = 2.9 Hz, 5H), 7.21 (td, *J* = 7.7, 1.1 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.91 (t, *J* = 2.1 Hz, 1H), 6.83 (t, *J* = 2.7 Hz, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 6.39 – 6.34 (m, 1H), 5.01 (d, *J* = 15.8 Hz, 1H), 4.86 (d, *J* = 15.8 Hz, 1H), 3.26 (s, 1H), 1.51 (s, 9H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$)** δ 177.8, 142.1, 135.6, 131.5, 129.1, 128.6 (2C), 127.4, 127.1 (2C), 124.5, 122.9, 122.0, 118.6, 116.7, 109.3, 106.4, 74.3, 55.0, 43.6, 30.6 (3C). **HRMS (ESI**) *m/z*: $[M + H]^+$Calcd for $C_{23}H_{25}N_2O_2$ 361.1916; Found: 361.1913.



3-(1-(2-(1*H*-indol-3-yl) ethyl)-1*H*-pyrrol-3-yl)-1-benzyl-3-hydroxyindolin-2-one (24nl). Purification with petroleum ether/EtOAc(3/2) as eluent; White solid (98 mg, 73% yield, mp =173-176 °C). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.11 (s, 1H), 7.52 – 7.45 (m, 2H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.28 (d, *J* = 3.6 Hz, 5H), 7.21 (t, *J* = 7.6 Hz, 2H), 7.10 (dt, *J* = 17.7, 7.5 Hz, 3H), 6.78 – 6.68 (m, 2H), 6.61 (d, *J* = 2.2 Hz, 1H), 6.33 (t, *J* = 2.2 Hz, 1H), 5.00 (d, *J* = 15.8 Hz, 1H), 4.84 (d, *J* = 15.8 Hz, 1H), 4.09 (t, *J* = 7.1 Hz, 2H), 3.17 (t, *J* = 7.1 Hz, 2H), 3.03 (s, 1H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 177.8, 142.2, 136.1, 135.7, 131.5, 129.2, 128.8 (2C), 127.6, 127.1 (3C), 124.6, 123.1, 122.6, 122.4, 122.0, 121.6, 119.8, 119.4, 118.3,

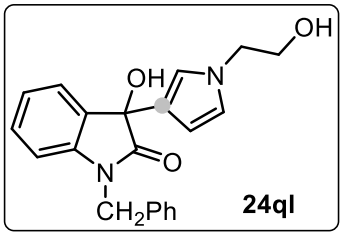


112.1, 111.3, 109.4, 106.8, 74.2, 50.5, 43.8, 27.7. **HRMS (ESI)** *m*/*z*: [M + H]$^+$Calcd for $C_{29}H_{26}N_3O_2$ 448.2025; Found: 448.2029.

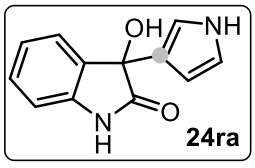


1-Benzyl-3-hydroxy-3-(1-(2-morpholinoethyl)-1*H*-pyrrol-3-yl) indolin-2-one (24pl). Purification with petroleum ether/EtOAc(4/1) as eluent; White solid (90 mg, 72% yield, mp =165-168 ^{o}C).**^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.53 (d, *J* = 7.3 Hz, 1H), 7.30 – 7.25 (m, 5H), 7.22 – 7.16 (m, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.74 (t, *J* = 2.1 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 6.66 (t, *J* = 2.6 Hz, 1H), 6.32 (t, *J* = 2.3 Hz, 1H), 5.03 – 4.79 (m, 2H), 3.94 (t, *J* = 6.9 Hz, 2H), 3.66 (t, *J* = 4.6 Hz, 4H), 2.68 (t, *J* = 6.9 Hz, 2H), 2.45 (t, *J* = 4.7 Hz, 4H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 177.1, 142.2, 135.6, 131.3, 129.3 (2C), 128.7, 127.6, 127.1 (2C), 124.5, 123.0 (2C), 121.9, 119.9, 109.5, 107.1, 74.1, 66.7 (2C), 59.3, 53.7 (2C), 47.1, 43.8. **HRMS (ESI)** *m*/*z*: [M + H]$^+$Calcd for $C_{25}H_{28}N_3O_3$ 418.2130; Found: 418.2128.

1-Benzyl-3-hydroxy-3-(1-(2-hydroxyethyl)-1*H*-pyrrol-3-yl) indolin-2-one (24ql). Purification with petroleum ether/EtOAc(3/2) as eluent; Light-yellow solid (85 mg, 81% yield, mp =167-170 ^{o}C).**^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.51 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.31 – 7.22 (m, 5H), 7.18 (td, *J* = 7.7, 1.3 Hz, 1H), 7.06 (td, *J* = 7.6, 1.0 Hz, 1H), 6.80 (t, *J* = 2.1 Hz, 1H), 6.69 (d, *J* = 7.8 Hz, 1H), 6.63 (t, *J* = 2.5 Hz, 1H), 6.27 (dd, *J* = 2.8, 1.8 Hz, 1H), 4.95 (d, *J* = 15.8 Hz, 1H), 4.80 (d, *J* = 15.8 Hz, 1H), 4.06 (s, 1H), 3.91 – 3.85 (m, 2H), 3.74 (t, *J* = 5.2 Hz, 2H), 2.85 (s, 1H). **^{13}C{^{1}H}NMR (101 MHz, CDCl$_3$)** δ 178.1, 142.0, 135.5, 131.6, 129.2, 128.7 (2C), 127.6, 127.1 (2C), 124.6, 123.2, 123.0, 122.0, 120.0, 109.5, 107.2, 74.3, 62.4, 52.2, 43.7. **HRMS (ESI)** *m*/*z*: [M + H]$^+$Calcd for $C_{21}H_{21}N_2O_3$ 349.1552; Found: 349.1546.

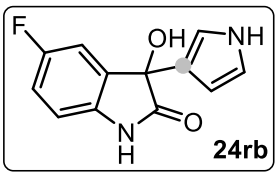


3-Hydroxy-3-(1*H*-pyrrol-3-yl) indolin-2-one (24ra). Purification with petroleum ether/EtOAc(1/1) as eluent; Brown solid (48 mg, 74% yield, mp =167-169 ^{o}C). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 7.30 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.19 (td, *J* = 7.7, 1.3 Hz, 1H), 6.97 (td, *J* = 7.5, 1.1 Hz, 1H), 6.82 (dd, *J* = 7.7, 0.8 Hz, 1H), 6.64 (dd, *J* = 2.8, 2.0 Hz, 1H), 6.48 (t, *J* = 1.8 Hz, 1H), 6.04

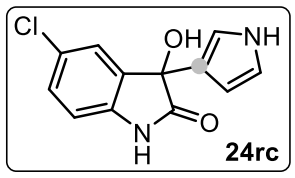


(dd, *J* = 2.8, 1.6 Hz, 1H), 3.74 (s, 1H). **$^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-*d*$_6$)** δ 179.6, 141.3, 134.0, 129.2, 125.0, 123.3, 122.2, 118.2, 116.5, 110.0, 107.1. **HRMS (ESI)** *m/z*: $[M + Na]^+$Calcd for $C_{12}H_{10}N_2O_2Na$ 237.0640; Found: 237.0632.

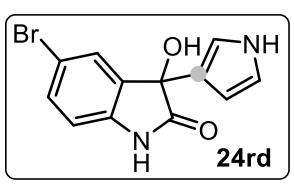
5-Fluoro-3-hydroxy-3-(1H-pyrrol-3-yl) indolin-2-one (24rb). Purification with petroleum ether/EtOAc(1/1) as eluent; Brown Solid (52 mg, 75% yield, mp =153-157 ^{o}C). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 7.12 (dd, *J* = 8.2, 2.7 Hz, 1H), 7.02 (ddd, *J* = 9.5, 8.4, 2.7 Hz, 1H), 6.82 (dd, *J* = 8.5, 4.4 Hz, 1H), 6.65 (t, *J* = 2.3 Hz, 1H), 6.51 (t, *J* = 1.8 Hz, 1H), 6.06 (dd, *J* = 2.8, 1.7 Hz, 1H). **$^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-*d*$_6$)** δ179.4, 158.5 (d, *J* = 237.2 Hz), 137.5, 136.9 (d, *J* = 7.4 Hz), 122.8, 118.4, 116.5, 115.3 (d, *J* = 23.4 Hz), 112.5 (d, *J* = 24.3 Hz), 110.9 (d, *J* = 7.8 Hz), 107.0, 74.5. **HRMS (ESI)** *m/z*: $[M + H]^+$Calcd for $C_{12}H_{10}FN_2O_2$ 233.0726; Found: 233.0723.



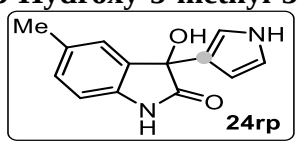
5-Chloro-3-hydroxy-3-(1*H*-pyrrol-3-yl) indolin-2-one (24rc). Purification with petroleum ether/EtOAc(1/1) as eluent; Brown Solid (54 mg, 73% yield, mp = 140-142^{o}C). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 7.40 (d, *J* = 1.9 Hz, 1H), 7.37 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.69 – 6.64 (m, 1H), 6.53 (s, 1H), 6.07 – 6.00 (m, 1H), 3.16 (s, 1H). **$^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-*d*$_6$)** δ 179.1, 140.3, 136.3, 128.9, 126.1, 124.9, 122.8, 118.5, 116.5, 111.6, 106.9, 74.3. **HRMS (ESI)** *m/z*: $[M + H]^+$Calcd for $C_{12}H_{10}ClN_2O_2$ 249.0431; Found: 249.0437.



5-Bromo-3-hydroxy-3-(1*H*-pyrrol-3-yl)indolin-2-one (24rd). Purification with petroleum ether/EtOAc(1/1) as eluent; Reddish solid (61 mg, 71% yield, mp = 156-158 ^{o}C). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 7.40 (d, *J* = 1.9 Hz, 1H), 7.37 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.68 – 6.65 (m, 1H), 6.53 (s, 1H), 6.04 (dd, *J* = 2.5, 1.5 Hz, 1H), 3.16 (s, 1H). **$^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-*d*$_6$)** δ 179.00, 140.8, 136.7, 131.8, 127.6, 122.8, 118.5, 116.5, 113.8, 112.2, 106.9, 74.3. **HRMS (ESI)** *m/z*: $[M + H]^+$Calcd for $C_{12}H_{10}BrN_2O_2$ 292.9925; Found: 292.9929.

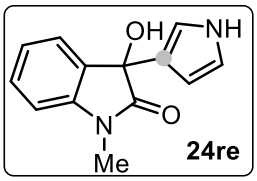


3-Hydroxy-5-methyl-3-(1*H*-pyrrol-3-yl)indolin-2-one (24rp). Purification with petroleum ether/EtOAc(3/2) as eluent; White solid (48 mg, 70% yield, mp = 161-164 °C).**^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 7.11 (s, 1H), 7.00 (d, *J* =

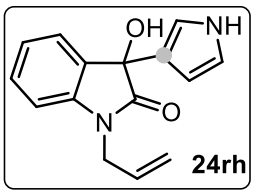


8.7 Hz, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 6.65 – 6.62 (m, 1H), 6.50 (t, *J* = 1.7 Hz, 1H), 6.04 (dd, *J* = 2.7, 1.6 Hz, 1H), 2.24 (s, 3H). **$^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-*d*$_6$)** δ 179.5, 138.9, 134.2, 131.0, 129.3, 125.6, 123.5, 118.1, 116.4, 109.7, 107.1, 74.3, 21.1. **HRMS (ESI)** *m*/*z*: $[M + H]^+$Calcd for $C_{13}H_{13}N_2O_2$ 229.0977; Found: 229.0983.

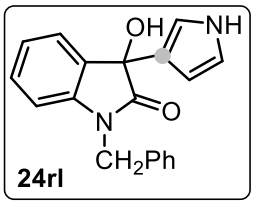
3-hydroxy-1-methyl-3-(1*H*-pyrrol-3-yl)indolin-2-one (24re). Purification with petroleum ether/EtOAc(3/2) as eluent; White solid (48 mg, 72% yield, mp = 181-184 °C). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 10.66 (s, 1H), 7.39 (dd, *J* = 7.3, 1.3 Hz, 1H), 7.31 (td, *J* = 7.7, 1.3 Hz, 1H), 7.06 (td, *J* = 7.5, 1.0 Hz, 1H), 6.98 (d, *J* = 7.7 Hz, 1H), 6.66 (q, *J* = 2.4 Hz, 1H), 6.50 (q, *J* = 2.1 Hz, 1H), 6.12 (s, 1H), 6.10 (dt, *J* = 4.1, 2.0 Hz, 1H), 3.10 (s, 3H). **$^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-*d*$_6$)** δ 177.2, 142.8, 133.2, 128.6, 124.1, 122.9, 122.1, 117.8, 116.3, 108.2, 106.8, 73.4, 25.8. **HRMS (ESI)** *m*/*z*: $[M + Na]^+$Calcd for $C_{13}H_{13}N_2O_2$ 251.0791; Found: 251.0782.



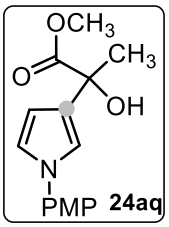
1-Allyl-3-hydroxy-3-(1*H*-pyrrol-3-yl) indolin-2-one (24rh). Purification with petroleum ether/EtOAc(3/2) as eluent; White solid (56 mg, 73% yield, mp = 170-174 °C).**^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 10.68 (s, 1H), 7.40 (d, *J* = 7.2 Hz, 1H), 7.27 (t, *J* = 7.7 Hz, 1H), 7.05 (t, *J* = 7.3 Hz, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 6.67 (p, *J* = 2.4 Hz, 1H), 6.53 (t, *J* = 2.2 Hz, 1H), 6.20 (d, *J* = 2.0 Hz, 1H), 6.09 (t, *J* = 2.3 Hz, 1H), 5.89 – 5.78 (m, 1H), 5.19 – 5.08 (m, 2H), 4.38 – 4.18 (m, 2H). **$^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-*d*$_6$)** δ 177.5, 142.3, 133.8, 132.5, 129.0, 124.7, 123.6, 122.6, 118.4, 117.0, 116.6, 109.3, 107.1, 74.0, 41.7. **HRMS (ESI)** *m*/*z*: $[M + H]^+$Calcd for $C_{15}H_{14}N_5O_2$ 255.1133; Found: 255.1129.



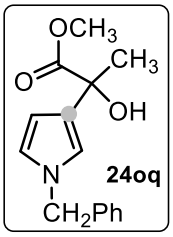
1-Benzyl-3-hydroxy-3-(1*H*-pyrrol-3-yl) indolin-2-one (24rl). Purification with petroleum ether/EtOAc(3/2) as eluent; Purple solid (65 mg, 71% yield, mp = 169-171 °C).**^{1}H NMR (400 MHz, CDCl$_3$)** δ 4.60 – 4.75 (m, 1H), 4.83 (dt, *J* = 16.2, 5.1 Hz, 1H), 6.22 (dd, *J* = 6.6, 3.4 Hz, 1H), 6.50 – 6.69 (m, 3H), 6.94 (td, *J* = 7.5, 2.8 Hz, 1H), 7.06 (td, *J* = 7.7, 2.6 Hz, 1H), 7.11 – 7.24 (m, 5H), 7.40 (dt, *J* = 9.9, 4.9 Hz, 1H), 9.50 (s, 1H). **$^{13}C\{^{1}H\}$ NMR (101 MHz, CDCl$_3$)** δ 177.8, 141.7, 135.4, 128.5, 128.3 (2C), 127.1, 126.7 (2C), 124.3, 122.5, 118.3, 118.1, 116.6, 116.4, 108.8, 106.4, 73.8, 43.2. **HRMS (ESI)** *m*/*z*: $[M + H]^+$Calcd for $C_{19}H_{17}N_2O_2$ 305.1290; Found: 305.1296.



Methyl 2-hydroxy-2-(1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)propanoate (24aq). Purification

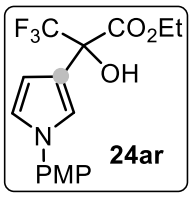


with petroleum ether/EtOAc(9/1) as eluent; Reddish oil (52 mg, 62% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.28 (d, *J* = 9.0 Hz, 2H), 7.02 (dd, *J* = 2.3, 1.8 Hz, 1H), 6.95 – 6.90 (m, 3H), 6.31 (dd, *J* = 2.9, 1.8 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 1.77 (s, 3H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)** δ 176.6, 157.8, 134.2, 128.6, 122.1 (2C), 120.0, 116.8, 114.6 (2C), 107.9, 72.8, 55.5, 53.0, 26.7. **HRMS (ESI)** *m*/*z*: [M + H]$^+$Calcd for $C_{15}H_{18}NO_4$ 276.1230; Found: 276.1236.



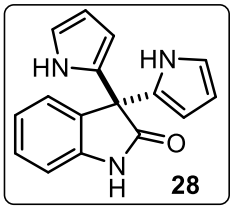
Methyl 2-(1-benzyl-1*H*-pyrrol-3-yl)-2-hydroxypropanoate (24oq). Purification with petroleum ether/EtOAc(9/1) as eluent; Brown oil (53 mg, 68% yield).**^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.37–7.26 (m, 3H), 7.17–7.11 (m, 2H), 6.74 (t, *J* = 2.1 Hz, 1H), 6.61 (t, *J* = 2.6 Hz, 1H), 6.21 (dd, *J* = 2.8, 1.8 Hz, 1H), 5.00 (s, 2H), 3.77 (s, 3H), 3.64 (s, 1H), 1.76 (s, 3H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)** δ 179.5, 137.5, 128.5 (2C), 127.6, 127.2, 127.0 (2C), 121.2, 118.1, 106.4, 72.7, 53.3, 52.7, 26.5. **HRMS (ESI)** *m*/*z*: [M + H]$^+$Calcd for $C_{15}H_{18}NO_3$ 260.1281; Found: 260.1276.

Ethyl 3,3,3-trifluoro-2-hydroxy-2-(1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)propanoate (24ar).



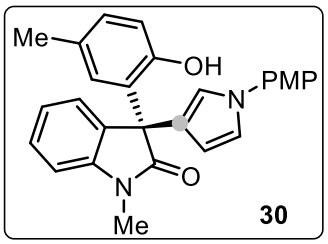
Purification with petroleum ether/EtOAc(9/1) as eluent; Slight yellow oil (74 mg, 72% yield).**^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.31 (d, *J* = 8.9 Hz, 2H), 7.23 (t, *J* = 2.1 Hz, 1H), 6.99 – 6.94 (m, 3H), 6.51 (DDT, *J* = 2.6, 1.7, 0.9 Hz, 1H), 4.50 – 4.37 (m, 2H), 4.34 – 4.21 (m, 1H), 3.85 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)** δ 169.4, 158.0, 133.9, 123.1 (q, *J* = 285.4 Hz), 122.3 (2C), 120.2, 119.3, 118.1, 114.7 (2C), 109.1, 75.8 (q, *J* = 31.5 Hz), 64.0, 55.5, 13.9. **HRMS (ESI)** *m*/*z*: [M + H]$^+$Calcd for $C_{16}H_{17}F_3NO_4$ 344.1104; Found: 260.1094.

3,3-di(1*H*-pyrrol-2-yl)indolin-2-one (28). Purification with petroleum ether/EtOAc(3/1) as

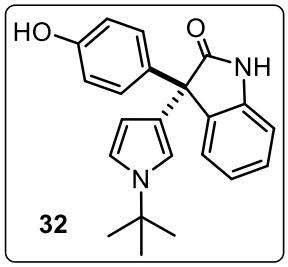


eluent; White solid (41 mg, 52% yield, mp =126-129 ^{o}C).**^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.74 (s, 2H), 7.54 (d, *J* = 7.4 Hz, 1H), 7.35 (t, *J* = 7.7 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 6.77 – 6.68 (m, 2H), 6.11 (q, *J* = 3.0 Hz, 2H), 5.98 (d, *J* = 3.3 Hz, 2H), 3.25 (s, 3H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)** δ 176.2, 142.9, 131.0, 128.8, 128.7, 125.2, 123.2, 118.4 (2C), 108.8, 108.4 (2C), 106.9 (2C), 52.1, 26.6. **HRMS (ESI)** *m*/*z*: [M + H]$^+$Calcd for $C_{16}H_{14}N_3O$264.1137; Found 264.1145.

3-(2-hydroxy-5-methylphenyl)-3-(1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)-1-methylindolin-2-one (30). Purification with petroleum ether/EtOAc(4/1) as eluent; White solid (108 mg, 85% yield, mp = 208–211 °C).**^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.57 (d, *J* = 7.2 Hz, 1H), 7.34 (q, *J* = 5.8, 3.6 Hz, 2H), 7.29 (d, *J* = 7.0 Hz, 1H), 7.22 (d, *J* = 8.9 Hz, 2H), 7.12 (dt, *J* = 14.2, 7.0 Hz, 3H), 6.97 – 6.94 (m, 1H), 6.94 – 6.91 (m, 1H), 6.87 (dd, *J* = 13.9, 8.4 Hz, 3H), 6.52 – 6.46 (m, 1H), 3.80 (s, 3H), 3.20 (s, 3H), 2.32 (s, 3H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)** δ 177.6, 157.8, 143.1, 140.1, 133.9, 132.0, 131.0, 129.7, 129.5, 128.4, 127.6, 124.5, 124.3, 123.1, 122.2 (3C), 120.7, 118.7, 114.5 (2C), 108.6, 108.5, 74.0, 55.5, 26.3, 21.1.**HRMS (ESI)** *m*/*z*: [M + H]$^+$Calcd for $C_{27}H_{25}N_2O_3$ 425.1865; Found 425.1871.



3-(1-(*tert*-butyl)-1H-pyrrol-3-yl)-3-(4-hydroxyphenyl)indolin-2-one (32). Purification with petroleum ether/EtOAc(3/2) as eluent; White solid (236 mg, 92% yield, mp = 203–206 °C).**^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.66 (s, 1H), 7.25 (s, 1H), 7.20 (td, *J* = 7.7, 1.3 Hz, 1H), 7.08 (d, *J* = 8.7 Hz, 2H), 7.04 (td, *J* = 7.6, 1.1 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 6.80 – 6.74 (m, 2H), 6.68 (d, *J* = 8.7 Hz, 2H), 6.12 (dd, *J* = 2.9, 1.9 Hz, 1H), 5.04 (s, 1H), 1.48 (s, 9H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, few drops of DMSO-d_6 was added)** δ 180.1, 155.5, 135.4, 133.0, 128.4 (2C), 127.0, 124.9, 121.8, 121.5, 117.3, 116.5, 114.7, 114.6 (2C), 109.4, 107.2, 56.5, 54.2, 30.3 (3C). **HRMS (ESI)** *m*/*z*: [M + H]$^+$Calcd for $C_{22}H_{23}N_2O_2$ 347.1754; Found 347.1745.



2.7 Single-crystal X-ray Diffraction Experiment and Analysis

2.7.1 Crystal Structure Data Tables for compound (24ae): The structure of the compound 3-hydroxy-3-(1-(4-methoxyphenyl)-1H-pyrrol-3-yl)-1-methylindolin-2-one **24ae** ($C_{20}H_{18}N_2O_3$) (**CCDC-1825913)** has been established by X-ray diffraction studies. The compound crystallizes in the triclinic space group P-1with unit cell parameters: a = 8.5340(5), b = 10.2010(5), c = 11.6720 (5) Å, α=90.880(5), β=110.076(5), ɤ=114.477(5)° and Z= 2. The crystal structure was solved by direct methods using single-crystal X-ray diffraction data and refined to R = 0.1463 for 1852 observed reflections.

Crystal Structure Determination and Refinement (24ae): X-ray intensity data of 5442 reflections (of which 2981 unique) were collected at 293(2) K *X'calibur system – Oxford*

diffraction make, U.K. equipped with graphite monochromatedMo$K\alpha$ radiation (λ=0.71073 Å). The crystal used for data collection was of dimensions 0.3 x 0.2 x 0.1 mm. The intensities were measured by ω scan mode for θ ranges 3.68 to 25.00°. 1852 reflections were treated as observed ($I > 2\sigma(I)$). Data were corrected for absorption, Extinction and Lorentz, and polarization factors. The structure was solved by direct methods using SHELXS97.[58]All non-hydrogen atoms of the molecule were in the best E-map. Full-matrix least-squares refinement was carried out using SHELXL97.[59]All the hydrogen atoms were geometrically fixed and allowed to ride on their parent carbon atoms with C-H= 0.84-0.96 Å. The final refinement cycles converged to an R = 0.1463 and $wR(F^2)$ = 0.4146 for the observed data. Residual electron densities ranged from -0.509 to 0.461 $eÅ^{-3}$. Atomic scattering factors were taken from International Tables for X-ray Crystallography. The crystallographic data of **24ae** are summarized in Table2.5The geometry of the molecule was calculated using the PLATON[60] and PARST[61] software. An ORTEP view of the title compound with atomic labeling and packing view of the molecules in the unit cell viewed down the a-axis is shown in Figure 2.2.

Table 2.5: Crystal and experimental data of compound (**24ae**).

CCDC No. 1825913	
Crystal description	block
Crystal color transparent	
Crystal size	0.30 x 0.20 x 0.10 mm
Empirical formula	$C_{20}H_{18}N_2O_3$
Formula weight	334.36
Radiation, Wavelength	Mo *K*α, 0.71073 Å
Unit cell dimensions	a=8.5340(5), b=10.2010(5), c=11.6720(5) Å
	α=90.880(5)°, β=110.076(5)°, ɤ=114.477(5)°
Crystal system	Triclinic
Space group	P-1

Unit cell volume	853.71(4)
No. of molecules per unit cell, Z	2
Temperature	293(2)
Absorption coefficient	0.089 mm^{-1}
F(000)	352
Scan mode	ω scan
θ range for entire data collection	3.76 <θ< 25.00 º
Range of indices	h= -9 to 10, k= -12 to 12, l= -11 to 13
Reflections collected / unique	5442 / 2981
Absorption correction	Multi-scan CrysAlis RED
Reflections observed (I > 2σ (I))	1852
R_{int}	0.0602
R_{sigma}	0.0924
Structure determination	direct methods
Refinement	Full-matrix least-squares on F^2
No. of parameters refined	241
No. of Restraints	1.425
Final R	0.1463
wR(F^2)	0.4146
Weight	$1/[\sigma^2(F_o^2)+(0.2000 P)^2+0.0000P]$
Where P = $[F_o^2 +2F_c^2] / 3$	
Goodness-of-fit	1.425
$(\Delta /\sigma)_{max}$	0.000
Final residual electron density	-0.509 <Δρ< 0.461 $eÅ^{-3}$

Measurement	*X'calibur system - Oxford diffraction make, U.K.*
Software for structure solution:	SHELXS97 (Sheldrick, 2008)
Software for refinement:	SHELXL97 (Sheldrick, 2008)
Software for molecular plotting:	ORTEP-3 (Farrugia, 2012)PLATON (Spek, 2009)

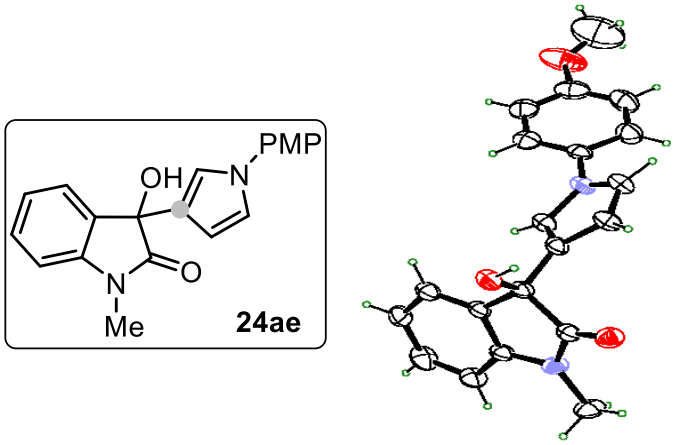


Figure 2.2: The ORTEP view of (**24ae**) and Packing view of the molecule viewed down the a-axis. (The thermal ellipsoids are drawn to the 40% probability level.)

2.7.2 Single Crystal XRD Experiments for 24ja

The single-crystal XRD data collection and data reduction were performed using CrysAlis PRO on a single-crystal Rigaku Oxford XtaLab Pro diffractometer. The crystals were kept at 93(2) K during data collection using CuKα (λ = 1.54184 Å) radiation. Using Olex2[62], the structure was solved with the ShelXT[63] structure solution program using Intrinsic Phasing and refined with the ShelXL[64] refinement package using Least Squares minimization.

Single Crystal structure data of compound (24ja)

Single Crystal structure, Cell parameters, and structure data of compound (24ja)

The single crystals suitable for XRD data collection were obtained from an ethyl acetate-hexane solvent mixture as light red blocks. The compound **24ja** ($C_{16}H_{18}N_2O_2$) crystallized in a monoclinic, P21/c crystal group and crystallized as a racemic mixture with a total of four molecules (Z=4), two enantiomers found per unit cell. The compound 24ja (CCDC 1973218) crystal structure is shown in Figure 2.3, whereas crystal packing is shown in Figure 2.4. The detailed crystallographic data of **24ja** are summarized in Table 2.6.

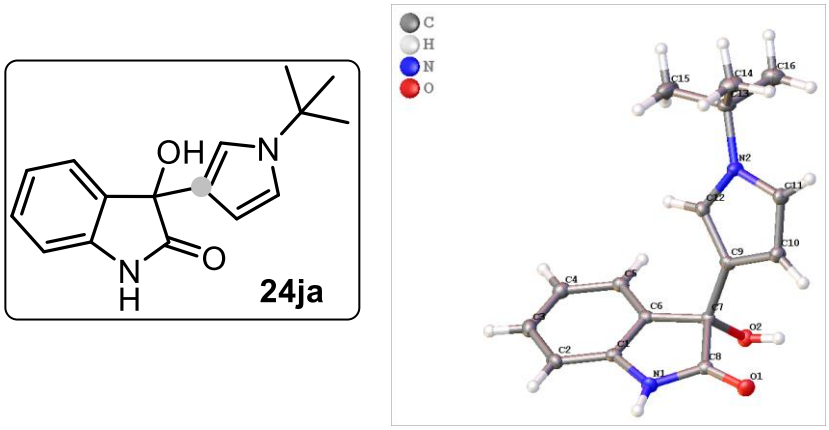


Figure 2.3. Crystal structure of compound **24ja** (**CCDC 1973218**)**.** (The thermal ellipsoids are drawn to the 50% probability level.)

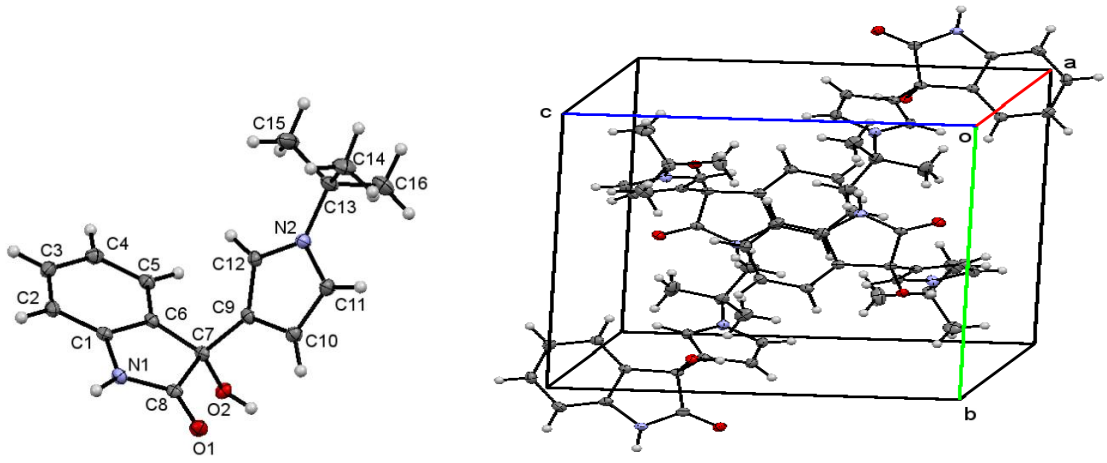


Figure 2.4 Crystal packing in a unit cell. Four molecules per unit cell (Z=4), consisting of a 1:1 enantiomeric racemic mixture.

The Crystal Data for $C_{16}H_{18}N_2O_2$ (**24ja**) (*M* =270.32 g/mol): monoclinic, space group $P2_1/c$ (no. 14), *a* = 10.8918(2) Å, *b* = 10.9673(2) Å, *c* = 11.9061(3) Å, *β* = 102.324(2)°, *V* = 1389.45(5) $Å^3$, *Z* = 4, *T* = 93(2) K, μ(CuKα) = 0.692 mm^{-1}, *Dcalc* = 1.292 g/cm^3, 7404 reflections measured (8.31° ≤ 2Θ ≤ 159.908°), 2934 unique (R_{int} = 0.0264, R_{sigma} = 0.0317) which were used in all calculations. The final R_1 was 0.0400 (I > 2σ(I)), and wR_2 was 0.1088 (all data).

Table 2.6: Crystal data and structure refinement for Compound (24ja).

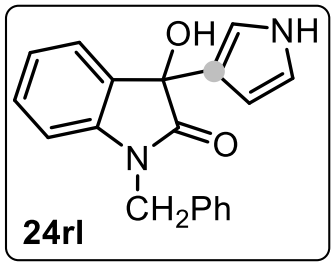
Identification code	exp_518_INDRESH-01
Empirical formula	$C_{16}H_{18}N_2O_2$
Formula weight	270.32
Temperature/K	93(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	10.8918(2)
b/Å	10.9673(2)
c/Å	11.9061(3)
α/°	90
β/°	102.324(2)
γ/°	90
Volume/Å^3	1389.45(5)
Z	4
ρ_{calc}g/cm^3	1.292
μ/mm^{-1}	0.692
F(000)	576.0
Crystal size/mm^3	0.1 × 0.08 × 0.03
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.31 to 159.908
Index ranges	$-13 \leq h \leq 13$, $-8 \leq k \leq 13$, $-15 \leq l \leq 14$
Reflections collected	7404
Independent reflections	2934 [R_{int} = 0.0264, R_{sigma} = 0.0317]
Data/restraints/parameters	2934/0/185
Goodness-of-fit on F^2	1.056
Final R indexes [I>=2σ (I)]	R_1 = 0.0400, wR_2 = 0.1058

Final R indexes [all data]	R_1 = 0.0433, wR_2 = 0.1088
Largest diff. peak/hole / e Å^{-3}	0.23/-0.28

2.7.3 Single Crystal XRD Experiments for 24rl

The single-crystal XRD data collection and data reduction were performed using CrysAlis PRO on a single-crystal Rigaku Oxford XtaLab Pro diffractometer. The crystals were kept at 93(2) K during data collection using CuKα (λ = 1.54184 Å) radiation. Using Olex2[62], the structure was solved with the ShelXT[63] structure solution program using Intrinsic Phasing and refined with the ShelXL[64] refinement package using Least Squares minimization.

The single crystals suitable for XRD data collection were obtained from Ethyl acetate-hexane solvent mixture as colorless blocks. The compound (**24rl**), $C_{19}H_{16}N_2O_2$, crystallized in a monoclinic, $P2_1/n$ crystal group and crystallized as a racemic mixture with a total of four molecules (Z=4), two each of enantiomers, found per unit cell. The crystal structure of the compound (**24rl**) **(CCDC 1973219)** is shown in Figure 2.5, whereas crystal packing is shown in Figure 2.6. The detailed crystallographic data of **24rl** are summarized in Table 2.7.



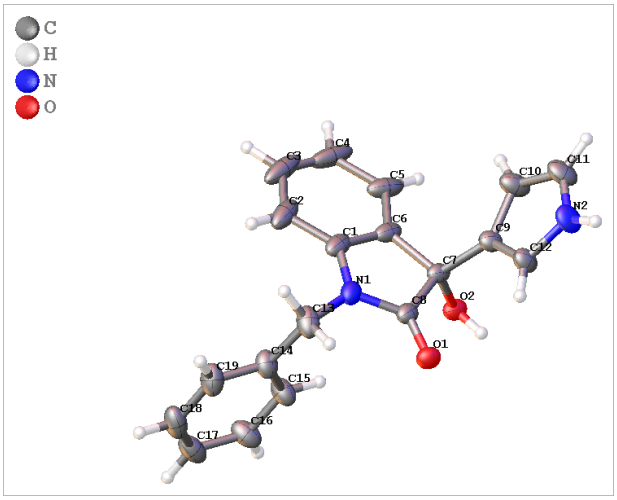


Figure 2.5. Crystal structure of compound (**24rl**) **(CCDC 1973219)**. (The thermal ellipsoids are drawn to the 50% probability level.)

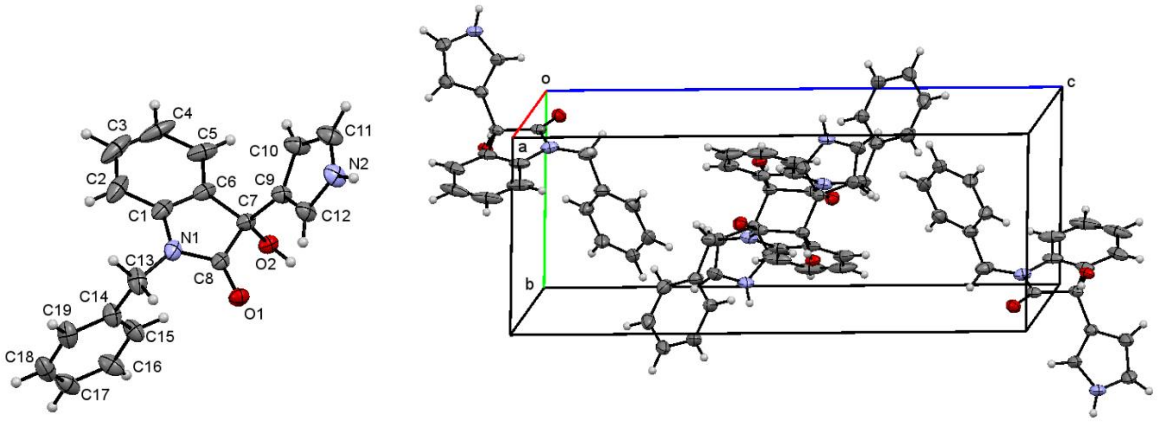


Figure 2.6. Crystal packing in a unit cell. Four molecules per unit cell (Z=4), consisting of a 1:1 enantiomeric racemic mixture.

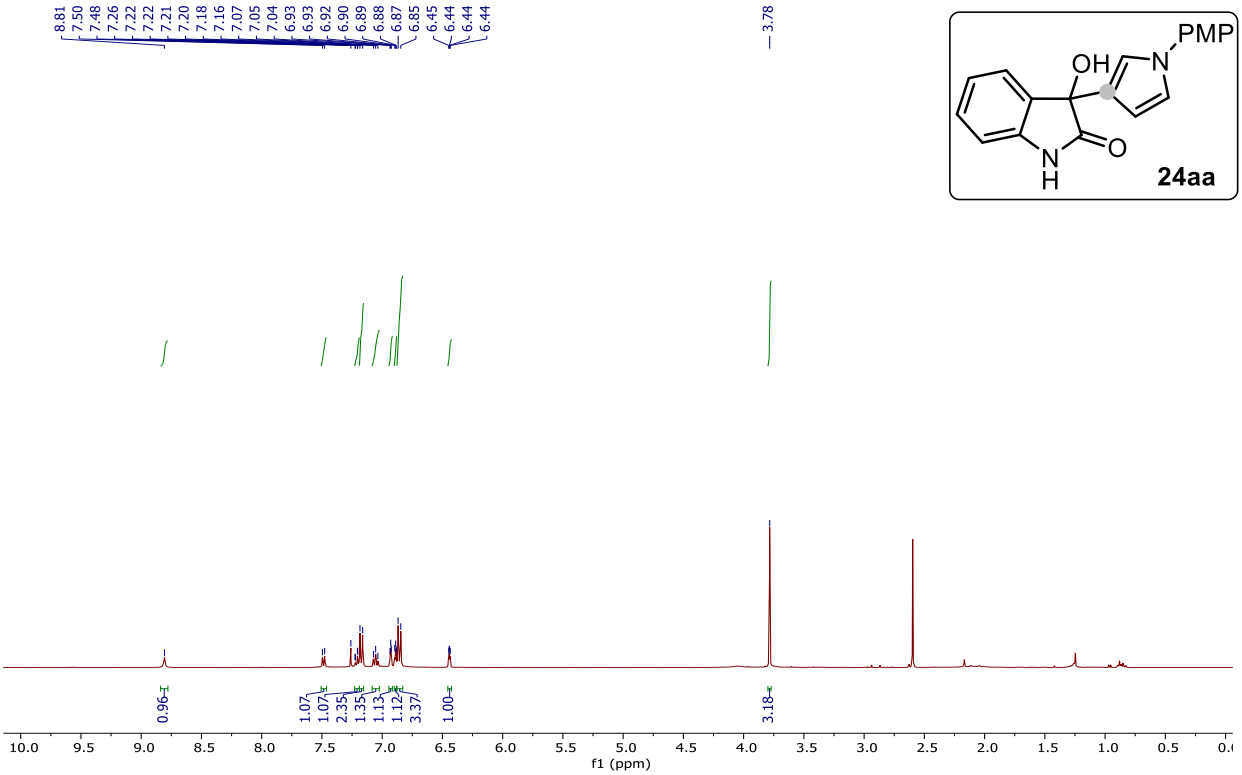
The Crystal Data for $C_{19}H_{16}N_2O_2$ (**24rl**) (*M* =304.34 g/mol): monoclinic, space group $P2_1/n$ (no. 14), *a* = 11.2879(2) Å, *b* = 7.27320(10) Å, *c* = 19.0032(3) Å, *β* = 103.460(2)°, *V* = 1517.29(4) $Å^3$, *Z* = 4, *T* = 93(2) K, μ(CuKα) = 0.705 mm^{-1}, *Dcalc* = 1.332 g/cm^3, 7899 reflections measured (8.356° ≤ 2Θ ≤ 160.764°), 3183 unique (R_{int} = 0.0296, R_{sigma} = 0.0339) which were used in all calculations. The final R_1 was 0.0442 (I > 2σ(I)), and wR_2 was 0.1213 (all data).

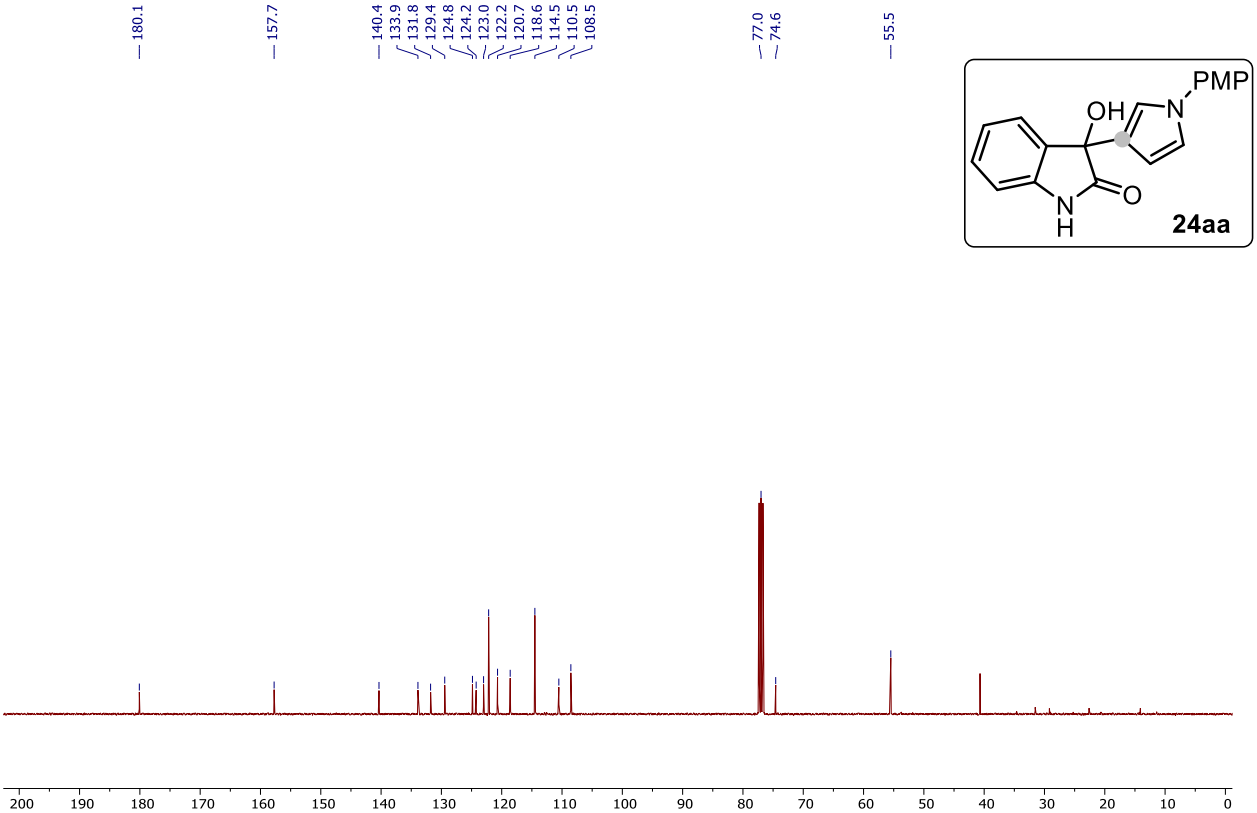
Table 2.7: Crystal data and structure refinement for compound (24rl).

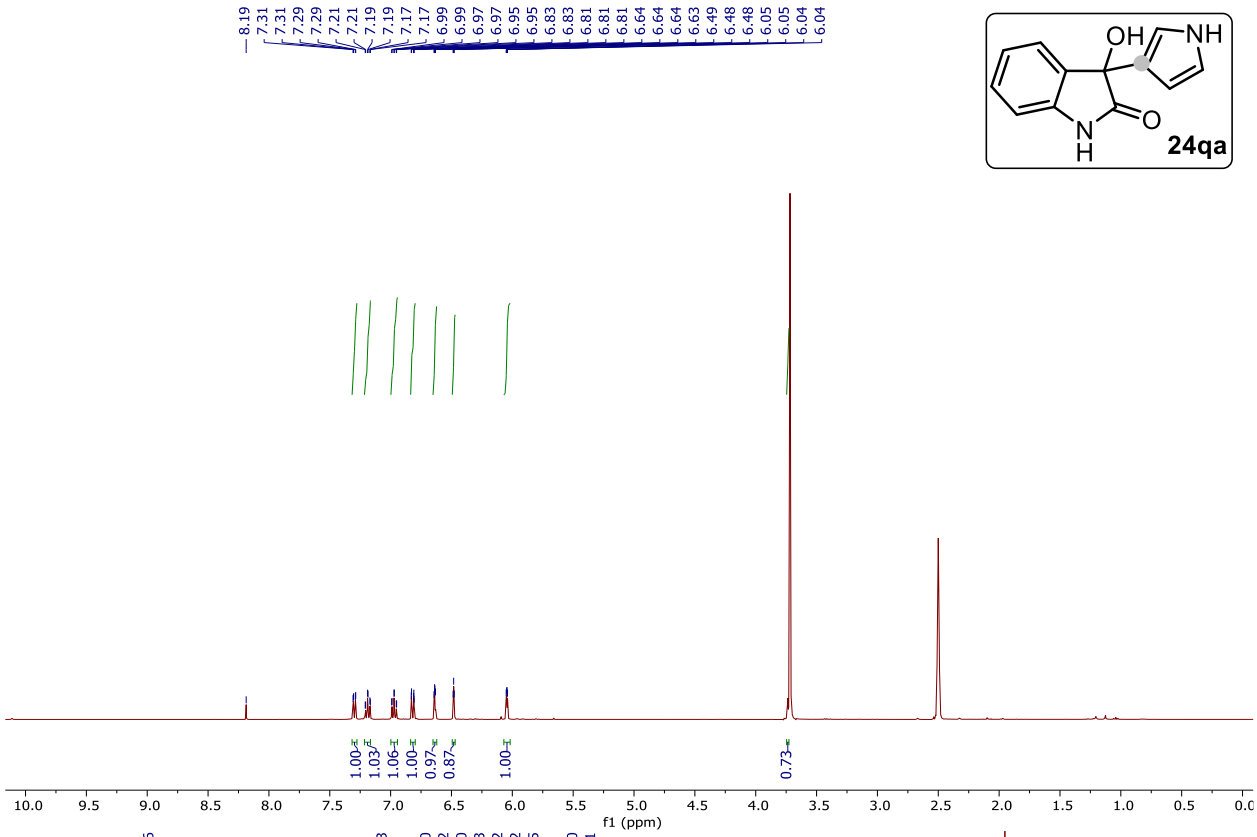
Identification code	exp_534_INDRESH-AP-CH2Ph-Fr-NH
Empirical formula	$C_{19}H_{16}N_2O_2$
Formula weight	304.34
Temperature/K	93(2)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	11.2879(2)
b/Å	7.27320(10)
c/Å	19.0032(3)
α/°	90
β/°	103.460(2)
γ/°	90
Volume/$Å^3$	1517.29(4)
Z	4

$\rho_{calc}g/cm^3$	1.332
μ/mm^{-1}	0.705
F(000)	640.0
Crystal size/mm^3	0.15 × 0.13 × 0.05
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.356 to 160.764
Index ranges	$-14 \leq h \leq 13$, $-8 \leq k \leq 8$, $-24 \leq l \leq 24$
Reflections collected	7899
Independent reflections	3183 [R_{int} = 0.0296, R_{sigma} = 0.0339]
Data/restraints/parameters	3183/0/209
Goodness-of-fit on F^2	1.082
Final R indexes [I>=2σ (I)]	R_1 = 0.0442, wR_2 = 0.1187
Final R indexes [all data]	R_1 = 0.0475, wR_2 = 0.1213
Largest diff. peak/hole / e $Å^{-3}$	0.18/-0.28

2.8 Spectral Information






8.19
7.31
7.31
7.29
7.29
7.21
7.21
7.19
7.19
7.17
7.17
6.99
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6.97
6.97
6.95
6.95
6.83
6.83
6.81
6.81
6.81
6.64
6.64
6.64
6.63
6.49
6.48
6.48
6.05
6.05
6.04
6.04
OH
NH
O
N
H
24qa
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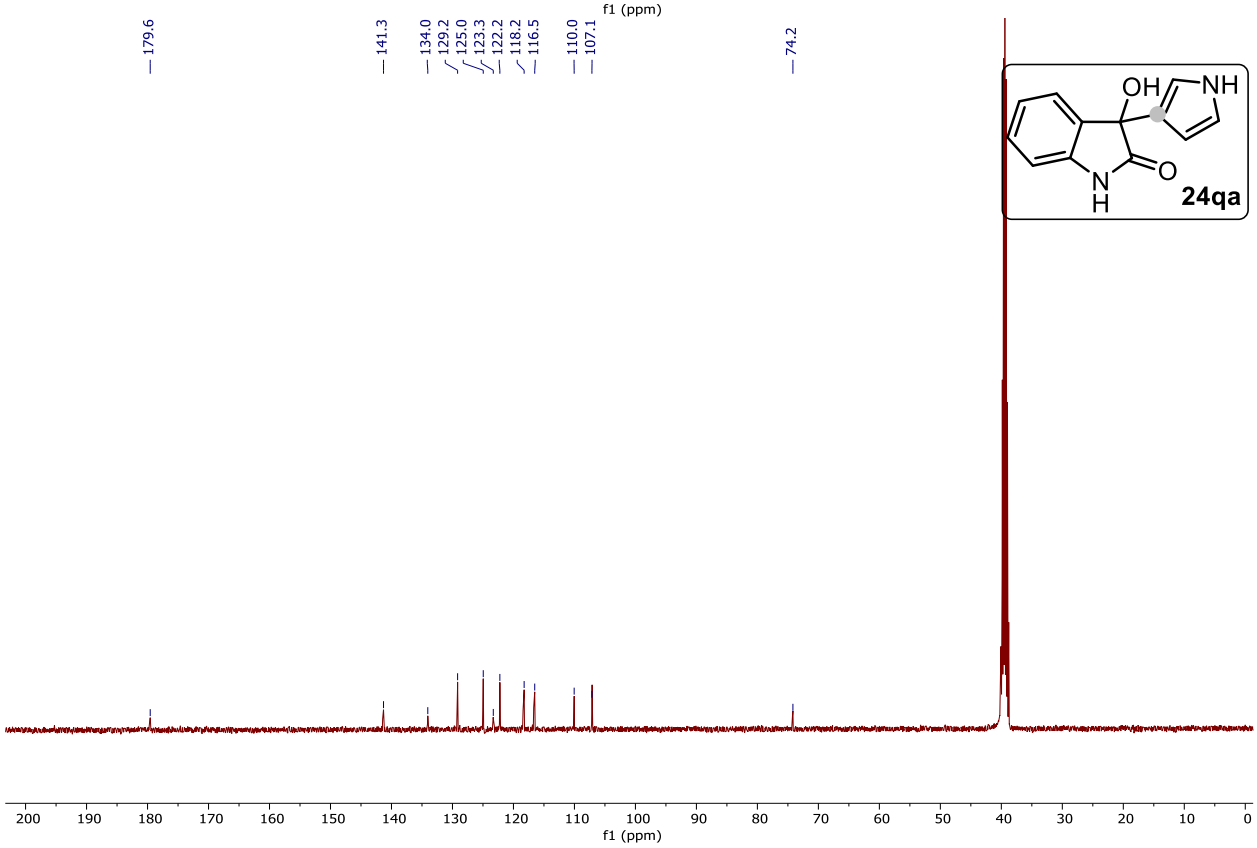
1.03
1.06
1.00
0.97
0.87
1.00
0.73
f1 (ppm)


179.6
141.3
134.0
129.2
125.0
123.3
122.2
118.2
116.5
110.0
107.1
74.2
OH
NH
O
N
H
24qa
f1 (ppm)

2.9 References

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Chapter 3

Catalyst-free Regiospecific Multicomponent Synthesis of C3-Functionalized Pyrroles

3.1 Introduction

Nitrogen-bearing heterocyclic compounds have gained significant attention in material chemistry, pharmaceutical chemistry, and synthetic organic chemistry. Nitrogen heterocyclic is more in number among the entire heterocyclic scaffold present in nature. The permutation of diversity-altered pharmacophores in a saturated ring has led to forming more active compounds. The five-member nitrogen heterocyclic system, i.e., Pyrrole, is essential to several natural products.[1a-d] Pyrrole is used in pharmaceuticals, and [1e-h is] also in the materials chemistry branch.[2] For this purpose, the chemist developed synthetic protocols such as metal-catalyzed reactions,[3] multicomponent reactions,[4] classical techniques,[5] and other strategies[6] to synthesize pyrrole-containing nine molecules. The Pyrrole was reactive at the C2-position because of the most stable resonating structure, which is well explored.[7] Comparatively, access to C3-functionalized Pyrrole is a challenging task that requires multistep/indirect strategies and is being studied with limited scope.[8-9] α-substitution often dominates pyrroles' electrophilic aromatic substitution (S_EAr) reaction. When a pyrrole protects with a bulky group or an electron-withdrawing group (EWG), the electrophile is forced into the C3-position. It must be an additional step to eliminate the EWG or bulky group. Nonetheless, the attachment/removal of the directing groups and the scarcity of readily available starting materials or catalysts posed a barrier to synthesizing the Pyrrole functionalized motif. To the stoichiometric conversions of Pyrrole and the isomeric mixture, formation is a limitation of this multistep approach.

Moreover, metal-catalyzed C-H activation helps synthesize pyrrole C3-arylation,[10] C3-alkylation[11-13] and other protocols were added in Chapter 1.[14-16] The critical intermediate in synthesizing Pyrrole, or a naturally occurring chemical is yet unknown when the compound is functionalized at the C3-position. Moreover, C3-functionalized pyrroles are present in bioactive compounds and serve as a suitable substrate for accessing more complex natural products. In that pyrrole motif containing alkaloids like as prodigiosin family is particularly remarkable for their diverse range of biological effects as synergistically with cyclosporine A or FK506, as drug-like molecules,[17] alkaloid rhazinicine acts as potent cytotoxicity toward human KB, HCT-116, MDA-MB-231, and MRC-5 cells overall as antitumor agent,[18] it also helps to synthesize pyroglutamic acid which is mainly used in human as memory recall,[19] also help to synthesis of alkaloids rhazinilam this primarily act as spindle poison to stop the

mitosis phase of cell division,[20] in same way synthesis of the Pyrrole intermediate like HIV inhibitor,[21a] Aloracetam for Alzheimer's disease treatment,[21b] resminostst where use antineoplastic agent is an orally bioavailable inhibitors of histone diacetylene,[21c] Spiroindimicin B alkaloid is used for cytotoxicity activity,[21d] Verrucarin-E for anti-mitotic,[21e] Pyrrolnitrin as antifungal and BODIPY as bis-pyrrole or polymeric compound in functional materials (selected examples **I-VIII** are shown in Figure 3.1).[22] Thus, developing a direct *de novo* synthesis of C3-substituted Pyrrole from simple starting material will be exciting to explore.

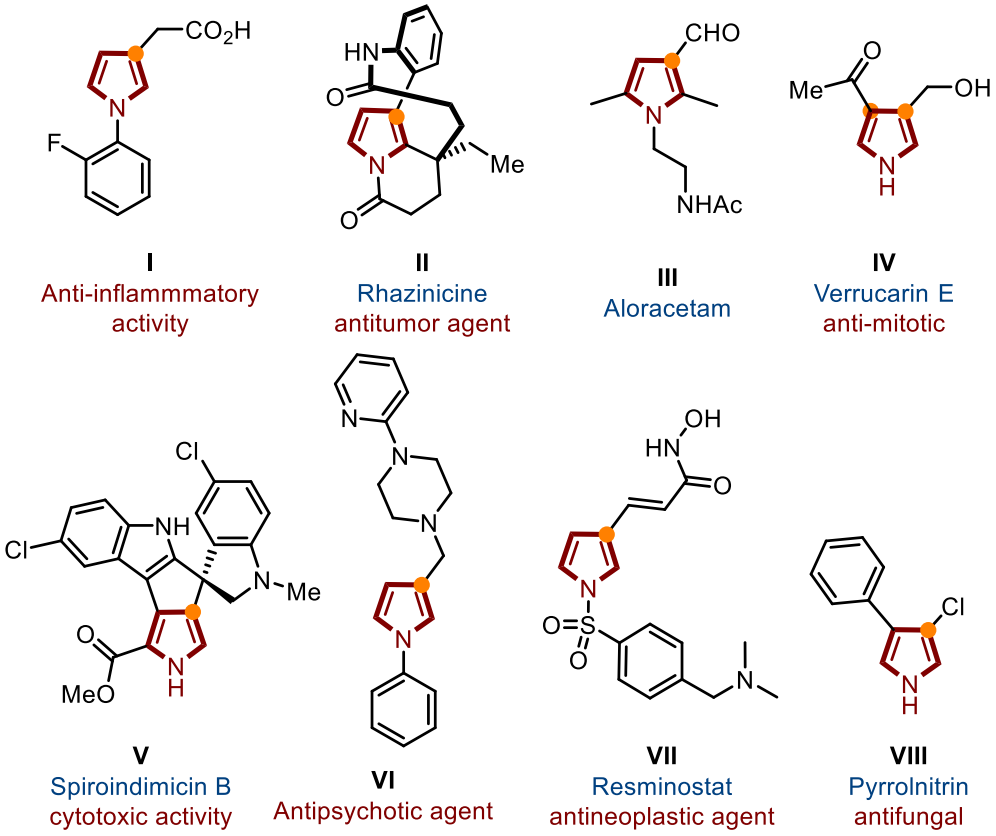


Figure 3.1 Representative examples of C3-functionalized pyrroles as bioactive compounds.

3.1.1 Importance and utilization of α–acyl carbonyl for pyrrole synthesis

α–Acyl carbonyl or 1,2-dicarbonyl compounds are commonly used in synthesizing heterocyclic compounds because of their reactive site. In this sequence, adjacent aldehyde and ketone functional groups with different reactivity show interesting chemical properties. The existence of

the ketone group, the reactivity of the aldehyde of the aromatic ring next to *α*–acyaloxalate is greater than that of other aldehydes, such as benzaldehydes, acetophenone, heteroaromatic aldehydes as shown in Figure 3.2.[23a] Taking help from the detailed study of carbonyl substrate customs in reaction, as coupling partner to the formation of C-N, C-O, C-S, and C-C bonds. an electron-withdrawing

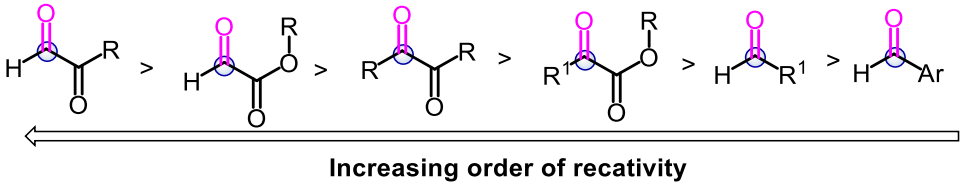
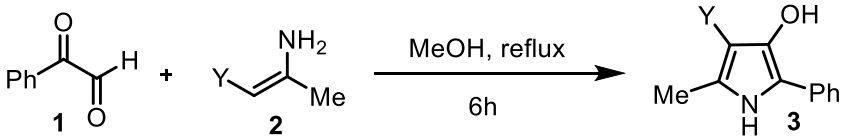


Figure 3.2 Virtual reactivity of carbonyl compounds.

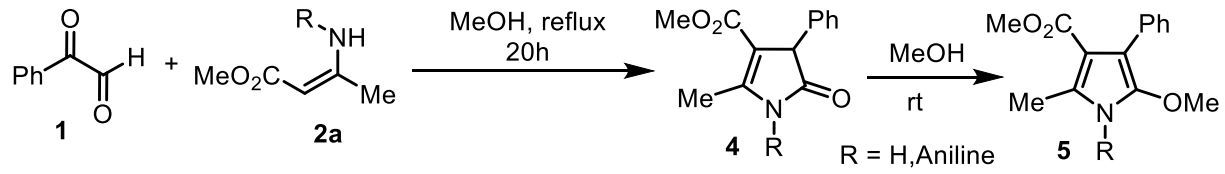
One part of reactive carbonyl is utilized frequently in aldol condensation, Dieckmann cyclization, 1, 3-dipolar cycloaddition reactions, cyclo-condensation, Fischer indole synthesis, Paal-Knorr, Pfitzinger-type condensation, Pictet−Spengler reaction, modulated Wittig reaction followed by reduction, Ugi reaction, and Michael addition type reaction.[23b]

Interestingly, active carbonyls have been extensively utilized in synthesizing important heterocycles in the past two decades. In this context, Feliciano and co-workers developed a direct synthesis of 3-hydroxy pyrroles **3** by reacting phenyl glyoxal **1** with enamine **2** via nucleophilic addition/cyclization/ aromatization sequence.[23c]



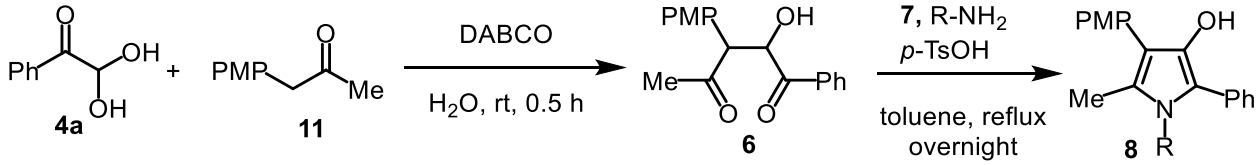
Scheme 3.1 Synthesis of pyrrole from enamine and glyoxal.

A similar strategy was reported to prepare 2-methoxy-NH-pyrrole or 2-methoxy-*N*-aryl-pyrrole with good yields from 2-pyrrolic-5-one **4** intermediate, generated from phenyl glyoxal **1** and enamine **2a**, followed by the reaction with MeOH at rt (Scheme 3.2).[23d]



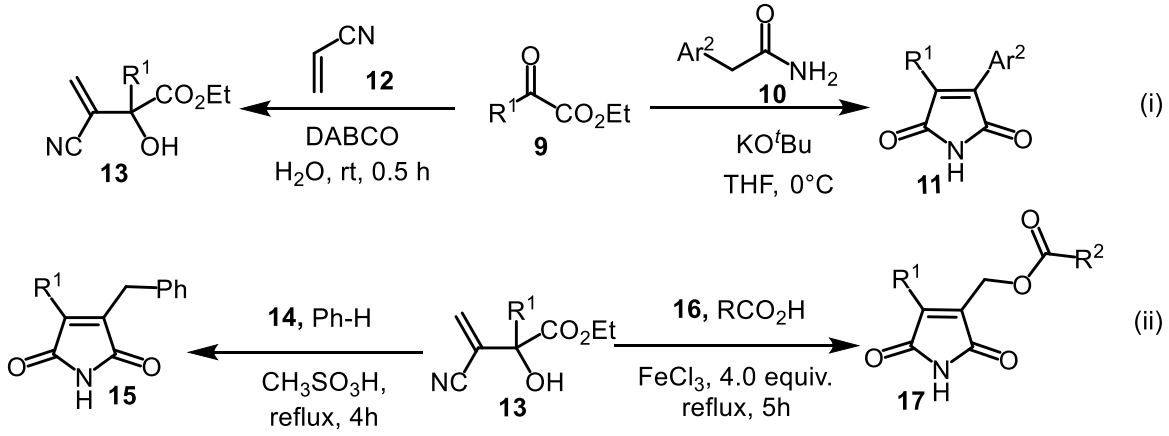
Scheme 3.2 Direct synthesis of pyrrole from glyoxal.

In 2010, Eftekhari and co-workers reported a DABCO-catalyzed reaction to generate a 1,4-dicarbonyl compound from **4a** and react with ketone **11** followed by Paal-Knorr reaction with aromatic /aliphatic amines **7** in the presence of acid under the refluxed condition to synthesize *N*-alkyl (aryl)-2, 4-diaryl-2-methyl-1H-pyrrole-3-of **8 (**Scheme 3.3).[23e]



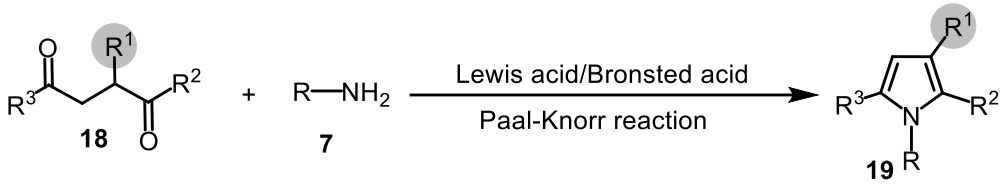
Scheme 3.3 Direct synthesis of pyrrole from hydroxy-glyoxal.

Basavaiah and co-workers described an acid-catalyzed reaction for synthesizing 3,4-disubstituted maleimides **15** and **17**. Where using Baylis-Hillman (BH) adduct **13**, they were derived through the coupling of α-oxoesters **9** with acrylonitrile in the presence of DABCO (30 mol%) at room temperature (Scheme 3.4(i)).[23f-g] A similar reaction with glyoxylates and acetamides **10** gives maleimides **11** was reported by Faul *et al.* in 1999. The reactions were carried out by adding KO^{t}Bu to a mixture of glyoxylate **9** and acetamide **10** in THF at 0 °C and afforded the corresponding maleimides **11** with 67−99% yields (Scheme 3.4 (ii)).[23h]



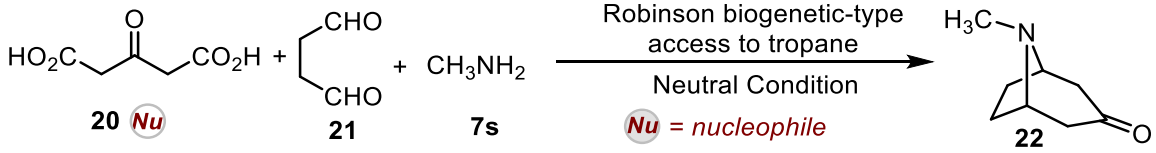
Scheme 3.4 Synthesis of maleimide from glyoxylate.

In 2015, Török and co-workers utilized the linear functionalized 1, 4-dicarbonyls **18,** and amines **7** in the presence of acid to synthesize C3-substituted pyrrole **19**. This protocol is complementary to the Paal-Knorr reaction (Scheme 3.5).[24]



Scheme 3.5 The Paal-Knorr reaction to pyrrole synthesis.

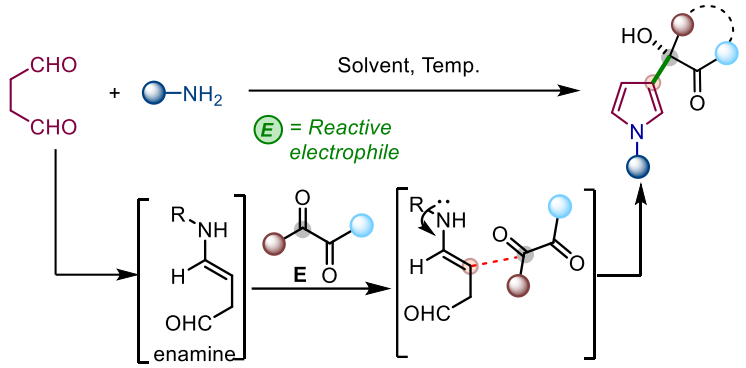
The 1,4-dicarbonyl compounds are also utilized for synthesizing natural products.[25] In this direction, Robinson and co-workers used biogenetic-type synthesis of tropinone **22** by using succinaldehyde **21**, primary amine **7s,** and acetone dicarboxylic acid **20** as a suitable nucleophilic reaction carried out in a test tube. This is the best example of illustrating synthetic creativity reminiscent of nature (Scheme 3.6).[26]



Scheme 3.6 Synthesis of tropinone from succinaldehyde.

3.1.2 Hypothesis of the present work:

Our group is continually exploring the metal-free synthesis of nitrogen heterocycles using 1,4-dicarbonyls.[27] We have recently developed a direct method to access C3-substituted pyrroles.[28,32] During the investigation, we questioned whether more reactive carbonyls could be employed as suitable electrophiles to harness the nucleophilic reactivity of enamine-intermediate, in situ generated from succinaldehyde and a primary amine before the Paal-Knorr cyclization to access C3-substituted Pyrrole directly under catalysts-free conditions. Herein, we report our success in developing a new catalyst-free, greener protocol for directly synthesizing C3-substituted Pyrrole from succinaldehyde, amines, and α-acyl carbonyls under mild conditions (Scheme 3.7).

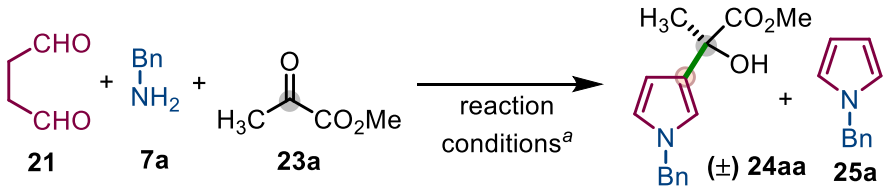


Scheme 3.7 Synthesis of C3-substituted pyrrole from succinaldehyde.

3.2 Results and discussion

Having this idea in mind, we began our study by choosing methyl pyruvate **23a** as a suitably reactive α-acyl carbonyl unit, aqueous succinaldehyde **21**, and benzylamine **7a**. Initially, we obtained product **24aa** (36%) as a minor product accompanied by pyrrole **25a** (58%) as a significant product by just mixing the substrates in EtOH at room temperature (entry 1, Table 3.1). In comparison, **24aa** (42%) was obtained as the primary product and **25a** (35%) in CH_2Cl_2 under similar conditions. These initial results showed that in situ generated enamine intermediate reacts with activated carbonyls; however, the Paal-Knorr reaction is competitive in the polar protic solvent, which could be crucial in improving this protocol. With these motivating results, we intended to explore other conditions and obtain. An improved yield of **24aa** (54%) at 5 ^oC (entry 3, Table 3.1). Additional variation in terms of acid as an additive (entry 4, Table 3.1) and solvents like $CHCl_3$, CH_3CN, and EtOH did not improve the reaction yield (entries (5-7, Table 3.1). Gratifyingly, an improvement in the protocol was when the mixture of solvents (CH_2Cl_2: EtOH, 1:1) was employed as a reaction medium, and product **24aa** (76% yield) was obtained along with **25a** (10% yield). Further changes in the reaction conditions, either by low loading of methyl pyruvate **23a** (entry 9, Table 3.1), using acid-additive (entry 10, Table 3.1), reducing the reaction temperature (entry 11, Table 3.1), solvent ratio (entries 12-13, Table 3.1), and varying solvents (entries 14-15, Table 3.1), did not improve the outcome. Thus, we preferred to operate the reaction under optimized conditions (entry 8, Table 3.1).

Table 3.1 Optimization of Reaction Conditions[a]



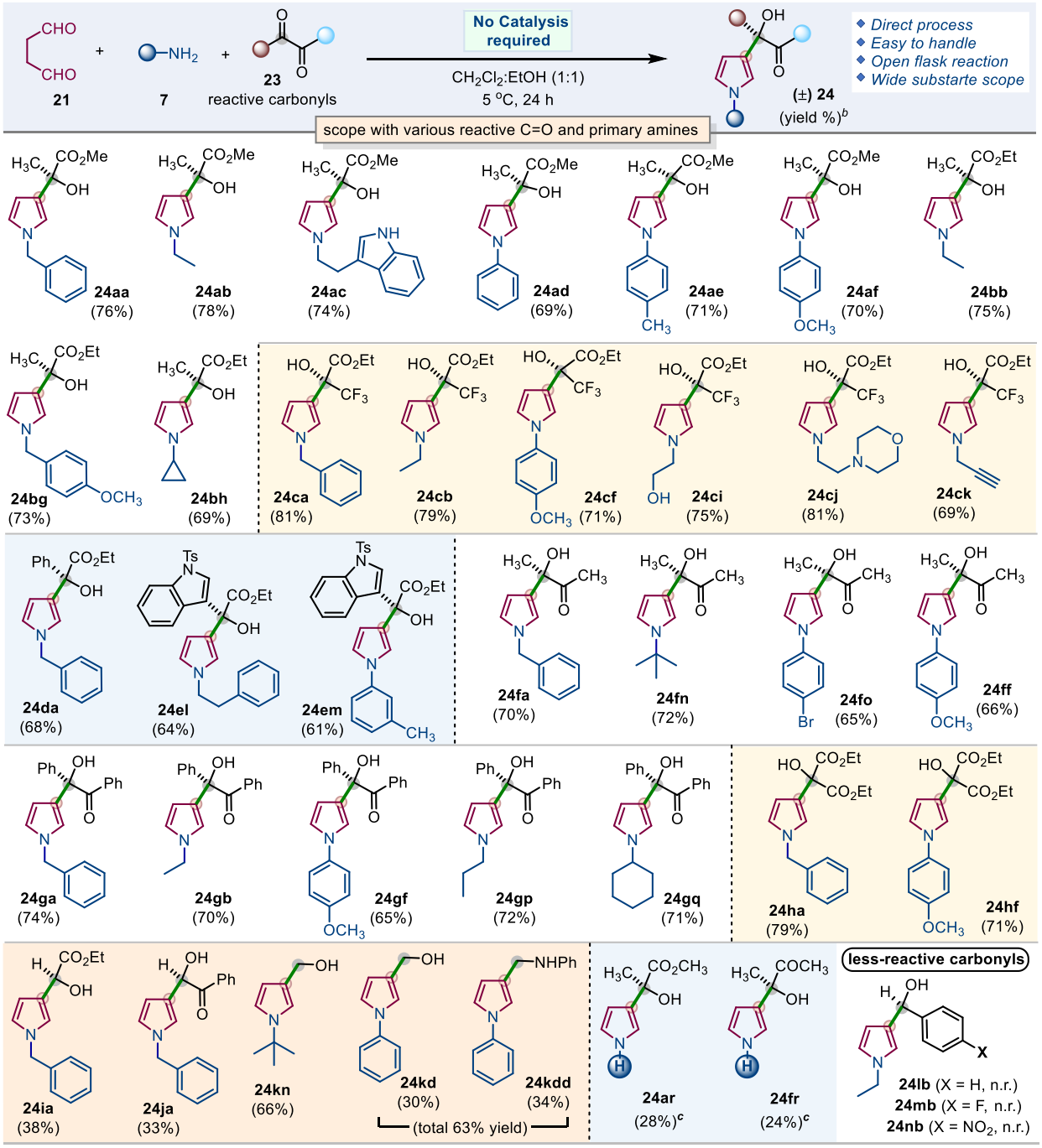
entry	reaction conditions[a]	yield **24aa/25a** (%)[b]
1	EtOH, rt, 24 h	36/58
2	CH_2Cl_2, rt, 24 h	42/35
3	CH_2Cl_2, 5 °C, 20 h	54/28
4	CH_2Cl_2, CH_3CO_2H (10 mol%), 5 °C, 22 h	20/65
5	$CHCl_3$, 5 °C, 24 h	46/36
6	CH_3CN, 5 °C, 14 h	21/64
7	EtOH, 5 °C, 24 h	54/32
8	**CH_2Cl_2:EtOH (1:1), 5 °C, 24 h**	**76/10**
9[c]	CH_2Cl_2:EtOH (1:1), 5 °C, 24 h	43/26
10	CH_2Cl_2:EtOH (1:1), CH_3CO_2H (10 mol%), 5 °C, 14 h	45/38
11	CH_2Cl_2:EtOH (1:1), 0 °C, 24 h	68/15
12	CH_2Cl_2:EtOH (2:1), 5 °C, 24 h	58/25
13	CH_2Cl_2:EtOH (1:2), 5 °C, 24 h	60/28
14	CH_2Cl_2:MeOH (1:1), 0 °C, 24 h	65/17
15	*i*-PrOH, 5 °C, 24 h	42/39

[a]Unless otherwise indicated, the reaction was carried out with succinaldehyde **21** (3.0 M sol, 0.6 mmol, 2.0 equiv.), benzylamine **15a** (0.3 mmol, 1.0 equiv.), methyl pyruvate **23a** (0.6 mmol, 2.0 equiv.), Solvent (3.0 mL), 5 °C. [b]Isolated yield of **24aa**/**25a** refers to **7a**. [c]methyl pyruvate **23a** (0.3 mmol, 1.0 equiv.) was used.

Under the optimized condition, we found that a series of primary amines **7** and activated carbonyls **23** provided the desired product **24** in good yield (Table 3.2). In this direction, methyl pyruvate **23a** was initially explored as reactive carbonyl and furnished products (**24aa**-**24af**) in good yields (69-78%) with various aliphatic/aromatic amines. Similar results were obtained with ethyl pyruvate **23b** to furnish products (**24bb**, **24bg**, and **24bh**) with comparable yields. Next, ethyl trifluoropyruvate **23c** was tested as a reactive electrophile with amines, and various C3-substituted pyrroles as heteroaromatic hydroxy-trifluoromethyl ethyl esters **24ca**-**24ck** (69-81% yields) were prepared. Interestingly, organofluorine compounds are attractive targets in multiple

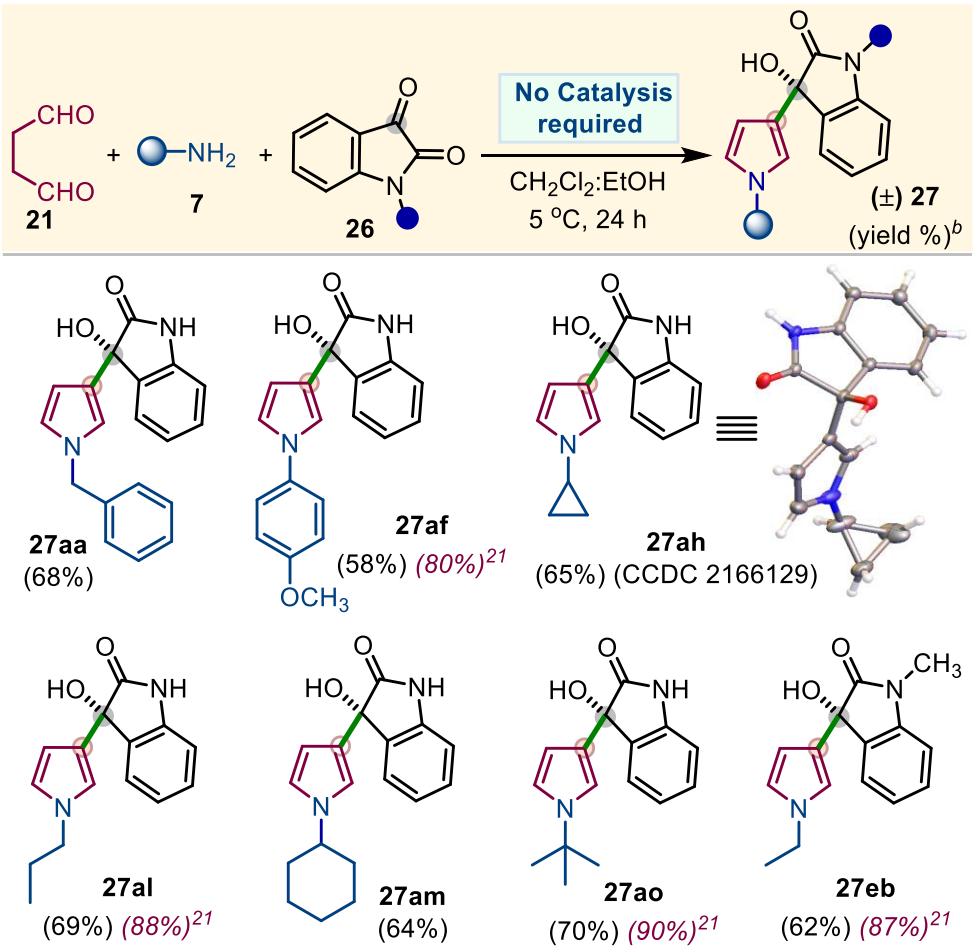
fields of chemistry, especially the trifluoromethyl group, which plays a vital role in improving the bireceptor selectivities of such fluorinated compounds.[29] Other keto-esters **23d** and **23e** also furnished the corresponding compounds **24da** and **24el**-**24em** (61-68% yields). Next, 1,2-diketo carbonyls such as 1,2-butanedione **23f** and benzil **23g** were applied successfully with aliphatic and aromatic amines to furnished products **24fa**-**24ff** and **24ga**-**24gq** in good yields, respectively Diethyl 2-oxomalonate **23h,** a more reactive carbonyl, produced the desired products **24ha** (79% yield) and **24hf** (71% yield) with aliphatic/aromatic amines. Besides, reactive aldehydes such as ethyl glyoxalate **23i** and glyoxal **23j** successfully furnished related products **24ia** (38% yield) and **24ja** (33% yield); however, low results are probably due to other side reactions. Interestingly, product **24kn** (66% yield) was obtained when formaldehyde **23k** was employed as reactive carbonyl for a similar response with sterically bulky *tert*-butylamine **7n**. While a mixture of products such as (1-phenyl-1*H*-pyrrol-3-yl)methanol **24kd** (30% yield) and *N*-((1-phenyl-1*H*-pyrrol-3-yl)methyl)aniline **24kdd** (34% yield) was obtained when aniline was employed under optimized conditions. Interestingly, direct access to C3- substituted NH-pyrrole was examined using NH_4OAc as an amine source, and corresponding products **24ar** (28%) and **24fr** (24%) were obtained with low yields. This protocol failed to produce products (**24lb**, **24mb**, and **24nb**) with less-reactive aromatic aldehydes (**23l**-**23n**) under standardized conditions could be the protocol limitation. Next, we focused on extending the reaction scope with isatin as an activated cyclic carbonyl under similar conditions (Table 3.3). A series of compounds **27aa**-**27eb** were prepared with moderate to good yields (58-70%) under optimized conditions with aliphatic and aromatic amines. The single-crystal X-ray analysis confirmed the structure of product **27ah**(CCDC 2166129).[30] However, the reaction produces fewer yields than our earlier catalytic method.[28]

Table 3.2 Reaction scope with primary amines 7 and acyclic reactive carbonyls 23[a]



Reagents and conditions: [a]Unless otherwise indicated, reactions were carried out with succinaldehyde **21** (3.0 M sol, 0.6 mmol), amine **7** (0.3 mmol), activate carbonyls **23** (0.6 mmol), CH_2Cl_2:MeOH (1:1, 3.0 mL), 5 °C, 24 h. [b]Isolated yields of **24** refer to **23**. (≤10% of *N*-alkyl/aryl-pyrrole **25** was obtained in all the cases as a direct Paal-Knorr reaction). [c]NH_4OAc (0.3 mmol) was used as an amine source.

Table 3.3 Reaction scope with primary amines 7 and isatins 26.

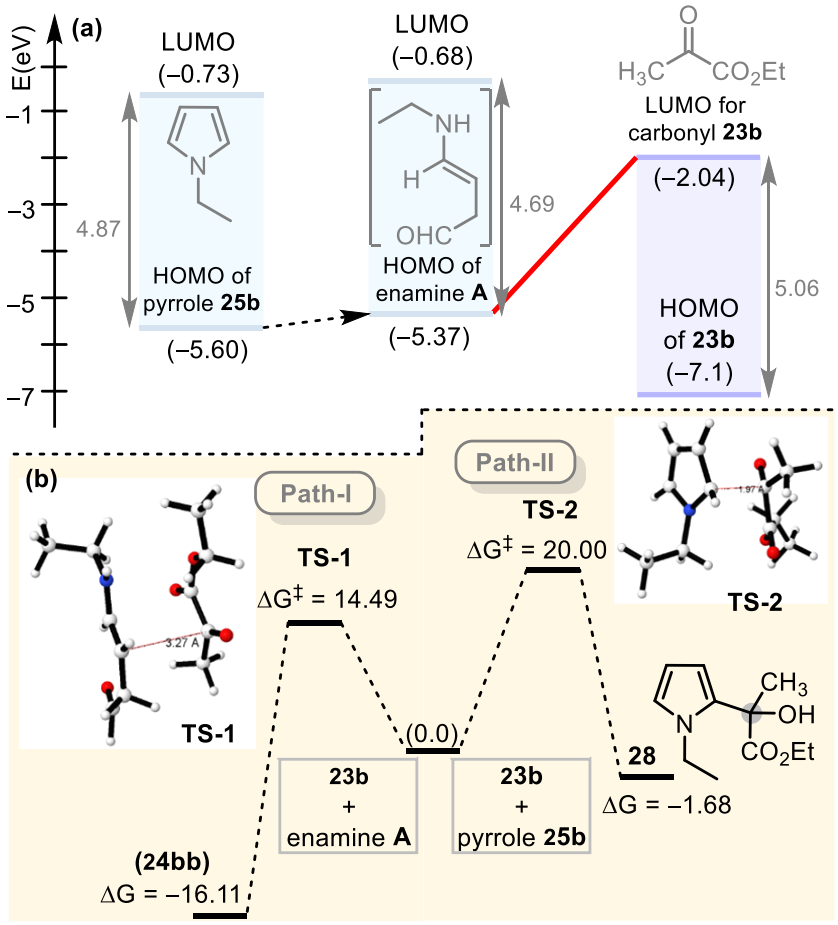


Reagents and conditions: [a]Unless otherwise indicated, the reaction was carried out with succinaldehyde **21** (3.0 M sol, 0.6 mmol), primary amine **7** (0.3 mmol), isatin **26** (0.6 mmol), CH_2Cl_2:MeOH (1:1, 3.0 mL), rt, 24 h. [b]Isolated yields of **26** refer to **7** (≤10% of *N*-alkyl/aryl-pyrrole **25** were obtained in all the cases as direct Paal-Knorr reaction).

3.3.1 Theoretical Calculations at the DFT Level

Density functional theory (DFT) calculations were performed using B3LYP hybrid exchange-correlation functional[31,32] with a def2-TZVP basis set[33] to gain more mechanistic insight (Scheme 3.8). All the analyses, including geometry optimization and frequencies, were performed using ORCA 4.2 program in the gas phase, with RIJCOSX approximation for Coulomb and exchange integrals.[34] A correction for dispersion interaction was added using Grimme D3 with Becke-Johnson damping.[35] The HOMO-energy profile data

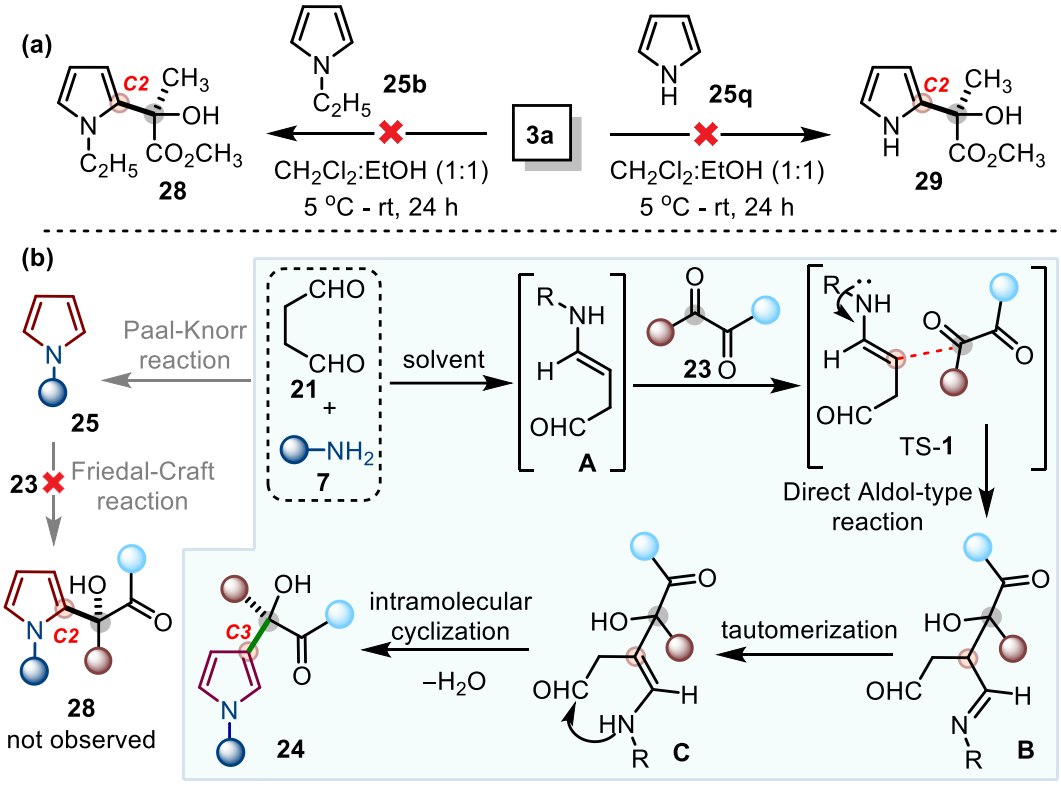
confirmed the higher nucleophilicity of in situ generated enamine-**A** (–5.37 eV) over pyrrole **25b** (–5.6 eV) and showed an improved interface with the LUMO of ethyl pyruvate **23b** (–2.04 eV) (Scheme 3.8a). Next, the combination of enamine-**A** (Path-I), and pyrrole **25b** (Path-II) with ethyl pyruvate **23b** was studied, in which the Gibbs free energy (G) is denoted relative to the separate reactants (Scheme 3.8b). The combination of ethyl pyruvate **23b** with enamine-**A** took place through TS-**1** ($\Delta G^{\ddagger}$ = 14.49 kcal/mol), followed by a Paal-Knorr reaction that yielded C3-substituted pyrrole **24bb** (ΔG = –16.11 kcal/mol) (Path-I). The formation of C2-pyrrole **28** was realized through TS-**2** ($\Delta G^{\ddagger}$ = 20.0 kcal/mol) via the reaction between pyrrole **25b** and ethyl pyruvate **23b** (Path-II). The DFT-calculations outcome for energy favorability of TS-**1** over TS-**2** by 5.51 kcal/mol and more excellent stability of **24bb** over **29** by 14.43 kcal/mol support the experimental observations.



Scheme 3.8 (a) The HOMO-LUMO energy profile of pyrrole **25b**, enamine **A**, ethyl pyruvate **23b**. (b) Transition State Geometries and Relative Activation Energies for (i) **TS-1** represents the

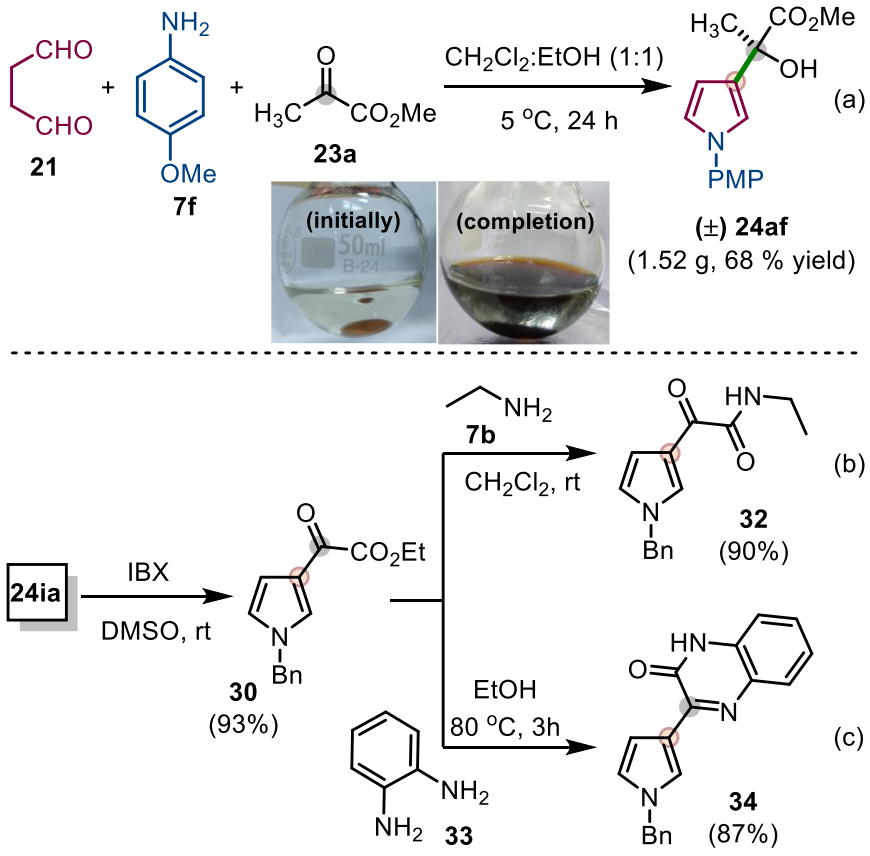
reaction between enamine-**A** and ethyl pyruvate **23b** (Path-I), (ii) **TS-2** represents the reaction between pyrrole **25b** with ethyl pyruvate **23b**. Gibbs activation energies ($\Delta G^{\ddagger}$, kcal/mol) and Gibbs reaction energies (ΔG, kcal/mol) are shown and computed at B3LYP-D3BJ/def2-TZVP.

Next, the reactivity of preformed *N*-ethyl pyrrole **25b** and Pyrrole **25q** was tested with methyl pyruvate **23a** as controlled experiments. These combinations failed to yield the expected products **28** and **29** under standard conditions (Scheme 3.9a). These results verify the association of in situ generated enamine with reactive carbonyls for developing this protocol. A tentative reaction mechanism is proposed based on DFT calculations and controlled experiments (Scheme 3.9b). A direct aldol-type response between enamine-**A** and reactive carbonyls **23** via TS-1 resulted in the formation of intermediate-**B**, which followed a tautomerization-cyclization sequence as an overall Paal-Knorr reaction to furnish C3-substituted pyrrole **24**. While the construction of C2-substituted pyrrole **28** was not observed, which was expected through the Friedel-Craft response of pyrrole **25** with activated carbonyls **23**.



Scheme 3.9 (a) Control experiments under standard conditions, and (b) the plausible reaction mechanism.

Additional transformations were performed to showcase the utility of the pyrrole products (Scheme 3.10). Initially, the reaction was tested at the gram-scale synthesis and compound **24af** (1.52 g, 68%) was obtained when **7f** (1.0 g) was employed under optimized conditions (Scheme 3.4a). Next, pyrrole **24ia** prepared herein could be readily oxidized with IBX to furnish pyrrole-oxo-ester **30** (93% yield). Furthermore, pyrrole-oxo-amide **32** (90% yield, Scheme 3.10b) and pyrrolo-quinoxalinone **34** (87% yield, Scheme 3.10c) were obtained when pyrrole-oxo-ester **30** was subjected to react with ethylamine **7b** and o-phenylenediamine **33**, respectively, under mild conditions.



Scheme 3.10 Gram-scale synthesis of **24af** and synthetic transformations on **24ia**.

3.4 Conclusion

We have developed a direct method for synthesizing *β*-functionalized pyrroles under open-flask catalyst-free conditions. The suitability of reactive carbonyls as electrophilic substrates for enamine, in situ generated from succinaldehyde and amines, just before the Paal-Knorr reaction

was a crucial parameter for developing this protocol. A broad substrate scope with readily available and inexpensive starting materials such as reactive carbonyls and amines has been established for the rapid and atom-economical synthesis of high-value C3-substituted pyrroles with moderate to good yields. This transformation was further probed computationally and well-supported with close energy profiles, and late-stage modifications on Pyrrole were established.

3.5 General Experimental Methods

Unless otherwise stated, all commercially available compounds were used as received without further purification. All solvents employed in the reactions were distilled from appropriate drying agents. Aqueous succinaldehyde **21** (3M solutions) was prepared using the reported procedure.[36]The reactions under the standard conditions were monitored by thin-layer chromatography (TLC) on Merck silica gel 60 F254 pre-coated plates (0.25 mm). Column chromatographic purification was performed on silica gel (100–200 mesh) using petroleum ether/EtOAc. Mixture. Chemical yields refer to pure, isolated substances. ^{1}H and ^{13}C-NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solution on a BRUKER-AV400 spectrometer. High-resolution mass spectra were recorded on Agilent 6545 Q-TOF LC/MS. Melting points were determined by EZ–Melt Automated Melting Point Apparatus and are incorrect.

3.5.1 General procedure for the preparation of C3-substituted Pyrrole (24/27)

An oven-dried Schlenk tube (25 mL) was charged with aqueous succinaldehyde **21** (3.0 M sol, 0.6 mmol, 2.0 equiv.), amine **15** (0.3 mmol, 1.0 equiv.) and reactive carbonyls **23** (0.6 mmol, 2.0 equiv.) in CH_2Cl_2: EtOH (1:1) (3.0 mL) at 5 °C. The combined reaction mixture was stirred at the same temperature and monitored as the reaction progressed by TLC. Upon completion, the solvent was removed under reduced pressure, and the response was initiated between CH_2Cl_2 (5.0 mL) and water (5.0 mL) for five minutes. The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The product **24/27** (up to 81% yield) was obtained by passing through a silica-gel column by eluting with petroleum ether/EtOAc.

3.5.2 pH-study during the reaction

In the detailed study of the reaction, we checked the response's pH, from set up to end at 25 ^{o}C, with the help of a digital pH-meter electrode. So we observed that all starting material was mixed, then the pH (10.45) and completion was almost neutral (7.88); detail is shown in table

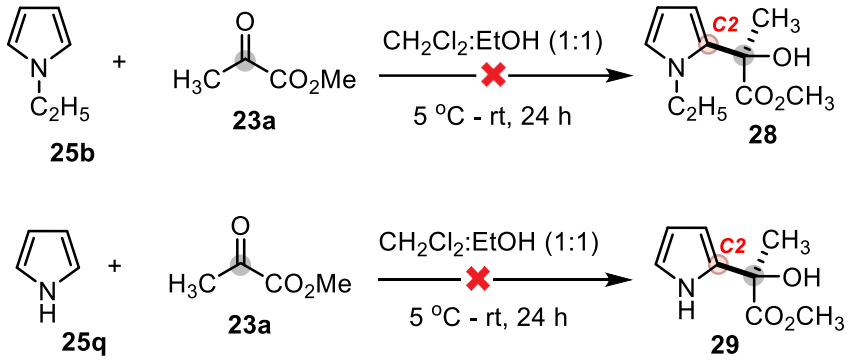
3.4. It is clear from this study initially; pH was basic; after the formation of the product, it got Neutral.

(a) Standard buffer solution at 25 °C using digital pH-meter electrode (pH = 4.05)	(b) Succinaldehyde (3.0 M aqueous sol) at 25 °C (pH = 2.41)
(c) All the substreat at 25 °C in CH_2Cl_2:EtOH (1.:1) reading was (pH =10.45)	(d) Reaction while completed CH_2Cl_2:EtOH (1.:1) at 25 °C (pH=7.88)

Table 3.4 pH-study during the progress of the reaction

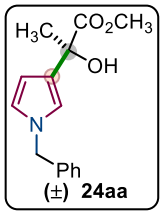
3.5.3 Controlled experiments

The model reaction between methyl pyruvate 23a and preformed N-ethyl pyrrole 25b/pyrrole 25q: An oven-dried Schlenk tube (25 mL) was charged with methyl pyruvate **23a** (0.3 mmol, 1.0 equiv.) and *N*-ethyl pyrrole **25b** (0.6 mmol, 2.0 equiv.)/pyrrole **25q** (0.6 mmol, 2.0 equiv.) in CH_2Cl_2:EtOH (1:1) (3.0 mL) and stirred from 5 °C to room temperature; no reactions were observed between them even after 24 h.

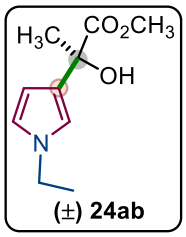


3.6 Spectral data for compounds

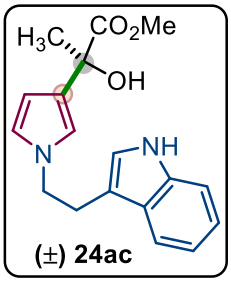
Methyl-2-(1-benzyl-1*H*-pyrrol-3-yl)-2-hydroxypropanoate (± 24aa). Purification with petroleum ether/EtOAc(8/2) as eluent; Brown oil (59 mg, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.26 (m, 3H), 7.17–7.11 (m, 2H), 6.74 (t, *J* = 2.1 Hz, 1H), 6.61 (t, *J* = 2.6 Hz, 1H), 6.21 (dd, *J* = 2.8, 1.8 Hz, 1H), 5.00 (s, 2H), 3.77 (s, 3H), 3.64 (s, 1H), 1.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.5, 137.5, 128.5 (2C), 127.6, 127.2, 127.0 (2C), 121.2, 118.1, 106.4, 72.7, 53.3, 52.7, 26.5 HRMS (ESI) *m/z*: [M + H]$^{+}$ Calcd for $C_{15}H_{18}NO_3$ 260.1281; Found 260.1276.



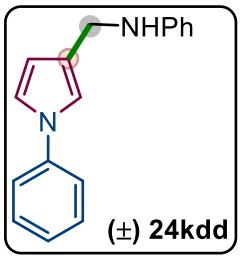
Methyl-2-(1-ethyl-1*H*-pyrrol-3-yl)-2-hydroxypropanoate (± 24ab). Purification with petroleum ether/EtOAc (8/2) as eluent; Reddish oil (46 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$)δ 6.71 (t, *J* =2.1 Hz, 1H,), 6.60 (t, *J* =2.5 Hz, 1H), 6.15 (dd, *J* =2.8, 1.8 Hz, 1H), 3.89 (q, *J* =7.3 Hz, 2H), 3.78 (s, 3H), 3.63 (s, 1H), 1.53 (s, 3H), 1.43 (t, *J* =7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$)δ 176.6, 126.6, 120.0, 116.9, 105.7, 72.7, 52.6, 44.1, 26.4, 16.2. HRMS (ESI) *m/z*: [M + H]$^{+}$ Calcd for $C_{10}H_{16}NO_3$ 198.1125 Found 198.1129.



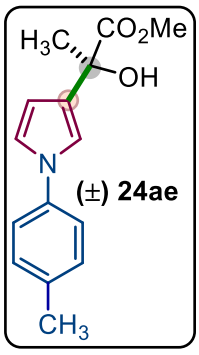
Methyl2-(1-(2-(1*H*-indol-3-yl)ethyl)-1*H*-pyrrol-3-yl)-2-hydroxypropanoate (± 24ac). Purification with petroleum ether/EtOAc (6/4) as eluent; Yellow oil (69 mg, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.20 – 7.13 (m, 1H), 6.76 (d, *J* = 2.4 Hz, 1H), 6.68 (d, *J* = 2.2 Hz, 1H), 6.62 – 6.57 (m, 1H), 6.18 – 6.11 (m, 1H), 4.11 (t, *J* = 7.3 Hz, 2H), 3.79 (s, 3H), 3.20 (t, *J* = 7.3 Hz, 2H), 1.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 136.1, 127.0, 126.6, 122.2, 121.9, 120.8, 119.2, 118.2, 117.7, 112.0, 111.2, 105.8, 72.9, 52.8, 50.3, 27.6, 26.5. HRMS (ESI) *m/z*: [M + H]$^{+}$ Calcd for$C_{18}H_{21}N_2O_3$ 313.1547; Found 313.1541.



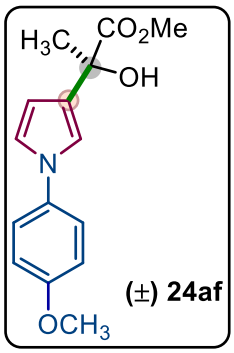
Methyl 2-hydroxy-2-(1-phenyl-1*H*-pyrrol-3-yl)propanoate (± 24ad). Purification with petroleum ether/EtOAc(8/2) as eluent; Yellowish oil (51 mg, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$)δ7.44 – 7.38 (m, 2H), 7.38 – 7.34 (m, 2H), 7.27 – 7.22 (m, 1H), 7.11 (dd, *J* = 2.3, 1.8 Hz, 1H), 7.01 (dd, *J* = 3.0, 2.3 Hz, 1H), 6.35 (dd, *J* = 2.9, 1.8 Hz, 1H), 3.81 (s, 3H), 3.61 (s, 1H), 1.78 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$)δ 176.6, 140.5, 129.5(2C), 129.1, 125.8, 120.4(2C), 119.6, 116.4, 108.5, 72.8, 53.1, 26.7. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{16}NO_3$ 246.1125; Found 246.1129.



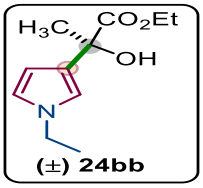
Methyl-2-hydroxy-2-(1-(*p*-tolyl)-1*H*-pyrrol-3-yl)propanoate (± 24ae). Purification with petroleum ether/EtOAc(8/2) as eluent; Yellowish oil (55 mg, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.28 (d, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 8.2 Hz, 2H), 7.11 (d, *J* = 2.2 Hz, 1H), 7.00 (t, *J* = 2.6 Hz, 1H), 6.36 (t, *J* = 2.3 Hz, 1H), 3.83 (s, 3H), 3.64 (s, 1H), 2.39 (s, 3H), 1.81 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$)δ176.6, 138.1, 135.5, 130.0 (2C), 128.8, 120.3(2C), 119.6, 116.4, 108.1, 72.8, 53.0, 26.7, 20.8. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{18}NO_3$ 260.1281; Found 260.1287.



Methyl-2-hydroxy-2-(1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)propanoate (± 24af). Purification with petroleum ether/EtOAc (8/2) as eluent; Reddish oil (58 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 9.0 Hz, 2H), 7.02 (dd, *J* = 2.3, 1.8 Hz, 1H), 6.95 – 6.90 (m, 3H), 6.31 (dd, *J* = 2.9, 1.8 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 1.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 157.8, 134.2, 128.6, 122.6 (2C), 120.0, 116.8, 114.6 (2C), 107.9, 72.8, 55.5, 53.0, 26.7. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{18}NO_4$ 276.1230; Found 276.1236.

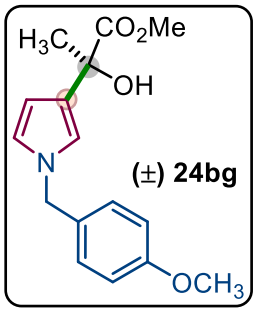


Ethyl-2-(1-ethyl-1*H*-pyrrol-3-yl)-2-hydroxypropanoate (± 24bb). Purification with petroleum ether/EtOAc (8/2) as eluent; Reddish oil (47 mg, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (d, *J* = 2.1 Hz, 1H), 6.58 (t, *J* = 2.5 Hz, 1H), 6.13 (dd, *J* = 2.8, 1.8 Hz, 1H), 4.30 – 4.15 (m, 2H), 3.87 (q, *J* = 7.3 Hz, 2H), 3.55 (s, 1H),



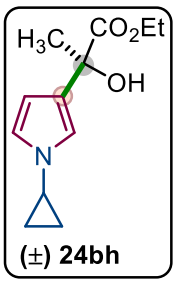
1.72 (s, 3H), 1.40 (t, *J* = 7.3 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 126.9, 120.1, 117.0, 105.8, 72.7, 61.8, 44.2, 26.6, 16.3, 14.0. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{18}NO_3$ 212.1281; Found 212.1279.

Ethyl 2-hydroxy-2-(1-(4-methoxybenzyl)-1*H*-pyrrol-3-yl) propanoate (±24bg). Purification



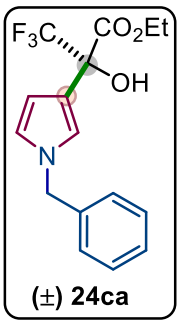
with petroleum ether/EtOAc (9/1) as eluent; Reddish oil (66 mg, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.68 (t, *J* = 2.1 Hz, 1H), 6.57 (t, *J* = 2.5 Hz, 1H), 6.16 (dd, *J* = 2.8, 1.8 Hz, 1H), 4.93 (s, 2H), 4.29 – 4.15 (m, 2H), 3.79 (s, 3H), 3.53 (s, 1H), 1.71 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 159.2, 129.6, 128.7 (2C), 127.4, 121.1, 118.0, 114.1 (2C), 106.4, 72.7, 61.9, 55.3, 52.9, 26.7, 14.0. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{22}NO_4$ 304.1543; Found 304.1549.

Ethyl 2-(1-cyclopropyl-1*H*-pyrrol-3-yl)-2-hydroxypropanoate (± 24bh). Purification with



petroleum ether/EtOAc (9/1) as eluent; Reddish oil (46 mg, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (t, *J* = 2.1 Hz, 1H), 6.63 (t, *J* = 2.5 Hz, 1H), 6.08 (dd, *J* = 2.8, 1.8 Hz, 1H), 4.28 – 4.13 (m, 2H), 3.66 (s, 1H), 3.31 – 3.23 (m, 1H), 1.69 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.93 – 0.87 (m, 2H), 0.87 – 0.81 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 126.7, 121.2, 118.0, 105.7, 72.4, 61.5, 29.7, 26.4, 13.8, 5.9. (2C). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{18}NO_3$ 224.1281; Found 224.1276.

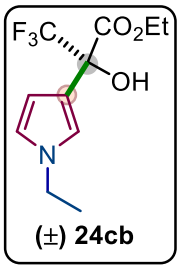
Ethyl-2-(1-benzyl-1*H*-pyrrol-3-yl)-3,3,3-trifluoro-2-hydroxypropanoate (± 24ca).



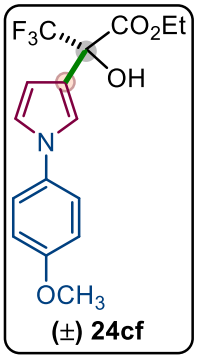
Purification with petroleum ether/EtOAc (9/1) as eluent; Reddish oil (79 mg, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 3H), 7.16 (d, *J* = 8.1 Hz, 2H), 6.98 (t, *J* = 2.1 Hz, 1H), 6.67 (t, *J* = 2.6 Hz, 1H), 6.43 (t, *J* = 1.9 Hz, 1H), 5.04 (s, 2H), 4.48 – 4.34 (m, 2H), 4.31 (s, 1H), 1.37 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ169.5, 137.2, 128.7 (2C), 127.8, 127.1 (2C), 123.2 (q, *J* = 285.3 Hz), 121.4, 120.7, 116.7, 107.9, 75.8 (q, *J* = 31.0 Hz), 63.7, 53.5,

13.7. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{17}F_3NO_3$ 328.1155. Found 328.1163.

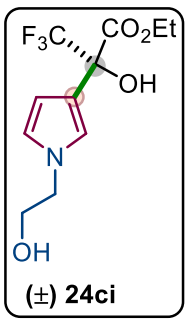
Ethyl-2-(1-ethyl-1*H*-pyrrol-3-yl)-3,3,3-trifluoro-2-hydroxypropanoate (± 24cb). Purification with petroleum ether/EtOAc (9/1) as eluent; Reddish oil (63 mg, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (t, *J* = 2.1 Hz, 1H), 6.63 (t, *J* = 2.6 Hz, 1H), 6.31 (t, *J* = 1.9 Hz, 1H), 4.47 – 4.31 (m, 2H), 4.22 (s, 1H), 3.90 (q, *J* = 7.3 Hz, 2H), 1.42 (t, *J* = 7.3 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 123.2 (q, *J* = 285.2 Hz), 120.4, 119.6, 116.2, 107.4, 75.7 (q, *J* = 31.2 Hz), 63.8, 44.4, 16.3, 13.9. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{15}F_3NO_3$ 266.0999; Found 266.0987.



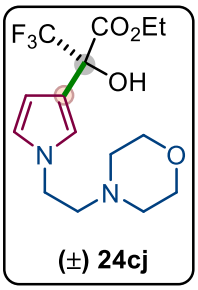
Ethyl-3,3,3-trifluoro-2-hydroxy-2-(1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)propanoate (± 24cf). Purification with petroleum ether/EtOAc (9/1) as eluent; Slight yellowish oil (73 mg, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.9 Hz, 2H), 7.21 (t, *J* = 2.1 Hz, 1H), 6.97 – 6.92 (m, 3H), 6.49 (t, *J* = 1.9 Hz, 1H), 4.50 – 4.34 (m, 2H), 4.27 (s, 1H), 3.83 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 158.0, 133.9, 123.1 (q, *J* = 285.4 Hz), 122.3 (2C), 120.2, 119.3, 118.1, 114.7 (2C), 109.1, 75.8 (q, *J* = 31.5 Hz), 64.0, 55.5, 13.9. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{17}F_3NO_4$ 344.1104; Found 344.1094.



Ethyl-3,3,3-trifluoro-2-hydroxy-2-(1-(2-hydroxyethyl)-1*H*-pyrrol-3-yl)propanoate (± 24ci). Purification with petroleum ether/EtOAc (8/2) as eluent; Yellowish oil (63 mg, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (t, *J* = 2.1 Hz, 1H), 6.67 (t, *J* = 2.6 Hz, 1H), 6.33 (m, 1H), 4.47 – 4.31 (m, 3H), 3.97 (dd, *J* = 5.7, 4.7 Hz, 2H), 3.81 (t, *J* = 5.2 Hz, 2H), 2.36 (s, 1H), 1.37 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 123.2 (q, *J* = 285.3 Hz), 121.4, 120.5, 116.8, 107.8, 75.8 (q, *J* = 31.2 Hz), 63.8, 62.5, 52.1, 13.8. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{15}F_3NO_4$ 282.0948; Found 282.0957.

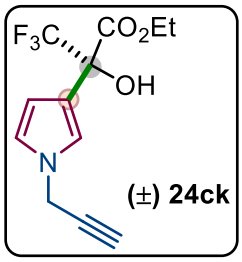


Ethyl-3,3,3-trifluoro-2-hydroxy-2-(1-(2-morpholinoethyl)-1*H*-pyrrol-3-yl)propanoate



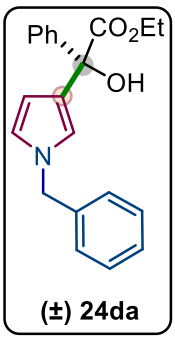
(± 24cj). Purification with petroleum ether/EtOAc (6/4) as eluent; Yellowish oil (85 mg, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (t, *J* = 2.1 Hz, 1H), 6.64 (t, *J* = 2.6 Hz, 1H), 6.29 (m, 1H), 4.46 – 4.29 (m, 2H), 3.96 (t, *J* = 6.8 Hz, 3H), 3.73 – 3.63 (m, 4H), 2.68 (t, *J* = 6.8 Hz, 2H), 2.46 – 2.41 (m, 4H), 1.36 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 123.2 (q, *J* = 285.3 Hz), 121.8, 120.5, 116.5, 107.6, 75.8 (q, *J* = 31.1 Hz), 66.8 (2C), 63.7, 59.3, 53.7 (2C), 47.5, 13.9. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{22}F_3N_2O_4$ 351.1526; Found 351.1529.

Ethyl-3,3,3-trifluoro-2-hydroxy-2-(1-(prop-2-yn-1-yl)-1*H*-pyrrol-3-yl)propanoate (± 24ck).

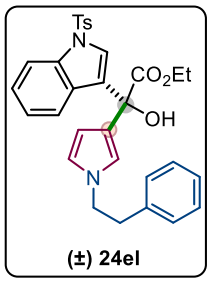


Purification with petroleum ether/EtOAc (8/2) as eluent; Yellowish oil (57 mg, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$)) δ 6.99 (t, *J* = 2.1 Hz, 1H), 6.73 (t, *J* = 2.7 Hz, 1H), 6.38 – 6.34 (m, 1H), 4.65 (d, *J* = 2.6 Hz, 2H), 4.46 – 4.31 (m, 2H), 4.18 (s, 1H), 2.45 (t, *J* = 2.6 Hz, 1H), 1.37 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 123.1 (q, *J* = 285.4 Hz), 120.8, 120.1, 117.2, 108.4, 75.8 (q, *J* = 31.3 Hz), 74.2, 63.9, 38.9, 13.9. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{13}F_3NO_3$ 276.0842; Found 276.0847.

Ethyl-2-(1-benzyl-1*H*-pyrrol-3-yl)-2-hydroxy-2-phenylacetate (± 24da). Purification with petroleum ether/EtOAc(8/2) as eluent; Yellowish oil (68 mg, 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.54 (m, 2H), 7.37 – 7.29 (m, 6H), 7.18 – 7.13 (m, 2H), 6.74 (t, *J* = 2.1 Hz, 1H), 6.66 (t, *J* = 2.6 Hz, 1H), 6.24 (dd, *J* = 2.9, 1.8 Hz, 1H), 5.03 (s, 2H), 4.29 (d, *J* = 8.4 Hz, 2H), 4.12 (s, 1H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 174.8, 142.6, 137.7, 128.7 (2C), 127.8 (2C), 127.7, 127.6, 127.1 (2C), 126.8 (2C), 125.8, 121.2, 120.2, 108.3, 77.4, 62.4, 53.5, 14.0. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{22}NO_3$ 336.1594; Found 336.1588.

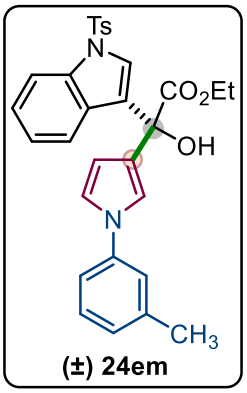


Ethyl-2-hydroxy-2-(1-phenethyl-1*H*-pyrrol-3-yl)-2-(1-tosyl-1*H*-indol-3-yl)acetate (± 24el).



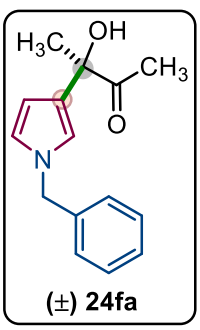
Purification with petroleum ether/EtOAc (4/1) as eluent; Orange oil (104 mg, 64% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.56 – 7.50 (m, 2H), 7.32 – 7.14 (m, 7H), 7.09 – 7.05 (m, 2H), 6.61 (t, *J* = 2.1 Hz, 1H), 6.53 (t, *J* = 2.6 Hz, 1H), 6.13 (dd, *J* = 2.8, 1.8 Hz, 1H), 4.30 – 4.13 (m, 2H), 4.10 – 4.03 (m, 3H), 3.04 (t, *J* = 7.2 Hz, 2H), 2.34 (s, 3H), 1.16 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 144.8, 138.2, 135.6, 135.2, 129.8 (2C), 128.8, 128.6 (2C), 128.5 (2C), 126.8 (2C), 126.7, 125.8, 124.8, 124.5, 124.1, 123.1, 121.6, 121.0, 119.1, 113.4, 107.2, 73.7, 62.6, 51.4, 38.2, 21.5, 13.9. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{31}H_{31}N_2O_5S$ 543.1948; Found 543.1952.

Ethyl-2-hydroxy-2-(1-(m-tolyl)-1*H*-pyrrol-3-yl)-2-(1-tosyl-1*H*-indol-3-yl)acetate (± 24em).



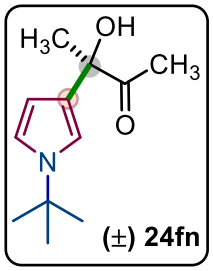
Purification with petroleum ether/EtOAc (4/1) as eluent; Orange oil (97 mg, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7 δ 7.94 (dt, *J* = 8.4, 1.0 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.62 – 7.55 (m, 2H), 7.35 – 7.27 (m, 2H), 7.23 – 7.15 (m, 5H), 7.13 (t, *J* = 2.1 Hz, 1H), 7.11 – 7.02 (m, 2H), 6.36 (dd, *J* = 3.0, 1.8 Hz, 1H), 4.36 – 4.20 (m, 2H), 4.19 (s, 1H), 2.41 (s, 3H), 2.34 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 144.9, 140.4, 139.6, 135.6, 135.2, 129.9 (2C), 129.4, 128.7, 126.9 (2C), 126.7, 126.2, 125.8, 124.6, 124.4, 123.2, 121.5, 121.2, 119.8, 117.9, 117.6, 113.5, 109.5, 73.7, 62.9, 21.5 (2C) 14.0. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{30}H_{29}N_2O_5S$ 529.1792; Found 529.1796.

3-(1-benzyl-1*H*-pyrrol-3-yl)-3-hydroxybutan-2-one (± 24fa). Purification with petroleum ether/EtOAc (9/1) as eluent; Yellowish oil (51 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 3H), 7.10 (m, 2H), 6.68 (t, *J* = 2.1 Hz, 1H), 6.63 (t, *J* = 2.5 Hz, 1H), 6.10 (dd, *J* = 2.8, 1.8 Hz, 1H), 5.01 (s, 2H), 4.36 (s, 1H), 2.17 (s, 3H), 1.68 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.3, 137.6, 128.7 (2C), 127.7, 127.0 (2C), 126.1, 121.9, 118.9, 106.9, 76.8, 53.5, 24.6, 23.3. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{15}H_{18}NO_2$ 244.1332; Found

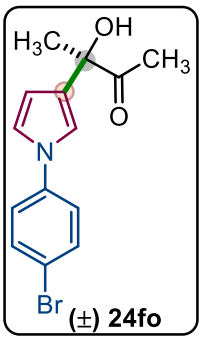


244.1338.

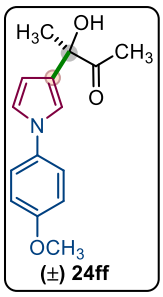
3-(1-(tert-butyl)-1*H*-pyrrol-3-yl)-3-hydroxybutan-2-one (± 24fn). Purification with petroleum ether/EtOAc (9/1) as eluent; Yellowish oil (45 mg, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 – 6.77 (m, 1H), 6.75 (t, *J* = 2.7 Hz, 1H), 6.04 (dd, *J* = 2.9, 1.9 Hz, 1H), 4.35 (s, 1H), 2.17 (s, 3H), 1.68 (s, 3H), 1.49 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.5, 124.8, 118.2, 115.4, 105.8, 76.9, 54.9, 30.6 (3C), 24.7, 23.4. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{20}NO_2$ 210.1489; Found 210.1487.



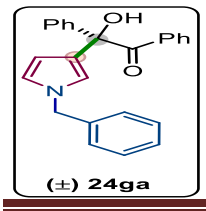
3-(1-(4-bromophenyl)-1*H*-pyrrol-3-yl)-3-hydroxybutan-2-one (± 24fo). Purification with petroleum ether/EtOAc (8/2) as eluent; Reddish oil (60 mg, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.04 (t, *J* = 1.9 Hz, 1H), 6.99 (t, *J* = 2.5 Hz, 1H), 6.29 – 6.25 (m, 1H), 4.45 (s, 1H), 2.22 (s, 3H), 1.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.8, 139.3, 132.5 (2C), 128.4, 121.7(2C), 119.9, 119.0, 116.9, 109.2, 76.7, 24.7, 23.4. HRMS (ESI) *m/z*: $[M + H]^+$Calcd for$C_{14}H_{15}NBrO_2$ 308.0281; Found 308.0285.



3-hydroxy-3-(1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)butan-2-one (± 24ff). Purification with petroleum ether/EtOAc (9/1) as eluent; Orange oil (51 mg, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 9.0 Hz, 2H), 6.99 (t, *J* = 2.1 Hz, 1H), 6.96 – 6.91 (m, 3H), 6.23 (dd, *J* = 2.9, 1.8 Hz, 1H), 4.44 (s, 1H), 3.83 (s, 3H), 2.23 (s, 3H), 1.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.1, 157.8, 134.1, 127.4, 122.1 (2C), 120.5, 117.5, 114.6 (2C), 108.2, 76.8, 55.6, 24.7, 23.4. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{18}NO_3$ 260.1281; Found 260.1283.

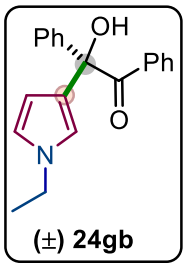


2-(1-benzyl-1*H*-pyrrol-3-yl)-2-hydroxy-1,2-diphenylethan-1-one (± 24ga). Purification with petroleum ether/EtOAc (9/1) as eluent; Reddish oil (81 mg, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.71 – 7.64 (m, 2H), 7.47 – 7.41 (m, 2H), 7.38 – 7.32 (m, 1H), 7.28 – 7.15 (m, 8H), 7.00 –

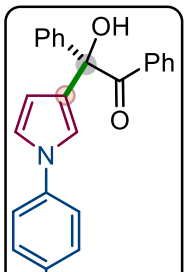


6.96 (m, 2H), 6.56 – 6.51 (m, 2H), 6.04 (dd, *J* = 2.6, 2.0 Hz, 1H), 5.09 (s, 1H), 4.89 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 142.9, 137.6, 134.8, 132.6, 130.8 (2C), 128.6 (2C), 128.3 (2C), 127.9, 127.8 (2C), 127.7 (2C), 127.6, 126.9 (2C), 124.8, 121.4, 121.3, 109.2, 81.4, 53.4. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{25}H_{22}NO_2$ 368.1645; Found 368.1649.

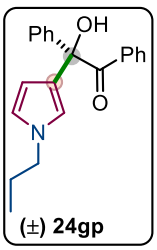
2-(1-ethyl-1*H*-pyrrol-3-yl)-2-hydroxy-1,2-diphenylethan-1-one (± 24gb). Purification with petroleum ether/EtOAc (9/1) as eluent; Reddish oil (64 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.74 (m, 2H), 7.53 (dd, *J* = 8.2, 1.6 Hz, 2H), 7.47 – 7.41 (m, 1H), 7.38 – 7.25 (m, 5H), 6.63 (t, *J* = 2.6 Hz, 1H), 6.59 (t, *J* = 2.1 Hz, 1H), 6.07 (dd, *J* = 2.8, 1.9 Hz, 1H), 5.15 (s, 1H), 3.85 (q, *J* = 7.3 Hz, 2H), 1.37 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.3, 143.0, 134.9, 132.6, 130.8 (2C), 128.2 (2C), 127.8 (3C), 127.6 (2C), 124.2, 120.2, 120.1, 108.6, 81.5, 44.2, 16.3. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{20}H_{20}NO_2$ 306.1489; Found 306.1493.



2-hydroxy-2-(1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)-1, 2-diphenylethan-1-one (± 24gf). Purification with petroleum ether/EtOAc (8/2) as eluent; Reddish oil (75 mg, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.72 (m, 2H), 7.56 – 7.51 (m, 2H), 7.48 – 7.43 (m, 1H), 7.38 – 7.29 (m, 4H), 7.28 (d, *J* = 7.4 Hz, 1H), 7.23 (d, *J* = 8.9 Hz, 2H), 6.96 – 6.93 (m, 1H), 6.93 – 6.88 (m, 3H), 6.23 (dd, *J* = 2.9, 1.8 Hz, 1H), 5.20 (s, 1H), 3.81 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.2, 157.8, 142.8, 134.8, 134.1, 132.9, 131.0 (2C), 128.5 (2C), 128.1, 128.0 (2C), 127.7 (2C), 126.3, 122.0 (3C), 120.0, 119.7, 114.6, 110.6, 81.5, 55.6. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{25}H_{22}NO_3$ 384.1594; Found 384.1592.

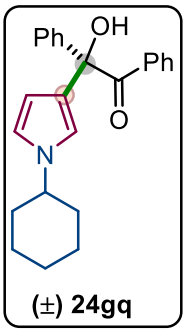


2-hydroxy-1,2-diphenyl-2-(1-propyl-1*H*-pyrrol-3-yl)ethan-1-one (± 24gp). Purification with petroleum ether/EtOAc (8/2) as eluent; Reddish oil (69 mg, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.72 (m, 2H), 7.53 – 7.49 (m, 2H), 7.47 – 7.42 (m, 1H), 7.37 – 7.27 (m, 5H), 6.61 (t, *J* = 2.5 Hz, 1H), 6.55 (t, *J* = 2.1 Hz, 1H), 6.06 (dd, *J* = 2.8, 1.8 Hz, 1H), 5.15 (s, 1H), 3.76 (t, *J* = 7.1 Hz, 2H), 1.79 – 1.69 (m,

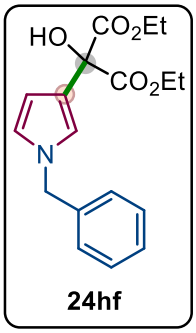


2H), 0.87 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.4, 143.1, 134.9, 132.6, 130.9 (2C), 128.3 (2C), 127.9, 127.8 (2C), 127.7 (2C), 124.1, 120.8, 120.7, 108.5, 81.5, 51.4, 24.6, 11.1. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{21}H_{22}NO_2$ 320.1645; Found 320.1653.

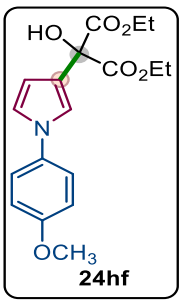
2-(1-cyclohexyl-1*H*-pyrrol-3-yl)-2-hydroxy-1,2-diphenylethan-1-one (± 24gq). Purification with petroleum ether/EtOAc (9/1) as eluent; Yellowish oil (76 mg, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.73 (m, 2H), 7.55 – 7.50 (m, 2H), 7.46 – 7.41 (m, 1H), 7.36 – 7.25 (m, 5H), 6.69 (t, *J* = 2.6 Hz, 1H), 6.64 (t, *J* = 2.1 Hz, 1H), 6.05 (dd, *J* = 2.9, 1.9 Hz, 1H), 5.15 (s, 1H), 3.72 (tt, *J* = 11.8, 3.7 Hz, 1H), 2.10 – 2.01 (m, 2H), 1.85 (dt, *J* = 13.8, 3.5 Hz, 2H), 1.75 – 1.66 (m, 1H), 1.56 (m, 2H), 1.42 – 1.29 (m, 2H), 1.19 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.4, 143.0, 134.9, 132.5, 130.8 (2C), 128.2 (2C), 127.7 (3C), 127.6 (2C), 123.6, 118.7, 118.6, 108.0, 81.5, 58.6, 34.4 (2C), 25.5 (2C), 25.3. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{24}H_{26}NO_2$ 360.1958; Found 360.1964.



Diethyl-2-(1-benzyl-1*H*-pyrrol-3-yl)-2-hydroxymalonate (24ha). Purification with petroleum ether/EtOAc (9/1) as eluent; Yellowish oil (78 mg, 79% yield).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.25 (m, 3H), 7.12 (m, 2H), 6.91 (dd, *J* = 2.3, 1.8 Hz, 1H), 6.61 (t, *J* = 2.6 Hz, 1H), 6.32 (dd, *J* = 2.8, 1.7 Hz, 1H), 5.00 (s, 2H), 4.28 (qt, *J* = 7.1, 3.5 Hz, 5H), 4.15 (s, 1H), 1.28 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1 (2C), 137.5, 128.5 (2C), 127.6, 127.1 (2C), 121.0, 120.1, 119.7, 108.0, 63.2, 62.4 (2C), 53.4, 13.8(2C). HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{18}H_{22}NO_5$ 332.1492; Found 332.1494.

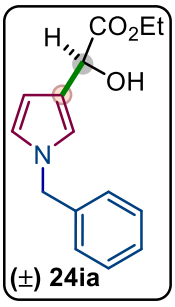


Diethyl-2-hydroxy-2-(1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl) malonate (24hf). Purification with petroleum ether/EtOAc (8/2) as eluent; Reddish oil (73 mg, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H), 7.21 (dd, *J* = 2.4, 1.7 Hz, 1H), 6.95 – 6.90 (m, 3H), 6.46 (dd, *J* = 2.9, 1.7 Hz, 1H), 4.36 – 4.26 (m, 4H), 4.22 (s, 1H), 3.81 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1 (2C), 157.7, 134.1, 122.0 (2C), 121.2, 119.7, 118.6, 114.5 (2C), 109.4, 63.3,

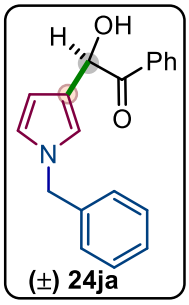


62.6 (2C), 55.4, 13.9 (2C). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{22}NO_6$ 348.1442; Found 348.1428.

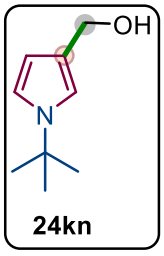
Ethyl-2-(1-benzyl-1*H*-pyrrol-3-yl)-2-hydroxyacetate (± 24ia). Purification with petroleum ether/EtOAc (8/2) as eluent; Yellowish oil (30 mg, 38% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 3H), 7.17 – 7.07 (m, 2H), 6.79 – 6.69 (m, 1H), 6.62 (t, *J* = 2.5 Hz, 1H), 6.19 (dd, *J* = 2.8, 1.7 Hz, 1H), 5.13 (s, 1H), 5.01 (s, 2H), 4.30 – 4.20 (m, 2H), 3.09 (s, 1H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 137.5, 128.7 (2C), 127.7, 127.1 (2C), 122.0, 121.6, 119.4, 106.9, 67.9, 61.6, 53.4, 14.1. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{18}NO_3$ 260.1281; Found 260.1277.



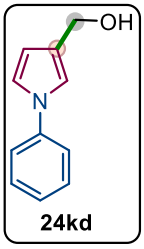
2-(1-benzyl-1H-pyrrol-3-yl)-2-hydroxy-1-phenylethan-1-one (± 24ja). Purification with petroleum ether/EtOAc (8/2) as eluent; Yellowish semi-solid (29 mg, 33% yield).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.93 (m, 2H), 7.58 – 7.51 (m, 1H), 7.41 (ddt, *J* = 7.9, 6.6, 1.2 Hz, 2H), 7.28 – 7.24 (m, 3H), 7.03 – 6.96 (m, 2H), 6.65 (t, *J* = 2.0 Hz, 1H), 6.56 (t, *J* = 2.5 Hz, 1H), 6.08 (dd, *J* = 2.8, 1.8 Hz, 1H), 5.95 (d, *J* = 5.9 Hz, 1H), 4.97 (s, 3H), 4.17 (d, *J* = 6.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 137.5, 133.9, 133.5, 129.1 (2C), 128.7 (2C), 128.5 (2C), 127.7, 126.9 (2C), 122.5, 122.1, 120.2, 107.8, 70.1, 53.4. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{18}NO_2$ 292.1332; Found 292.1338.



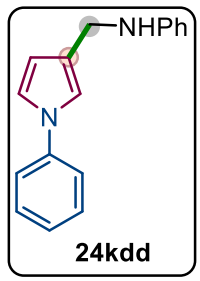
(1-(*tert*-butyl)-1*H*-pyrrol-3-yl) methanol (24kn). Purification with petroleum ether/EtOAc (9/1) as eluent; Yellow oil (30 mg, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 – 6.82 (m, 1H), 6.79 (t, *J* = 2.6 Hz, 1H), 6.18 (dd, *J* = 2.8, 1.8 Hz, 1H), 4.55 (s, 2H), 1.52 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.3, 118.0, 116.3, 107.2, 59.0, 54.7, 30.7 (3C). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_9H_{16}NO$ 154.1226; Found 154.1234.



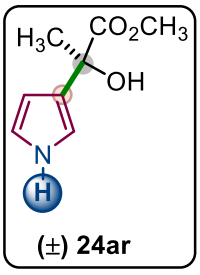
(1-phenyl-1*H*-pyrrol-3-yl)methanol (24kd). Purification with petroleum ether/EtOAc (8/2) as eluent; Reddish oil (16 mg, 30% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.35 (m, 4H), 7.28 – 7.22 (m, 1H), 7.10 (t, *J* = 2.0 Hz, 1H), 7.05 (t, *J* = 2.6 Hz, 1H), 6.38 (dd, *J* = 2.9, 1.8 Hz, 1H), 4.63 (s, 2H), 1.47 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 129.6 (2C), 126.1, 125.7, 120.4 (2C), 119.9, 117.8, 110.1, 58.8. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{11}H_{12}NO$ 174.0913; Found 174.0919.



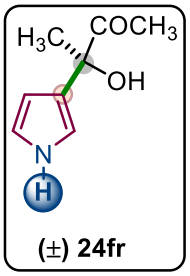
***N*-((1-phenyl-1*H*-pyrrol-3-yl)methyl)aniline (24kdd).** Purification with petroleum ether/EtOAc (8/2) as eluent; Reddish oil (25 mg, 34% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.38 (m, 4H), 7.31 – 7.22 (m, 3H), 7.12 (d, *J* = 2.0 Hz, 1H), 7.10 (t, *J* = 2.6 Hz, 1H), 6.80 – 6.72 (m, 3H), 6.40 (dd, *J* = 2.9, 1.7 Hz, 1H), 4.28 (s, 2H), 3.91 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 140.5, 129.5 (2C), 129.2 (2C), 125.6, 124.0, 120.2 (2C), 119.6, 117.5, 117.4, 112.9 (2C), 110.3, 41.5. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{17}H_{17}N_2$ 249.1386; Found: 249.1378.



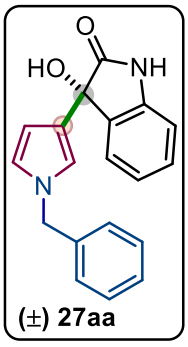
Ethyl 2-hydroxy-2-(1*H*-pyrrol-3-yl) propanoate (± 24ar). Purification with petroleum ether/EtOAc (8/2) as eluent; Yellow oil; (14 mg, 28% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 6.79 (dt, *J* = 2.7, 1.8 Hz, 1H), 6.71 (td, *J* = 2.7, 2.1 Hz, 1H), 6.23 (td, *J* = 2.8, 1.7 Hz, 1H), 3.77 (s, 3H), 1.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 127.0, 118.2, 114.9, 106.2, 72.8, 52.9, 26.6. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_8H_{12}NO_3$: 170.0812; Found 170.0818.



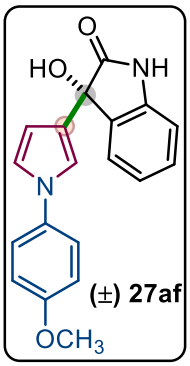
3-hydroxy-3-(1*H*-pyrrol-3-yl) butan-2-one (± 24fr). Purification with petroleum ether/EtOAc (6/4) as eluent; Yellow oil; (11 mg, 24% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 6.78 (dt, *J* = 2.7, 1.8 Hz, 1H), 6.75 (td, *J* = 2.8, 2.1 Hz, 1H), 6.15 (td, *J* = 2.8, 1.7 Hz, 1H), 4.39 (s, 1H), 2.17 (s, 3H), 1.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.4, 125.9, 118.7, 115.6, 106.7, 76.8, 24.7, 23.3. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_8H_{12}NO_2$ 154.0863; Found 154.0859.



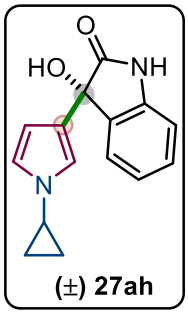
3-(1-benzyl-1*H*-pyrrol-3-yl)-3-hydroxyindolin-2-one (± 27aa). Purification with petroleum ether/EtOAc (4/1 as eluent; Red solid (62 mg, 68% yield, mp = 166-168 °C). ^{1}H NMR (400 MHz, $CDCl_3$ & few drops of DMSO-d_6 was added) δ 9.79 (s, 1H), 7.31 (d, *J* = 7.2 Hz, 1H), 7.28 – 7.15 (m, 3H), 7.14 – 7.02 (m, 3H), 6.91 (q, *J* = 7.2 Hz, 1H), 6.77 (t, *J* = 7.3 Hz, 1H), 6.56 (dq, *J* = 18.7, 2.8 Hz, 2H), 6.16 (td, *J* = 4.6, 2.2 Hz, 1H), 5.86 – 5.73 (m, 1H), 4.89 (d, *J* = 6.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$& few drops of DMSO-d_6 was added) δ 178.5, 140.4, 136.8, 132.3, 127.6, 127.5 (2C), 126.5, 126.3 (2C), 123.6, 123.0, 120.7, 120.1, 118.7, 108.8, 106.7, 72.9, 52.2. HRMS (ESI)*m/z*: $[M + H]^+$ Calcd for $C_{19}H_{17}N_2O_2$ 305.1285. Found 305.1291.



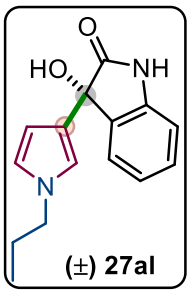
3-hydroxy-3-(1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)indolin-2-one (± 27af). Purification with petroleum ether/EtOAc (3/2) as eluent; Yellow solid (56 mg, 58% yield, mp = 122-124 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 7.38 (d, *J* = 8.0 Hz, 3H), 7.22 (t, *J* = 7.7 Hz, 1H), 7.16 (s, 1H), 6.98 (q, *J* = 8.5 Hz, 4H), 6.84 (d, *J* = 7.7 Hz, 1H), 6.24 (d, *J* = 9.0 Hz, 2H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.1, 157.5, 141.9, 133.9, 133.8, 129.3, 126.5, 125.1, 122.1, 121.4 (2C), 120.0, 117.6, 115.2 (2C), 110.0, 109.6, 74.1, 55.8. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{17}N_2O_3$ 321.1239; Found 321.1244.



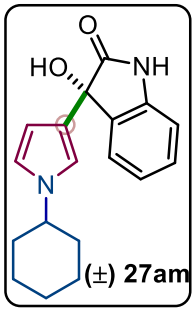
3-(1-cyclopropyl-1*H*-pyrrol-3-yl)-3-hydroxyindolin-2-one (± 27ah). Purification with petroleum ether/EtOAc (4/1 as eluent; Red solid (49 mg, 65% yield, mp = 166-168 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (s, 1H), 7.33 – 7.29 (m, 1H), 7.19 (td, *J* = 7.7, 1.3 Hz, 1H), 6.96 (td, *J* = 7.5, 1.1 Hz, 1H), 6.79 (dt, *J* = 7.6, 0.8 Hz, 1H), 6.67 (t, *J* = 2.5 Hz, 1H), 6.51 (t, *J* = 2.0 Hz, 1H), 6.05 (s, 1H), 6.00 (dd, *J* = 2.8, 1.8 Hz, 1H), 3.31 (m, 1H), 0.83 – 0.76 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.3, 141.8, 134.1, 129.1, 125.0, 124.1, 122.0, 121.4, 119.8, 109.9, 107.6, 74.0, 30.3, 6.5 (2C). HRMS (ESI)*m/z*: $[M + H]^+$ Calcd for $C_{15}H_{15}N_2O_2$ 255.1128; Found 255.1134.



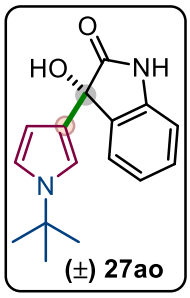
3-hydroxy-3-(1-propyl-1H-pyrrol-3-yl)indolin-2-one (± 27al). Purification with petroleum ether/EtOAc (4/1 as eluent; Red solid (53 mg, 69% yield, mp = 166-168 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.14 (s, 1H), 7.32 (d, *J* = 7.2 Hz, 1H), 7.19 (td, *J* = 7.7, 1.2 Hz, 1H), 7.00 – 6.93 (m, 1H), 6.80 (d, *J* = 7.7 Hz, 1H), 6.64 (t, *J* = 2.4 Hz, 1H), 6.50 (t, *J* = 1.9 Hz, 1H), 6.05 (s, 1H), 6.04 – 6.01 (m, 1H), 3.72 (t, *J* = 7.1 Hz, 2H), 1.62 (h, *J* = 7.3 Hz, 2H), 0.79 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.4, 141.8, 134.3, 129.0, 125.0, 123.7, 121.9, 121.1, 119.5, 109.9, 107.4, 74.1, 50.8, 24.8, 11.5. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{17}N_2O_2$ 257.1285; Found 257.1291.



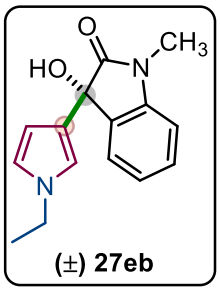
3-(1-cyclohexyl-1*H*-pyrrol-3-yl)-3-hydroxyindolin-2-one (± 27am). Purification with petroleum ether/EtOAc (9/1) as eluent; Orange oil (56 mg, 64% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.51 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.27 – 7.21 (m, 1H), 7.08 (td, *J* = 7.6, 1.0 Hz, 1H), 6.88 (d, *J* = 7.7 Hz, 1H), 6.71 (t, *J* = 2.1 Hz, 1H), 6.66 (t, *J* = 2.6 Hz, 1H), 6.30 (dd, *J* = 2.9, 1.8 Hz, 1H), 3.68 (tt, *J* = 11.8, 3.8 Hz, 1H), 3.34 (s, 1H), 2.06 – 1.95 (m, 2H), 1.82 (dt, *J* = 13.4, 3.4 Hz, 2H), 1.72 – 1.63 (m, 1H), 1.52 (m, 2H), 1.41 – 1.24 (m, 2H), 1.16 (qt, *J* = 12.8, 3.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 140.3, 132.0, 129.3, 124.9, 122.9, 121.6, 119.5, 117.9, 110.3, 106.4, 74.6, 58.9, 34.5 (2C), 25.6 (2C), 25.4. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{21}N_2O_2$ 297.1598; Found 297.1592.



3-(1-(tert-butyl)-1*H*-pyrrol-3-yl)-3-hydroxyindolin-2-one (± 27ao). Purification with petroleum ether/EtOAc (7/3) as eluent; Brownish solid (56 mg, 70% yield, mp = 178–181 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (s, 1H), 7.48 (d, *J*= 7.3 Hz, 1H), 7.18 (td, *J* = 8.7, 7.7, 1.0 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.88 – 6.82 (m, 2H), 6.74 (t, *J* = 2.7 Hz, 1H), 6.28 (dd, *J* = 2.8, 1.9 Hz, 1H), 4.15 (s, 1H), 1.41 (s, 9H). ^{13}CNMR (100 MHz, $CDCl_3$) δ 180.8, 140.4, 132.1, 129.0, 124.6, 122.7, 121.5 118.3, 116.7, 110.6, 106.4, 74.8, 54.9, 30.5 (3C). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{19}N_2O_2$ 271.1446; Found: 271.1449.

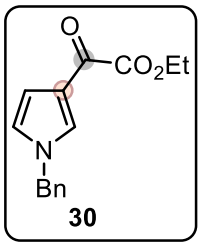


3-(1-ethyl-1*H*-pyrrol-3-yl)-3-hydroxy-1-methylindolin-2-one (± 27eb). Purification with petroleum ether/EtOAc (4/1) as eluent; White solid (47 mg, 62% yield, mp = 123-126 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 1H), 7.32 (td, *J* = 7.8, 1.3 Hz, 1H), 7.11 (td, *J* = 7.6, 1.0 Hz, 1H), 6.83 (dt, *J* = 7.7, 0.8 Hz, 1H), 6.68 (t, *J* = 2.0 Hz, 1H), 6.60 (t, *J* = 2.5 Hz, 1H), 6.31 (dd, *J* = 2.8, 1.8 Hz, 1H), 3.83 (q, *J* = 7.3 Hz, 2H), 3.23 (s, 1H), 3.18 (s, 3H), 1.36 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 143.2, 131.3, 129.3, 124.4, 122.9, 122.3, 120.8, 119.2, 108.3, 106.9, 74.0, 44.3, 6.3, 16.3. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{17}N_2O_2$ 257.1290; Found 257.1287.

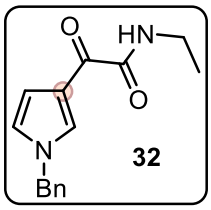


3.6.1 Gram-Scale synthesis of (±)24af: To a solution of succinaldehyde **21** (3.0 M sol, 5.39 mL, 16.3 mmol, 2.0 equiv.), *p*-anisidine **7f** (1.0 g, 8.13 mmol, 1.0 equiv.) in CH_2Cl_2:EtOH (1:1) (20.0 mL) was added methyl pyruvate **23a** (1.65 g, 16.3 mmol, 2.0 equiv.) and further stirred at 5 °C for 24 h. Upon completion, the solvents were removed under reduced pressure, and the reaction was stirred between CH_2Cl_2 (10.0 mL) and water (10.0 mL) for five minutes. The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The product **24af** (1.52 g, 68% yield) was obtained by passing through the silica-gel column by eluting with petroleum ether/EtOAc.

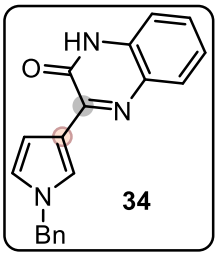
3.6.2 Ethyl 2-(1-benzyl-1*H*-pyrrol-3-yl)-2-oxoacetate (30). To the stirred solution of **24ia** (0.08 g, 0.3 mmol) in DMSO (4.0 mL) was added IBX (0.90 0.35 mmol) at rt and stirred the combined mixture for 4 h at the same temperature. Upon completion, the reaction was stirred between saturated $NaHCO_3$ solution (5.0 mL) and EtOAc (5.0 mL). The organic layer was separated and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Passing through a small pad of silica-gel column using petroleum ether/EtOAc (9/1) as eluent gave a-ketoester **30** (74 mg, 93% yield) as little orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (t, *J* = 1.9 Hz, 1H), 7.39 – 7.29 (m, 3H), 7.20 – 7.12 (m, 2H), 6.81 (dd, *J* = 3.0, 1.7 Hz, 1H), 6.66 (dd, *J* = 3.0, 2.1 Hz, 1H), 5.08 (s, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3, 163.0, 135.9, 130.6, 129.0 (2C), 128.3, 127.3 (2C), 123.4, 121.6, 111.1, 61.9, 54.0, 14.0. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{16}NO_3$ 258.1125; Found 258.1121.



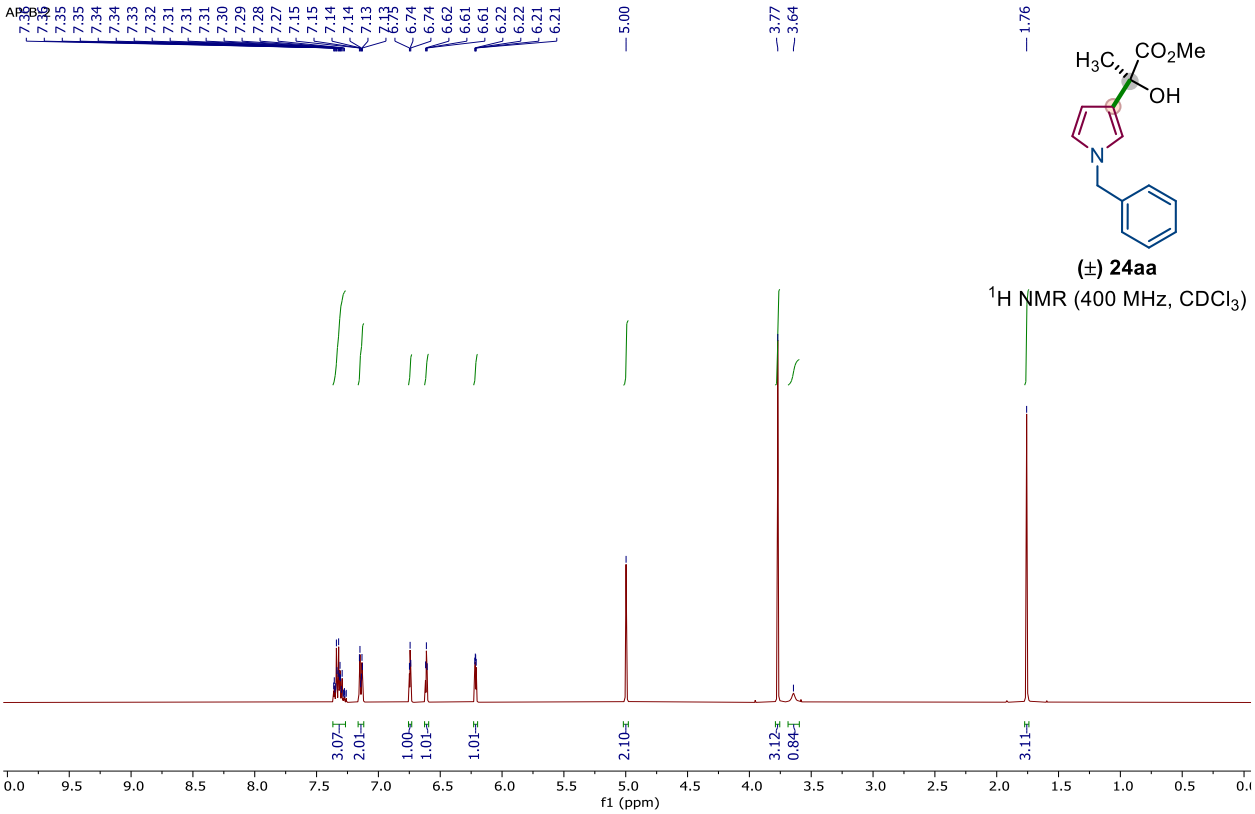
2-(1-benzyl-1*H*-pyrrol-3-yl)-*N*-ethyl-2-oxoacetamide (32). An over-dried Schlenk tube (25 mL) was charged with α-ketoester compound **30** (0.70 mg, 0.27 mmol) and ethyl amine **7b** (25 mg, 0.54 mmol) in CH_2Cl_2 (4.0 mL) and stirred at rt for 24 h. Upon completion, the reaction mixture was concentrated under reduced pressure. Compound **32** was obtained by directly passing the crude mass through a small pad of silica-gel column using petroleum ether/ethyl acetate (8:2) as eluent. White solid (63 mg, 90% yield, mp = 91-94ºC). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (t, *J* = 1.9 Hz, 1H), 7.41 – 7.27 (m, 4H), 7.18 – 7.14 (m, 2H), 6.84 (dd, *J* = 3.0, 1.6 Hz, 1H), 6.63 (dd, *J* = 3.1, 2.1 Hz, 1H), 5.07 (s, 2H), 3.36 (qd, *J* = 7.3, 5.9 Hz, 2H), 1.20 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.6, 162.0, 136.1, 132.6, 128.9 (2C), 128.2, 127.3 (2C), 122.8, 120.9, 111.4, 53.9, 34.0, 14.4. IR (KBr)/cm^{-1} 3417, 2916, 1717,1651, 1605, 1512, 1350, 1250, 1188, 1049, HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{15}H_{17}N_2O_2$ 257.1285; Found 257.1291.



3-(1-benzyl-1*H*-pyrrol-3-yl) quinoxalin-2(1*H*)-one (34). An over-dried Schlenk tube (25 mL) was charged with α-ketoester compound **30** (0.80 mg, 0.31 mmol) and 1,2-diaminobenzene **33** (50 mg, 0.47 mmol, 1.5 equiv.) in EtOH (5.0 mL) and heating to 80 ºC for 3 h. Upon completion, the reaction mass was concentrated under reduced pressure. Compound 34 was obtained by directly passing through a small pad of silica-gel column using petroleum ether/ethyl acetate (6:4) as eluent. Yellow solid (82 mg, 87% yield, mp = 269-271ºC). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (t, *J* = 1.9 Hz, 1H), 7.70 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.44 – 7.37 (m, 1H), 7.35 (dt, *J* = 6.8, 1.4 Hz, 2H), 7.32 – 7.23 (m, 6H), 6.95 (dd, *J* = 2.9, 2.1 Hz, 1H), 6.89 (dd, *J* = 2.9, 1.6 Hz, 1H), 5.18 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.5, 151.2, 138.6, 132.8, 130.8, 129.2 (2C), 128.8, 128.2, 127.9 (3C), 127.3, 123.9, 123.0, 120.7, 115.3, 109.2, 53.0. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{19}H_{16}N_3O$ 302.1288; Found 302.1292.

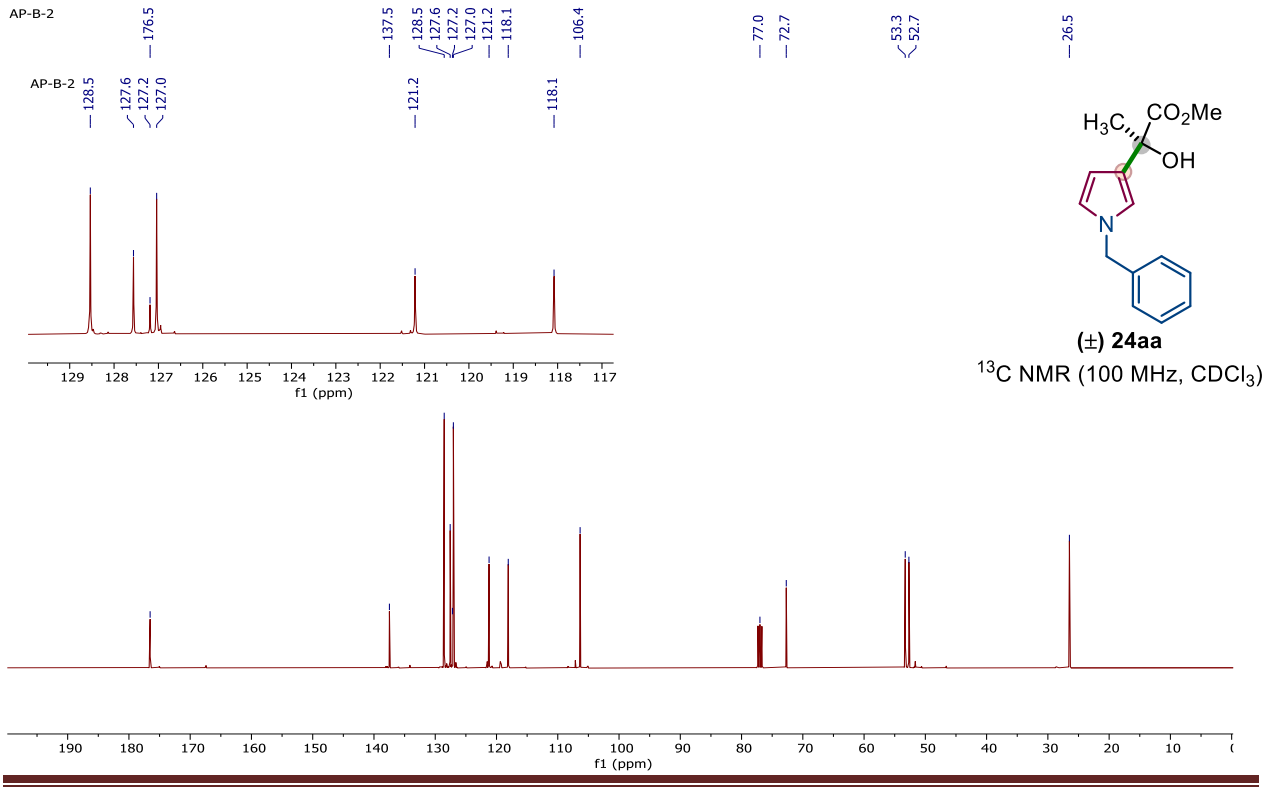


3.7 Spectral Information



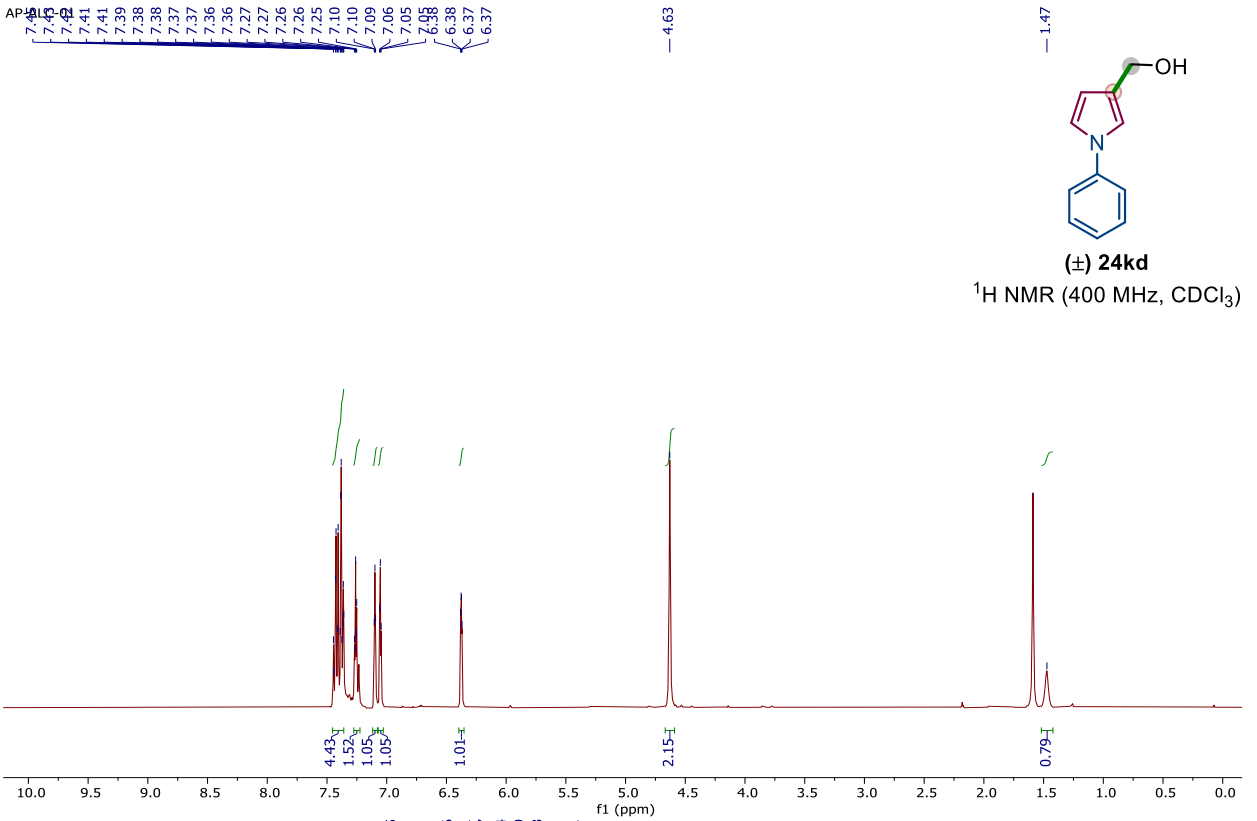
(±) **24aa**

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



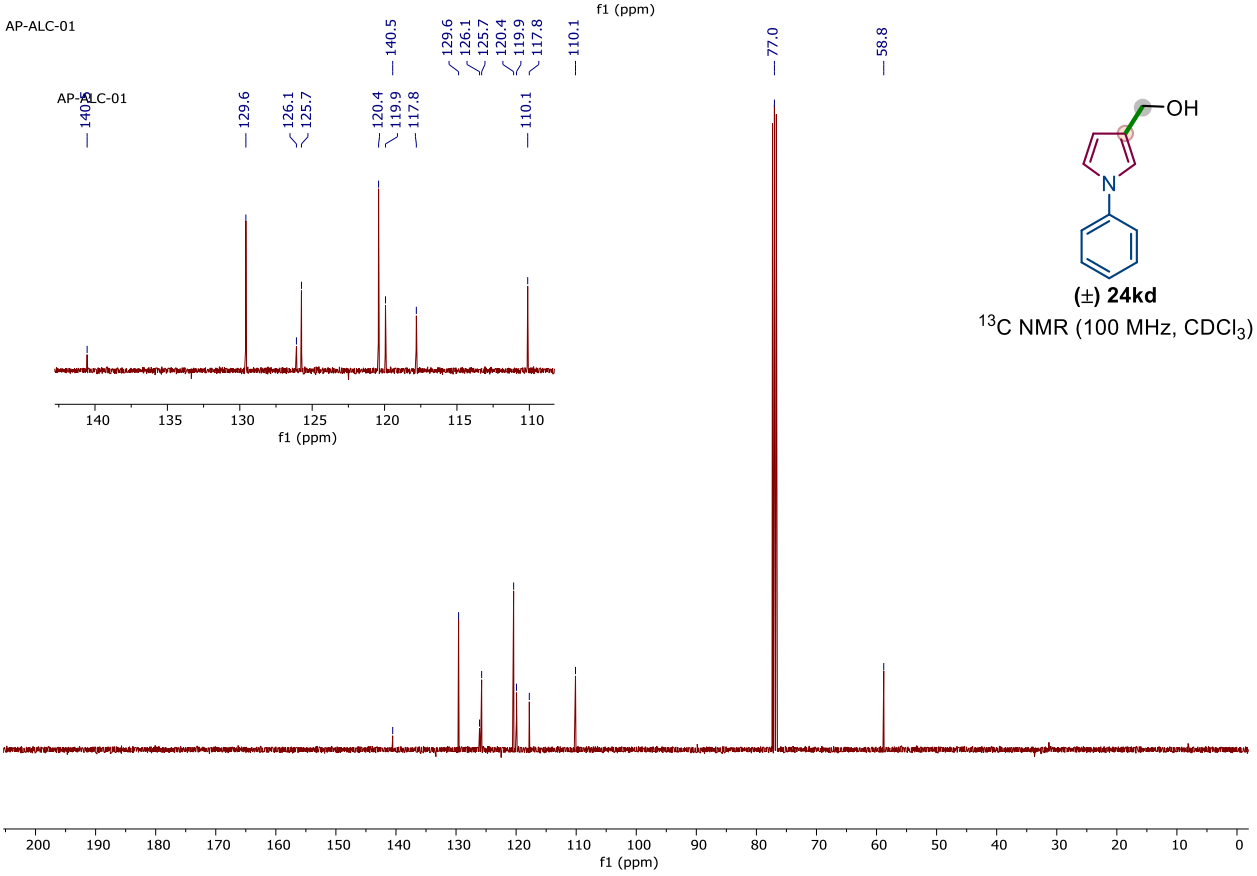
(±) **24aa**

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



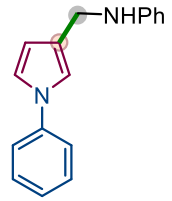
(±) 24kd

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



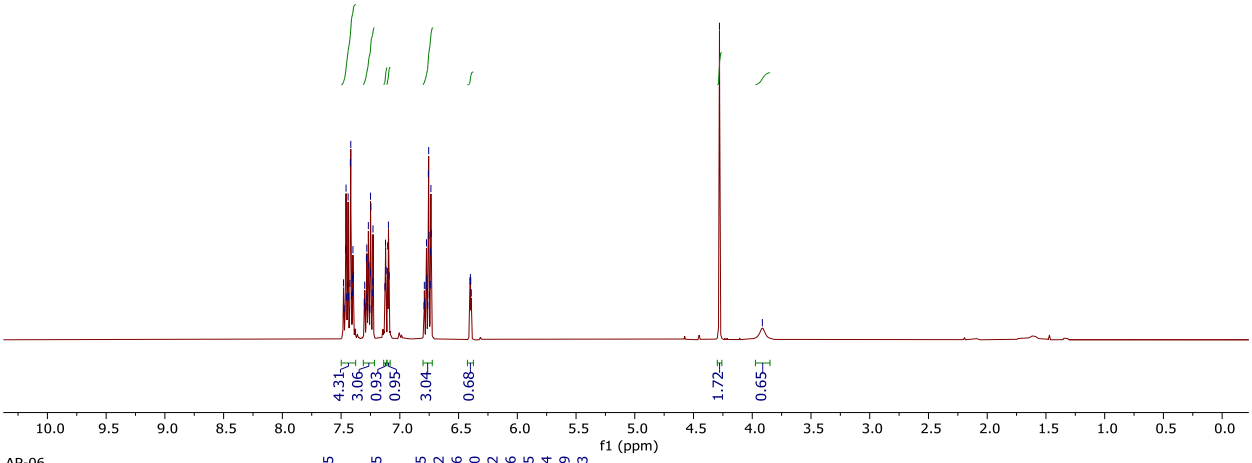
(±) 24kd

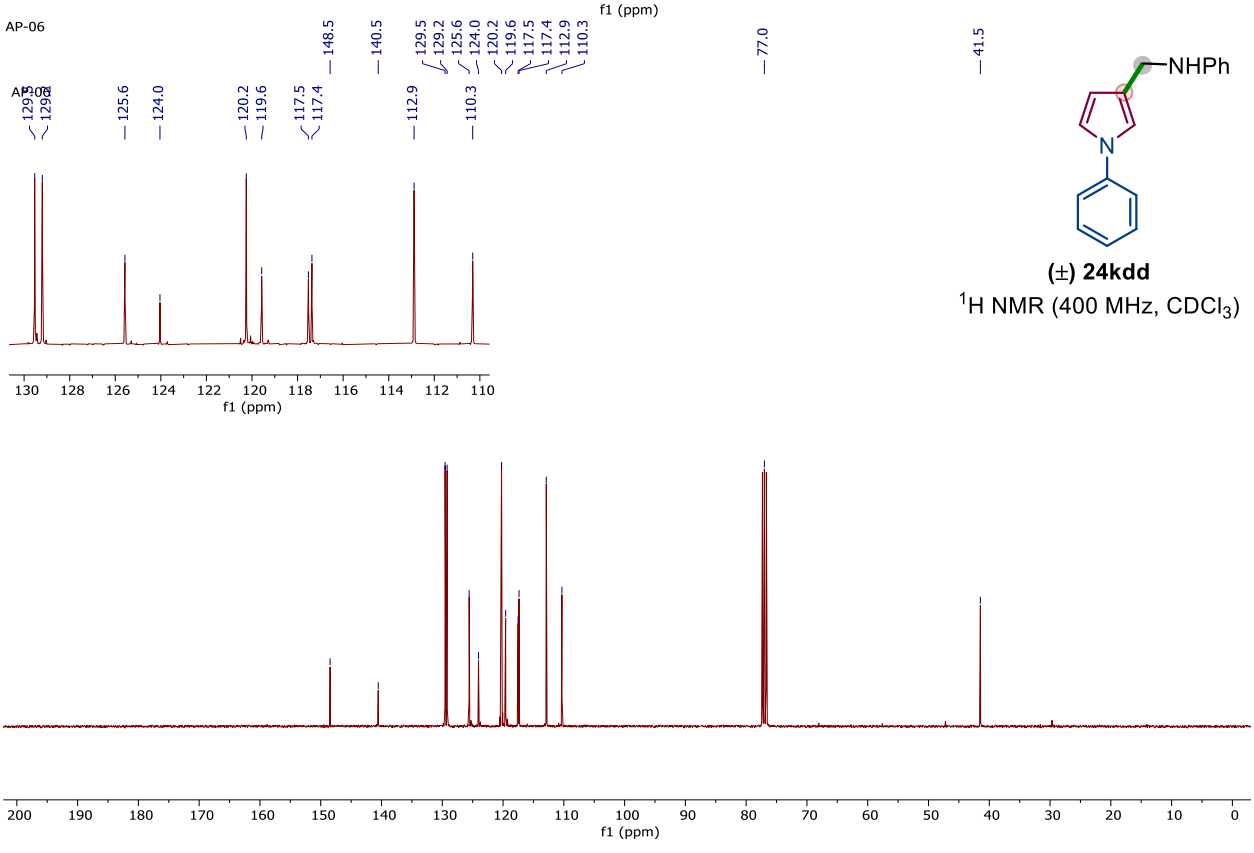
^{13}C NMR (100 MHz, $CDCl_3$)



(±) 24kdd

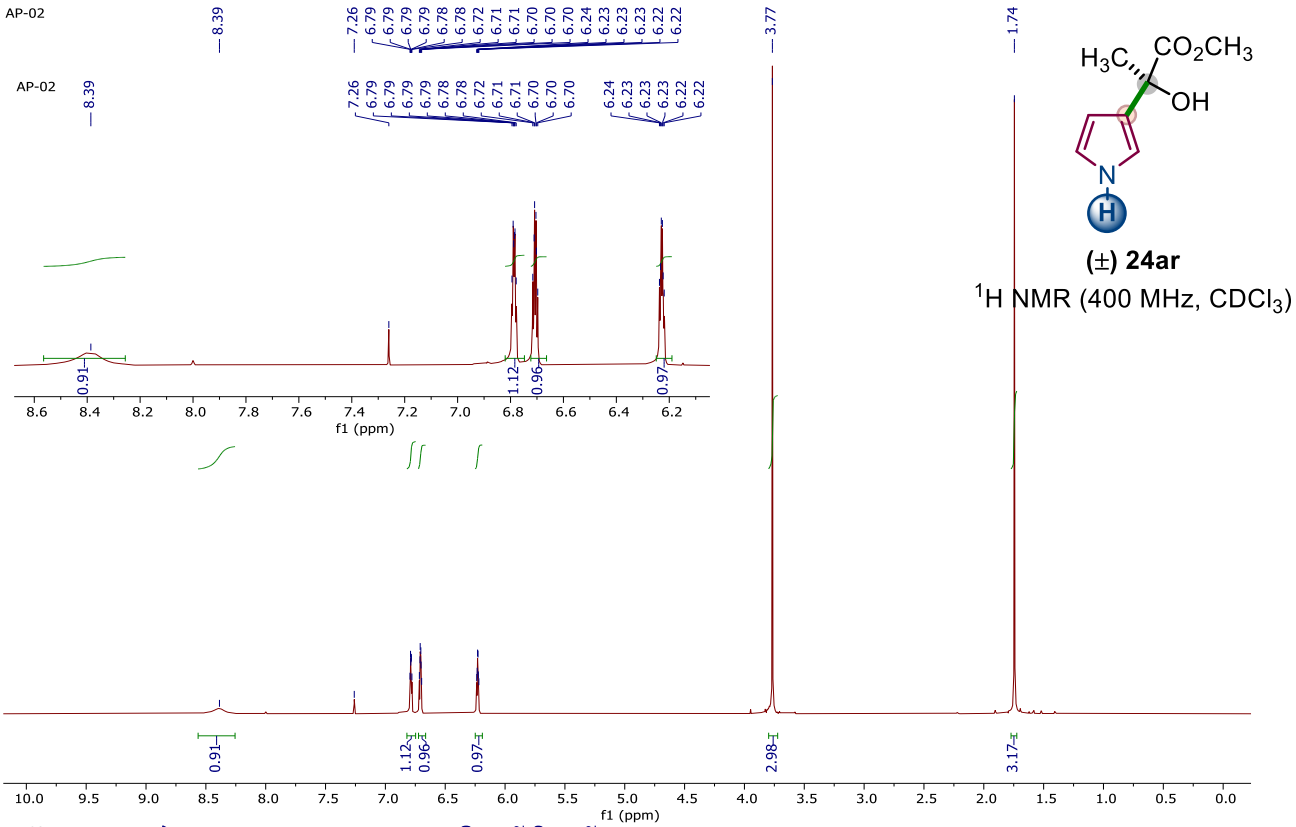
^{13}C NMR (100 MHz, $CDCl_3$)





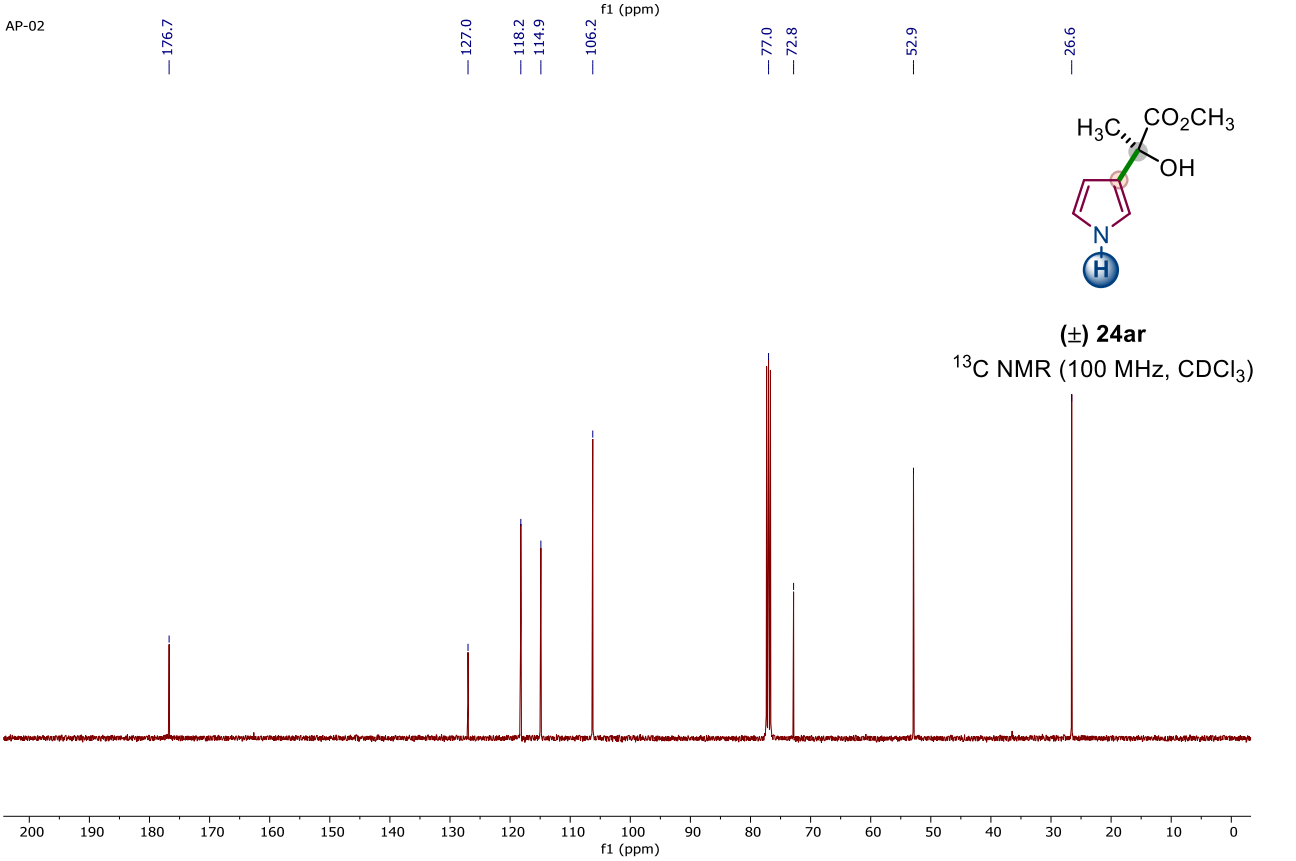
(±) 24kdd

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



(±) 24ar

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



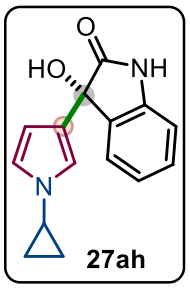
(±) 24ar

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

3.8 Single-crystal X-ray Diffraction Experiment and Analysis

Single Crystal XRD Experiments for 27ah: The single crystal XRD data collection and data reduction were performed using CrysAlis PRO on a single crystal Rigaku Oxford XtaLab Pro Kappa dual home/near diffractometer. The crystals were kept at 93(2) K during data collection using CuKα (λ = 1.54184 Å) radiation. Using Olex2[37], the structure was solved with the ShelXT[38] structure solution program using Intrinsic Phasing and refined with the ShelXL[39] refinement package using Least Squares minimization.

Single Crystal structure, Cell parameters, and structure data of compound (27ah)



The single crystal of compound (**27ah**) $C_{15}H_{14}N_2O_2$ **[exp_968_IK-APIS-CP]** was crystalized as a colorless block through the slow evaporation of (ethyl acetate + hexane + acetone) solvent mixture solution at room temperature. The compound **[exp_968_IK-APIS-CP]** crystallized in a monoclinic crystal system with a $P2_1/c$ space group. One molecule appeared in the structure solution in an asymmetric unit ($Z'=1$) with the following crystal unit cell data.

Crystal Data for $C_{15}H_{14}N_2O_2$ (M =254.28 g/mol): monoclinic, space group $P2_1/c$ (no. 14), a = 11.1124(2) Å, b = 11.30100(10) Å, c = 10.6161(2) Å, β = 109.698(2)°, V = 1255.17(4) Å^3, Z = 4, T = 93(2) K, μ(Cu Kα) = 0.737 mm^{-1}, *Dcalc* = 1.346 g/cm^3, 13555 reflections measured (8.452° ≤ 2Θ ≤ 159.236°), 2695 unique (R_{int} = 0.0296, R_{sigma} = 0.0230) which were used in all calculations. The final R_1 was 0.0386 (I > 2σ(I)), and wR_2 was 0.0980 (all data). The crystallographic details of compound **27ah** are deposited to the Cambridge Crystallographic (CCDC 2166129). The ORTEP diagram as the crystal structure of **27ah [exp_968_IK-APIS-CP]** is illustrated in Figure 3.3. The molecule has one chiral center (C7–*R*).

The compound crystallized as a colorless block in a monoclinic $P2_1/c$ space group (CCDC 2166129). One neutral molecule, $C_{15}H_{14}N_2O_2$ found in an asymmetric unit, and four molecules are found in a unit cell. The compound has two hydrogen bond donors, N1-H and O2-H, and two hydrogen bond acceptors, O1 and O2. The 3D supramolecular structure is stabilized by hydrogen bond and non-covalent bond interactions.

Table 3.5: Crystal data and structure refinement for (27ah) exp_968_IK_APIS-CP_autored

Identification code	exp_968_IK_APIS-CP_autored
Empirical formula	$C_{15}H_{14}N_2O_2$
Formula weight	254.28
Temperature/K	93(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	11.1124(2)
b/Å	11.30100(10)
c/Å	10.6161(2)
α/°	90
β/°	109.698(2)
γ/°	90
Volume/Å^3	1255.17(4)
Z	4
ρ_{calc}g/cm^3	1.346
μ/mm^{-1}	0.737
F(000)	536.0
Crystal size/mm^3	0.2 × 0.15 × 0.05
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	8.452 to 159.236
Index ranges	$-14 \leq h \leq 13$, $-13 \leq k \leq 14$, $-12 \leq l \leq 13$
Reflections collected	13555
Independent reflections	2695 [R_{int} = 0.0296, R_{sigma} = 0.0230]
Data/restraints/parameters	2695/0/173
Goodness-of-fit on F^2	1.066
Final R indexes [I>=2σ (I)]	R_1 = 0.0386, wR_2 = 0.0964
Final R indexes [all data]	R_1 = 0.0411, wR_2 = 0.0980

Largest diff. peak/hole / e $Å^{-3}$	0.27/-0.34
CCDC	2166129

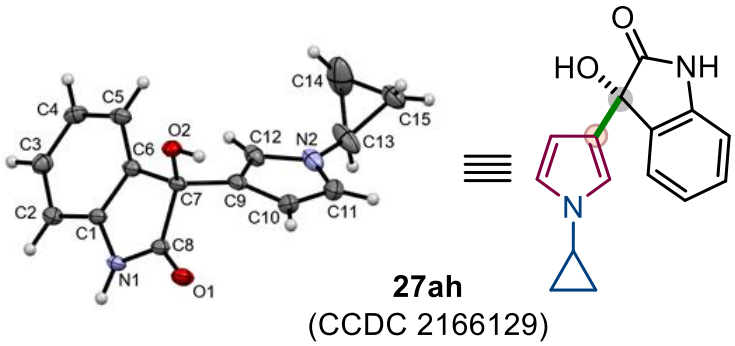


Figure 3.3: The ORTEP diagram of compound 27ah **[exp_968_IK-APIS-CP]**. The thermal ellipsoid is drawn at the 50 % probability level, and hydrogen atoms are shown as small spheres of arbitrary radii **(CCDC 2166129).**

3.9 References

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Chapter – 4

Amine-Catalyzed Direct Enantioselective Synthesis of C3-Hydroxyalkylated Pyrrole

4.1 Introduction

Developing a method to create chirality around pyrrole is an exciting task in asymmetric synthesis. The pyrrole ring system is essential to several biologically active natural products and marketed drugs.[1] In particular, chiral pyrrole-derived molecules such as (+)-heronapyrrole A, D, and C antibiotic natural products, (+)-nitropyrrole in A, B, and D showed cytotoxicity towards human colon carcinoma cells. Streptorubin B, pyrrole derived compound having a chiral center at the C3-position, is also known to have anti-bacterial activity against MRSA strain.[2] Asymmetric techniques for the selective functionalization of pyrrole are exciting because these electron-rich heterocycles are constituents of numerous natural products and pharmaceutical agents. In this context, several Friedel-Craft reactions[3] have been established to access chiral pyrrole under metal-catalysis[4] and organocatalysis[5] since the initial development of MacMillan and co-workers in this direction (Figure 4.1).[6] The most broadly utilized methodology has been the conjugate addition of heterocycles to α, β-unsaturated carbonyl compounds using chiral transition-metal catalysts or organocatalysts. Interestingly, these methods create chirality at the favorable C2-position of pyrrole due to its intrinsic reactivity.[7]

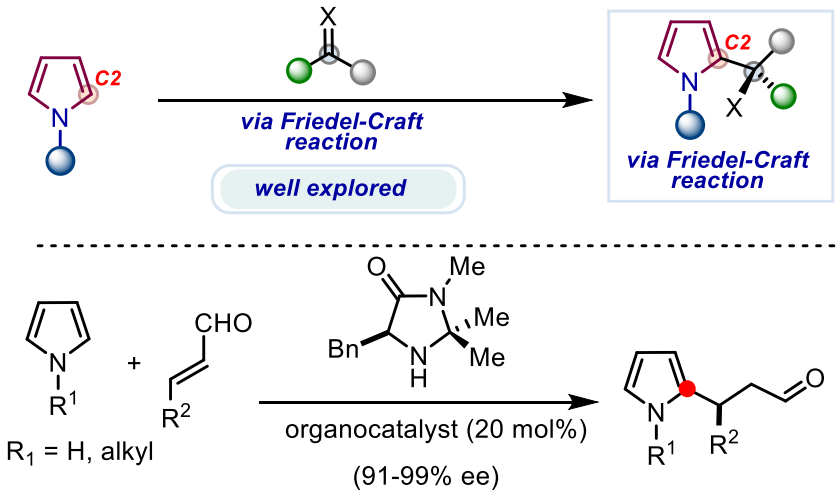


Figure 4.1 A general approach for the S_EAr reaction with pyrrole at C2-position.

4.1.1 Approaches toward the enantioselective synthesis of C3-substituted pyrroles

The creation of substitution with a chiral center at the C3-position of pyrrole via S_EAr reactions is difficult to achieve,[8] compared to the C2-position. Alternative methods have been developed to induce chirality at the C3-position that strictly requires the pre-functionalization at the C2/C5-

positions of pyrrole. The general approach to synthesizing C3-substituted pyrrole from pre-functionalized pyrrole is shown in Figure 4.2.

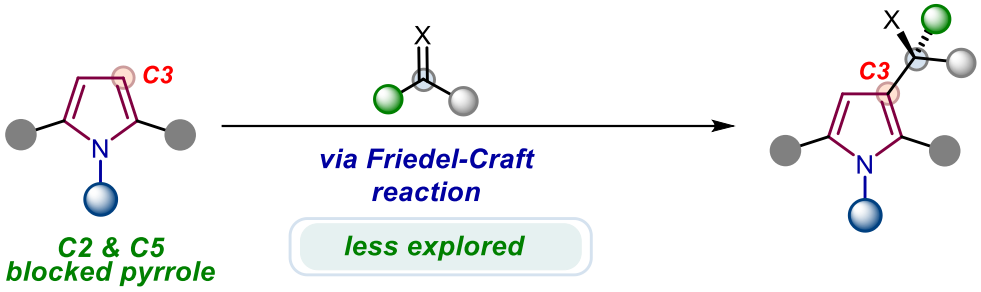
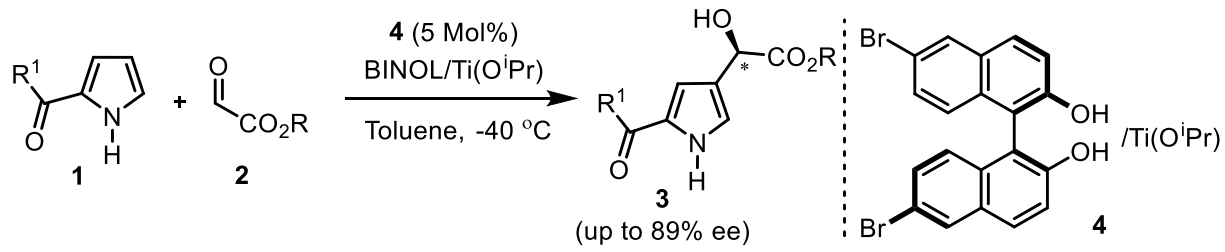


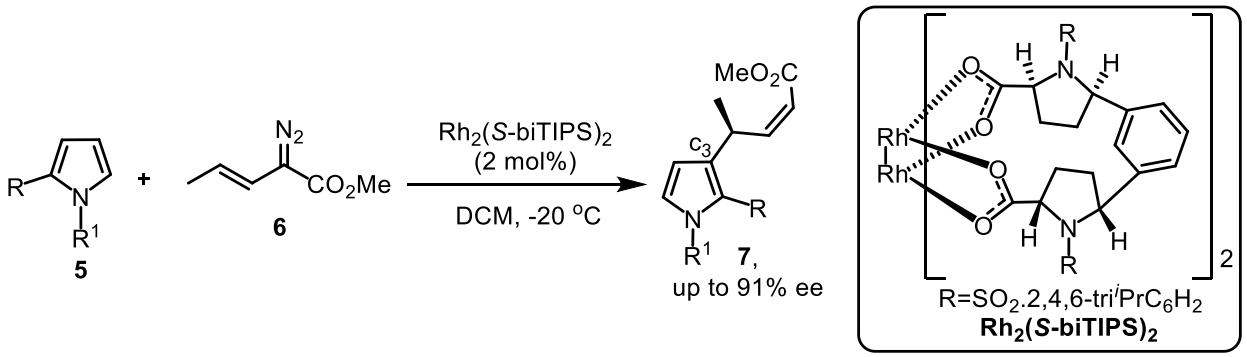
Figure 4.2 Alternative approach for the S_EAr reaction at the C3-position of pyrrole.

Thus, developing a method for creating chirality at the C3-position of pyrrole is an interesting problem to resolve. Several methods have been developed in this direction that utilizes the strategy mentioned in Figure 4.2. In this direction, the first report appeared from the Jurczak group. They developed the Friedel-Crafts reaction of decorated 2-acylpyrrole **1** with n-butylglyoxylate **2** to produce β-functionalized pyrrole **3** in an asymmetric fashion using readily available chiral BINOL–Ti(IV) **4** complexes as a catalyst. An electron-withdrawing group at α or *N*-positions to facilitate the regioselective and highly enantioselective 2,4-disubstituted pyrroles **3** (Scheme 4.1).[9]



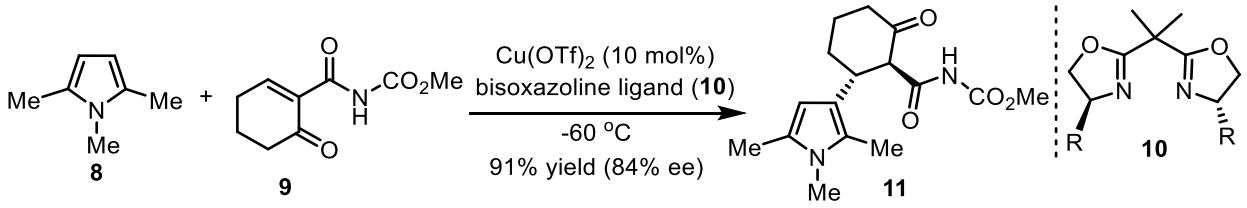
Scheme 4.1 Ti(IV)-BINOL catalyst first asymmetric Friedel–Crafts reactions on pyrroles.

In 2012, Davies co-workers reported Rh_2(*S*-biTISP)$_2$ catalyzed asymmetric vinylogous alkylation between *N*-heterocycles **5** (indoles and pyrroles) and methyl (*E*)-2-diazo-3-pentanoate **6** yielding C3 functionalized products **7**. In their study, a bridged dirhodium catalyst is responsible for the induction of chirality at the C3-position of pyrrole with the vinylogous position of the carbenoid (Scheme 4.2).[10]



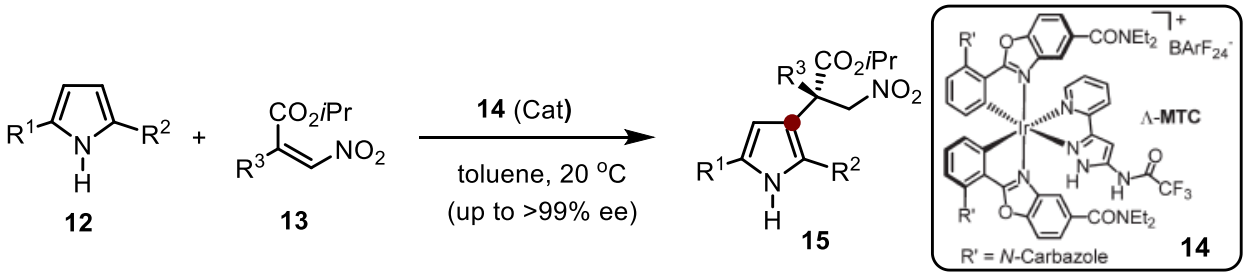
Scheme 4.2 Rh-catalyzed asymmetric vinylogous alkylation reaction.

Nakada and co-workers developed an enantioselective Friedel–Crafts β-alkylation reaction of 1,2,5-trimethyl pyrrole **8** with cyclic α-alkylidene *β*-oxoimide **9** using a bisoxazoline $Cu(OTf)_2$ catalyst to furnish **11** (Scheme 4.3).[11]



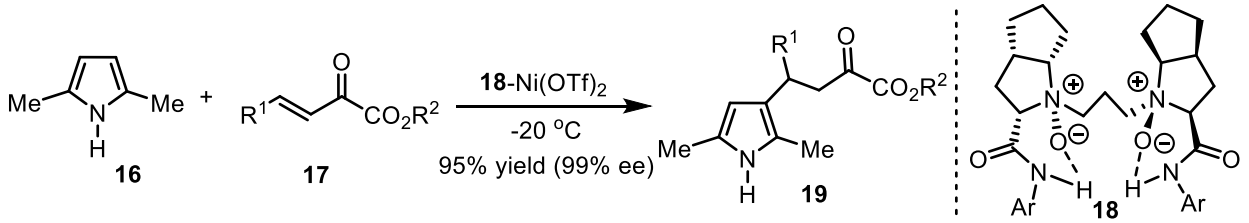
Scheme 4.3 Cu-catalyst asymmetric Friedel–Crafts reactions with pyrrole.

In 2016, Meggers and co-workers developed a highly enantioselective Friedel–Crafts β-alkylation of 2,5-disubstituted pyrroles **12** with nitroacrylates **13** to access C3-substituted pyrrole **15** having all-carbon quaternary stereocenters. The developed method utilizes many CF_3-substituted aromatic/alkyl/heteroaromatic nitro-styrene as Michael acceptors under mild catalytic conditions (Scheme 4.4).[12]



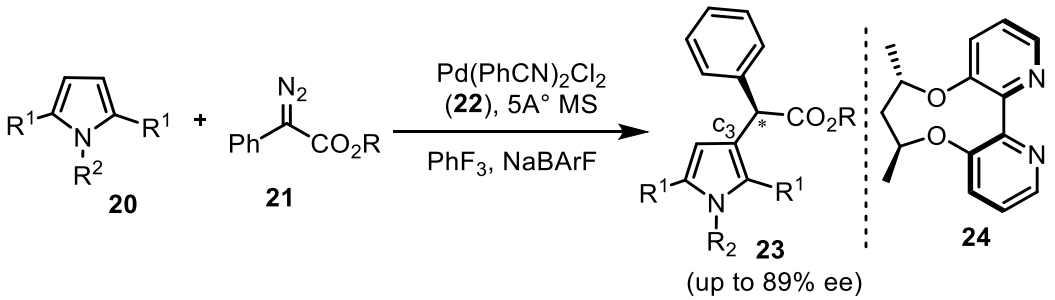
Scheme 4.4 The enantioselective C3-alkylation at C3-position of pyrrole.

In 2015, Feng and co-workers demonstrated the asymmetric Friedel-Crafts C3-alkylation of 2,5-dimethyl pyrrole **16** to β, γ-unsaturated α-ketoesters **17**, by using chiral Ni (II)-complexes of *N*, *N*'- dioxides ligand **18** to furnish compound **19** with high yields and enantioselectivity. A remarkable inversion of enantioselectivity was recognized by changing ligands. The single crystal X-ray analysis confirms that the stereochemistry and DFT calculations clarified the experimentally observed high enantioselectivity at the low temperature (Scheme 4.5).[13]



Scheme 4.5 The asymmetric Friedel–Crafts *β*-alkylation reaction on pyrrole.

In 2018, Zhou and co-workers developed an enantioselective C–H functionalization of highly substituted pyrrole **20** with diazo compounds **21** using Pd-catalyst (5 mol%) and chiral bipyridine ligand C3-ACBP **24** to furnish C3-substituted pyrrole **23** with high enantioselectivity (Scheme 4.6). A great deal of reactivity and enantioselectivity towards C–H functionalization was reported when the same reaction was performed on a gram scale.[14]

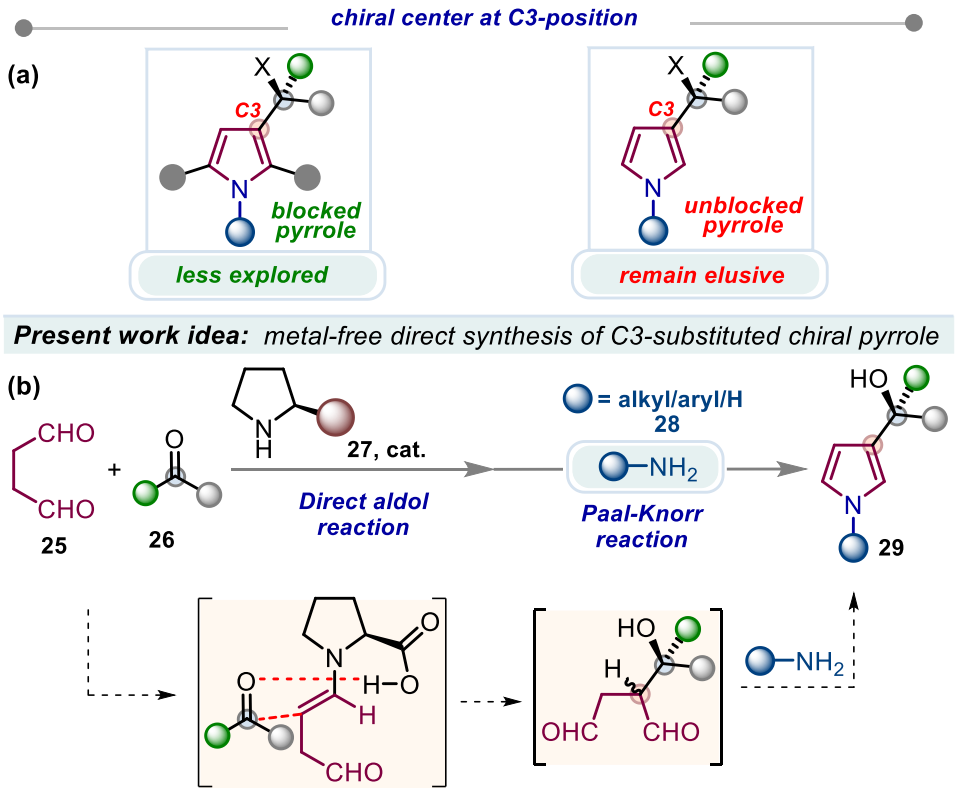


Scheme 4.6 Asymmetric synthesis of C3-functionalized pyrrole from diazo compounds.

4.1.2 Concept and hypothesis of present work

It is clear from the literature analysis that the asymmetric synthesis of C3-substituted pyrrole is increasing attention due to its importance in biologically active compounds. However, the reported approaches are limited to using C2/C5-substituted pyrrole as suitable starting material for further derivation at the C3-position (remained unfunctionalized). However, these alternative

strategies to create chirality at the C3-position of masked pyrrole (Scheme 4.7a). however, similar transformations on unblocked pyrrole or direct asymmetric access to such unit remained unmapped, as far as we know. Thus, developing a direct asymmetric method for β-substituted pyrrole is highly motivating.



Scheme 4.7 Direct asymmetric synthesis of C3-hydroxy alkylated pyrrole.

In this context, we envision that the chiral enamine-intermediate, *in*-situ generated from succinaldehyde **25** and amine catalyst **27,** react with carbonyl-compound **26** through a direct aldol reaction to deliver a suitably functionalized 1,4-dicarbonyl compound that may react with primary amine for a Paal-Knorr reaction, will eventually furnish a pyrrole having substitution with a chiral center at the C3 position (Scheme 4.7b).

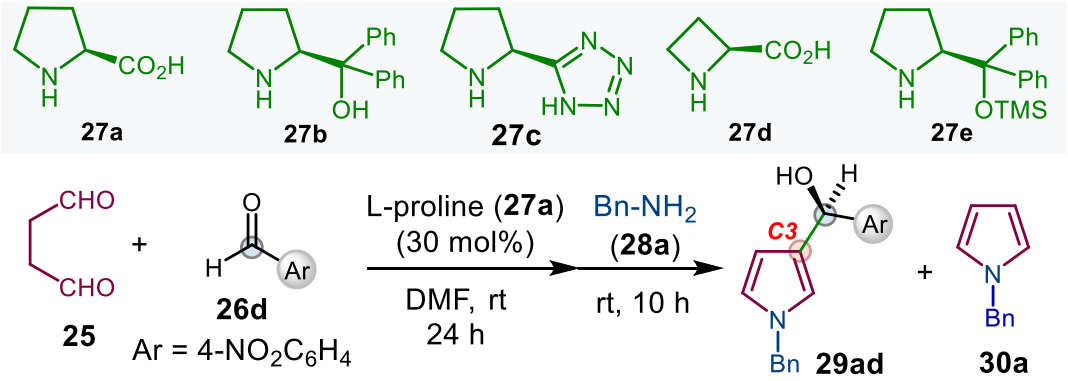
In this context, succinaldehyde **25**, a simple 1,4-dialdehyde compound, has recently been exploited extensively for metal-free cascade transformations,[15] apart from its early utilization in tropinone synthesis[16] and the Paal–Knorr reaction,[17] along with other reactions.[18] In our continued research interest in utilizing succinaldehyde for metal-free transformations,[19] we recently developed stimulating direct access to C3-substituted pyrrole using mild Lewis acid[20]

and catalyst-free conditions.[21] The present study focuses on exploiting the potential of chiral amine-catalyzed direct aldol reaction of succinaldehyde with acceptor carbonyls before it undergoes the Paal-Knorr response with a primary amine **28** to deliver C3-functionalized pyrrole asymmetrically in one-pot fashion. Herein, we present a chronologically multicomponent domino sequence first direct synthesis of unblocked β-hydroxy alkylated-alkyl/Ar/H-pyrroles **29** (Scheme 4.7). Such chiral hydroxy alkylated *N*-heteroaromatics are exciting targets and versatile intermediates in synthesizing pharmaceuticals/agrochemicals.[22]

4.2 Results and discussion

Our study began by investigating transformations using succinaldehyde **25** and 4-nitrobenzaldehyde **26d** under amine catalysts **27**, followed by the addition of benzylamine **28a** as model substrates (Table 4.1). We obtained pyrrole **29ad** (68%) with enantioselectivity (94:6 er) in our initial experiment along with corresponding un-substituted Paal-Knorr product **30a** (18%) when the reaction was carried out in DMF at room temperature using L-proline (30 mol%) as amine catalyst (entry 1, Table 4.1). With the initial encouraging result, we optimize the reaction conditions with different parameters (entries 2-16, in Table 4.1). Initially, deviation in the reaction medium using other solvents like DMSO, 1,4-dioxane, CH_3CN, CH_2Cl_2, and CH_2Cl_2: EtOH mixture failed to advance the results (entries 2-6, Table 4.1). A slight improvement in the reaction yield; however, less enantioselectivity was observed when benzoic acid was used as an additive (entry 7, Table 4.1). No improvement in the reaction outcome was seen when the Paal-Knorr reaction (step-II) was carried out using benzylamine **28a** with the varying amount (entries 8-9, Table 4.1) or with other amine catalysts **27b**-**27e** (entries 10-13, Table 4.1). Pleasingly, the formation of product **29ad** with 74% yield and enantioselectivity (>99:1 er) was observed when the direct aldol reaction was carried out at 10 ^{o}C (entry 14, Table 4.1) while optimizing the temperature parameters for both steps (entries 14-16, Table 4.1) and catalyst loading (entry 14, Table 4.1). However, the formation of **30a** could not be suppressed completely; we consider the standard condition (entry 14) for the rest of our study.

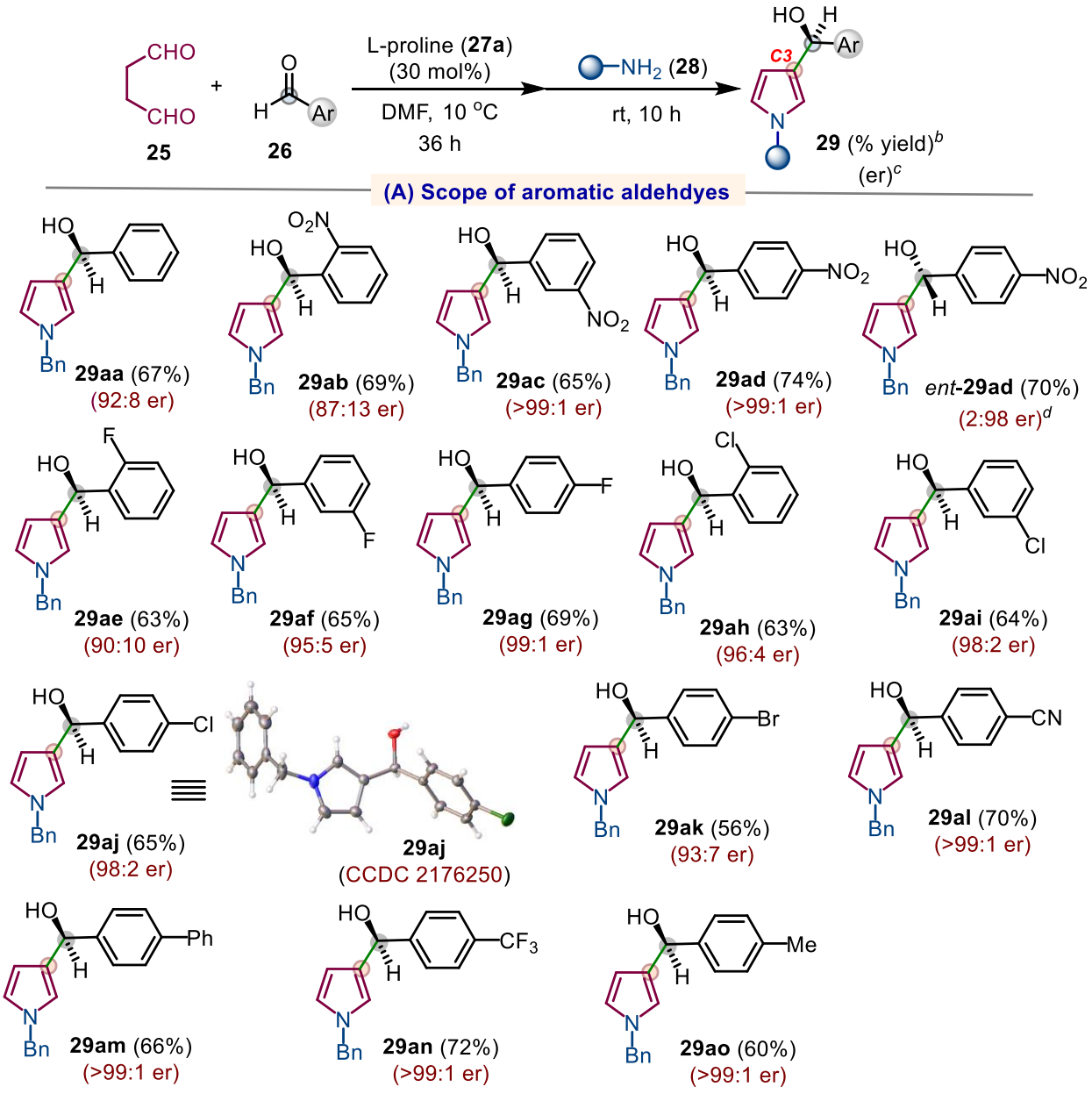
Table 4.1 Optimization of reaction conditions[a]

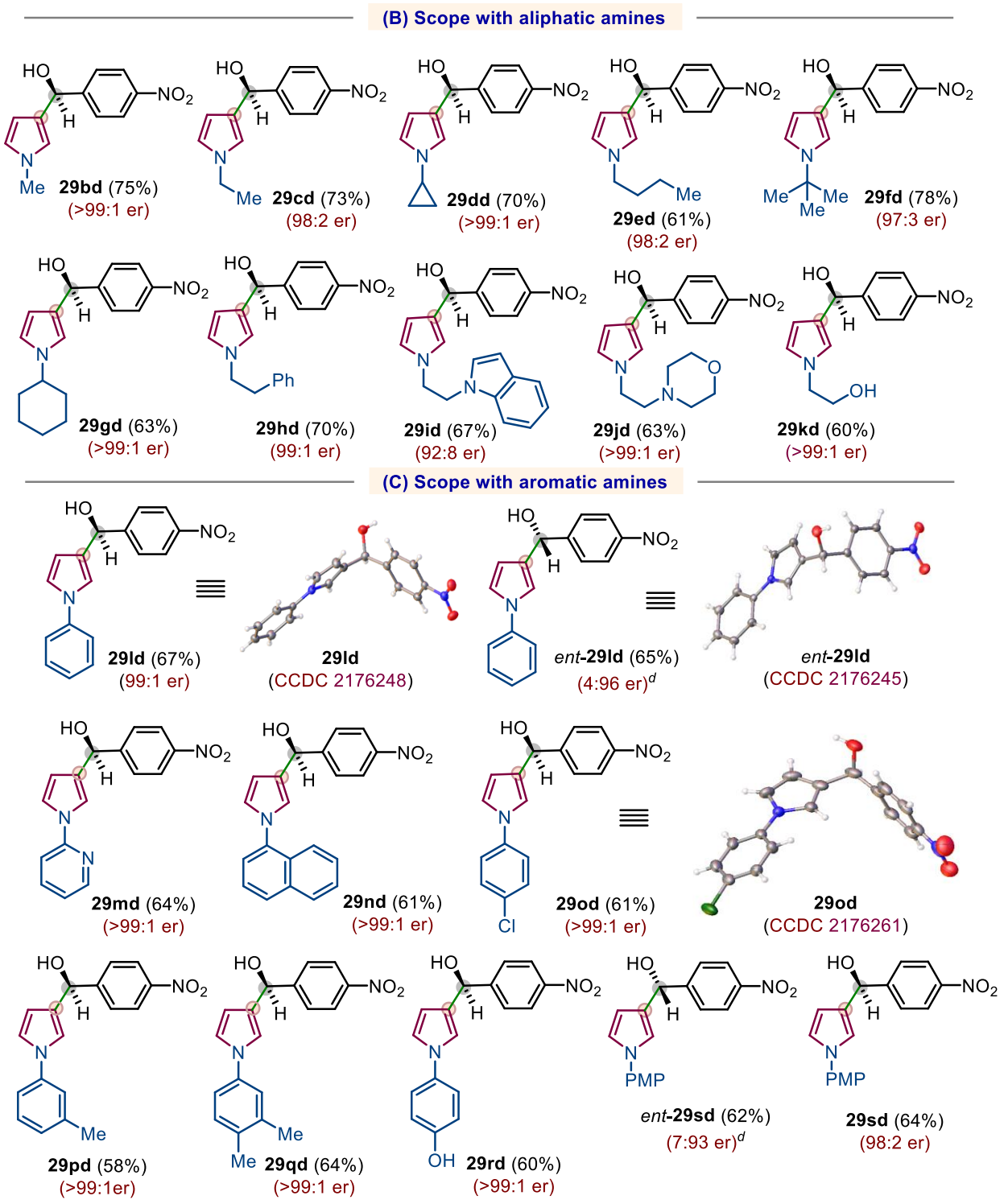


entry	Variation from above (step-I) / (step-II)	yield (%)[b] **29ad**/**30a**	(er)[c] for **29ad**
1	None	68/18	94:6
2	DMSO as solvent / -	56/20	89:11
3	1,4-dioxane as solvent / -	38/28	nd
4	CH_3CN as solvent / -	39/25	nd
5	CH_2Cl_2 as solvent / -	45/32	85:15
6	CH_2Cl_2:EtOH (2:1) as solvent / -	54/25	91:9
7	$PhCO_2H$ (30 mol%) used as additive / -	70/15	93:7
8	- / **28a** (1.0 equiv) was used	50/12	95:5
9	- / **28a** (2.0 equiv) was used	70/25	95:5
10	Catalyst **27b** was used / -	48/30	90:10
11	Catalyst **27c** was used / -	53/25	93:7
12	Catalyst **27d** was used / -	55/28	94:6
13[d]	Catalyst **27e** was used / -	45/30	6:94
14	**10 °C, 36 h** / -	**74/<10**	**>99:1**
15	0 °C, 48 h / -	65/<10	>99:1
16	10 °C, 36 h / 10 °C, 10 h	68/15	>99:1
17	Cat **27a** (20 mol%), 10 °C, 36 h / -	66/15	>99:1

[a]The reaction was carried out using succinaldehyde **25** (3.0 M sol, 1.8 mmol, 3.0 equiv), 4-nitrobenzaldehyde **26d** (0.6 mmol, 1.0 equiv), L-Proline **27a** (0.18 mmol, 0.3 equiv), DMF (3.0 mL), rt, 24 h (step-I); **28a** (0.9 mmol, 1.5 equiv), rt, 10 h (step-II). [b]Isolated yield of **29ad** refers to **26d**.[c]Determined using stationary chiral columns. [d]$PhCO_2H$ (30 mol%) was used as an additive.

Table 4.2 Reaction scope with primary amines **28** and aromatic aldehydes **26**[a].



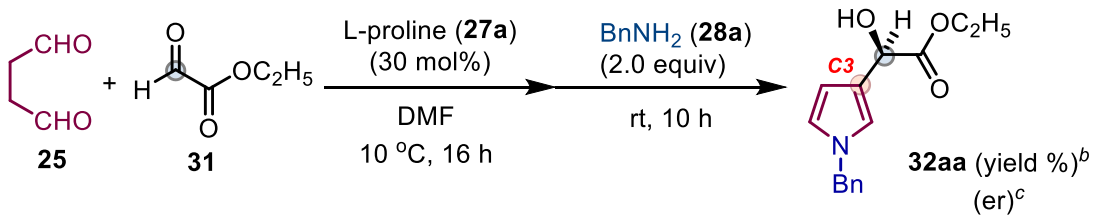


[a]The reaction was carried out using succinaldehyde **25** (3.0 M sol, 1.8 mmol, 3.0 equiv), aromatic aldehyde **26** (0.6 mmol, 1.0 equiv), L-Proline **27a** (0.18 mmol, 0.3 equiv), DMF (3.0 mL), 10 °C, 36 h (step-I); **28** (0.9 mmol, 1.5 equiv), rt, 10 h (step-II). [b]Isolated yield of **29** refers

to **26** (≤10% of *N*-alkyl/aryl-pyrrole **30** was obtained in all the cases). [c]Determined using stationary chiral columns. [d]D-proline (*ent*-**27a**) was used instead of L-proline.

Under optimized conditions, the reaction scope was checked with various aromatic aldehydes **26** with primary amine **28** (Table 4.2). Initially, a series of aromatic aldehydes **26a-26o**, irrespective of their electronic features, underwent proline-catalyzed aldol reaction with succinaldehyde **25** followed by Paal-Knorr reaction with benzylamine **28a** corresponding furnished products **29aa-29ao** with Overall good yields and high enantioselectivity (up to >99:1 er). Next, the generality of primary aliphatic amines **28b-28k** has been tested with succinaldehyde **25** and 4-nitrobenzaldehyde **26a** to furnish the corresponding products **29bd-29kd** with comparable yields and enantioselectivity. Besides, a series of aromatic/heteroaromatic primary amines **28l-28s** also supplied corresponding chiral pyrrole **29ld-29sd** with good to high results and excellent enantioselectivity (up to >99:1 er). Access to both enantiomers of any chiral compounds is highly demanded for evaluating their biological/pharmaceutical activity. In this regard, opposite enantiomers *ent*-**29ad**, *ent*-**29ld,** and *ent*-**2,9sd** were prepared with comparable yields and enantioselectivity using D-proline as an amine catalyst. The absolute configuration of **29aj**, **29ld**, and **29od** was determined to be (*R*), and for *ent*-**29ld** to be (*S*) based on single crystal X-ray analysis and earlier literature, the stereochemistry of others was assigned by analogy.[23]

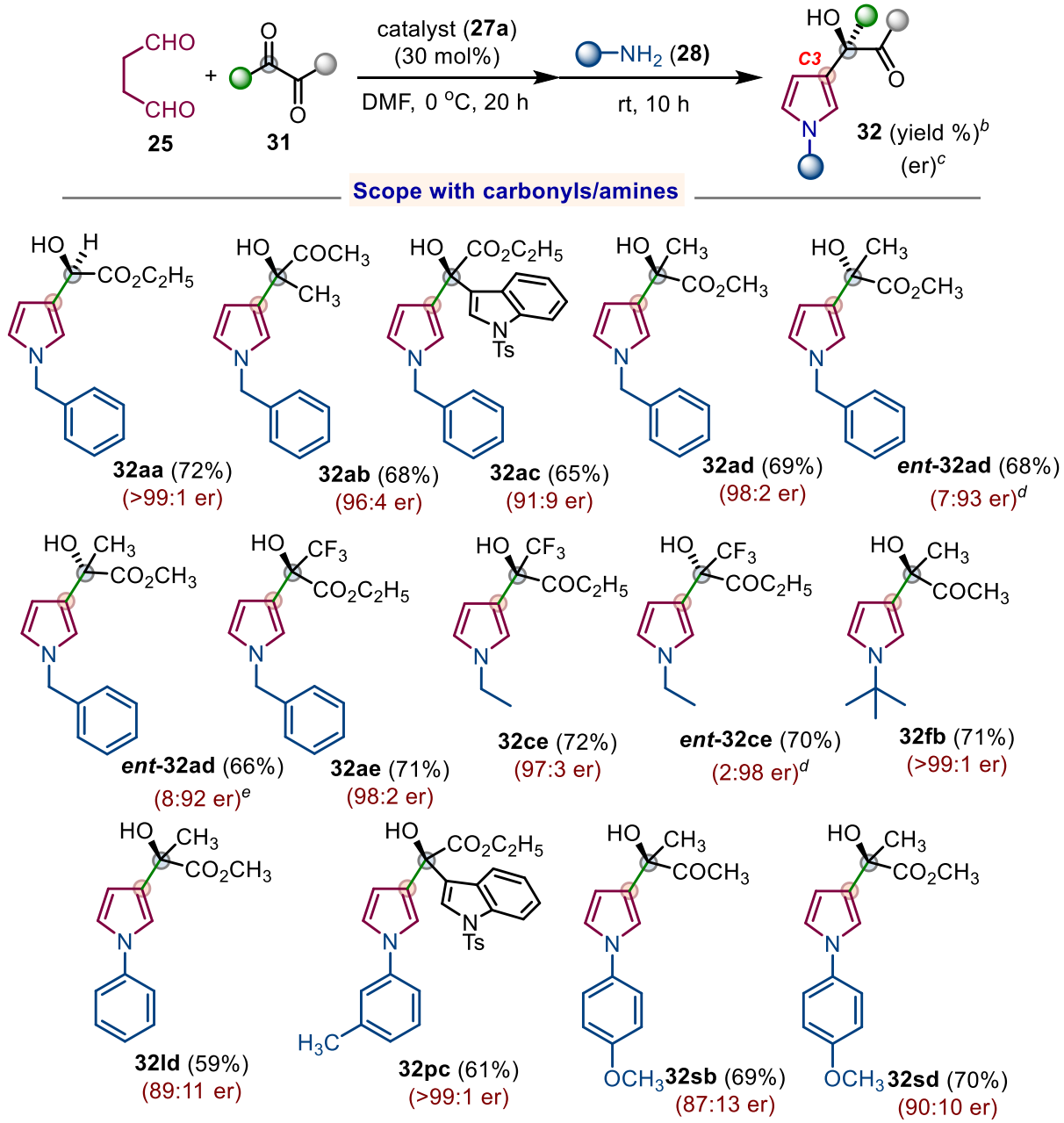
Table 4.3 Optimization of reaction conditions for reactive carbonyls **31**[a]



entry	Variation from above (step-I) / (step-II)	yield **32aa**/**30a** (%)[b]	er for **32aa**[c]
1	None	68/15	96:4
2	**0 °C, 20 h / -**	**72/<10**	**>99:1**
3	-5 °C, 20 h/ -	66/15	>99:1
4	Cat **27a** (20 mol%), 0 °C, 20 h / -	61/18	>99:1

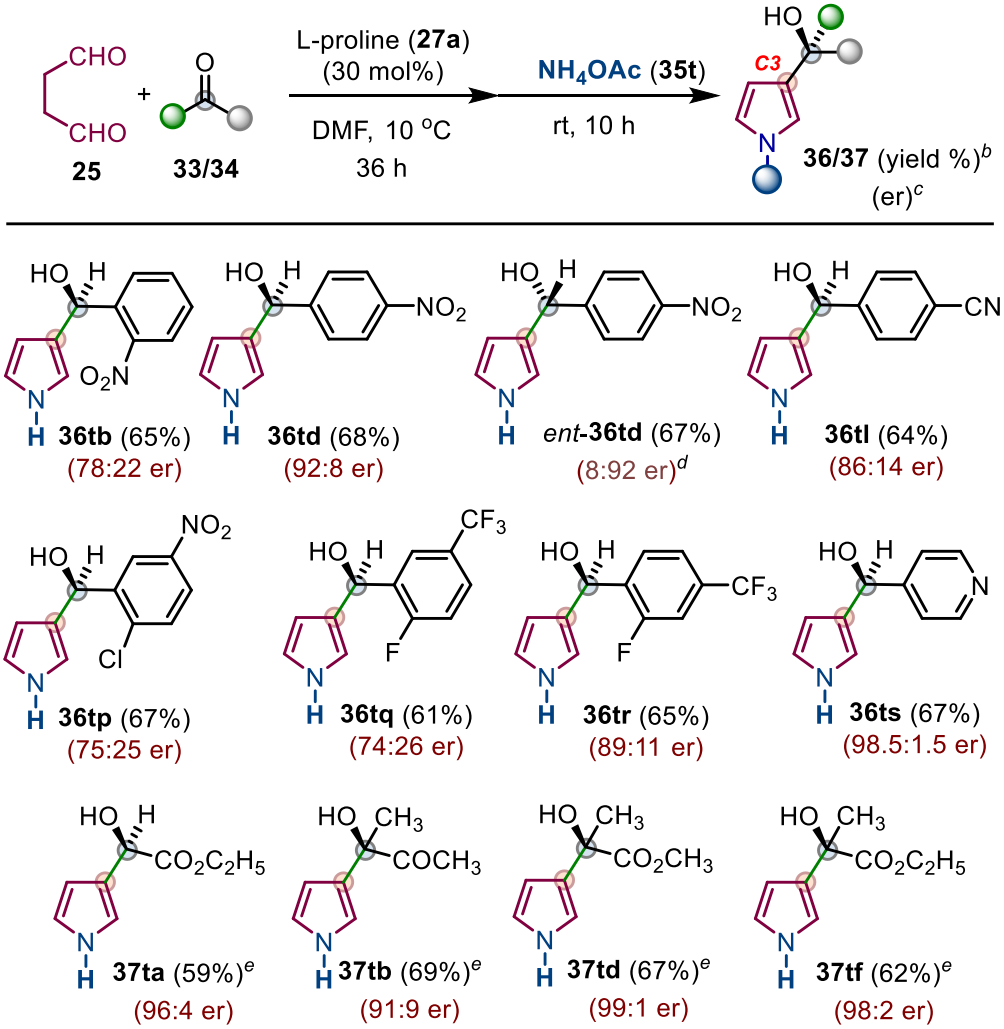
[a]The reaction was carried out using succinaldehyde **25** (3.0 M sol, 1.8 mmol, 3.0 equiv), ethyl glyoxalate **31a** (0.6 mmol, 1.0 equiv), L-Proline **27a** (0.18 mmol., 0.3 equiv), DMF (3.0 mL), 0 ^{o}C, 20 h (step-I); $BnNH_2$ **28a** (0.9 mmol, 1.5 equiv), rt, 10 h (step-II). [c]Determined using stationary chiral columns.

Table 4.4 Reaction scope with primary amines **28** and reactive carbonyls **31**[a]



[a]The reaction was carried out using succinaldehyde **25** (3.0 M sol, 1.8 mmol, 3.0 equiv), reactive carbonyls **31** (0.6 mmol, 1.0 equiv), L-Proline **27a** (0.18 mmol, 0.3 equiv), DMF (3.0 mL), 0 °C, 20 h(step-I); **28** (0.9 mmol, 1.5 equiv), rt, 10 h (step-II).[b]Isolated yield of **32** refers to **31** (≤10% of N-alkyl/aryl-pyrroles were obtained in all the cases).[c]Determined using stationary chiral columns. [d]D-proline (*ent*-**27a**) was used instead of L-proline. [e]Reaction was carried out with catalyst **27e** (30 mol%) and $PhCO_2H$ (30 mol%) as an additive.

Table 4.5 Reaction scope of acceptor carbonyls **33**/**34** with NH_4OAc **35**[a]



[a]The reaction was carried out using succinaldehyde **25** (3.0 M sol, 1.8 mmol, 3.0 equiv), **33/34** (0.6 mmol, 1.0 equiv), L-proline **27a** (0.18 mmol, 0.3 equiv), DMF (3.0 mL), 10 °C, 36 h (step-I); NH_4OAc **35t** (0.9 mmol, 1.5 equiv), rt, 10 h (step-II). [b]Isolated yield of **36/37** refers to **33/34**(≤10% of N-H pyrroles **30** were obtained in all the cases). [c]Determined using stationary

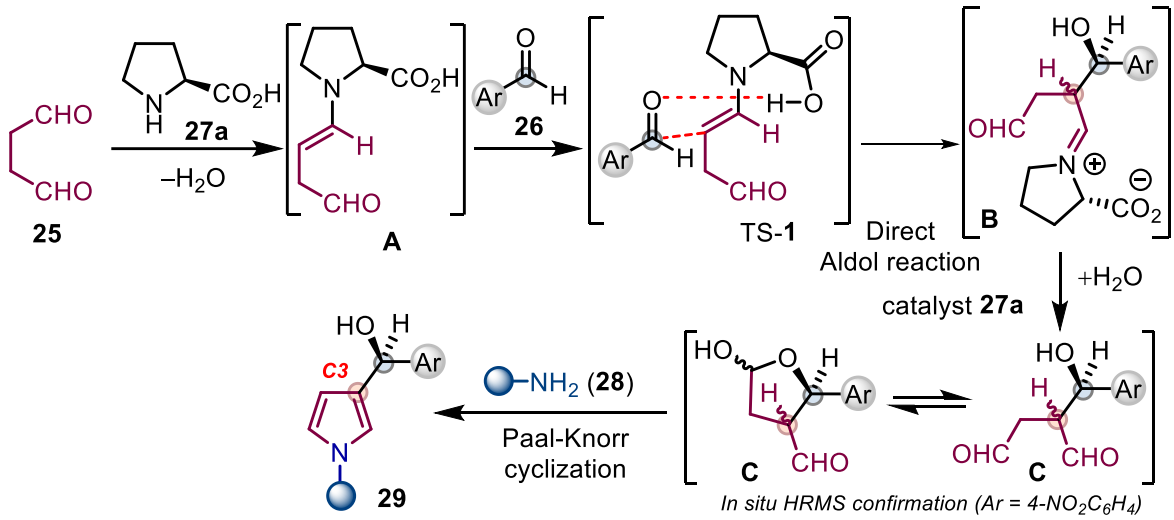
chiral columns. [d]D-proline (*ent*-**27a**) was used in place of L-proline. [e]Reaction was carried out at 0 ^{o}C for 20 h (step-I).

Next, we screened the reactive α-oxocarbonyls and other modification **31s** as suitable electrophiles for a similar conversion at slight modification conditions (Table 4.3). Notably, α-oxocarbonyls[24] are important substrates to access chiral α-hydroxycarboxylic acid derivatives with challenging quaternary stereogenic centers through metal-and organocatalytic transformations.[25,26] As shown in Table 4.5. Initially, α-oxocarbonyls such as ethyl glyoxylate **31a**,1,2-butanedione **33b**, ketoester **34c,** and **34d** were tested to furnish the corresponding **36aa-36ad** by quenching the intermediate with benzylamine **28a** with good yields (65-72%) and high enantioselectivity (91:9 to >99:1 er). The opposite enantiomer *ent*-**36ad** was also achieved with comparable products and stereoselectivity using D-proline *ent*-**27a** (7:93 er) and diphenylprolinol silyl ether **27e** as catalysts under similar conditions. Next, chiral trifluoromethane α-hydroxy ester **32ae**, **32ce** and *ent*-**3,2ce** were obtained (70-72% yield) with high enantioselectivity when ethyl trifluoropyruvate **34e** was used as reactive electrophile followed by reaction with amines **28a** and **28c** respectively. Access to such trifluoromethylated units, especially in an asymmetric fashion, is quite appealing due to their various applications in pharmaceutical chemistry.[27]A similar set of compounds were tested with *tert*-butylamine **28f** and other aromatic amines **28l**, **28p**, and **28s** and furnished the corresponding products **32fb**, **32ld**, **32pc**, **32sb,** and **32sd**, respectively, with comparable yield and enantioselectivity (Table 4.5).

Gratifyingly, the most challenging C3-substituted free NH-pyrroles (**36**/**37**) were accessed asymmetrically using NH_4OAc as an amine source under optimized conditions (Table 4.5). Initially, aromatic aldehydes **26b**, **26d**, **26l**, and **26p**-**26s** furnished corresponding pyrrole **29tb, 29td, 29tl,** and **29tp-29ts** with yield (up to 68%) and enantioselectivity (up to 92:8 er). Additionally, pyrroles **32ta**, **32te**, **32tg,** and **32th** were obtained with good yield and excellent enantioselectivity (up to 99:1 er) from corresponding reactive ketones **31a, 31e, 31g** and **31h** following a two-step protocol in the same vessel. Remarkably, asymmetric synthesis of C3-substituted free NH-pyrrole has been presented for the first time, as far as we know, thus, proving the novelty of the developed protocol.

4.3 Reaction Mechanism

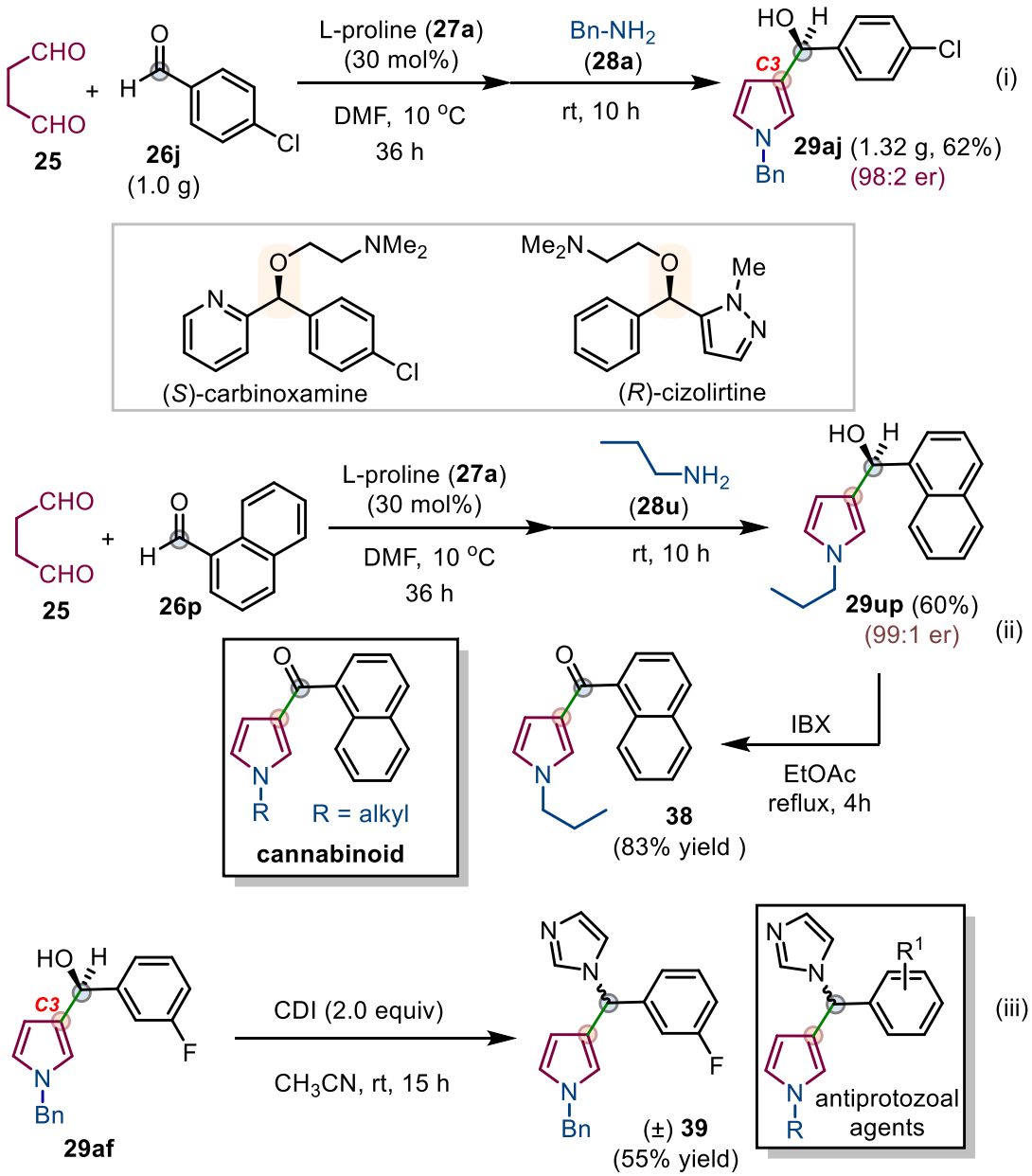
Based on the earlier reports on direct aldol reaction and present reaction outcome, a tentative reaction mechanism has been proposed (Scheme 4.8). A proline-catalyzed direct aldol reaction between enamine-**A** and acceptor carbonyls **26** proceeded through TS-**1**, leading to intermediate-**B**. A resulting suitably functionalized 1,4-dialdehyde **C** could generate through the regeneration of catalyst **27a** from **B**. The resulting compound **C** underwent a Paal-Knorr reaction with a primary amine **28** to furnish chiral C3-substituted pyrrole **29**. Based on the earlier reports and the present outcome, a tentative mechanism has been proposed that is supported by the *in situ* HRMS study of intermediate lactol as an aldol-product before the Paal-Knorr reaction (Scheme 4.8).



Scheme 4.8 Plausible reaction mechanism for the developed protocol.

Additionally, the synthetic utility of the method was shown at the gram-scale preparation of **29aj** (1.32g, 62% yield) (Scheme 4.9(i)) under standard conditions. The rapid access to both enantiomers of such hyxroxyalkylated heteroaromatics, even at the gram-scale, is quite interesting as identical units are found in many bioactive compounds/existing drugs like (*S*)-carbinoxamine or (*R*)-cizolirtine. Next, 1-naphthaldehyde **26p** as a bulkier aldehyde was tested under standard conditions to initially furnish **29up** (60%, 99:1 er), which on subsequent IBX-oxidation yielded 1-propyl-3-(1-naphthyl) pyrroles **38** (83%); thus, a two-pot rapid synthesis of pyrrole-based cannabinoid[28] has been developed (Scheme 4.9(ii)), despite of losing chirality during oxidation. The current method provides easy access to heteroaryl methanols/3-

acylpyrroles, which are attractive substrates for *N*-confused calix[5]pyrroles[29] and *meso*-triaryl 22-oxanorroles.[30] Additionally,1-(aryl(1*H*-pyrrol-3-yl)methyl)-1*H*-imidazole **39** (55% yield) was obtained as a racemic mixture when **29af** was reacted with 1,1'-carbonyldiimidazole (CDI), similar units were recently established as antiprotozoal agents (Scheme 4.9(iii)).[31]



Scheme 4.9 (i) Gram-scale synthesis of **29aj**; (ii) Synthesis of **29up** and corresponding 3-acylpyrrole **38** as bioactive cannabinoid; (iii) Synthesis of imidazole-based pyrrole **39**.

4.4 Conclusion

In summary, we have developed the first enantioselective synthesis of unblocked β-hydroxy alkylated *N*-alkyl/Ar/H-pyrrole under metal-free conditions. The one-pot, two-step sequential multicomponent protocol proceeds via amine-catalyzed direct aldol reaction of aqueous succinaldehyde with acceptor carbonyls followed by Paal-Knorr response of intermediate with primary amines. A broad substrate scope with acceptor aldehydes/ketones and aliphatic/aromatic primary amines has been developed to access both enantiomers of β-hydroxy alkylated pyrroles in good yield and excellent enantioselectivity. The reaction has been established at the gram scale, along with other late-stage conversions.

4.5 General Experimental Information

Unless otherwise stated, all commercially available compounds were used as received without further purification. All solvents employed in the reactions were distilled from appropriate drying agents. All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on Merck silica gel 60 F254 precoated plates (0.25 mm). Column chromatographic purification was performed on silica gel (100−200 mesh) using a petroleum ether/EtOAc mixture. Chemical yields refer to pure, isolated substances. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$/DMSO-$d_6$on a BRUKER-AV400 and spectral data were reported in ppm. ^{13}C NMR spectra were recorded on a BRUKER-AV400 (100 MHz) spectrometer with complete proton decoupling.^{19}F NMR spectra were recorded on a BRUKER-AV400 (376 MHz). High-resolution mass spectra were recorded using the quadrupole electrospray ionization (ESI) technique. Infrared (FT-IR) spectra were recorded on a Perkin-Elmer Spectrometer, ν_{max} in cm^{-1}. Melting points were determined by an EZ-Melt, Automated Melting Point Apparatus, and specific rotation was measured through a RUDOLPH Polarimeter. Enantiomeric ratio (er) was determined on a Water-2998 instrument with CHIRALPAK columns using hexane/2-propanol.

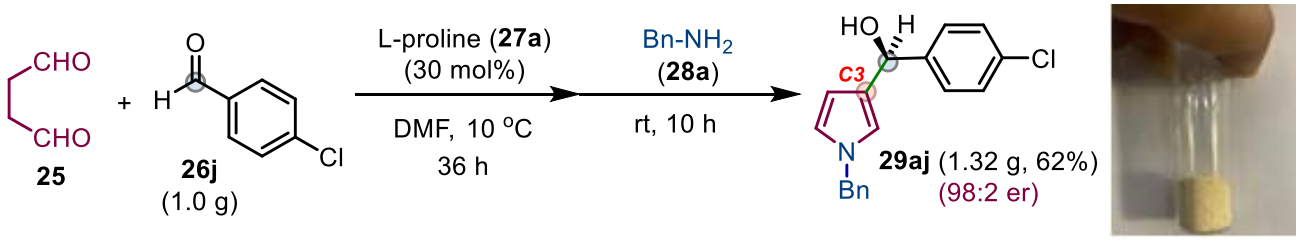
General procedure for the synthesis of 29

An oven-dried Schlenk tube was charged with L-Proline **27a** (0.18 mmol, 0.3 equiv, 21 mg), succinaldehyde **25** (3.0 M sol, 1.8 mmol, 600µl, 3.0 equiv), and aromatic aldehyde **26** (0.6 mmol, 1.0 equiv) in DMF (3.0 mL) at 10°C. The reaction mixture was stirred for 36 h at the same temperature. Primary aliphatic/aromatic amine **28** (0.9 mmol, 1.5 equiv) was added to the

same vessel and stirred for 10 h at room temperature. The reaction mixture was quenched with ice-cold water (3.0 mL) and extracted with EtOAc (3 × 5.0 mL). The combined organic layer was washed with brine (3.0 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The column chromatographic purification on silica gel using petroleum ether/EtOAc as eluent furnished chiral pyrrole **29** (up to 78% yield).

Typical Procedure for the Enantioselective Synthesis of 32. An oven-dried Schlenck tube was charged with L-Proline **27a** (0.18 mmol, 0.3 equiv, 21 mg), succinaldehyde **25** (3.0 M sol, 1.8 mmol, 600µl, 3.0 equiv), and reactive carbonyl **31** (0.6 mmol, 1.0 equiv) in DMF (3.0 mL) at 0°C. The reaction mixture was stirred for 20 h at the same temperature. Primary aliphatic/aromatic amine **28** (0.9 mmol, 1.5 equiv) was added to the same vessel and stirred for 10 h at room temperature. The reaction mixture was quenched with ice-cold water (3.0 mL) and extracted with EtOAc (3 × 5.0 mL). The combined organic layer was washed with brine (3.0 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The column chromatographic purification on silica gel using petroleum ether/EtOAc as eluent furnished chiral pyrrole **32** (up to 72% yield).

Gram Scale synthesis of 29aj



Scheme 4.10 Gram-scale synthesis of **29aj.**

An oven-dried 100 ml round bottom flask was charged with L-proline **27a** (2.14 mmol, 24.6 mg, 0.3 equiv), succinaldehyde **25** (3.0 M sol, 21.42 mmol, 3.0 equiv.), and 4-chlorobenzaldehyde **26j** (1.0 g, 7.14 mmol, 1.0 equiv) in DMF (35 mL) catalyst at 10 °C. The reaction mixture was stirred for 36 h at the same temperature. Benzylamine **28a** (1.15 g, 10.71 mmol, and 1.5 equiv) was added to the same vessel and stirred for 10 h at room temperature. The reaction mixture was quenched with ice-cold water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated

under reduced pressure. The column chromatographic purification on silica gel using petroleum ether/EtOAc as eluent furnished chiral pyrrole **29aj** (1.32 g, 62 % yield).

(*S*)-naphthalen-1-yl(1-propyl-1*H*-pyrrol-3-yl) methanol (29up).

An oven-dried Schlenk tube was charged with L-Proline **27a** (0.18 mmol, 0.3 equiv, 21 mg), succinaldehyde **25** (3.0 M sol, 1.8 mmol, 600 µl, 3.0 equiv), and 1-naphthaldehyde **26p** (0.6 mmol, 1.0 equiv, 94 mg) in DMF (3.0 mL) at 10 °C. The reaction mixture was stirred for 36 h at the same temperature. N-propyl amine **28u** (0.9 mmol, 1.5 equiv, 53 mg) was added to the same vessel and stirred for 10 h at room temperature. The reaction mixture was quenched with ice-cold water (3.0 mL) and extracted with EtOAc (3 × 5.0 mL). The combined organic layer was washed with brine (3.0 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The column chromatographic purification on silica gel using petroleum ether/EtOAc (8/2) as eluent furnished chiral pyrrole **29up** (95 mg, 60% yield)

Naphthalen-1-yl (1-propyl-1*H*-pyrrol-3-yl) methanone (32).

An over-dried Schlenk tube (25 mL) was charged with **29up** (0.34 mmol, 1.0 equiv., 90 mg) and IBX (1.2 mmol, 2.0 equiv., 190 mg) in EtOAc (5.0 mL) and heated to 80 ^oC for 4 h. Upon complete oxidation; the flask was cooled and stirred $NaHCO_3$ (10%-sol, 5.0 mL) for five minutes. The organic layer was separated and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Compound 38 (74 mg, 83% yield) was obtained as a brown semi-solid after passing through a small pad of silica-gel column using petroleum ether/EtOAc (9/1) as the eluent.

1-((1-benzyl-1*H*-pyrrol-3-yl)(3-fluorophenyl)methyl)-1*H*-imidazole (±39).

An over-dried Schlenk tube (25 mL) was charged with compound **29af** (83 mg, 0.3 mmol, 1 equiv) and 1,1'-carbonyldiimidazole (CDI) (97 mg, 0.6 mmol, 2.0 equiv.) in dry CH_3CN (2.0 mL) at room temperature and stirred for 15 h. Upon completion, the reaction mass was concentrated under reduced pressure. Yellowish semi-solid compound **39** (55 mg, 55% yield) was obtained in racemic form by directly passing through a small pad of column using petroleum ether/EtOAc (3:2) as eluent.

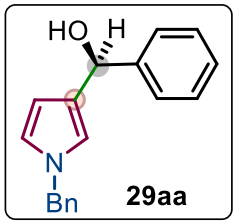
(4-Nitrophenyl)(1*H*-pyrrol-3-yl)methanone (40).

An over-dried Schlenk tube (25 mL) was charged with **29td** (0.6 mmol, 1.0 equiv, 132 mg) and IBX (1.2 mmol, 2.0 equiv, 339 mg) in EtOAc (10.0 mL) and heated to 80 ^oC for 4 h. Upon complete oxidation; the flask was cooled and stirred $NaHCO_3$ (10%-sol, 10.0 mL) for five

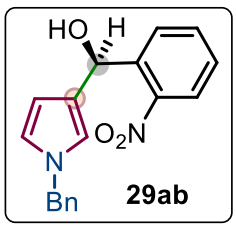
minutes. The organic layer was separated and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Compound 38 (122 mg, 94% yield) was obtained as a brown semi-solid after passing through a small pad of silica-gel column using petroleum ether/EtOAc (8/2) as the eluent.

4.6 Characterization data

(*S*)-(1-benzyl-1*H*-pyrrol-3-yl)(phenyl)methanol (29aa). The general procedure was followed with benzaldehyde (**26a**, 64 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), benzylamine (**28a**, 96 mg, 0.9 mmol) to furnish **29aa** after purification using petroleum ether/EtOAc (8/2) as eluent; Yellow solid (106 mg, 67% yield, mp = 75–78°C); **HPLC** (IA column, *n*-hexane/2-propanol = 90/10, flow rate 1.0 mL/min, *I* = 253 nm) was used to measure the enantiomeric ratio (er = 92:8), t_R = 8.13 min (major), 17.17 min (minor). $[\alpha]_D^{25}$= –38.2 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.38 (dd, *J* = 7.5, 1.5 Hz, 2H), 7.30 – 7.18 (m, 6H), 7.06 – 7.04 (m, 2H), 6.54 (t, *J* = 2.5 Hz, 1H), 6.47 (t, *J* = 2.1 Hz, 1H), 6.05 (dd, *J* = 2.8, 1.8 Hz, 1H), 5.73 (s, 1H), 4.92 (s, 2H), 2.02 (bs, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 143.4, 136.8, 127.7 (2C), 127.2 (2C), 127.1, 126.7, 126.1, 126.1 (2C), 125.3 (2C), 120.7, 118.3, 106.4, 70.0, 52.4. **IR** (neat) υ cm^{-1} 3350 (OH), 1511. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{18}NO$ 264.1383; found 264.1378.

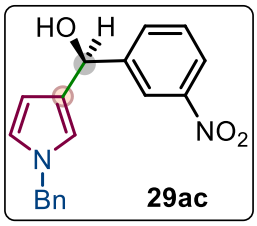


(*S*)-(1-benzyl-1*H*-pyrrol-3-yl)(2-nitrophenyl)methanol (29ab). The general procedure was followed with 2-nitrobenzaldehyde (**26b**, 91 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), benzylamine (**28a**, 96 mg, 0.9 mmol) to furnish **29ab** after purification using petroleum ether/EtOAc (8/2) as eluent; Yellow solid (127 mg, 69% yield, mp = 91–93°C); **HPLC** (IA column, *n*-hexane/2-propanol= 85:15, flow rate 1.0 mL/min, *I* = 252 nm) was used to measure the enantiomeric ratio (er = 87:13), t_R = 6.77 min (major), 14.28 min (minor). $[\alpha]_D^{25}$ = –35.9 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.95 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.87 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.63 (td, *J* = 7.6, 1.4 Hz, 1H), 7.41 (m, 1H), 7.31 (m, 3H), 7.11 – 7.05 (m, 2H), 6.59 (m, 2H), 6.40 (s, 1H), 6.05 (dd, *J* = 2.7, 1.9 Hz, 1H), 4.98 (s, 2H), 2.53 (s, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 147.2, 138.5, 136.7, 132.1, 127.7 (2C), 127.5, 126.8, 126.7,

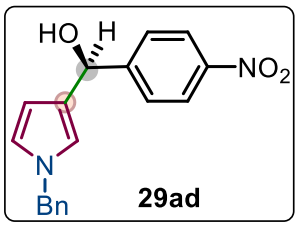


126.0 (2C), 124.7, 123.4, 121.7, 118.7, 106.4, 65.5, 52.4. **IR** (neat) υ cm^{-1} 3350 (OH), 1511, 1336. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{17}N_2O_3$ 309.1234; found 309.1238.

(*S*)-(1-benzyl-1*H*-pyrrol-3-yl)(3-nitrophenyl)methanol (29ac). The general procedure was followed with 3-nitrobenzaldehyde (**26c**, 91 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), benzylamine (**28a**, 96 mg, 0.9 mmol) to furnish **29ac** after purification using petroleum ether/EtOAc (8/2) as eluent; Yellow solid (120 mg, 65% yield, mp = 93–95 °C); **HPLC** (IA column, *n*-hexane/2-propanol = 85/15, flow rate 1.0 mL/min, *I* = 301 nm) was used to measure the enantiomeric ratio (er = >99:1), t_R = 15.46 min (minor), 17.32 min (major). $[\alpha]_D^{25}$ = –39.1 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.31 (t, *J* = 2.1 Hz, 1H), 8.12 (m, 1H), 7.80 (m, 1H), 7.50 (t, *J* = 7.9 Hz, 1H), 7.33 (m, 3H), 7.18 – 7.08 (m, 2H), 6.64 (d, *J* = 2.6 Hz, 1H), 6.58 (t, *J* = 2.1 Hz, 1H), 6.08 (dd, *J* = 2.8, 1.8 Hz, 1H), 5.88 (d, *J* = 3.6 Hz, 1H), 5.01 (s, 2H), 2.20 (d, *J* = 3.7 Hz, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 147.2, 145.6, 136.4, 131.4, 128.0, 127.8 (2C), 126.9, 126.1 (2C), 126.1, 121.3, 121.0, 120.3, 118.4, 106.1, 68.9, 52.5. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{17}N_2O_3$ 309.1234; found 309.1230.

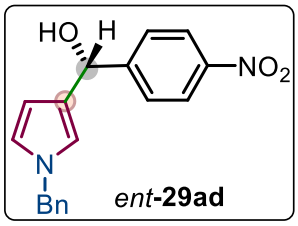


(*S*)-(1-benzyl-1*H*-pyrrol-3-yl)(4-nitrophenyl)methanol (29ad). The general procedure was followed with 4-nitrobenzaldehyde (**26d**, 91 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), benzylamine (**28a**, 96 mg, 0.9 mmol) to furnish **29ad** after purification using petroleum ether/EtOAc (8/2) as eluent; Yellow solid (137 mg, 74% yield, mp = 102–104 °C); **HPLC** (IA column, *n*-hexane/2-propanol = 85/15, flow rate 1.0 mL/min, *I* = 263 nm) was used to measure the enantiomeric ratio (er = >99:1), t_R = 5.46 min (minor), 10.06 min (major). $[\alpha]_D^{25}$= – 86.0 (*c* 0.4, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.19 (d, *J* = 8.6 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.39 – 7.28 (m, 3H), 7.19 – 7.04 (m, 2H), 6.60 (dt, *J* = 34.4, 2.4 Hz, 2H), 6.07 (t, *J* = 2.4 Hz, 1H), 5.87 (d, *J* = 2.7 Hz, 1H), 4.99 (s, 2H), 2.16 (d, *J* = 3.5 Hz, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 150.7, 146.0, 136.4, 127.8 (2C), 126.9, 126.1 (2C), 126.0, 156.9 (2C), 122.4 (2C), 112.2, 118.4, 106.1, 69.0, 52.5. **IR** (neat) υ cm^{-1} 3350

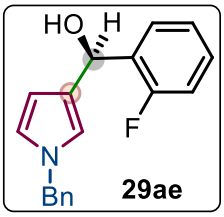


(OH), 1511, 1336. **HRMS (ESI-TOF)** *m/z*: [M + H] $^{+}$ Calcd for $C_{18}H_{17}N_2O_3$ 309.1234; found 309.1233.

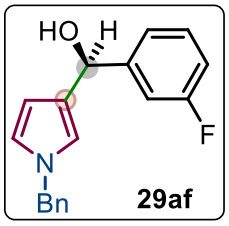
(*S*)-(1-benzyl-1*H*-pyrrol-3-yl)(4-nitrophenyl)methanol (*ent*-29ad). The general procedure was followed with 4-nitrobenzaldehyde (**26d**, 91 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), benzylamine (**28a**, 96 mg, 0.9 mmol) to furnish *ent*-**29ad** after purification using petroleum ether/EtOAc (8/2) as eluent; Yellow solid (129 mg, 70% yield); **HPLC** (IA column, *n*-hexane/2-propanol = 85/15, flow rate 1.0 mL/min, *I* = 263 nm) was used to measure the enantiomeric ratio (er = 2:98), t_R = 5.41 min (major). 10.29 min (minor). $[\alpha]_D^{25}$ = + 37.4 (*c* 0.1, CH_2Cl_2).



(*S*)-(1-benzyl-1*H*-pyrrol-3-yl)(2-fluorophenyl)methanol (29ae). The general procedure was followed with 2-fluorobenzaldehyde (**26e**, 74 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), benzylamine (**28a**, 96 mg, 0.9 mmol) to furnish **29ae** after purification using petroleum ether/EtOAc (8/2) as eluent; White solid (106 mg, 63% yield, mp = 72–75 °C); **HPLC** (IA column, *n*-hexane/2-propanol= 85/15, flow rate 1.0 mL/min, *I* = 232 nm) was used to measure the enantiomeric ratio (er =90:10), t_R= 12.84 min (minor), 13.95 min (major). $[\alpha]_D^{25}$= – 31.5 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.62 (td, *J* = 7.6, 1.9 Hz, 1H), 7.38 – 7.24 (m, 4H), 7.18 (td, *J* = 7.5, 1.3 Hz, 1H), 7.16 – 7.12 (m, 2H), 7.05 (m, 1H), 6.61 (t, *J* = 2.5 Hz, 1H), 6.61 (t, *J* = 2.1 Hz, 1H), 6.15 (dd, *J* = 2.8, 1.8 Hz, 1H), 6.11 (s, 1H), 5.01 (s, 2H), 2.22 (bs, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 159.9 (d, *J* = 246.0 Hz), 137.7, 131.6 (d, *J* = 12.8 Hz), 128.7 (2C), 128.6 (d, *J* = 8.3 Hz), 127.7, 127.6, 127.1 (2C), 126.8, 124.0 (d, *J* = 3.4 Hz), 121.6, 119.2, 115.2 (d, *J* = 21.6 Hz), 107.3, 65.3 (d, *J* = 3.8 Hz), 53.4. **HRMS (ESI-TOF)** *m/z*: [M + H] $^{+}$ Calcd for $C_{18}H_{17}FNO$ 282.1289; found 282.1285.

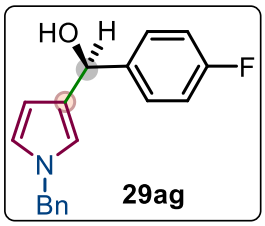


(*S*)-(1-benzyl-1*H*-pyrrol-3-yl)(3-fluorophenyl)methanol (29af). The general procedure was followed with 3-fluorobenzaldehyde (**26f**, 74 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), benzylamine (**28a**, 96 mg, 0.9 mmol) to furnish **29af** after purification using petroleum ether/EtOAc (8/2) as eluent; White solid (110 mg, 65% yield, mp = 78–81 °C); **HPLC** (IA column, *n*-

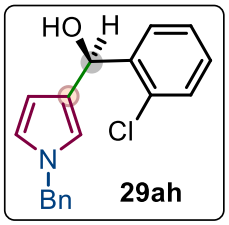


hexane/2-propanol = 85/15, flow rate 1.0 mL/min, *I* = 337 nm) was used to measure the enantiomeric ratio (er = 95:5), t_R= 11.47 min (minor), 12.46 min (major). $[\alpha]_D^{25}$= – 34.8 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.39 – 7.27 (m, 4H), 7.23–7.16 (m, 2H), 7.15 – 7.10 (m, 2H), 6.98 – 6.92 (m, 1H), 6.63 (t, *J* = 2.5 Hz, 1H), 6.56 (t, *J* = 2.1 Hz, 1H), 6.10 (dd, *J* = 2.8, 1.8 Hz, 1H), 5.78 (d, *J* = 3.0 Hz, 1H), 5.00 (s, 2H), 2.15 (d, *J* = 3.5 Hz, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 162.8 (d, *J* = 245.3 Hz), 147.2 (d, *J* = 6.6 Hz), 137.6, 129.5 (d, *J* = 8.2 Hz), 128.7 (2C), 127.8, 127.6, 127.1 (2C), 121.8 (2C), 119.3, 113.9 (d, *J* = 21.2 Hz), 113.2 (d, *J* = 22.1 Hz), 107.3, 70.3 (d, *J* = 1.3 Hz), 53.4. **HRMS (ESI-TOF)** *m/z*: [M + H] $^+$ Calcd for $C_{18}H_{17}FNO$282.1289; found 282.1295.

(*S*)-(1-benzyl-1*H*-pyrrol-3-yl)(4-fluorophenyl)methanol (29ag). The general procedure was followed with 4-fluorobenzaldehyde (**26g**, 74 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), benzylamine (**28a**, 96 mg, 0.9 mmol) to furnish **29ag** after purification using petroleum ether/EtOAc (8/2) as eluent; Brown semi-solid (116 mg, 69% yield); **HPLC** (IA column, *n*-hexane/2-propanol = 85/15, flow rate 1.0 mL/min, *I* = 250 nm) was used to measure the enantiomeric ratio (er =99:1), t_R = 8.16 min (major), 16.27 min (minor). $[\alpha]_D^{25}$= – 38.0 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.45 – 7.40 (m, 2H), 7.37 – 7.29 (m, 3H), 7.16 – 7.12 (m, 2H), 7.06 – 7.01 (m, 2H), 6.64 (t, *J* = 2.5 Hz, 1H), 6.55 – 6.54 (m, 1H), 6.11 (dd, *J* = 2.8, 1.8 Hz, 1H), 5.78 (s, 1H), 5.00 (s, 2H), 2.24 (S, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 161.9 (d, *J* = 244.6 Hz), 140.2 (d, *J* = 3.0 Hz), 137.7, 128.7 (2C), 128.0, 127.9 (2C, d, *J* = 8.0 Hz),127.7, 127.0 (2C), 121.7, 119.2, 114.8 (2C, d, *J* = 21.3 Hz), 107.2, 70.3, 53.3. **^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$)** δ –115.8; **HRMS (ESI-TOF)** *m/z*: [M + H] $^+$ Calcd for $C_{18}H_{17}FNO$ 282.1289; found 282.1290.

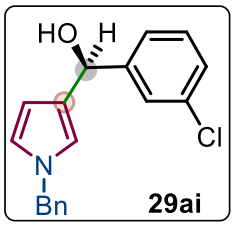


(*R*)-(1-benzyl-1*H*-pyrrol-3-yl)(2-chlorophenyl)methanol (29ah). The general procedure was followed with 2-chlorobenzaldehyde (**26h**, 84 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), benzylamine (**28a**, 96 mg, 0.9 mmol) to furnish **29ah** after purification using petroleum ether/EtOAc (8/2) as eluent; slight yellow solid (112 mg, 63% yield, mp = 117–119°C); **HPLC** (IA column, *n*-hexane/2-propanol = 90/10, flow rate 1.0 mL/min, *I* =

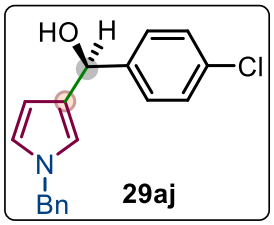


250 nm) was used to measure the enantiomeric ratio (er = 96:4), t_R = 4.48 min (minor), 10.80 min (major). $[\alpha]_D^{25}$ = – 43.5 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.74 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.35 – 7.28 (m, 5H), 7.22 (td, *J* = 7.6, 1.7 Hz, 1H), 7.11 – 7.09 (m, 2H), 6.62 (t, *J* = 2.5 Hz, 1H), 6.57 (t, *J* = 2.1 Hz, 1H), 6.17 (s, 1H), 6.14 (dd, *J* = 2.8, 1.8 Hz, 1H), 4.99 (s, 2H), 2.26 (s, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 140.8, 136.8, 131.1, 128.3, 127.7 (2C), 127.2, 126.6, 126.5, 126.0 (2C), 125.8, 125.3, 120.6, 118.6, 106.4, 66.7, 52.4. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$Calcd for $C_{18}H_{17}ClNO$ 298.0993; found 298.0995.

(*S*)-(1-benzyl-1*H*-pyrrol-3-yl)(3-chlorophenyl)methanol (29ai). The general procedure was followed with 3-chlorobenzaldehyde (**26i**, 84 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), benzylamine (**28a**, 96 mg, 0.9 mmol) to furnish **29ai** after purification using petroleum ether/EtOAc (8/2) as eluent; slight yellow solid (114 mg, 64% yield, mp = 96–99°C); **HPLC** (IA column, *n*-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, *I* = 253 nm) was used to measure the enantiomeric ratio (er = 98:2), t_R = 5.90 min (major), 16.11 min (minor). $[\alpha]_D^{25}$ = – 40.1 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.46 (dd, *J* = 2.3, 1.4 Hz, 1H), 7.36 – 7.21 (m, 6H), 7.13 – 7.11 (m, 2H), 6.63 (t, *J* = 2.5 Hz, 1H), 6.55 (t, *J* = 2.1 Hz, 1H), 6.09 (dd, *J* = 2.8, 1.8 Hz, 1H), 5.76 (d, *J* = 3.7 Hz, 1H), 5.00 (s, 2H), 2.09 (d, *J* = 3.9 Hz, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 145.5, 136.6, 133.1, 128.4, 1287.7 (2C), 126.8, 126.5, 126.2, 126.1 (2C), 125.4, 123.4, 120.9, 118.4, 106.3, 69.3, 52.4. **HRMS (ESI-TOF)** m/z: $[M + H]^+$Calcd for $C_{18}H_{17}ClNO$ 298.0993; found 298.0997.

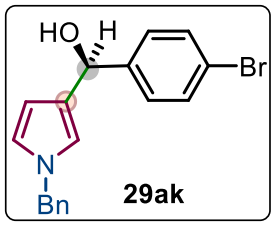


(*S*)-(1-benzyl-1*H*-pyrrol-3-yl)(4-chlorophenyl)methanol (29aj). The general procedure was followed with 4-chlorobenzaldehyde (**26j**, 84 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), benzylamine (**28a**, 96 mg, 0.9 mmol) to furnish **29aj** after purification using petroleum ether/EtOAc (8/2) as eluent; slight yellow solid (116 mg, 65% yield, mp = 111–114°C); **HPLC** (IA column, *n*-hexane/2-propanol= 80/20, flow rate 1.0 mL/min, *I* = 255 nm) was used to measure the enantiomeric ratio (er= 98:2), t_R = 13.70 min (minor), 15.59 min (major). $[\alpha]_D^{25}$ = –28.7 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.40 – 7.38 (m, 2H), 7.37 – 7.34 (m, 5H), 7.11 (m, 2H), 6.63 (t, *J* = 2.5 Hz, 1H), 6.53 (s, 1H),

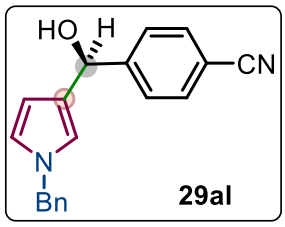


6.08 (dd, *J* = 2.8, 1.8 Hz, 1H), 5.76 (d, *J* = 3.9 Hz, 1H), 4.99 (s, 2H), 2.06 (d, *J* = 4.0 Hz, 1H). **^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)** δ 141.9, 136.6, 131.7, 127.7 (2C), 127.3 (2C), 126.8, 126.8, 126.7 (2C), 126.1 (2C), 120.9, 118.3, 106.3, 69.3, 52.4. **IR** (neat) υ cm^{-1} 3302 (OH), 1489, 1149, 1033, 756. **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$Calcd for $C_{18}H_{17}ClNO$ 298.0993; found 298.1001.

(*S*)-(1-benzyl-1*H*-pyrrol-3-yl)(4-bromophenyl)methanol (29ak). The general procedure was followed with 4-bromobenzaldehyde (**26k**, 111 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), benzylamine (**28a**, 96 mg, 0.9 mmol) to furnish **29ak** after purification using petroleum ether/EtOAc (8/2) as eluent; Yellow solid (115 mg, 56% yield, mp = 117–119°C); **HPLC** (IA column, *n*-hexane/2-propanol = 90/10, flow rate 1.0 mL/min, *I* = 250 nm) was used to measure the enantiomeric ratio (er = 93:7), t_R= 4.61 min (major), 7.88 min (minor). $[\alpha]_D^{25}$ = – 56.4 (*c* 0.2, CH_2Cl_2). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.47–7.44 (m, 2H), 7.35–7.29 (m, 5H), 7.13–7.10 (m, 2H), 6.63 (t, *J* = 2.5 Hz, 1H), 6.53–6.51 (m, 1H), 6.08 (dd, *J* = 2.8, 1.8 Hz, 1H), 5.75 (s, 1H), 4.99 (s, 2H), 2.08 (m, 1H). **^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)** δ 141.9, 136.6, 131.7, 127.6 (2C), 127.3 (2C), 125.8, 126.8, 126.7 (2C), 126.1 (2C), 120.9, 118.3, 106.3, 69.3, 52.4. **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$ Calcd for $C_{18}H_{17}BrNO$ 342.0488; found 342.0482.

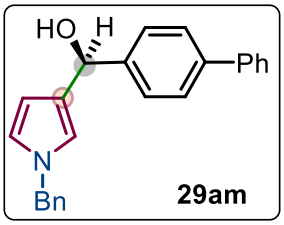


(*S*)-4-((1-benzyl-1*H*-pyrrol-3-yl)(hydroxy)methyl)benzonitrile (29al).The general procedure was followed with 4-cyanobenzaldehyde (**26l**, 78 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), benzylamine (**28a**, 96 mg, 0.9 mmol) to furnish **29al** after purification using petroleum ether/EtOAc (8/2) as eluent; White solid (121 mg, 70% yield, mp = 110–112°C); **HPLC** (IA column, *n*-hexane/2-propanol = 90/10, flow rate 1.0 mL/min, *I* = 337 nm) was used to measure the enantiomeric ratio (er = >99:1), t_R = 4.70 min (major), 12.87 min (minor). $[\alpha]_D^{25}$ = – 38.0 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.63 – 7.60 (m, 2H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.36 – 7.29 (m, 3H), 7.12 – 7.10 (m, 2H), 6.64 (t, *J* = 2.5 Hz, 1H), 6.54 (t, *J* = 2.0 Hz, 1H), 6.05 (dd, *J* = 2.8, 1.8 Hz, 1H), 5.81 (s, 1H), 4.99 (s, 2H), 2.20 (m, 1H). **^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)** δ 148.7, 136.4, 131.0 (2C), 127.7 (2C), 126.8,

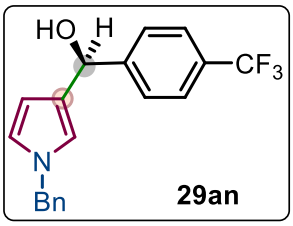


126.1 (2C), 126.0, 125.8 (2C), 121.1, 118.4, 118.0, 109.6, 106.2, 69.1, 52.5. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{17}N_2O$ 289.1335; found 289.1328.

(*S*)-[1,1'-biphenyl]-4-yl(1-benzyl-1*H*-pyrrol-3-yl)methanol (29am). The general procedure was followed with 4-phenylbenzaldehyde (**26m**, 109 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), benzylamine (**28a**, 96 mg, 0.9 mmol) to furnish **29am** after purification using petroleum ether/EtOAc (8/2) as eluent; Brown solid (134 mg, 66% yield, mp =127–129°C); **HPLC** (IA column, *n*-hexane/2-propanol = 85/15, flow rate 1.0 mL/min, *I* = 252 nm) was used to measure the enantiomeric ratio (er = >99:1), t_R = 5.50 min (major), 10.97 min (minor). $[\alpha]_D^{25}$ = – 33.3 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.61 – 7.57 (m, 4H), 7.53 – 7.51 (m, 2H), 7.46 – 7.42 (m, 2H), 7.36 – 7.28 (m, 4H), 7.13 (m,2H), 6.64 (t, *J* = 2.49, 2.49 Hz, 1H), 6.60 – 6.59 (m, 1H), 6.16 (dd, *J* = 2.77, 1.76 Hz, 1H), 5.86 (d, *J* = 3.92 Hz, 1H), 5.00 (s, 2H), 2.10 (s, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 142.5, 140.0, 139.0, 136.8, 127.7 (2C), 127.7 (2C), 127.0, 126.7, 126.1, 126.1 (2C), 126.1 (2C), 126.0 (2C), 125.7 (2C), 120.8, 118.4, 106.4, 69.8, 52.4. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{22}NO$ 340.1696; found 340.1724.

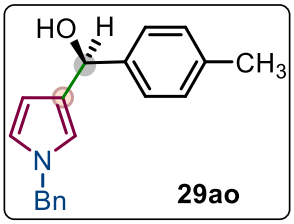


(*S*)-(1-benzyl-1*H*-pyrrol-3-yl)(4-(trifluoromethyl)phenyl)methanol (29an). The general procedure was followed with 4-(trifluoromethyl)benzaldehyde (**26n**, 104 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), benzylamine (**28a**, 96 mg, 0.9 mmol) to furnish **29an** after purification using petroleum ether/EtOAc (8/2) as eluent; White solid (143 mg, 72% yield, mp = 91–93°C); **HPLC** (IA column, *n*-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, *I* = 254 nm) was used to measure the enantiomeric ratio (er = >99:1), t_R = 8.82 min (minor), 10.81 min (major). $[\alpha]_D^{25}$ = – 28.2 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.61–7.55 (q, *J* = 8.4 Hz, 4H), 7.37 – 7.26 (m, 3H), 7.14 – 7.11 (m, 2H), 6.64 (t, *J* = 2.5 Hz, 1H), 6.55 (t, *J* = 2.0 Hz, 1H), 6.10 (dd, *J* = 2.8, 1.8 Hz, 1H), 5.84 (d, *J* = 3.8 Hz, 1H), 5.00 (s, 2H), 2.21 (d, *J* = 3.9 Hz, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 148.3, 137.6, 129.1 (q, *J* = 32.2Hz), 128.7 (2C), 127.8, 127.4, 127.1 (2C), 126.5 (2C), 125.1 (2C, q, *J* = 3.7 Hz),

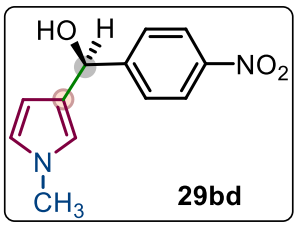


124.5 (q, *J* = 271.9 Hz), 122.0, 119.4, 107.3, 70.3, 53.4. **HRMS (ESI-TOF)** *m/z*: [M + H] $^{+}$ Calcd for $C_{19}H_{17}F_3NO$ 332.1257; found 332.1261.

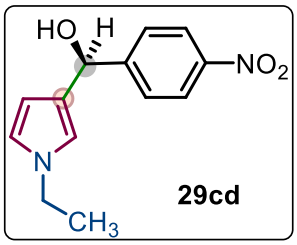
(*S*)-(1-benzyl-1*H*-pyrrol-3-yl)(*p*-tolyl)methanol (29ao). The general procedure was followed with 4-methylbenzaldehyde (**26o**, 72 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), benzylamine (**28a**, 96 mg, 0.9 mmol) to furnish **29ao** after purification using petroleum ether/EtOAc (8/2) as eluent; orange semi-solid (100 mg, 60% yield); **HPLC** (IA column, *n*-hexane/EtOAc = 80/20, flow rate 1.0 mL/min, *I* = 254 nm) was used to measure the enantiomeric ratio (er = >99:1), t_R = 11.55 min (minor), 5.52 min (major). $[\alpha]_D^{25}$ = – 55.8 (*c* 0.2, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.35 – 7.34 (m, 4H), 7.30 – 7.28 (m, 1H), 7.17–7.11 (dd, *J* = 16.25, 8.31 Hz, 4H), 6.61 (t, *J* = 2.50, 2.50 Hz, 1H), 6.55 (t, *J* = 1.77, 1.77 Hz, 1H), 6.12 – 6.11 (m, 1H), 5.78 (d, *J* = 2.32 Hz, 1H), 4.99 (s, 2H), 2.35 (s, 3H), 2.31 (s, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 140.6, 136.9, 127.9 (2C), 127.7 (2C), 127.6, 127.3, 126.7, 126.1 (2C), 125.3 (2C), 120.7, 118.3, 106.5, 70.0, 52.4, 20.1. **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$Calcd for $C_{19}H_{20}NO$ 278.1539; Found 278.1534.



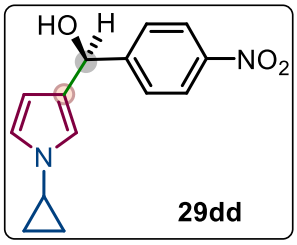
(*S*)-(1-methyl-1*H*-pyrrol-3-yl)(4-nitrophenyl)methanol (29bd). The general procedure was followed with 4-nitrobenzaldehyde (**26d**, 91 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), *n*-methylamine (**28b**, 28 mg, 0.9 mmol) to furnish **29bd** after purification using petroleum ether/EtOAc (8/2) as eluent; Yellow solid (104 mg, 75% yield, mp = 55–57°C); **HPLC** (IA column, *n*-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, *I* = 263 nm) was used to measure the enantiomeric ratio (er = >99:1), t_R = 9.78 min (major), 19.15 min (minor). $[\alpha]_D^{25}$ = – 68.3 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.20 – 8.17 (m, 2H), 7.62 – 7.59 (m, 2H), 6.56 (t, *J* = 2.48, 2.48 Hz, 1H), 6.45 (t, *J* = 2.08, 2.08 Hz, 1H), 6.02 (dd, *J* = 2.74, 1.80 Hz, 1H), 5.85 (s, 1H), 3.60 (s, 3H), 2.23 (s, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 150.8, 145.9, 125.8 (2C), 125.7, 122.4 (2C), 121.7, 119.0, 105.9, 68.9, 35.2; **IR**(neat) υ cm^{-1}3400, 3080, 3040, 1511, 1342, (NO_2), 1149, 1033, 756, 609. **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$Calcd for $C_{12}H_{13}N_2O_3$ 233.0921; found 233.0918.



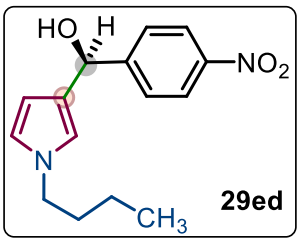
(*S*)-(1-ethyl-1*H*-pyrrol-3-yl)(4-nitrophenyl)methanol (29cd). The general procedure was followed with 4-nitrobenzaldehyde (**26d**, 91 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), *n*-ethylamine (**28c**, 41 mg, 0.9 mmol) to furnish **29cd** after purification using petroleum ether/EtOAc (8/2) as eluent; Yellow solid (108 mg, 73% yield, mp = 56–59°C); **HPLC** (IA column, *n*-hexane/2-propanol =80/20, flow rate 1.0 mL/min, *I* = 252 nm) was used to measure the enantiomeric ratio (er = 98:2), t_R= 6.22 min (minor), 17.42 min (major). $[\alpha]_D^{25}$ = – 60.8 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.20 – 8.18 (m, 2H), 7.64 – 7.61 (m, 2H), 6.62 (t, *J* = 2.51, 2.51 Hz, 1H), 6.52 (t, *J* = 2.06, 2.06 Hz, 1H), 6.03 (dd, *J* = 2.76, 1.82 Hz, 1H), 5.87 (m, 1H), 3.87 (q, *J* = 7.32, 7.32, 7.32 Hz, 2H), 2.29 (d, *J* = 3.21 Hz, 1H), 1.38 (t, *J* = 7.34, 7.34 Hz, 3H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 150.8, 145.9, 125.9 (2C), 125.4, 122.4 (2C), 120.0, 117.4, 105.6, 69.0, 43.3, 15.4. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$Calcd for $C_{13}H_{15}N_2O_3$ 247.1077; found 247.1082.



(*S*)-(1-cyclopropyl-1*H*-pyrrol-3-yl)(4-nitrophenyl)methanol (29dd). The general procedure was followed with 4-nitrobenzaldehyde (**26d**, 91 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), cyclopropylamine (**28d**, 51 mg, 0.9 mmol) to furnish **29dd** after purification using petroleum ether/EtOAc (8/2) as eluent; Yellow solid (108 mg, 70% yield, mp = 83–86°C); **HPLC** (IA column, *n*-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, *I* = 337 nm) was used to measure the enantiomeric ratio (er = >99:1), t_R= 8.81 min (minor), 21.23 min (major). $[\alpha]_D^{25}$ = – 54.7 (*c* 0.1, CH_2Cl_2).**^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.20 – 8.16 (m, 2H), 7.62 – 7.58 (m, 2H), 6.69 (t, *J* = 2.52, 2.52 Hz, 1H), 6.69–6.57 (t, *J* = 2.06, 2.06 Hz, 1H), 5.98 (dd, *J* = 2.88, 1.84 Hz, 1H), 5.83 (s, 1H), 3.30–3.25 (m, 1H), 2.28 (s, 1H), 0.90 – 0.86 (m, 4H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 150.7, 146.0, 125.9 (2C), 125.4, 122.4 (2C), 121.3, 118.6, 105.7, 69.0, 29.0, 5.2 (2C)**. HRMS (ESI-TOF)** *m/z*: $[M + H]^+$Calcd for $C_{14}H_{15}N_2O_3$ 259.1077; found 259.1074.

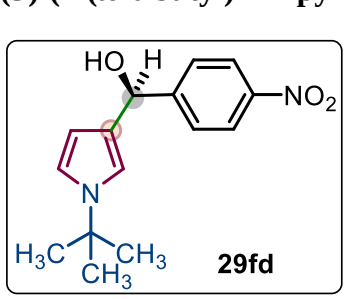


(*S*)-(1-butyl-1*H*-pyrrol-3-yl)(4-nitrophenyl)methanol (29ed). The general procedure was followed with 4-nitrobenzaldehyde (**26d**, 91 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), *n*-butylamine (**28e**, 66 mg, 0.9 mmol) to furnish **29ed** after purification using petroleum ether/EtOAc (8/2) as eluent; orange semi-solid (100 mg, 61% yield); **HPLC** (IA

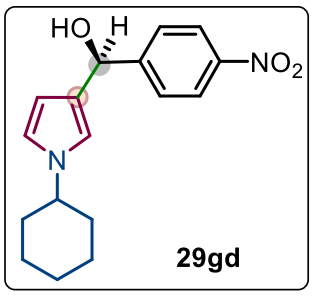


column, *n*-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, *I* = 252 nm) was used to measure the enantiomeric ratio (er = 99:1), t_R = 4.25 min (major), 12.36 min (minor). $[\alpha]_D^{25} = -56$ (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.16 – 8.14 (m, 2H), 7.60 – 7.58 (m, 2H), 6.59 (t, *J* = 2.49, 2.49 Hz, 1H), 6.48 (t, *J* = 2.10, 2.10 Hz, 1H), 6.01 (dd, *J* = 2.82, 1.75 Hz, 1H), 5.88 (d, *J* = 3.72 Hz, 1H), 3.78 (m, 2H), 2.53(s, 1H) 1.73 – 1.66 (m, 2H), 1.33 – 1.24 (m, 2H), 0.93–0.89 (t, *J* = 7.36, 7.36 Hz, 3H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 151.9, 144.9, 126.9 (2C), 125.4, 122.4 (2C), 120.6, 117.9, 105.6, 69.1, 48.5, 32.4, 18.9, 12.6. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$Calcd for $C_{15}H_{19}N_2O_3$ 275.1390; found 275.1394.

(*S*)-(1-(*tert*-butyl)-1*H*-pyrrol-3-yl)(4-nitrophenyl)methanol (29fd). The general procedure was followed with 4-nitrobenzaldehyde (**26d**, 91 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), *tert*-butylamine (**28f**, 66 mg, 0.9 mmol) to furnish **29fd** after purification using petroleum ether/EtOAc (8/2) as eluent; Faint yellow solid (128 mg, 78% yield, mp =131–134°C); **HPLC** (IA column, *n*-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, *I* = 245 nm) was used to measure the enantiomeric ratio (er = 97:3), t_R = 4.92 min (major), 9.27 min (minor). $[\alpha]_D^{25} = -59.1$ (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.23 – 8.20 (m, 2H), 7.64 (dd, *J* = 8.99, 0.72 Hz, 2H), 6.80 (t, *J* = 2.66, 2.66 Hz, 1H), 6.72 (m, 1H), 6.02 (dd, *J* = 2.90, 1.84 Hz, 1H), 5.89 (d, *J* = 3.01 Hz, 1H), 2.24 (d, *J* = 3.52 Hz, 1H), 1.52 (s, 9H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 149.9, 145.0, 125.0 (2C), 145.8, 122.4 (2C), 117.7, 114.1, 103.2, 69.3, 54.0, 29.7 (3C); **IR** (neat) υ cm^{-1} 3400 (OH), 1512, 1342. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$Calcd for $C_{15}H_{19}N_2O_3$ 275.1390; found 275.1396.

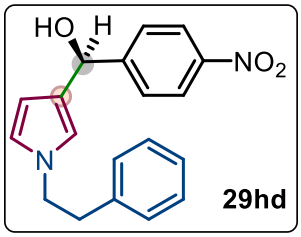


(*S*)-(1-cyclohexyl-1*H*-pyrrol-3-yl)(4-nitrophenyl)methanol (29gd). The general procedure was followed with 4-nitrobenzaldehyde (**26d**, 91 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), cyclohexylamine (**28g**, 89 mg, 0.9 mmol) to furnish **29gd** after purification using petroleum ether/EtOAc (8/2) as eluent; Yellow solid (113 mg, 63% yield, mp = 117–119°C); **HPLC** (IA column, *n*-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, *I* = 303 nm) was used to measure the

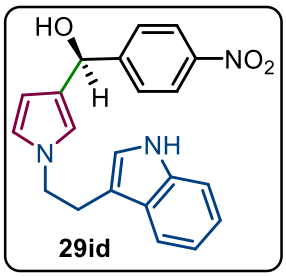


enantiomeric ratio (er = >99:1), t_R = 6.34 min (minor), 15.16 min (major). $[\alpha]_D^{25}$ = – 44.1 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.19 (d, *J* = 8.70 Hz, 2H), 7.62 (d, *J* = 8.69 Hz, 2H), 6.67 (t, *J* = 2.57, 2.57 Hz, 1H), 6.55 (d, *J* = 2.16 Hz, 1H), 6.02 (t, *J* = 2.39, 2.39 Hz, 1H), 5.86 (s, 1H), 3.73 (m, 1H), 2.28 (s, 1H), 2.07 – 2.01 (m, 2H), 1.87 (dt, *J* = 13.70, 3.33, 3.33 Hz, 2H), 1.74 – 1.69 (m, 1H), 1.57 (m, 2H), 1.37 (m, 2H), 1.29 – 1.18 (m, 1H).**^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)**δ 150.9, 145.9, 128.3, 125.9 (2C), 124.8, 122.3 (2C), 118.4, 115.9, 105.1, 69.2, 57.8, 33.5, 33.5, 24.5 (2C), 24.3. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$Calcd for $C_{17}H_{21}N_2O_3$ 301.1547; found 301.1553.

(*S*)-(4-nitrophenyl)(1-phenethyl-1*H*-pyrrol-3-yl)methanol (29hd). The general procedure was followed with 4-nitrobenzaldehyde (**26d**, 91 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), phenethylamine (**28h**, 109 mg, 0.9 mmol) to furnish **29hd** after purification using petroleum ether/EtOAc (8/2) as eluent; Orange solid (135 mg, 70% yield, mp = 90–92°C); **HPLC** (IA column, *n*-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, *I* = 253 nm) was used to measure the enantiomeric ratio (er = 99:1), t_R = 6.01 min (minor), 10.15 min (major). $[\alpha]_D^{25}$ = – 52.4 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.58 – 7.56 (m, 2H), 7.30 – 7.27 (m, 2H), 7.24 (m, 3H), 7.08 – 7.05 (m, 2H), 6.58 (t, *J* = 2.51, 2.51 Hz, 1H), 6.37 (t, *J* = 2.03, 2.03 Hz, 1H), 6.02 (dd, *J* = 2.76, 1.79 Hz, 1H), 5.81 (s, 1H), 4.04 (t, *J* = 7.26, 7.26 Hz, 2H), 3.01 (t, *J* = 7.27, 7.27 Hz, 2H), 2.53 (s, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 150.8, 145.7, 137.0, 127.5 (2C), 127.4 (2C), 125.8 (2C), 125.5, 125.1, 122.2 (2C), 120.3, 118.0, 105.7, 68.8, 50.1, 37.0. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$Calcd for $C_{19}H_{19}N_2O_3$ 323.1390; found 323.1395.

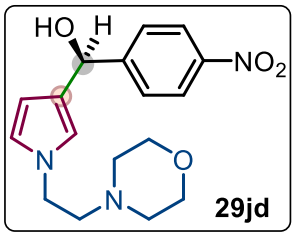


(*S*)-(1-(2-(1*H*-indol-3-yl)ethyl)-1*H*-pyrrol-3-yl)(4-nitrophenyl)methanol (29id). The general procedure was followed with 4-nitrobenzaldehyde (**26d**, 91 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), tryptamine (**28i**, 144 mg, 0.9 mmol) to furnish **29id** after purification using petroleum ether/EtOAc (8/2) as eluent; Brown semi-solid (145 mg, 67% yield); **HPLC** (IA column, *n*-hexane/*iso*-propanol= 80/20, flow rate 1.0 mL/min, *I* = 337 nm) was used to measure the enantiomeric ratio (er = 92:8), t_R = 11.85 min (minor), 4.33 min (major). $[\alpha]_D^{25}$ = – 63.6 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.22

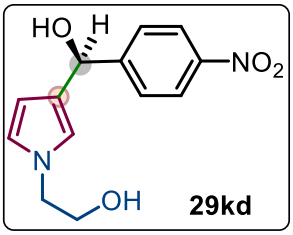


(s, 1H), 8.18 – 8.16 (m, 2H), 7.54 – 7.52 (m, 2H), 7.48 – 7.45 (m, 1H), 7.38 (d, *J* = 8.13 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.18–7.14 (td, *J* = 7.44, 7.37, 2.11 Hz, 1H), 6.82 (d, *J* = 2.46 Hz, 1H), 6.64 (t, *J* = 2.42, 2.42 Hz, 1H), 6.36 (d, *J* = 2.28 Hz, 1H), 6.07 – 6.06 (m, 1H), 5.80 (s, 1H), 4.12 (t, *J* = 7.06, 7.06 Hz, 2H), 3.19 (t, *J* = 7.07, 7.07 Hz, 2H), 2.59 (d, *J* = 14.78 Hz, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 150.8, 145.6, 135.0, 126.0, 125.7 (2C), 124.9, 122.2 (2C), 121.1, 120.9, 120.3, 118.2, 118.1, 117.2, 111.0, 110.2, 105.7, 68.8, 49.3, 26.6. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{20}N_3O_3$ 362.1499; found 362.1502.

(*S*)-(1-(2-morpholinoethyl)-1*H*-pyrrol-3-yl)(4-nitrophenyl)methanol (29jd). The general procedure was followed with 4-nitrobenzaldehyde (**26d**, 91 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), 2-morphlinoethanamine (**28j**, 117 mg, 0.9 mmol) to furnish **29jd** after purification using petroleum ether/EtOAc (8/2) as eluent; Red semi-solid (125 mg, 63% yield,); **HPLC** (IA column, *n*-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, *I* = 246 nm) was used to measure the enantiomeric ratio (er = >99:1), t_R = 3.72 min (minor), 9.23 min (major). $[\alpha]_D^{25}$ = – 39.2 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.51 – 7.48 (m, 2H), 6.96 – 6.92 (m, 2H), 5.98 (t, *J* = 2.51, 2.51 Hz, 1H), 5.89 (t, *J* = 2.08, 2.08 Hz, 1H), 5.36 (dd, *J* = 2.76, 1.76 Hz, 1H), 5.16 (s, 1H), 3.26 (t, *J* = 6.87, 6.87 Hz, 2H), 3.00 – 2.97 (m, 4H), 2.00 (t, *J* = 6.88, 6.88 Hz, 2H), 1.76 – 1.74 (m, 4H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 151.1, 145.6, 125.7 (2C), 125.5, 122.1 (2C), 120.5, 117.9, 105.7, 68.6, 65.5 (2C), 58.2, 52.4 (2C), 45.8. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{22}N_3O_4$ 332.1605; found 332.1611.

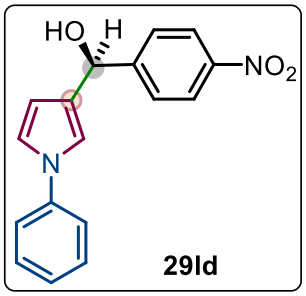


(*S*)-2-(3-(hydroxy (4-nitrophenyl) methyl)-1*H*-pyrrol-1-yl) ethan-1-ol (29kd). The general procedure was followed with 4-nitrobenzaldehyde (**26d**, 91 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), ethanolamine (**28k**, 55 mg, 0.9 mmol) to furnish **29kd** after purification using petroleum ether/EtOAc (8/2) as eluent; Red semi-solid (94 mg, 60% yield,); **HPLC** (IA column, *n*-hexane/EtOAc = 80/20, flow rate 1.0 mL/min, *I* = 254 nm) was used to measure the enantiomeric ratio (er = >99:1), t_R = 7.02 min (minor), 11.86 min (major). $[\alpha]_D^{25}$ = – 33.4 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.54 – 7.51 (m, 2H), 6.96 – 6.93 (m, 2H), 5.99 (s, 1H), 5.92 (t, *J* = 1.87, 1.87 Hz, 1H), 5.38 (dd, *J* =

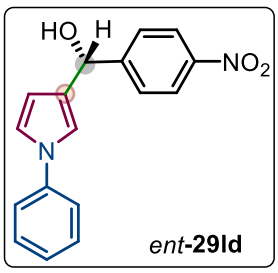


2.75, 1.77 Hz, 1H), 5.17 (s, 1H), 3.28 (dd, *J* = 5.54, 4.20 Hz, 2H), 3.14 (t, *J* = 5.13, 5.13 Hz, 2H), 1.94 (d, 1H). **^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)** δ 150.6, 145.9, 125.8 (2C), 122.4 (2C), 120.9, 118.4, 106.3, 68.9, 61.6, 51.0. **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$Calcd for $C_{13}H_{15}N_2O_4$ 263.1026; found 263.1032.

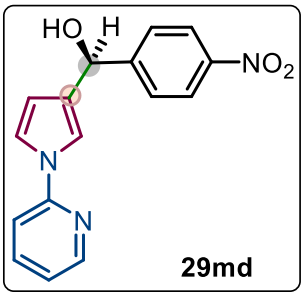
(*S*)-(4-nitrophenyl)(1-phenyl-1*H*-pyrrol-3-yl)methanol (29ld). The general procedure was followed with 4-nitrobenzaldehyde (**26d**, 91 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), aniline (**28l**, 84 mg, 0.9 mmol) to furnish **29ld** after purification using petroleum ether/EtOAc (8/2) as eluent; Brown solid (118 mg, 67% yield, mp = 87–90°C); **HPLC** (IA column, *n*-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, *I* = 253 nm) was used to measure the enantiomeric ratio (er = 99:1), t_R = 4.34 min (major), 11.50 min (minor). $[\alpha]_D^{25}$ = – 56.3 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.17 – 8.14 (m, 2H), 7.62 – 7.59 (m, 2H), 7.40 – 7.32 (m, 2H), 7.32 – 7.25 (m, 2H), 7.21 (tt, *J* = 6.87, 6.87, 1.29, 1.29 Hz, 1H), 6.99 (p, *J* = 2.44, 2.44, 2.34, 2.34 Hz, 1H), 6.90 (t, *J* = 2.10, 2.10 Hz, 1H), 6.19 (dd, *J* = 2.96, 1.78 Hz, 1H), 5.90 (s, 1H), 2.24 (d, 1H). **^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)** δ 150.3, 146.1, 139.2, 128.6 (2C), 127.6, 126.0 (2C), 125.1, 122.6(2C), 119.5 (3C),116.6, 108.0, 69.0. **HRMS (ESI-TOF)** *m/z*: [M+H]$^+$Calcd for $C_{17}H_{15}N_2O_3$ 295.1077; found 295.1069.



(*R*)-(4-nitrophenyl)(1-phenyl-1*H*-pyrrol-3-yl)methanol (*ent*-29ld). The general procedure was followed with 4-nitrobenzaldehyde (**26d**, 91 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), aniline (**28l**, 84 mg, 0.9 mmol) to furnish ***ent*-29ld** after purification using petroleum ether/EtOAc (8/2) as eluent; Brown solid (115 mg, 65% yield); **HPLC** (IA column, *n*-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, *I* = 253 nm) was used to measure the enantiomeric ratio (er = 4:96), t_R = 5.52 min (minor), 12.59 min (major). $[\alpha]_D^{25}$ = + 53.6 (*c* 0.1, CH_2Cl_2).

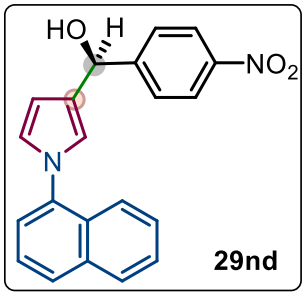


(*S*)-(4-nitrophenyl)(1-(pyridin-2-yl)-1*H*-pyrrol-3-yl)methanol (29md). The general procedure was followed with 4-nitrobenzaldehyde (**26d**, 91 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), 2-aminopyridine (**28m**, 85 mg, 0.9 mmol) to furnish **29md** after purification

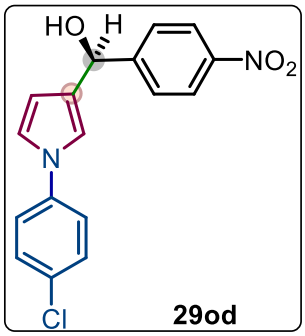


using petroleum ether/EtOAc (8/2) as eluent; pink solid (113 mg, 64% yield, mp = 126–129 °C); **HPLC** (IA column, *n*-hexane/2-propanol = 90/10, flow rate 1.0 mL/min, *I* = 250 nm) was used to measure the enantiomeric ratio (er = >99:1), t_R = 18.45 min (major), 20.38 min (minor). $[\alpha]_D^{25}$ = – 66.2 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.35 (m, 1H), 8.19 – 8.09 (m, 2H), 7.71 (m, 1H), 7.63 – 7.57 (m, 2H), 7.39 (p, *J* = 2.28, 2.28, 2.23, 2.23 Hz, 2H), 7.23 (dt, *J* = 8.30, 0.95, 0.95 Hz, 1H), 7.09 (m, 1H), 6.21 (dd, *J* = 3.07, 1.86 Hz, 1H), 5.87 (s, 1H), 3.22 (d, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 150.2, 149.7, 147.5, 145.9, 137.6, 128.2, 125.9 (2C), 122.4 (2C), 119.5, 118.0, 115.2, 110.3, 108.9, 68.7. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{14}N_3O_3$ 296.1030; found 296.1032.

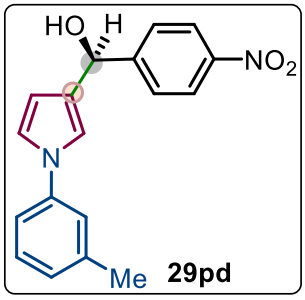
(*S*)-(1-(naphthalen-1-yl)-1*H*-pyrrol-3-yl)(4-nitrophenyl)methanol (29nd). The general procedure was followed with 4-nitrobenzaldehyde (**26d**, 91 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), 1-naphthylamine (**28n**, 129 mg, 0.9 mmol) to furnish **29nd** after purification using petroleum ether/EtOAc (8/2) as eluent; Brown semi-solid (126 mg, 61% yield, mp = 135–137°C); **HPLC** (IA column, *n*-hexane/2-propanol = 90/10, flow rate 1.0 mL/min, *I* = 337 nm) was used to measure the enantiomeric ratio (er = >99:1), t_R = 6.16 min (major), 15.93 min (minor). $[\alpha]_D^{25}$ = – 56.1 (*c* 0.1, CH_2Cl_2).**^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.24 – 8.21 (m, 2H), 7.93 – 7.86 (m, 2H), 7.75 – 7.67 (m, 3H), 7.58 – 7.46 (m, 4H), 7.42 (dd, *J* = 7.33, 1.25 Hz, 1H), 7.00 – 6.91 (m, 1H), 6.89 – 6.81 (m, 1H), 6.31 (dd, *J* = 2.87, 1.77 Hz, 1H), 6.04 – 6.01 (m, 1H), 2.38 (s, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 150.5, 146.1, 136.5, 133.2, 128.5, 127.2, 127.2, 126.4, 126.1, 126.0 (2C), 125.6, 124.2, 123.3, 122.5 (2C), 122.3, 121.8, 120.4, 106.7, 69.0. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{17}N_2O_3$ 345.1234; found 345.1238.



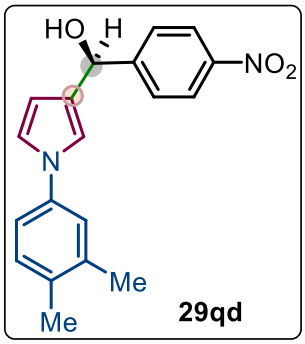
(*S*)-(1-(4-chlorophenyl)-1*H*-pyrrol-3-yl)(4-nitrophenyl)methanol (29od). The general procedure was followed with 4-nitrobenzaldehyde (**26d**, 91 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), 4-chloroaniline (**28o**, 115 mg, 0.9 mmol) to furnish **29od** after purification using petroleum ether/EtOAc (8/2) as eluent; Yellow solid (120 mg, 61% yield, mp = 81–84°C); **HPLC** (IA column, *n*-hexane/2-propanol= 80/20, flow rate 1.0 mL/min, *I* = 253 nm) was used to measure the enantiomeric ratio (er=>99:1), t_R = 4.81 min (major), 8.75 min (minor). $[\alpha]_D^{25}$ = – 39 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.23 – 8.17 (m, 2H), 7.69 – 7.61 (m, 2H), 7.43 – 7.32 (m, 2H), 7.31 – 7.22 (m, 2H), 7.00 (dd, *J* = 2.95, 2.33 Hz, 1H), 6.94 – 6.89 (m, 1H), 6.24 (dd, *J* = 3.00, 1.77 Hz, 1H), 5.94 (s, 1H), 2.44 (s, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 150.2, 146.1, 137.7, 130.5, 128.7 (2C), 127.9, 125.9 (2C), 122.5 (2C), 120.5 (2C), 119.3, 116.4,108.4, 68.9. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$Calcd for $C_{17}H_{14}ClN_2O_3$ 329.0687; found 329.0679.



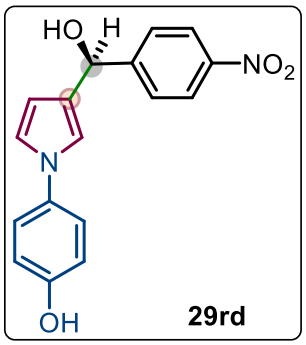
(*S*)-(4-nitrophenyl)(1-(*m*-tolyl)-1*H*-pyrrol-3-yl)methanol (29pd). The general procedure was followed with 4-nitrobenzaldehyde (**26d**, 91 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), 3-methyl aniline (**28p**, 96 mg, 0.9 mmol) to furnish **29pd** after purification using petroleum ether/EtOAc (8/2) as eluent; Brown solid (107 mg, 58% yield, mp = 107–109°C); **HPLC** (IA column, *n*-hexane/2-propanol=80/20, flow rate 1.0 mL/min, *I* = 254 nm) was used to measure the enantiomeric ratio (er = >99:1), t_R = 7.12 min (major), 13.18 min (minor). $[\alpha]_D^{25}$ = – 70.6 (*c* 0.3, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.22 – 8.14 (m, 2H), 7.67 – 7.58 (m, 2H), 7.30 (t, *J* = 7.72, 7.72 Hz, 1H), 7.17 – 7.10 (m, 2H), 7.11 – 7.06 (m, 1H), 7.04 (t, *J* = 2.63, 2.63 Hz, 1H), 6.94 (t, *J* = 2.04, 2.04 Hz, 1H), 6.23 (dd, *J* = 2.94, 1.74 Hz, 1H), 5.91 (s, 1H), 2.40 (s, 3H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 150.4, 145.8, 139.0, 138.5, 128.3, 127.3, 125.8 (2C), 125.6, 122.3 (2C), 119.9, 119.2, 116.4, 116.3, 107.8, 68.8, 20.3. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{17}N_2O_3$ 309.1234; found 309.1238.



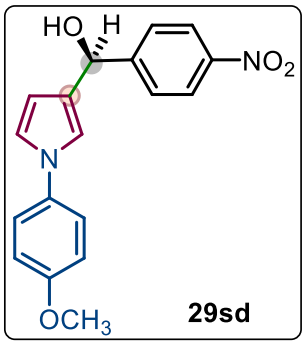
(*S*)-(1-(3,4-dimethylphenyl)-1*H*-pyrrol-3-yl)(4-nitrophenyl)methanol (29qd). The general procedure was followed with 4-nitrobenzaldehyde (**26d**, 91 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), 3,4-dimethylaniline (**28q**, 109 mg, 0.9 mmol) to furnish **29qd** after purification using petroleum ether/EtOAc (8/2) as eluent; Brown solid (124 mg, 64% yield, mp = 94–98°C); **HPLC** (IA column, *n*-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, *I* = 250 nm) was used to measure the enantiomeric ratio (er = >99:1), t_R = 9.02 min (minor), 17.21 min (major). $[\alpha]_D^{25}$ = – 55.2 (*c* 0.2, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.22 – 8.19 (m, 2H), 7.67 – 7.64 (m, 2H), 7.15 (d, *J* = 8.07 Hz, 1H), 7.11 (d, *J* = 2.36 Hz, 1H), 7.06 (dd, *J* = 8.07, 2.48 Hz, 1H), 7.00 (t, *J* = 2.60, 2.60 Hz, 1H), 6.91 (t, *J* = 2.08, 2.08 Hz, 1H), 6.21 (dd, *J* = 2.93, 1.76 Hz, 1H), 5.99 – 5.88 (m, 1H), 2.34 (d, *J* = 3.22 Hz, 1H), 2.30 (s, 3H), 2.28 (s, 3H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 150.4, 146.1, 137.2, 137.0, 133.6, 129.6, 127.2, 126.0 (2C), 122.6 (2C), 120.9, 119.6, 116.9, 116.7, 107.6, 69.0, 18.9, 18.2. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{19}N_2O_3$ 323.1390; found 323.1385.



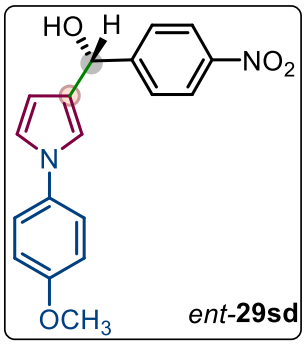
(*S*)-4-(3-(hydroxy(4-nitrophenyl)methyl)-1*H*-pyrrol-1-yl)phenol (29rd). The general procedure was followed with 4-nitrobenzaldehyde (**26d**, 91 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), 4-aminophenol (**28r**, 98 mg, 0.9 mmol) to furnish **29rd** after purification using petroleum ether/EtOAc (8/2) as eluent; Brown solid (112 mg, 60% yield, mp = 85–87°C); **HPLC** (IA column, *n*-hexane/2-propanol = 90/10, flow rate 1.0 mL/min, *I* = 254 nm) was used to measure the enantiomeric ratio (er = >99:1), t_R = 4.85 min (major), 8.51 min (minor). $[\alpha]_D^{25}$ = – 42.5 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$ few drop of DMSO-d_6)** δ 8.76 (d, *J* = 3.58 Hz, 1H), 7.85 – 7.79 (m, 2H), 7.32 (dd, *J* = 9.07, 2.15 Hz, 2H), 6.82 – 6.75 (m, 2H), 6.56 – 6.53 (m, 1H), 6.51 – 6.47 (m, 3H), 5.80 (dd, *J* = 2.95, 1.76 Hz, 1H), 5.50 (s, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$ few drop of DMSO-d_6)** δ 153.8, 151.5, 144.7, 130.9, 126.8, 125.3, 121.4, 121.3, 119.8 (2C), 118.1, 115.6, 114.3 (2C), 106.8, 96.3, 67.4. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$Calcd for $C_{17}H_{15}N_2O_4$ 311.1026; found 311.1022.



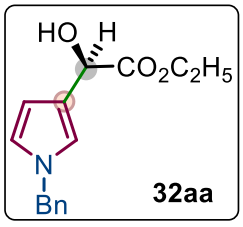
(*S*)-(1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)(4-nitrophenyl)methanol (29sd). The general procedure was followed with 4-nitrobenzaldehyde (**26d**, 91 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), 4-methoxyaniline (**28s**, 111 mg, 0.9 mmol) to furnish **29sd** after purification using petroleum ether/EtOAc (8/2) as eluent; Yellow solid (124 mg, 64% yield, mp = 94–97°C); **HPLC** (IA column, *n*-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, *I* = 310 nm) was used to measure the enantiomeric ratio (er = 98:2), t_R = 4.40 min (minor), 10.41 min (major). $[\alpha]_D^{25}$ = – 48.0 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.21 – 8.12 (m, 2H), 7.69 – 7.56 (m, 2H), 7.26 – 7.17 (m, 2H), 6.99 – 6.87 (m, 3H), 6.87 – 6.81 (m, 1H), 6.19 (dd, *J* = 2.92, 1.75 Hz, 1H), 5.90 (s, 1H), 3.81 (s, 3H), 2.98 (s, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 156.7, 150.5, 145.8, 132.7, 127.0, 125.8 (2C), 122.3 (2C), 120.8 (2C), 119.5, 116.7, 113.5 (2C), 107.4, 68.8, 54.4. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{17}N_2O_4$ 325.1183; found 325.1179.



(*R*)-(1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)(4-nitrophenyl)methanol (*ent*-29sd). The general procedure was followed with 4-nitrobenzaldehyde (**26d**, 91 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), 4-methoxyaniline (**28s**, 111 mg, 0.9 mmol) to furnish *ent*-**29sd** after purification using petroleum ether/ethyl acetate (8/2) as eluent;(120 mg, 62% yield). **HPLC** (IA column, *n*-hexane/2-propanol= 90/10, flow rate 1.0 mL/min, *I* = 240 nm) was used to measure the enantiomeric ratio (er =7:93), t_R = 6.46 min (major), 12.42 min (minor). $[\alpha]_D^{25}$ = + 46.5 (*c* 0.1, CH_2Cl_2).



(*S*)-Ethyl-2-(1-benzyl-1*H*-pyrrol-3-yl)-2-hydroxyacetate (32aa). The general procedure was followed with ethyl glyoxylate (**31a**, 61 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), benzylamine (**28a**, 96 mg, 0.9 mmol) to furnish **32aa** after purification using petroleum ether/EtOAc (8/2) as eluent; Yellowish oil (112 mg, 72% yield); **HPLC** (IA column, *n*-hexane/2-propanol = 90/10, flow rate 1.0 mL/min, *I* = 211 nm) was used to measure the enantiomeric ratio (er = >99:1), t_R = 4.25 min (major), 5.45 min (minor). $[\alpha]_D^{25}$ = – 28.5 (*c*



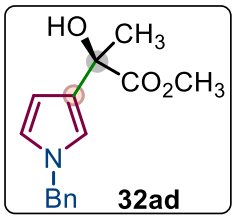
0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.38 – 7.27 (m, 3H), 7.17 – 7.07 (m, 2H), 6.79 – 6.69 (m, 1H), 6.62 (t, *J* = 2.5 Hz, 1H), 6.19 (dd, *J* = 2.8, 1.7 Hz, 1H), 5.13 (s, 1H), 5.01 (s, 2H), 4.30 – 4.20 (m, 2H),3.09 (s, 1H), 1.27 (t, *J* = 7.1 Hz, 3H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 174.0, 137.5, 128.7 (2C), 127.7, 127.1 (2C), 122.0, 121.6, 119.4, 106.9, 67.9, 61.6, 53.4, 14.1. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$Calcd for $C_{15}H_{18}NO_3$ 260.1281; Found 260.1276.

3-(1-benzyl-1*H*-pyrrol-3-yl)-3-hydroxybutan-2-one (32ab). The general procedure was followed with 2,3-butanedione (**31b**, 51 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), benzylamine (**28a**, 96 mg, 0.9 mmol) to furnish **32ab** after purification using petroleum ether/EtOAc (8/2) as eluent; Yellowish oil (99 mg, 68% yield); **HPLC** (IA column, *n*-hexane/2-propanol = 90/10, flow rate 1.0 mL/min, *I* = 268 nm) was used to measure the enantiomeric ratio (er = 96:4), t_R = 20.11 min (major), 22.62 min (minor). $[\alpha]_D^{25}$ = + 18.3 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.34 – 7.27 (m, 3H), 7.10 (m, 2H), 6.68 (t, *J* = 2.1 Hz, 1H), 6.63 (t, *J* = 2.5 Hz, 1H), 6.10 (dd, *J* = 2.8, 1.8 Hz, 1H), 5.01 (s, 2H), 4.36 (s, 1H), 2.17 (s, 3H), 1.68 (s, 3H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 209.3, 136.6, 127.7 (2C), 126.7, 126.0 (2C), 125.1, 120.9, 117.9, 105.9, 75.8, 52.5, 23.6, 22.3. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$Calcd for $C_{15}H_{18}NO_2$ 244.1332; Found 244.1338.

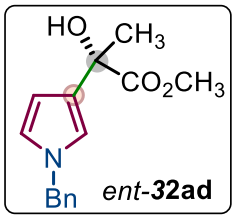
Ethyl-2-(1-benzyl-1*H*-pyrrol-3-yl)-2-hydroxy-2-(1-tosyl-1*H*-indol-3-yl)acetate (32ac). The general procedure was followed with ethyl 1-tosyl indol-3-ylglyoxylate (**31c**, 223 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), benzylamine (**28a**, 96 mg, 0.9 mmol) to furnish **32ac** after purification using petroleum ether/EtOAc (8/2) as eluent; Orange semi-solid (206 mg, 65% yield); **HPLC** (IA column, *n*-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, *I* = 256 nm) was used to measure the enantiomeric ratio (er = 91:9), t_R = 5.64 min (minor), 9.60 min (major). $[\alpha]_D^{25}$ = + 40.4 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.67 (dt, *J* = 8.36, 0.95, 0.95 Hz, 1H), 7.49 – 7.43 (m, 2H), 7.33 – 7.27 (m, 1H), 7.12 – 6.98 (m, 5H), 6.94 – 6.89 (m, 3H), 6.88 – 6.84 (m, 2H), 6.47 (t, *J* = 2.07, 2.07 Hz, 1H), 6.40 (t, *J* = 2.56, 2.56 Hz, 1H), 5.96 (dd, *J* = 2.80, 1.75 Hz, 1H), 4.77 (s, 2H), 4.05 – 3.97 (m, 1H), 3.97 – 3.88 (m, 1H), 3.84 (s, 1H), 2.06 (s, 3H), 0.89 (t, *J* = 7.13, 7.13 Hz, 3H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 173.3, 143.8, 136.7, 134.6, 134.1, 128.8 (2C), 127.8, 127.7 (2C), 126.7, 126.0 (2C), 125.8 (2C),

124.7, 123.8, 123.5, 123.5, 122.0, 120.6, 120.5, 118.8, 112.4, 106.7, 72.7, 61.7, 52.5, 20.5, 12.9. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$Calcd for $C_{30}H_{29}N2O_5S$ 529.1792; Found 529.1797.

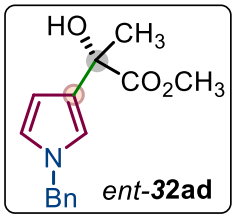
Methyl-2-(1-benzyl-1*H*-pyrrol-3-yl)-2-hydroxypropanoate (32ad). The general procedure was followed methyl pyruvate (**31d**, 61 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), benzylamine (**28a**, 96 mg, 0.9 mmol) to furnish **32ad** after purification using petroleum ether/EtOAc (8/2) as eluent; Brownish oil (107 mg, 69% yield); **HPLC** (IA column, *n*-hexane/2-propanol = 90/10, flow rate 1.0 mL/min, *I* = 299 nm) was used to measure the enantiomeric ratio (er = 98:2), t_R = 8.33 min (minor), 9.39 min (major). $[\alpha]_D^{25}$ = + 30.0 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.36–7.26 (m, 3H), 7.17–7.11 (m, 2H), 6.74 (t, *J* = 2.1 Hz, 1H), 6.61 (t, *J* = 2.6 Hz, 1H), 6.21 (dd, *J* = 2.8, 1.8 Hz, 1H), 5.00 (s, 2H), 3.77 (s, 3H), 3.64 (s, 1H), 1.76 (s, 3H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 175.5, 136.5, 127.5 (2C), 126.6, 126.2, 126.0 (2C), 120.2, 117.1, 105.4, 71.7, 52.3, 51.7, 25.5. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$Calcd for $C_{15}H_{18}NO_3$ 260.1281; Found 260.1276.



Methyl-2-(1-benzyl-1*H*-pyrrol-3-yl)-2-hydroxypropanoate (*ent*-32ad). The general procedure was followed with methyl pyruvate (**31d**, 61 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), benzylamine (**28a**, 96 mg, 0.9 mmol) to furnish ***ent* -32ad** after purification using petroleum ether/EtOAc (8/2) as eluent; (105 mg, 68% yield) **HPLC** (IA column, *n*-hexane/2-propanol = 90/10, flow rate 1.0 mL/min, *I* = 299 nm) was used to measure the enantiomeric ratio (er =7:93), t_R = 8.32 min (major), 9.38 min (minor). $[\alpha]_D^{25}$ = – 31.2 (*c* 0.1, CH_2Cl_2).

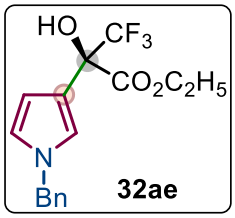


Methyl-2-(1-benzyl-1*H*-pyrrol-3-yl)-2-hydroxypropanoate (*ent*-32ad) (prepared using catalyst **27e** (30 mol%) and $PhCO_2H$ (30 mol%) as an additive).The general procedure was followed with methyl pyruvate (**31d**, 61 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), benzylamine (**28a**, 96 mg, 0.9 mmol) to furnish ***ent* -32ad** after purification using petroleum ether/EtOAc (8/2) as eluent; (102 mg, 66% yield); **HPLC** (IA column, *n*-hexane/2-propanol = 90/10, flow rate 1.0 mL/min, *I* = 299 nm) was used to measure the

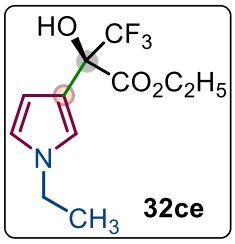


enantiomeric ratio (er = 8:92), t_R = 8.34 min (major), 9.38 min (minor). $[\alpha]_D^{25}$ = – 29.8 (*c* 0.1, CH_2Cl_2).

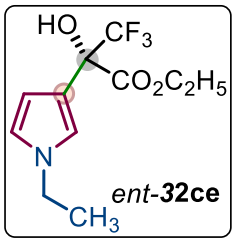
Ethyl-2-(1-benzyl-1*H*-pyrrol-3-yl)-3,3,3-trifluoro-2-hydroxypropanoate (32ae). The general procedure was followed with ethyl trifluoro pyruvate (**31e**, 102 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), benzylamine (**28a**, 96 mg, 0.9 mmol) to furnish **32ae** after purification using petroleum ether/EtOAc (8/2) as eluent; Reddish oil (136 mg, 71% yield); **HPLC** (IA column, *n*-hexane/2-propanol = 90/10, flow rate 1.0 mL/min, *I* = 228 nm) was used to measure the enantiomeric ratio (er = 98:2), t_R = 6.98 min (minor), 12.00 min (major). $[\alpha]_D^{25}$ = + 28.7 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.39 – 7.31 (m, 3H), 7.16 (d, *J* = 8.1 Hz, 2H), 6.98 (t, *J* = 2.1 Hz, 1H), 6.67 (t, *J* = 2.6 Hz, 1H), 6.43 (t, *J* = 1.9 Hz, 1H), 5.04 (s, 2H), 4.48 – 4.34 (m, 2H), 4.31 (s, 1H), 1.37 (t, *J* = 7.1 Hz, 3H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 169.5, 137.2, 128.7 (2C), 127.8, 127.1 (2C), 122.2 (q, *J* = 285.3 Hz), 121.4, 120.7, 116.7, 107.9, 77.8 (q, *J* = 31.0 Hz), 63.7, 53.5, 13.7. **HRMS (ESI–TOF)** *m/z*: [M + H]$^+$Calcd for $C_{16}H_{17}F_3NO_3$ 328.1155; Found. 328.1161.



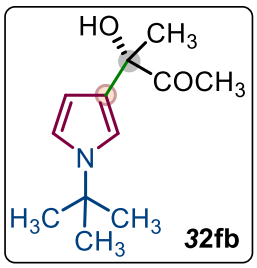
Ethyl-2-(1-ethyl-1*H*-pyrrol-3-yl)-3,3,3-trifluoro-2-hydroxypropanoate (32ce). The general procedure was followed with trifluoro pyruvate (**31e**, 102 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), ethylamine (**28c**, 41 mg, 0.9 mmol) to furnish **32ce** after purification using petroleum ether/EtOAc (8/2) as eluent; Reddish Oil (115 mg, 72% yield,); **HPLC** (IA column, *n*-hexane/2-propanol= 90/10, flow rate 1.0 mL/min, *I* = 258 nm) was used to measure the enantiomeric ratio (er = 97:3), t_R = 4.46 min (minor), 6.84 min (major). $[\alpha]_D^{25}$ = + 34.2 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.89 (t, *J* = 2.1 Hz, 1H), 6.63 (t, *J* = 2.6 Hz, 1H), 6.31 (t, *J* = 1.9 Hz, 1H), 4.47 – 4.31 (m, 2H), 4.22 (s, 1H), 3.90 (q, *J* = 7.3 Hz, 2H), 1.42 (t, *J* = 7.3 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 168.6, 122.2 (q, *J* = 285.2 Hz), 119.4, 118.6, 115.2, 106.4, 74.7 (q, *J* = 31.2 Hz), 62.8, 43.4, 15.3, 12.9. **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$Calcd for $C_{11}H_{15}F_3NO_3$ 266.0999; Found 266.0990.



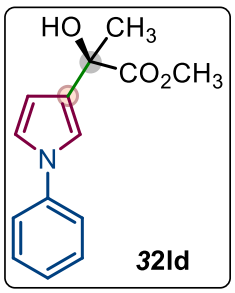
Ethyl-2-(1-ethyl-1*H*-pyrrol-3-yl)-3,3,3-trifluoro-2-hydroxypropanoate (*ent*-32ce). The general procedure was followed with ethyl trifluoropyruvate (**31e**, 102 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), ethylamine (**28c**, 41 mg, 0.9 mmol) to furnish ***ent*-32ce** after purification using petroleum ether/EtOAc (8/2) as eluent; Reddish Oil (111 mg, 70% yield); **HPLC** (IA column, *n*-hexane/2-propanol = 90/10, flow rate 1.0 mL/min, *I* = 258 nm) was used to measure the enantiomeric ratio (er = 2:98), t_R = 4.48 min (major), 6.61 min (minor). $[\alpha]_D^{25}$ = – 36.0 (*c* 0.1, CH_2Cl_2).



3-(1-(*tert*-butyl)-1*H*-pyrrol-3-yl)-3-hydroxybutan-2-one (32fb). The general procedure was followed with 2,3-butanedione (**31b**, 51 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), *tert*-butylamine (**28f**, 66 mg, 0.9 mmol) to furnish **32fb** after purification using petroleum ether/EtOAc (8/2) as eluent; Yellowish oil (89 mg, 71% yield); **HPLC** (IA column, *n*-hexane/2-propanol = 90/10, flow rate 1.0 mL/min, *I* = 220 nm) was used to measure the enantiomeric ratio (er = >99:1), t_R = 3.09 min (minor), 4.84 min (major). $[\alpha]_D^{25}$ = + 33.1 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.79 – 6.77 (m, 1H), 6.75 (t, *J* = 2.7 Hz, 1H), 6.04 (dd, *J* = 2.9, 1.9 Hz, 1H), 4.35 (s, 1H), 2.17 (s, 3H), 1.68 (s, 3H), 1.49 (s, 9H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 209.5, 123.8, 117.2, 114.4, 104.8, 75.9, 53.9, 29.6 (3C), 23.7, 22.4. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$Calcd for $C_{12}H_{20}NO_2$ 210.1489; Found 210.1485.

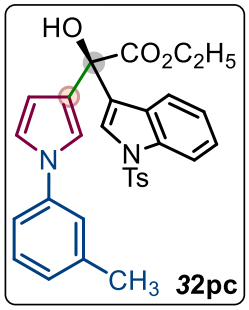


Methyl-2-hydroxy-2-(1-phenyl-1*H*-pyrrol-3-yl)propanoate (32ld). The general procedure was followed with methyl pyruvate **31d**, 61 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), aniline (**28l**, 84 mg, 0.9 mmol) to furnish **32ld** after purification using petroleum ether/EtOAc (8/2) as eluent; yellow semi-solid (87 mg, 59% yield); **HPLC** (IA column, *n*-hexane/2-propanol = 90/10, flow rate 1.0 mL/min, *I* = 256 nm) was used to measure the enantiomeric ratio (er = 89:11), t_R = 9.24 min (minor), 10.41 min (major). $[\alpha]_D^{25}$ = + 27.2 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ7.44 – 7.38 (m, 2H), 7.38 – 7.34 (m, 2H), 7.27 – 7.22 (m, 1H), 7.11 (dd, *J* = 2.3, 1.8 Hz, 1H), 7.01 (dd, *J* = 3.0, 2.3 Hz, 1H), 6.35 (dd, *J* = 2.9, 1.8 Hz, 1H), 3.81 (s, 3H), 3.61 (s, 1H), 1.78 (s, 3H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 175.6,



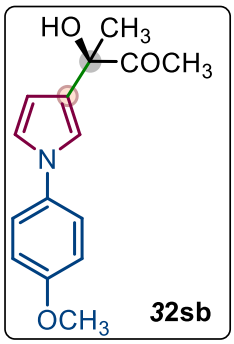
139.5, 128.5 (2C), 128.1, 124.8, 119.4 (2C), 118.6, 115.4, 107.5, 71.8, 52.1, 25.7. **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$Calcd for $C_{14}H_{16}NO_3$ 246.1125; Found 246.1129.

Ethyl-2-hydroxy-2-(1-(m-tolyl)-1*H*-pyrrol-3-yl)-2-(1-tosyl-1*H*-indol-3-yl)acetate (32pc). The



general procedure was followed with ethyl 1-tosyl indol-3-ylglyoxylate (**31c**, 223 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), 3-methyl aniline (**28p**, 96 mg, 0.9 mmol) to furnish **32pc** after purification using petroleum ether/EtOAc (8/2) as eluent; Orange semi-solid (193 mg, 61% yield); **HPLC** (IA column, *n*-hexane/2-propanol = 90/10, flow rate 1.0 mL/min, *I* = 224 nm) was used to measure the enantiomeric ratio (er = >99:1), t_R = 5.28 min (major),6.08 min (minor). $[\alpha]_D^{25}$= + 33.8 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.94 (dt, *J* = 8.4, 1.0 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.62 – 7.55 (m, 2H), 7.35 – 7.27 (m, 2H), 7.23 – 7.15 (m, 5H), 7.13 (t, *J* = 2.1 Hz, 1H), 7.11 – 7.02 (m, 2H), 6.36 (dd, *J* = 3.0, 1.8 Hz, 1H), 4.36 – 4.20 (m, 2H), 4.19 (s, 1H), 2.41 (s, 3H), 2.34 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 173.2, 143.9, 139.4, 138.6, 134.6, 134.2, 128.9 (2C), 128.4, 127.7, 125.9 (2C), 125.7, 125.2, 124.8, 123.6, 123.4, 122.2, 120.5, 120.2, 118.8, 116.9, 116.6, 112.5, 108.5, 72.7, 61.9, 20.5 (2C) 13.0. **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$Calcd for $C_{30}H_{29}N_2O_5S$ 529.1792; Found 529.1796.

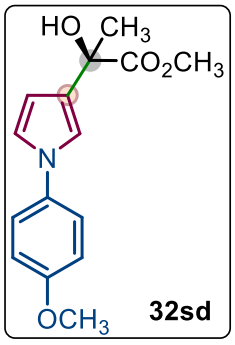
3-hydroxy-3-(1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl) butan-2-one (32sb). The general



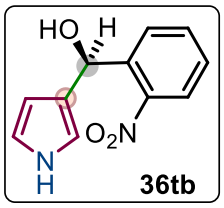
procedure was followed with 2,3-butanedione (**31b**, 51 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), 4-methoxyaniline (**28s**, 111 mg, 0.9 mmol) to furnish **32sb** after purification using petroleum ether/EtOAc (8/2) as eluent; Orange oil (107 mg, 69% yield); **HPLC** (IA column, *n*-hexane/2-propanol = 90/10, flow rate 1.0 mL/min, *I* = 257 nm) was used to measure the enantiomeric ratio (er = 87:13), t_R = 20.00 min (major), 20.48 min (minor). $[\alpha]_D^{25}$ = + 33.8 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.28 (d, *J* = 9.0 Hz, 2H), 6.99 (t, *J* = 2.1 Hz, 1H), 6.96 – 6.91 (m, 3H), 6.23 (dd, *J* = 2.9, 1.8 Hz, 1H), 4.44 (s, 1H), 3.83 (s, 3H), 2.23 (s, 3H), 1.74 (s, 3H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 210.1, 157.8, 134.1, 127.4, 122.1 (2C), 120.5, 117.5, 114.6 (2C), 108.2, 76.8,

55.6, 24.7, 23.4. **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$ Calcd for $C_{15}H_{18}NO_3$ 260.1281; Found 260.1283.

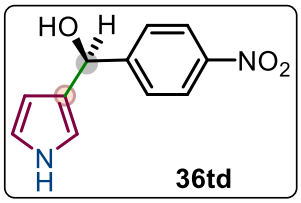
Methyl-2-hydroxy-2-(1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)propanoate (32sd). The general procedure was followed with methyl pyruvate (**31d**, 61 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), 4-methoxyaniline (**28s**, 111 mg, 0.9 mmol) to furnish **32sd** after purification using petroleum ether/EtOAc (8/2) as eluent; Reddish semi-solid (115 mg, 70% yield); **HPLC** (IA column, *n*-hexane/2-propanol = 90/10, flow rate 1.0 mL/min, *I* = 272 nm) was used to measure the enantiomeric ratio (er = 90:10), t_R = 5.60 min (minor), 6.34 min (major). $[\alpha]_D^{25}$ = + 33.5 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.28 (d, *J* = 9.0 Hz, 2H), 7.02 (dd, *J* = 2.3, 1.8 Hz, 1H), 6.95 – 6.90 (m, 3H), 6.31 (dd, *J* = 2.9, 1.8 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 1.77 (s, 3H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 176.6, 157.8, 134.2, 128.6, 122.6 (2C), 120.0, 116.8, 114.6 (2C), 107.9, 72.8, 55.5, 53.0, 26.7. **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$ Calcd for $C_{15}H_{18}NO_4$ 276.1230; Found 276.1236.



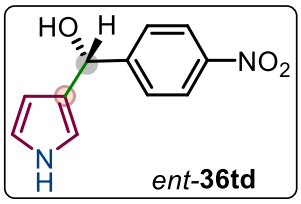
(*R*)-(2-nitrophenyl)(1*H*-pyrrol-3-yl)methanol (36tb). The general procedure was followed with 2-nitrobenzaldehyde (**33b**, 91 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), ammonium acetate (**35t**, 69 mg, 0.9 mmol) to furnish **36tb** after purification using petroleum ether/EtOAc (7/3) as eluent; Yellow solid (85 mg, 65% yield, mp = 94-97°C); **HPLC** (IA column, *n*-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, *I* = 220 nm) was used to measure the enantiomeric ratio (er = 78:22), t_R = 43.12 min (major), 49.10 min (minor). $[\alpha]_D^{25}$ = – 39.1 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.26 (s, 1H), 7.94 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.88 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.63 (td, *J* = 7.6, 1.4 Hz, 1H), 7.41 (td, *J* = 7.8, 1.5 Hz, 1H), 6.69 (q, *J* = 2.5 Hz, 1H), 6.65 (q, *J* = 2.1 Hz, 1H), 6.42 (s, 1H), 6.10 (td, *J* = 2.7, 1.6 Hz, 1H), 2.67 (s, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 147.0, 138.5, 132.2, 127.5, 126.9, 124.3, 123.4, 117.5, 115.3, 106.0, 65.4. **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$ Calcd for $C_{11}H_{11}N_2O_3$ 219.0764; found 219.0770.



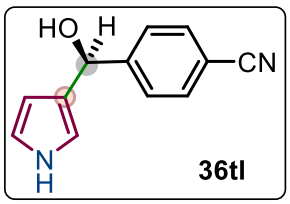
***(S)*-(4-nitrophenyl)(1*H*-pyrrol-3-yl)methanol (36td).** The general procedure was followed with 4-nitrobenzaldehyde (**33d**, 91 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), ammonium acetate (**35t**, 69 mg, 0.9 mmol) to furnish **36tb** after purification using petroleum ether/EtOAc (7/3) as eluent; Brown solid (89 mg, 68% yield, mp = 66–69°C); **HPLC** (IA column, *n*-hexane/2-propanol = 90/10, flow rate 0.5 mL/min, *I* = 273 nm) was used to measure the enantiomeric ratio (er = 92:8), t_R = 41.25 min (minor), 45.28 min (major); $[\alpha]_D^{25}$ = – 36.2 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.28 – 8.23 (m, 1H), 8.21 – 8.17 (m, 2H), 7.66 – 7.60 (m, 2H), 6.78 (q, *J* = 2.58, 2.53, 2.53 Hz, 1H), 6.67 (q, *J* = 2.14, 2.14, 2.08 Hz, 1H), 6.13 (td, *J* = 2.78, 2.74, 1.62 Hz, 1H), 5.92 (s, 1H), 2.22 (s, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 150.7, 146.0, 126.0 (2C), 125.7, 122.5 (2C), 118.0, 115.2, 106.1, 69.0. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{11}N_2O_3$ 219.0764; found 219.0772.



***(R)*-(4-nitrophenyl)(1*H*-pyrrol-3-yl)methanol (*ent*-36td).** The general procedure was followed with 4-nitrobenzaldehyde (**33d**, 91 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), ammonium acetate (**35t**, 69 mg, 0.9 mmol) to furnish ***ent*-36tb** after purification using petroleum ether/ethyl acetate (7/3) as eluent (88 mg, 67%); **HPLC** (IA column, *n*-hexane/2-propanol = 90/10, flow rate 0.5 mL/min, *I* = 246 nm) was used to measure the enantiomeric ratio (er = 8:92), t_R = 42.15 min (minor), 45.35 min (major). $[\alpha]_D^{25}$ = + 36.0 (*c* 0.1, CH_2Cl_2).

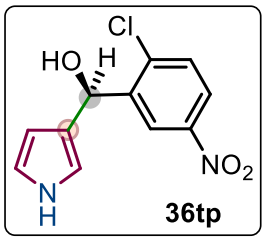


(*S*)-4-(hydroxy(1*H*-pyrrol-3-yl)methyl)benzonitrile (36tl). The general procedure was followed with 4-cyanobenzaldehyde (**33l**, 79 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), ammonium acetate (**35t**, 69 mg, 0.9 mmol) to furnish **36tl** after purification using petroleum ether/EtOAc (7/3) as eluent; White solid (76 mg, 64% yield, mp = 89–92°C); **HPLC** (IA column, *n*-hexane/2-propanol = 90/10, flow rate 1.0 mL/min, *I* = 258 nm) was used to measure the enantiomeric ratio (er = 86:14), t_R = 29.19 min (minor), 33.21 min (major). $[\alpha]_D^{25}$ = –41.2 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.30 (s, 1H), 7.62 (d, *J* = 8.38 Hz, 2H), 7.57 (d, *J* = 8.25 Hz, 2H), 6.76 (q, *J* = 2.57, 2.53, 2.53 Hz, 1H), 6.64 (q, *J* = 2.11, 2.11, 2.04 Hz, 1H), 6.12 (td, *J* = 2.74, 2.73, 1.58 Hz, 1H), 5.87 (s, 1H), 2.32 (d, *J* = 14.78 Hz,

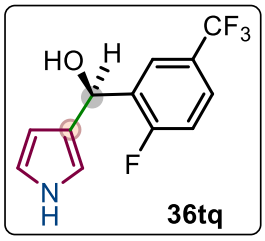


1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 148.7, 131.0 (2C), 125.9 (2C), 125.7, 118.0, 117.9, 115.1, 109.6, 106.0, 69.1. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$Calcd for $C_{12}H_{11}N_2O$ 199.0866; found 199.0859.

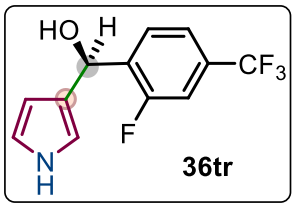
(*R*)-(2-chloro-5-nitrophenyl)(1*H*-pyrrol-3-yl)methanol (36tp). The general procedure was followed with 2-chloro 4-nitrobenzaldehyde (**33p**, 111 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), ammonium acetate (**35t**, 69 mg, 0.9 mmol) to furnish **36tp** after purification using petroleum ether/EtOAc (7/3) as eluent; Brown semi-solid (102 mg, 67% yield); **HPLC** (IA column, *n*-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, *I* = 257 nm) was used to measure the enantiomeric ratio (er = 75:24), t_R = 20.31 min (major), 23.23 min (minor). $[\alpha]_D^{25}$ = –39.3 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.69 (s, 1H), 8.64 (t, *J* = 3.5 Hz, 1H), 7.94 (dd, *J* = 8.6, 3.0 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 6.65 – 6.49 (m, 2H), 6.04 (d, *J* = 4.8 Hz, 2H), 4.96 (t, *J* = 3.7 Hz, 1H), 2.76 (s, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 145.7, 143.9, 137.6, 129.0, 123.8, 121.7, 121.5, 117.3, 115.1, 105.7, 65.7. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$Calcd for $C_{11}H_{10}ClN_2O_3$ 253.0374; Found 253.0380.



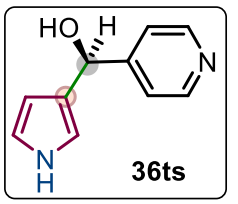
(*S*)-(2-fluoro-6-(trifluoromethyl)phenyl)(1*H*-pyrrol-3-yl)methanol (36tq). The general procedure was followed with 2-fluoro 5-trifluoromethyl benzaldehyde (**33q**,115 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), ammonium acetate (**35t**, 69 mg, 0.9 mmol) to furnish **36tq** after purification using petroleum ether/EtOAc (7/3) as eluent; Yellowish semi-solid (95 mg, 61% yield); **HPLC** (IA column, *n*-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, *I* = 275 nm) was used to measure the enantiomeric ratio (er =74:26), t_R = 10.17 min (major), 12.72 min (minor). $[\alpha]_D^{25}$ = – 43.3 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.23 (s, 1H), 7.96 (dd, *J* = 6.7, 2.2 Hz, 1H), 7.53 (m, 1H), 7.11 (t, *J* = 9.1 Hz, 1H), 6.78 – 6.71 (m, 1H), 6.69 – 6.63 (m, 1H), 6.23 – 6.16 (m, 1H), 6.13 (s, 1H), 2.31 (s, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 161.4 (d, *J* = 252.0 Hz), 132.8 (d, *J* = 14.1 Hz), 126.8 (d, *J* = 3.4 Hz), 126.6 (dq, *J* = 33.1, 3.4 Hz), 125.8, 125.1, (q, *J* = 3.8 Hz), 123.8 (q, *J* = 271.9 Hz), 118.7, 115.9, 115.7, 106.9, 64.6 (d, *J* = 3.4 Hz).**HRMS (ESI-TOF)** *m/z*: $[M + H]^+$Calcd for $C_{12}H_{10}F_4NO$ 260.0693; found 260.0697.



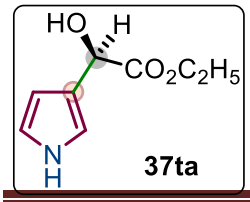
(*S*)-(2-fluoro-4-(trifluoromethyl)phenyl)(1*H*-pyrrol-3-yl)methanol (36tr). The general procedure was followed with 2-fluor-4-trifluoromethyl benzaldehyde (**33r**, 115 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), ammonium acetate (**35t**, 69 mg, 0.9 mmol) to furnish **36tr** after purification using petroleum ether/EtOAc (7/3) as eluent; Yellowish semi-solid (101 mg, 65% yield); **HPLC** (IA column, *n*-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, *I* = 275 nm) was used to measure the enantiomeric ratio (er = 89:11), t_R = 13.60 min (minor), 16.39 min (major). $[\alpha]_D^{25}$ = –44.3 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.23 (s, 1H), 7.96 (dd, *J* = 6.67, 2.19 Hz, 1H), 7.53 (m, 1H), 7.11 (t, *J* = 9.11, 9.11 Hz, 1H), 6.78 – 6.71 (m, 1H), 6.69 – 6.63 (m, 1H), 6.23 – 6.16 (m, 1H), 6.13 (s, 1H), 2.31 (s, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 159.2 (d, *J* = 248.4 Hz), 135.7 (d, *J* = 12.7 Hz), 130.9 (dq, *J* = 33.0, 8.1 Hz), 128.1 (d, *J* = 4.4 Hz), 125.8, 123.4 (dq, *J* = 272.2, 2.8 Hz), 121.1 (q, *J* = 3.8 Hz), 118.7, 115.9, 112.7 (dq, *J* = 25.0, 3.7 Hz), 106.9, 64.7 (d, *J* = 3.5 Hz).**HRMS (ESI-TOF)** *m/z*: $[M + H]^+$Calcd for $C_{12}H_{10}F_4NO$ 260.0693; found 260.0697.



(*S*)-pyridin-4-yl(1*H*-pyrrol-3-yl)methanol (36ts). The general procedure was followed with isonicotinaldehyde (**3s**,64 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), ammonium acetate (**35t**, 69 mg, 0.9 mmol) to furnish **36ts** after purification using petroleum ether/EtOAc (1/1) as eluent; Brown semi-solid (70 mg, 67% yield); **HPLC** (IA column, *n*-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, *I* = 220 nm) was used to measure the enantiomeric ratio (er = 99:1), t_R = 24.01 min (major), 30.15 min (minor). $[\alpha]_D^{25}$ = – 18.3 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, DMSO-d_6)** δ 10.61 (s, 1H), 8.47 (d, *J* = 5.1 Hz, 2H), 7.35 (d, *J* = 5.5 Hz, 2H), 6.62 (dd, *J* = 22.2, 2.3 Hz, 2H), 5.92 (d, *J* = 2.1 Hz, 1H), 5.60 (t, *J* = 5.7 Hz, 2H). **^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6)** δ 155.7, 149.6(3C), 127.0, 121.7, 118.3, 115.8, 106.7, 68.8. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$Calcd for $C_{10}H_{11}N_2O$ 175.0866; Found 175.0870.

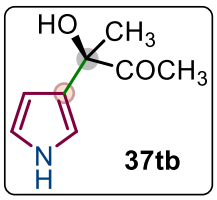


(*R*)-Ethyl-2-hydroxy-2-(1*H*-pyrrol-3-yl)acetate (37ta). The general procedure was followed with ethyl glyoxylate(**34a**, 61 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), ammonium acetate (**35t**, 69 mg, 0.9 mmol) to furnish **37ta** after purification using petroleum ether/EtOAc (7/3) as eluent;



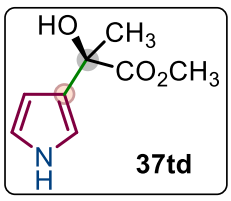
Yellowish oil (60 mg, 59% yield); **HPLC** (IA column, *n*-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, *I* = 293 nm) was used to measure the enantiomeric ratio (er = 96:4), t_R = 4.20 min (minor), 4.75 min (major). $[\alpha]_D^{25}$ = + 33.4 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.44 (s, 1H), 6.72 (s, 1H), 6.61 (s, 1H), 6.10 (s, 1H), 5.07 (s, 1H), 4.11 (q, 2H), 1.16 (t, 3H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 173.1, 120.8, 117.5, 115.2, 105.7, 66.9, 60.7, 13.13. **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$Calcd for $C_8H_{12}NO_3$ 170.0817 ; found 170.0819.

3-hydroxy-3-(1*H*-pyrrol-3-yl)butan-2-one (37tb).The general procedure was followed with



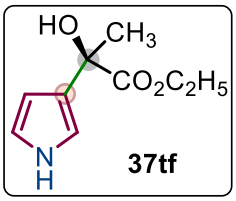
2,3-butanedione (**34b**, 51 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), ammonium acetate (**35t**, 69 mg, 0.9 mmol) to furnish **37tb** after purification using petroleum ether/EtOAc (7/3) as eluent; Yellowish oil (63 mg, 69% yield); **HPLC** (IA column, *n*-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, *I* = 337 nm) was used to measure the enantiomeric ratio (er = 91:9), t_R = 26.49 min (major), 29.76 min (minor). $[\alpha]_D^{25}$ = + 30.6 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.31 (s, 1H), 6.78 (dt, *J* = 2.7, 1.8 Hz, 1H), 6.75 (td, *J* = 2.8, 2.1 Hz, 1H), 6.15 (td, *J* = 2.8, 1.7 Hz, 1H), 4.39 (s, 1H), 2.17 (s, 3H), 1.71 (s, 3H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 210.4, 125.9, 118.7, 115.6, 106.7, 76.8, 24.7, 23.3. **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$Calcd for $C_8H_{12}NO_2$ 154.0863; Found 154.0859.

Ethyl-2-hydroxy-2-(1*H*-pyrrol-3-yl)propanoate (37td). The general procedure was followed

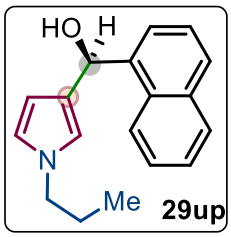


methyl pyruvatevate(**34d**, 61 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), ammonium acetate (**35t**, 69 mg, 0.9 mmol) to furnish **37td** after purification using petroleum ether/EtOAc (7/3) as eluent; Yellowish oil (66 mg, 67% yield); **HPLC** (IA column, *n*-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, *I* = 299 nm) was used to measure the enantiomeric ratio (er = 99:1), t_R = 3.41 min (minor), 4.29 min (major). $[\alpha]_D^{25}$ = + 32.1 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.39 (s, 1H), 6.79 (dt, *J* = 2.7, 1.8 Hz, 1H), 6.71 (td, *J* = 2.7, 2.1 Hz, 1H), 6.23 (td, *J* = 2.8, 1.7 Hz, 1H), 3.77 (s, 3H), 1.74 (s, 3H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 175.7, 126.0, 117.2, 113.9, 105.2, 71.8, 51.9, 25.6. **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$Calcd for $C_8H_{12}NO_3$: 170.0812; Found 170.0818.

Ethyl-2-hydroxy-2-(1*H*-pyrrol-3-yl)propanoate (37tf). The general procedure was followed with ethyl pyruvate(**34f**, 70 mg, 0.6 mmol), succinaldehyde (**25**, 600 µl, 3.0 M sol, 1.8 mmol), ammonium acetate (**35t**, 69 mg, 0.9 mmol) to furnish **37tf** after purification using petroleum ether/EtOAc (7/3) as eluent; yellow semi-solid (68 mg, 62% yield); **HPLC** (IA column, *n*-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, *I* = 259 nm) was used to measure the enantiomeric ratio (er = 98:2), t_R = 4.84 min (major), 6.16 min (minor). $[\alpha]_D^{25}$ = + 35.4 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.70 (s, 1 H), 6.77 (m, 1 H), 6.69 (m, 1H), 6.23 (td, *J* = 2.7, 1.5, 1 H), 4.23 (m, 2 H), 3.69 (m, 1 H), 1.75 (s, 3 H), 1.28 (t, *J* = 7.1, 3 H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 175.3, 125.9, 117.2, 113.9, 105.1, 71.9, 60.9, 25.6, 13.0. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ Calcd for $C_9H_{14}NO_3$ 184.0968 Found184.0970.

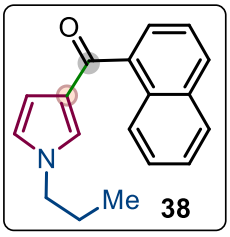


(*S*)-naphthalen-1-yl(1-propyl-1H-pyrrol-3-yl)methanol (29up). An oven-dried Schlenk tube was charged with L-Proline **27a** (0.18 mmol, 0.3 equiv, 21 mg), succinaldehyde **25** (3.0 M sol, 1.8 mmol, 600 µl,3.0 equiv), and 1-naphthaldehyde **26p** (0.6 mmol, 1.0 equiv, 94 mg) in DMF (3.0 mL) at 10 °C. The reaction mixture was stirred for 36 h at the same temperature. *N*-propyl amine **28u** (0.9 mmol, 1.5 equiv, 53 mg**)** was added to the same vessel and stirred for 10 h at room temperature. The reaction mixture was quenched with ice-cold water (3.0 mL) and extracted with EtOAc (3 × 5.0 mL). The combined organic layer was washed with brine (3.0 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The column chromatographic purification on silica gel using petroleum ether/EtOAc (8/2) as eluent furnished chiral pyrrole **29up** (95 mg, 60% yield) as brown semi-solid. **HPLC** (IA column, *n*-hexane/2-propanol = 80/20, flow rate 1.0 mL/min, *I* = 302 nm) was used to measure the enantiomeric ratio (er = 99:1), t_R = 4.95 min (minor), 11.80 min (major).$[\alpha]_D^{25}$ = –50.2 (*c* 0.1, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.09 – 8.07 (d, 1H), 7.89 – 7.87 (m, 1H), 7.85 – 7.81 (m, 2H), 7.53 (dd, *J* = 8.21, 7.11 Hz, 1H), 7.46 (m, 2H), 6.58 (t, *J* = 2.56, 2.56 Hz, 1H), 6.53 (s, 1H), 6.42 (d, *J* = 2.13 Hz, 1H), 6.17 – 6.11 (m, 1H), 3.70 (t, *J* = 7.17, 7.17 Hz, 2H), 2.32 (s, 1H), 1.72 (p, *J* = 7.35, 7.35, 7.31, 7.31 Hz, 2H), 0.86 (td, *J* = 7.42, 7.39, 0.91 Hz, 3H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 138.9, 132.7, 129.6, 127.5, 126.7, 125.9, 124.6, 124.4, 124.3, 123.2, 122.2,

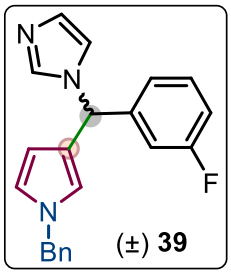


119.8, 118.2, 106.1, 67.2, 50.3, 23.6, 10.2. **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$Calcd for $C_{18}H_{20}NO$ 266.1539; Found 266.1541.

Naphthalen-1-yl (1-propyl-1*H*-pyrrol-3-yl)methanone (38). An over-dried Schlenk tube (25 mL) was charged with **29up** (0.34 mmol, 1.0 equiv, 90 mg) and IBX (1.2 mmol, 2.0 equiv, 190mg) in EtOAc (5.0 mL) and heated to 80 ^oC for 4 h. Upon complete oxidation; the flask was cooled and stirred $NaHCO_3$ (10%-sol, 5.0 mL) for five minutes. The organic layer was separated and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Compound **38** (74 mg, 83% yield) was obtained as a brown semi-solid after passing through a small pad of silica-gel column using petroleum ether/EtOAc (9/1) as the eluent.**^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.23 – 8.16 (m, 1H), 7.94 (dt, *J* = 8.22, 1.08, 1.08 Hz, 1H), 7.91 – 7.85 (m, 1H), 7.66 (dd, *J* = 6.99, 1.30 Hz, 1H), 7.54 – 7.47 (m, 3H), 7.07 (t, *J* = 1.94, 1.94 Hz, 1H), 6.71 (dd, *J* = 2.96, 1.72 Hz, 1H), 6.67 (dd, *J* = 2.96, 2.13 Hz, 1H), 3.81 (t, *J* = 7.12, 7.12 Hz, 2H), 1.77 (p, *J* = 7.29, 7.29, 7.29, 7.29 Hz, 2H), 0.90 (t, *J* = 7.38, 7.38 Hz, 3H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 191.0, 137.5, 132.7, 129.6, 129.0, 127.7, 127.1, 125.6, 125.2, 125.1, 125.0, 124.9, 123.3, 121.4, 109.5, 50.8, 23.3, 10.1. **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$ Calcd for $C_{18}H_{18}NO$ 264.1383; Found 264.1388.

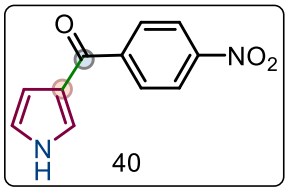


1-((1-benzyl-1*H*-pyrrol-3-yl)(3-fluorophenyl)methyl)-1*H*-imidazole (±39). An over-dried Schlenk tube (25 mL) was charged with compound **29af** (83 mg, 0.3 mmol, 1 equiv) and 1,1'-carbonyldiimidazole (CDI) (97 mg, 0.6 mmol, 2.0 equiv) in dry CH_3CN (2.0 mL) at room temperature and stirred for 15 h. Upon completion, the reaction mass was concentrated under reduced pressure. Yellowish semi-solid compound **39** (55 mg, 55% yield) was obtained in racemic form by directly passing through a small pad of column using petroleum ether/EtOAc (3:2) as eluent. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.52 (d, *J* = 4.27 Hz, 1H), 7.31 (m, 4H), 7.09 (dt, *J* = 7.95, 2.94, 2. 94 Hz, 3H), 6.98 (td, *J* = 8.37, 8.36, 2.84 Hz, 1H), 6.91 (d, *J* = 6.94 Hz, 2H), 6.84 (dt, *J* = 9.61, 2.22, 2.22 Hz, 1H), 6.68 (p, *J* = 3.28, 3.28, 3.18, 3.18 Hz, 1H), 6.45 – 6.35 (m, 2H), 6.03 (p, *J* = 3.35, 3.35, 3.31, 3.31 Hz, 1H), 4.99 (d, *J* = 3.88 Hz, 2H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 164.1 (d, *J* = 246.8 Hz), 143.5 (d, *J* = 6.8 Hz), 137.3 (d, *J* = 35.1 Hz), 130.1 (d, *J* = 8.1 Hz), 128.9, 128.8 (2C), 127.8, 126.9 (3C), 122.5 (d, *J* = 2.8 Hz), 122.3, 121.7, 120.9,



118.9, 114.7 (d, *J* = 21.0 Hz), 114.0, (d, *J* = 22.5 Hz), 108.7, 58.8, 53.4. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$Calcd for $C_{21}H_{19}FN_3$ 332.1558 Found 332.1555.

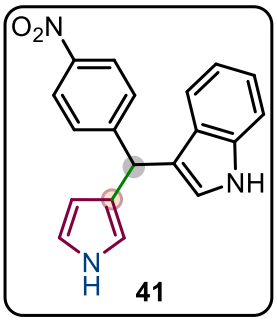
(4-Nitrophenyl)(1*H*-pyrrol-3-yl) methanone (40). An over-dried Schlenk tube (25 mL) was



40

charged with **29td** (0.6 mmol, 1.0 equiv, 132 m) and IBX (1.2 mmol, 2.0 equiv, 339mg) in EtOAc (10.0 mL) and heated to 80 ^oC for 4 h. Upon complete oxidation; the flask was cooled and stirred $NaHCO_3$ (10%-sol, 10.0 mL) for five minutes. The organic layer was separated and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Compound**40** (122 mg, 94% yield) was obtained as brown semi-solid after passing through a small pad of silica-gel column using petroleum ether/EtOAc (8/2) as the eluent;**^{1}H NMR (400 MHz, $CDCl_3$few drop of DMSO-*d*$_6$) δ** 10.56 (s, 1H), 8.35 – 8.17 (m, 2H), 7.96 – 7.81 (m, 2H), 7.28 (dt, *J*= 3.47, 1.69, 1.69 Hz, 1H), 6.82 (q, *J*= 2.70, 2.70, 2.64 Hz, 1H), 6.67 (q, *J*= 2.54, 2.54, 2.52 Hz, 1H).**^{13}C{^{1}H}NMR (100 MHz, Chloroform-*d* few drop of DMSO-*d*$_6$)** δ 188.8, 149.0, 145.4, 129.4(2C), 126.3, 123.6, 123.2(2C), 120.1, 109.0.**HRMS (ESI-TOF)***m/z*: $[M + H]^+$Calcd for $C_{18}H_{18}NO$264.1383; Found 264.1388.

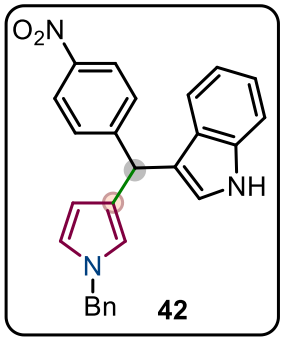
3-((4-nitrophenyl)(1*H*-pyrrol-3-yl)methyl)-1*H*-indole (41). Purification was done using



41

petroleum ether/ethyl acetate (8/2) as eluent; brown semi-solid (122 mg, 94% yield); **^{1}H NMR (400 MHz, $CDCl_3$** δ 8.22 – 8.02 (m, 5H), 7.53 – 7.47 (m, 2H), 7.39 (dd, *J*= 8.18, 0.98 Hz, 1H), 7.32 – 7.29 (m, 1H), 7.20 (ddd, *J*= 8.18, 7.02, 1.20 Hz, 1H), 7.04 (ddd, *J*= 7.99, 7.04, 1.02 Hz, 1H), 6.85 (dd, *J*= 2.28, 1.03 Hz, 1H), 6.80 (q, *J*= 2.46, 2.46, 2.44 Hz, 1H), 6.46 (q, *J*= 2.11, 2.11, 2.08 Hz, 1H), 6.13 (td, *J*= 2.65, 2.60, 1.55 Hz, 1H), 5.71 (s, 1H).**^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$)** δ 153.2, 146.4, 136.7, 129.4, 126.7, 125.5, 123.5, 123.4, 122.3, 119.6, 119.5, 119.5, 118.3, 116.6, 111.2, 108.9, 41.5.**HRMS (ESI-TOF)** *m/z*: $[M + H]^+$Calcd for $C_{19}H_{15}N_3O_2$ 318.1230; Found 318.1233.

3-((1-benzyl-1*H*-pyrrol-3-yl)(4-nitrophenyl)methyl)-1*H*-indole (42). Purification was done using petroleum ether/ethyl acetate (8/2) as eluent; brown semi-solid (122 mg, 94% yield);**^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.16 – 8.10 (m, 2H), 8.10 – 8.02 (m, 1H), 7.54 – 7.47 (m, 2H), 7.40 – 7.34 (m, 2H), 7.34 – 7.27 (m, 3H), 7.20 (ddd, J = 8.17, 7.02, 1.19 Hz, 1H), 7.15 – 7.08 (m, 2H), 7.04 (m, 1H), 6.84 (dd, J = 2.43, 1.07 Hz, 1H), 6.68 (t, J = 2.49, 2.49 Hz, 1H), 6.42 – 6.36 (m, 1H), 6.07 (dd, J = 2.75, 1.78 Hz, 1H), 5.67 (s, 1H), 5.00 (s, 2H).**^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$)** δ 153.2, 146.2, 138.1, 136.6, 129.3(2C), 128.6(2C), 127.6, 126.8(2C), 126.6, 125.7(2C), 123.4, 123.4, 122.1, 121.5, 120.0, 119.5, 119.4, 119.3, 111.1, 109.0, 53.3, 41.6.**HRMS (ESI-TOF)** *m/z*: [M + H]$^{+}$Calcd for $C_{26}H_{21}N_3O_2$ 407.163; Found 407.1628.



4.7 Single crystal X-ray Diffraction Experiment and Analysis

The single crystal XRD data collection and data reduction were performed using CrysAlis PRO on a single crystal Rigaku Oxford XtaLab Pro Kappa dual home/near diffractometer. The crystals were kept at 93(2) K during data collection using CuKα (λ = 1.54184 Å) radiation. Using Olex2,[32]the structure was solved with the ShelXT[33] structure solution program using Intrinsic Phasing and refined with the ShelXL[34] refinement package using Least Squares minimization.

4.7.1 Single Crystal structure, Cell parameters, and structure data of compound (29aj) (exp_1115-IK-AP-3Cl-bn, *S*-isomer) (CCDC 2176250): The single crystals of compound $C_{18}H_{16}ClNO$ (exp_1115-IK-AP-3Cl-bn, *S*-isomer) were obtained as colorless blocks through slow evaporation of this compound in CH_2Cl_2: *n*-hexane solvent mixture. The compound crystallized an orthorhombic crystal system and $P2_12_12_1$ space group with following unit cell parameters, $C_{18}H_{16}ClNO$ (M =297.77 g/mol), orthorhombic, space group $P2_12_12_1$ (no. 19), a = 4.65680(10) Å, b = 11.98330(10) Å, c = 26.5172(3) Å, V = 1479.76(4) Å^3, Z = 4, T = 123(2) K, μ(Cu Kα) = 2.256 mm^{-1}, *Dcalc* = 1.337 g/cm^3, 14685 reflections measured (8.096° ≤ 2Θ ≤ 148.896°), 2968 unique (R_{int} = 0.0304, R_{sigma} = 0.0191) which were used in all calculations. The final R_1 was 0.0249 (I > 2σ(I),) and wR_2 was 0.0621 (all data). The crystallographic details of the compound (exp_1115-IK-AP-3Cl-bn, *S*-isomer) are deposited to the Cambridge Crystallographic

(CCDC 2176250). The ORTEP diagram as the crystal structure of (exp_1115-IK-AP-3Cl-bn, *S*-isomer) is illustrated in Figure 4.3. The molecule has one chiral center (C12 – *S*).

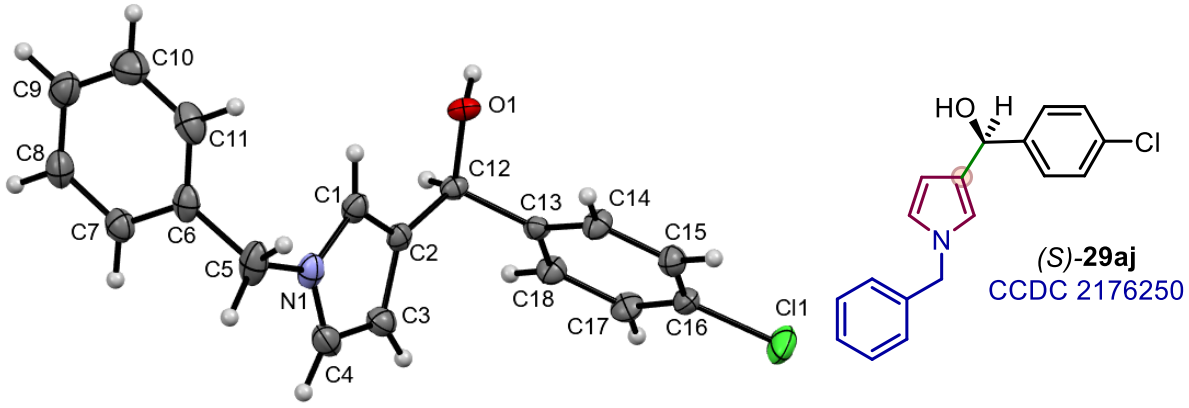


Figure 4.3. ORTEP diagram of compound **29aj** (exp_1115-IK-AP-3Cl-bn, *S*-isomer). The thermal ellipsoids are drawn at the 50 % probability level. (**CCDC 2176250**).

Table 4.6: Crystal data and structure refinement for exp_IK-AP-3Cl-Bn (29aj).

Identification code	exp_IK-AP-3Cl-Bn
Empirical formula	$C_{18}H_{16}ClNO$
Formula weight	297.77
Temperature/K	123(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	4.65680(10)
b/Å	11.98330(10)
c/Å	26.5172(3)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1479.76(4)
Z	4

ρ_{calc}g/cm^3	1.337
μ/mm^{-1}	2.256
F(000)	624.0
Crystal size/mm^3	0.27 × 0.1 × 0.08
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	8.096 to 148.896
Index ranges	$-3 \leq h \leq 5$, $-14 \leq k \leq 14$, $-33 \leq l \leq 32$
Reflections collected	14685
Independent reflections	2968 [R_{int} = 0.0304, R_{sigma} = 0.0191]
Data/restraints/parameters	2968/0/191
Goodness-of-fit on F^2	1.077
Final R indexes [I>=2σ (I)]	R_1 = 0.0249, wR_2 = 0.0619
Final R indexes [all data]	R_1 = 0.0251, wR_2 = 0.0621
Largest diff. peak/hole / e Å^{-3}	0.13/-0.19
Flack parameter	0.002(5)

Refinement model description

Number of restraints - 0, number of constraints - unknown.

Details:

```
1. Fixed Uiso
 At 1.2 times of:
  All C(H) groups, All C(H,H) groups
 At 1.5 times of:
  All O(H) groups
2.a Ternary CH refined with riding coordinates:
 C12(H12)
2.b Secondary CH2 refined with riding coordinates:
 C5(H5A,H5B)
2.c Aromatic/amide H refined with riding coordinates:
 C1(H1A), C3(H3), C4(H4), C7(H7), C8(H8), C9(H9), C10(H10),
```

C11(H11), C14(H14),
C15(H15), C17(H17), C18(H18)
2.d Idealised tetrahedral OH refined as a rotating group:
O1(H1)

4.7.2 Single Crystal structure, Cell parameters, and structure data of compound (29ld) (exp_1114-IK-AP-NO_2-ANI), *S*-isomer) (CCDC 2176248): The single crystal of compound **(**(exp_1114-IK-AP-NO_2-ANI), *S*-isomer**),** $C_{17}H_{14}N_2O_3$, obtained from chloroform: hexane solvent mixture as colorless blocks. The compound crystallized in an orthorhombic system, $P2_12_12_1$ space group with the following crystal data parameters, **Crystal Data** for $C_{17}H_{14}N_2O_3$ (M =294.30 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 5.57000(10) Å, b = 7.41440(10) Å, c = 33.2373(4) Å, V = 1372.64(3) Å^3, Z = 4, T = 123(2) K, μ(Cu Kα) = 0.815 mm^{-1}, *Dcalc* = 1.424 g/cm^3, 15993 reflections measured (10.646° ≤ 2Θ ≤ 148.684°), 2748 unique (R_{int} = 0.0446, R_{sigma} = 0.0263) which were used in all calculations. The final R_1 was 0.0299 (I > 2σ(I)), and wR_2 was 0.0762 (all data). The crystallographic details of the compound **(**(exp_1114-IK-AP-NO2-ANI), (*S*-isomer**)** are deposited to the Cambridge Crystallographic (CCDC 2176248). The ORTEP diagram as crystaz9l structure of **[**exp_1104-IK-AP-NO2-ANI**]** is illustrated in Figure 4.4. The molecule has one chiral center (C11 – *S*).

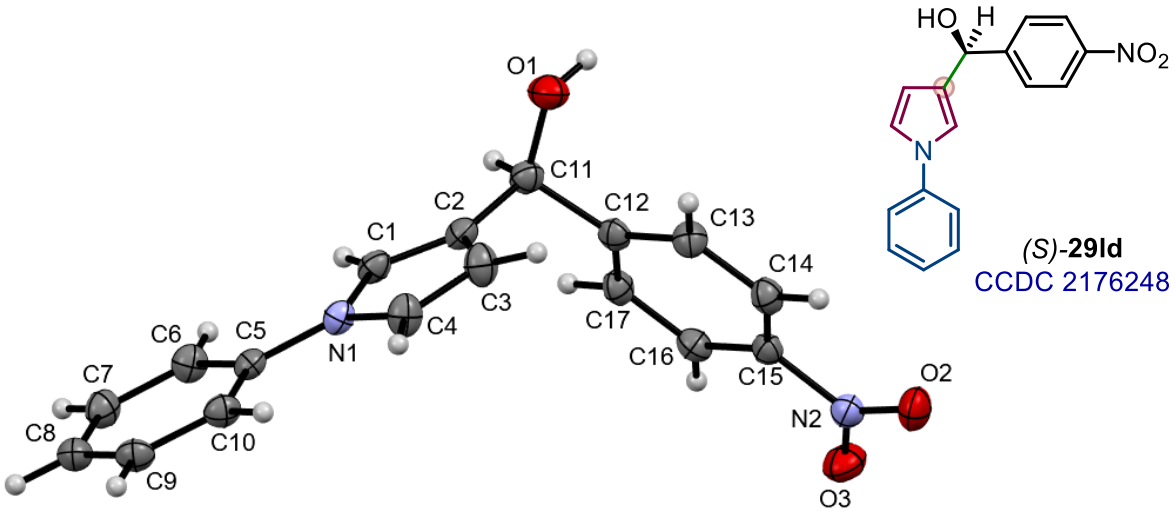


Figure 4.4. ORTEP diagram of compound **29ld** (exp_1114-IK-AP-NO_2_Repeat, *S*-isomer). The thermal ellipsoids are drawn at the 50 % probability level (**CCDC 2176248**). Flack parameter -0.05(10).

Table 4.7: Crystal data and structure refinement for exp_1114-IK-AP-NO_2-REPEAT (35ld).

Identification code	exp_1114-IK-AP-NO2-REPEAT
Empirical formula	$C_{17}H_{14}N_2O_3$
Formula weight	294.30
Temperature/K	123(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	5.57000(10)
b/Å	7.41440(10)
c/Å	33.2373(4)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1372.64(3)
Z	4
ρ_{calc}g/cm^3	1.424
μ/mm^{-1}	0.815
F(000)	616.0
Crystal size/mm^3	0.15 × 0.05 × 0.05
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	10.646 to 148.684
Index ranges	$-6 \leq h \leq 6$, $-9 \leq k \leq 9$, $-41 \leq l \leq 40$
Reflections collected	15993
Independent reflections	2748 [R_{int} = 0.0446, R_{sigma} = 0.0263]

Data/restraints/parameters	2748/0/200
Goodness-of-fit on F^2	1.048
Final R indexes [I>=2σ (I)]	R_1 = 0.0299, wR_2 = 0.0754
Final R indexes [all data]	R_1 = 0.0309, wR_2 = 0.0762
Largest diff. peak/hole / e $Å^{-3}$	0.18/-0.19
Flack parameter	-0.05(10)

Refinement model description

Number of restraints - 0, number of constraints - unknown.

Details:

```
1. Fixed Uiso
 At 1.2 times of:
  All C(H) groups
 At 1.5 times of:
  All O(H) groups
2.a Ternary CH refined with riding coordinates:
 C11(H11)
2.b Aromatic/amide H refined with riding coordinates:
 C1(H1A), C4(H4), C10(H10), C7(H7), C14(H14), C17(H17), C9(H9),
C16(H16),
 C13(H13), C6(H6), C8(H8), C3(H3)
2.c Idealised tetrahedral OH refined as a rotating group:
 O1(H1)
```

4.7.3 Single Crystal structure, Cell parameters, and structure data of compound (*ent*-29ld) (exp_1104-IK-AP-NO_2-ANI, *R*-isomer) (CCDC 2176245):

The single crystal of compound **(*ent*-29ld)** (exp_1104-IK-AP-NO_2-ANI), R-isomer**),** $C_{17}H_{14}N_2O_3$, obtained from the chloroform-hexane mixture as colorless blocks. The compound crystallized in an orthorhombic system, $P2_12_12_1$ space group with the following crystal data parameters, **Crystal Data** for $C_{17}H_{14}N_2O_3$ (M =294.30 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 5.57240(10) Å, b = 7.41840(10) Å, c = 33.2232(6) Å, V = 1373.39(4) $Å^3$, Z = 4, T = 123(2) K, μ(Cu Kα) = 0.814 mm^{-1}, *Dcalc* = 1.423 g/cm^3, 6612

reflections measured (10.652° ≤ 2Θ ≤ 159.71°), 2868 unique (R_{int} = 0.0256, R_{sigma} = 0.0328) which were used in all calculations. The final R_1 was 0.0375 (I > 2σ(I)), and wR_2 was 0.0963 (all data). The crystallographic details of the compound (exp_1104-IK-AP-NO2-ANI, *R*-isomer**)** are deposited to the Cambridge Crystallographic (CCDC 2176245). The ORTEP diagram as the crystal structure of compound **[**exp_1104-IK-AP-NO2-ANI**]** is illustrated in Figure 4.5. The molecule has one chiral center (C11 – *R*).

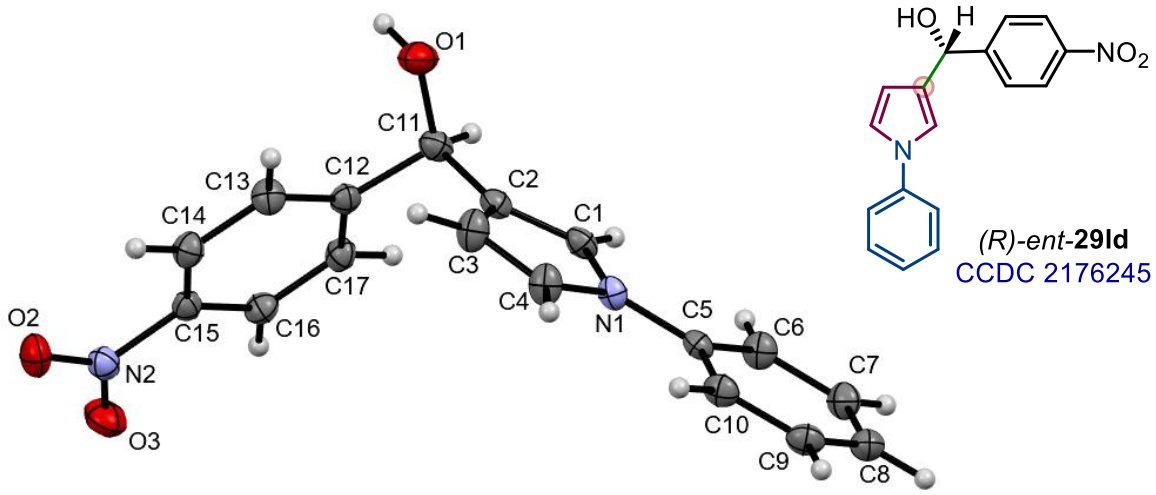


Figure 4.5. ORTEP diagram of compound (***ent*-29ld**) (exp_1104-IK-AP-NO_2-ANI, *R*-isomer). The thermal ellipsoids are drawn at the 50 % probability level (**CCDC 2176245**). Flack parameter -0.23(14).

Table 4.8: Crystal data and structure refinement for exp_1104_AK-AP-NO_2-ANI (*ent*-29ld).

Identification code	exp_1104_AK-AP-NO_2-ANI
Empirical formula	$C_{17}H_{14}N_2O_3$
Formula weight	294.30
Temperature/K	123(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$

a/Å	5.57240(10)
b/Å	7.41840(10)
c/Å	33.2232(6)
α/°	90
β/°	90
γ/°	90
Volume/$Å^3$	1373.39(4)
Z	4
$\rho_{calc}g/cm^3$	1.423
μ/mm^{-1}	0.814
F(000)	616.0
Crystal size/mm^3	0.16 × 0.08 × 0.05
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	10.652 to 159.71
Index ranges	$-6 \leq h \leq 4$, $-9 \leq k \leq 9$, $-41 \leq l \leq 42$
Reflections collected	6612
Independent reflections	2868 [R_{int} = 0.0256, R_{sigma} = 0.0328]
Data/restraints/parameters	2868/0/200
Goodness-of-fit on F^2	1.058
Final R indexes [I>=2σ (I)]	R_1 = 0.0375, wR_2 = 0.0956
Final R indexes [all data]	R_1 = 0.0386, wR_2 = 0.0963
Largest diff. peak/hole / e $Å^{-3}$	0.31/-0.21
Flack parameter	-0.23(14)

Refinement model description

Number of restraints - 0, number of constraints - unknown.

Details:

```
1.                  Fixed                  Uiso
 At          1.2           times           of:
  All                C(H)                groups
```

At 1.5 times of: All O(H) groups
2.a Ternary CH refined with riding coordinates: C11(H11)
2.b Aromatic/amide H refined with riding coordinates: C1(H1A), C10(H10), C14(H14), C4(H4), C7(H7), C17(H17), C16(H16), C6(H6), C13(H13), C9(H9), C8(H8), C3(H3)
2.c Idealised tetrahedral OH refined as a rotating group: O1(H1)

4.7.4 Single Crystal structure, Cell parameters and structure data of compound (29od) (exp_1129-IK-AP-NO_2-NAP-2, *S*-isomer) (CCDC 2176261):

The single crystals of compound (**29od**) $C_{17}H_{13}ClN_2O_3$ (exp_1129-IK-AP-NO_2-NAP-2, *S*-isomer) were obtained as a colorless block through slow evaporation of this compound in $CHCl_3$:Hexane solvent mixture. The compound crystallized in a tetragonal crystal system and $P4_32_12$ space group with following unit cell parameters, $C_{17}H_{13}ClN_2O_3$ (M =328.74 g/mol): tetragonal, space group $P4_32_12$ (no. 96), a = 7.09790(10) Å, c = 58.9621(14) Å, V = 2970.52(11) $Å^3$, Z = 8, T = 123(2) K, μ(Cu Kα) = 2.433 mm^{-1}, *Dcalc* = 1.470 g/cm^3, 8359 reflections measured (5.996° ≤ 2Θ ≤ 159.39°), 3121 unique (R_{int} = 0.0441, R_{sigma} = 0.0400) which were used in all calculations. The final R_1 was 0.0728 (I > 2σ(I)), and wR_2 was 0.1763 (all data). The crystallographic details of the compound (exp_1129-IK-AP-NO2-NAP-2, *S*-isomer) are deposited to the Cambridge Crystallographic (CCDC 2176261). The ORTEP diagram as the crystal structure of (exp_1129-IK-AP-NO2-NAP-2, *S*-isomer) is illustrated in Figure 4.6. The molecule has one chiral center (C11– *S*).

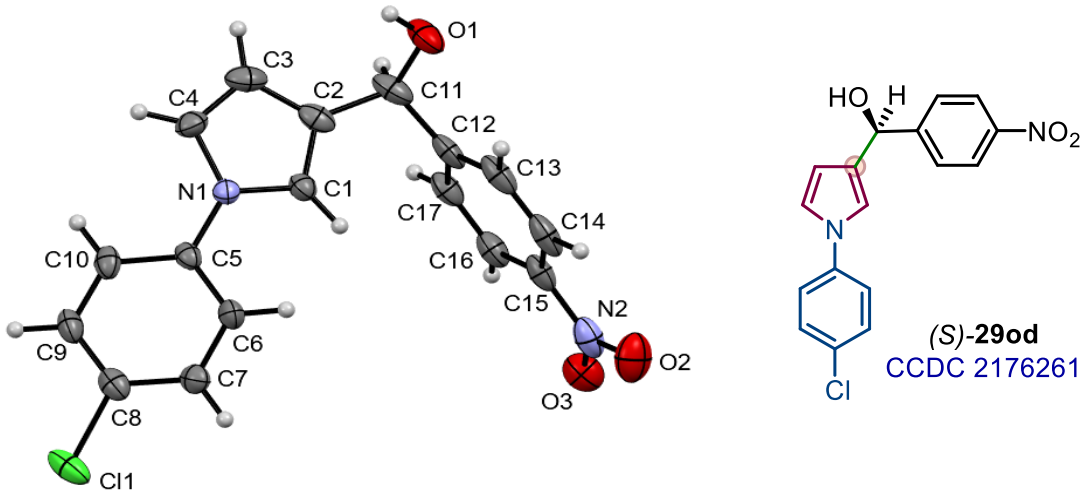


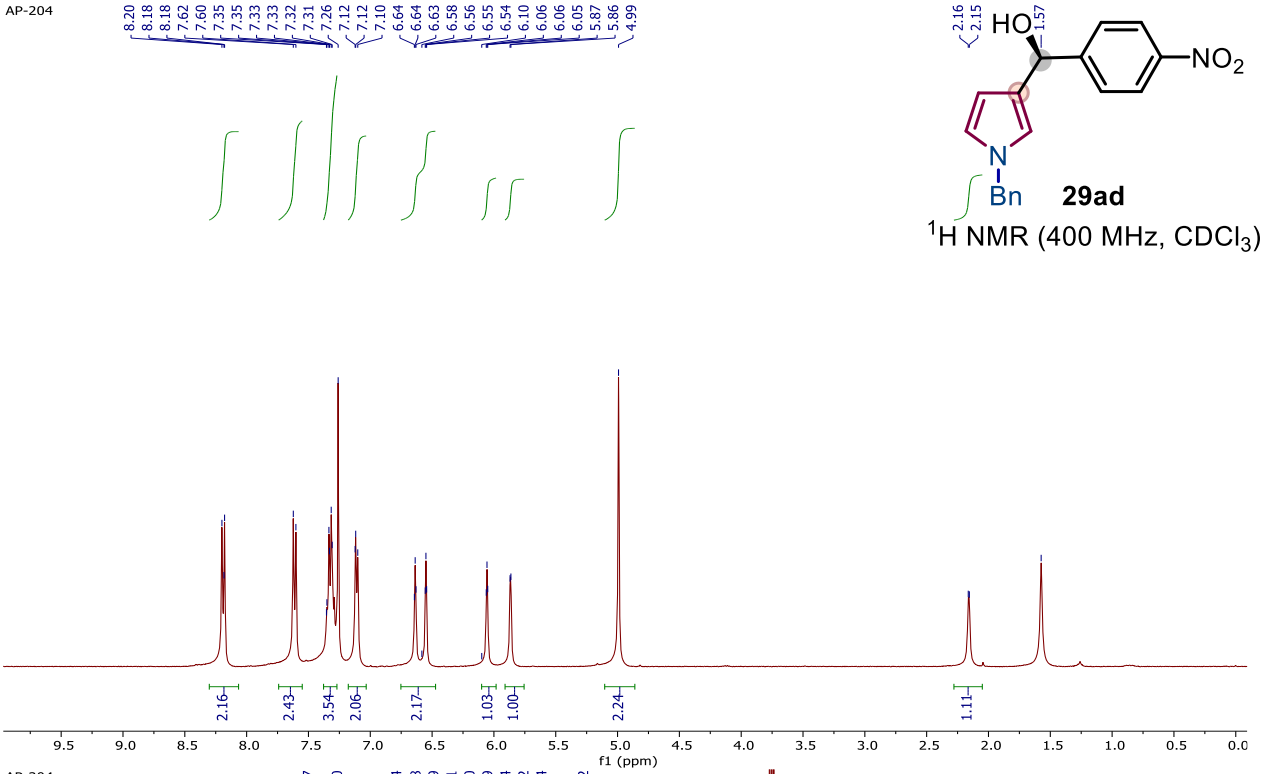
Figure 4.6. ORTEP diagram of compound **29od** (**exp_1129-IK-AP-NO$_2$-NAP-2**), S-isomer. The thermal ellipsoids are drawn at a 40 % probability level (**CCDC 2176261**). Flack parameter -0.14(5).

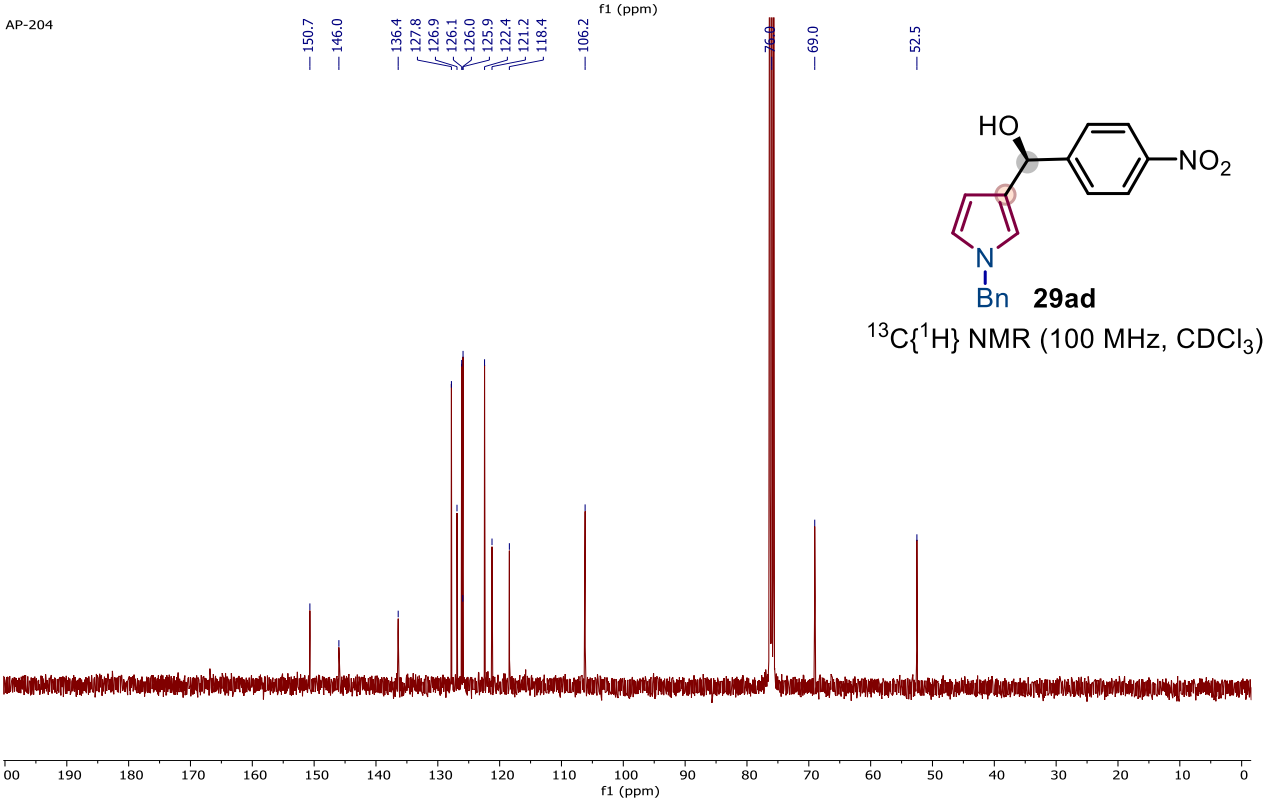
Table 4.9: Crystal data and structure refinement for exp_1129_IK-AP-NO2-NAP-2 (29od).

Identification code	exp_1129_IK-AP-NO2-NAP-2
Empirical formula	$C_{17}H_{13}ClN_2O_3$
Formula weight	328.74
Temperature/K	123(2)
Crystal system	tetragonal
Space group	$P4_32_12$
a/Å	7.09790(10)
b/Å	7.09790(10)
c/Å	58.9621(14)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2970.52(11)

Z	8
ρ_{calc}g/cm^3	1.470
μ/mm^{-1}	2.433
F(000)	1360.0
Crystal size/mm^3	0.17 × 0.13 × 0.06
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	5.996 to 159.39
Index ranges	$-8 \leq h \leq 7$, $-7 \leq k \leq 7$, $-36 \leq l \leq 73$
Reflections collected	8359
Independent reflections	3121 [R_{int} = 0.0441, R_{sigma} = 0.0400]
Data/restraints/parameters	3121/0/209
Goodness-of-fit on F^2	1.061
Final R indexes [I>=2σ (I)]	R_1 = 0.0728, wR_2 = 0.1748
Final R indexes [all data]	R_1 = 0.0754, wR_2 = 0.1763
Largest diff. peak/hole / e Å^{-3}	0.34/-0.28
Flack parameter	-0.14(5)

4.8. Spectral Information

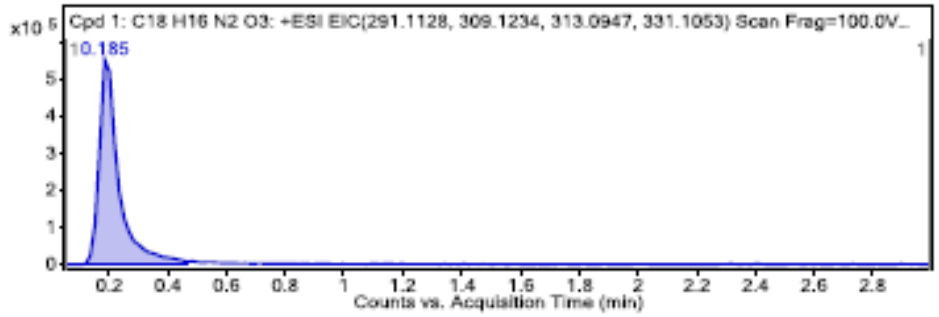




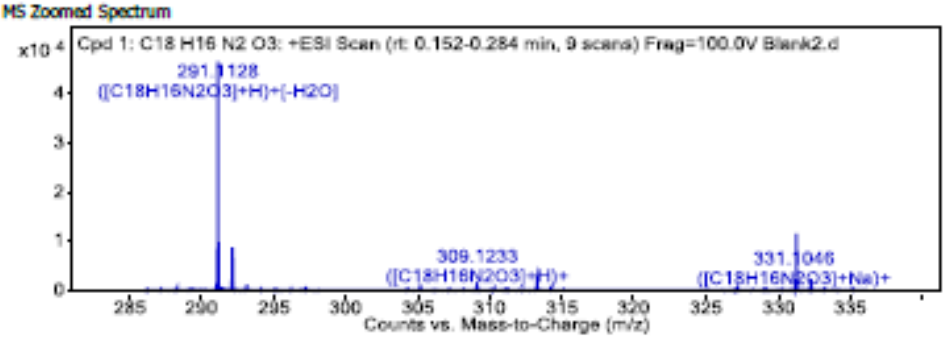
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C18 H16 N2 O3	0.185	308.1159	46792	C18 H16 N2 O3	308.1161	-0.59

Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C18 H16 N2 O3	291.1128	0.185	Find By Formula	308.1159

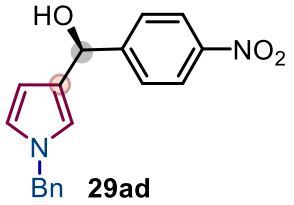


MS Zoomed Spectrum



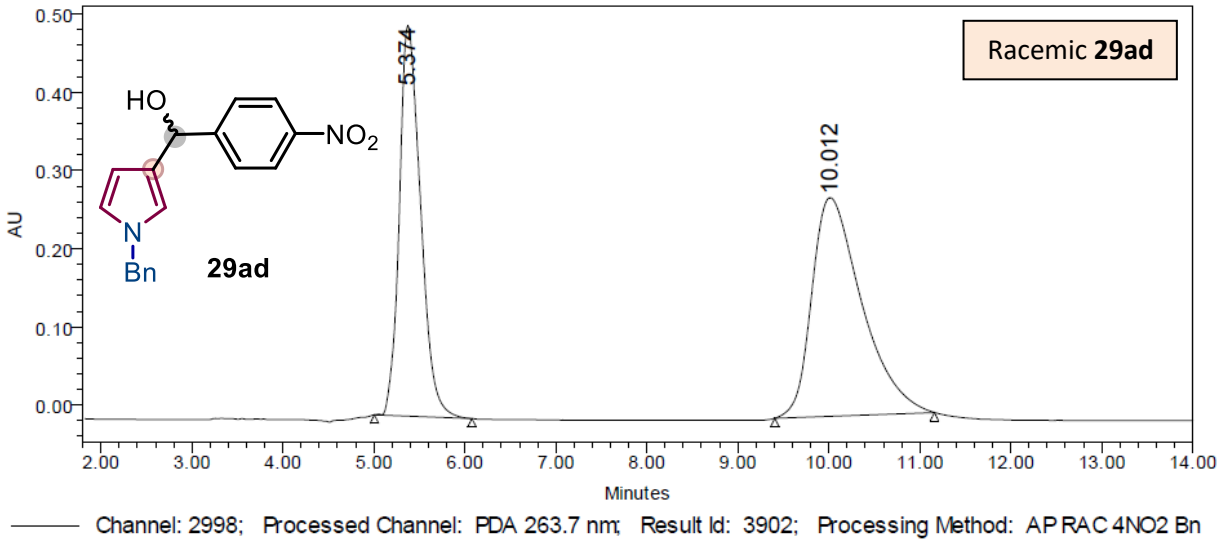
MS Spectrum Peak List

m/z	*Calc m/z*	Diff(ppm)	z	Abund	Formula	Ion
291.1128	291.1128	0.08	1	46792.4	C18H16N2O3	(M+H)+[-H2O]
292.1152	292.116	2.52	1	8719.62	C18H16N2O3	(M+H)+[-H2O]
293.116	293.1188	9.31	1	1188.63	C18H16N2O3	(M+H)+[-H2O]
309.1233	309.1234	0.28	1	526.52	C18H16N2O3	(M+H)+
310.1292	310.1265	-8.45	1	162.51	C18H16N2O3	(M+H)+
331.1046	331.1053	2.19	1	76.64	C18H16N2O3	(M+Na)+



29ad

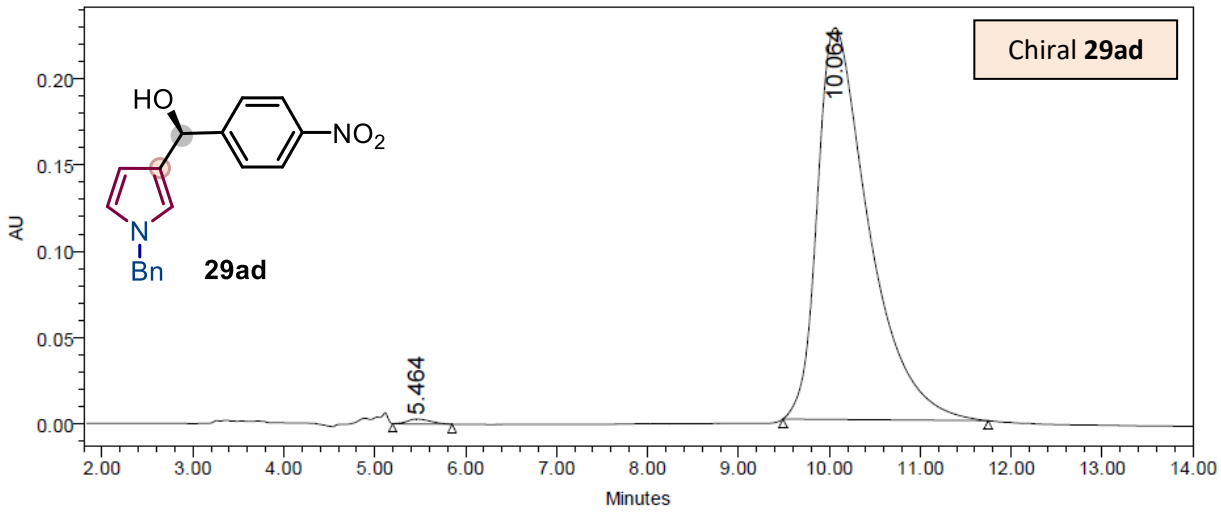
$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)



Channel: 2998; Processed Channel: PDA 263.7 nm; Result Id: 3902; Processing Method: AP RAC 4NO2 Bn

Processed Channel Descr.: PDA 263.7 nm

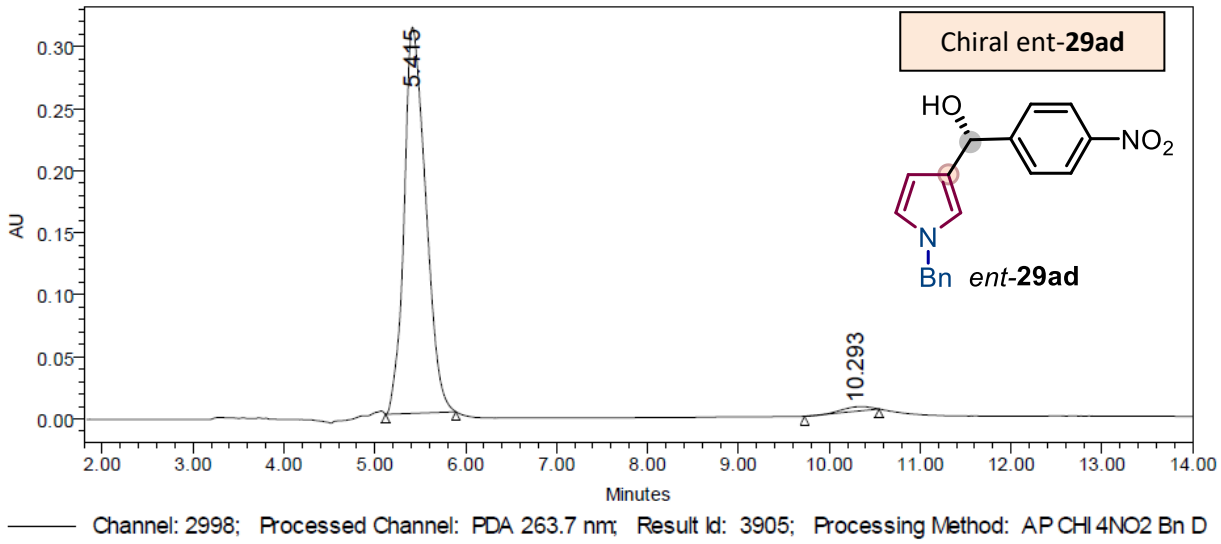
	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 263.7 nm	5.374	8106316	43.20	498937
2	PDA 263.7 nm	10.012	10658282	56.80	279445



Channel: 2998; Processed Channel: PDA 263.3 nm; Result Id: 3908; Processing Method: AP CHI 4NO2 Bn L

Processed Channel Descr.: PDA 263.3 nm

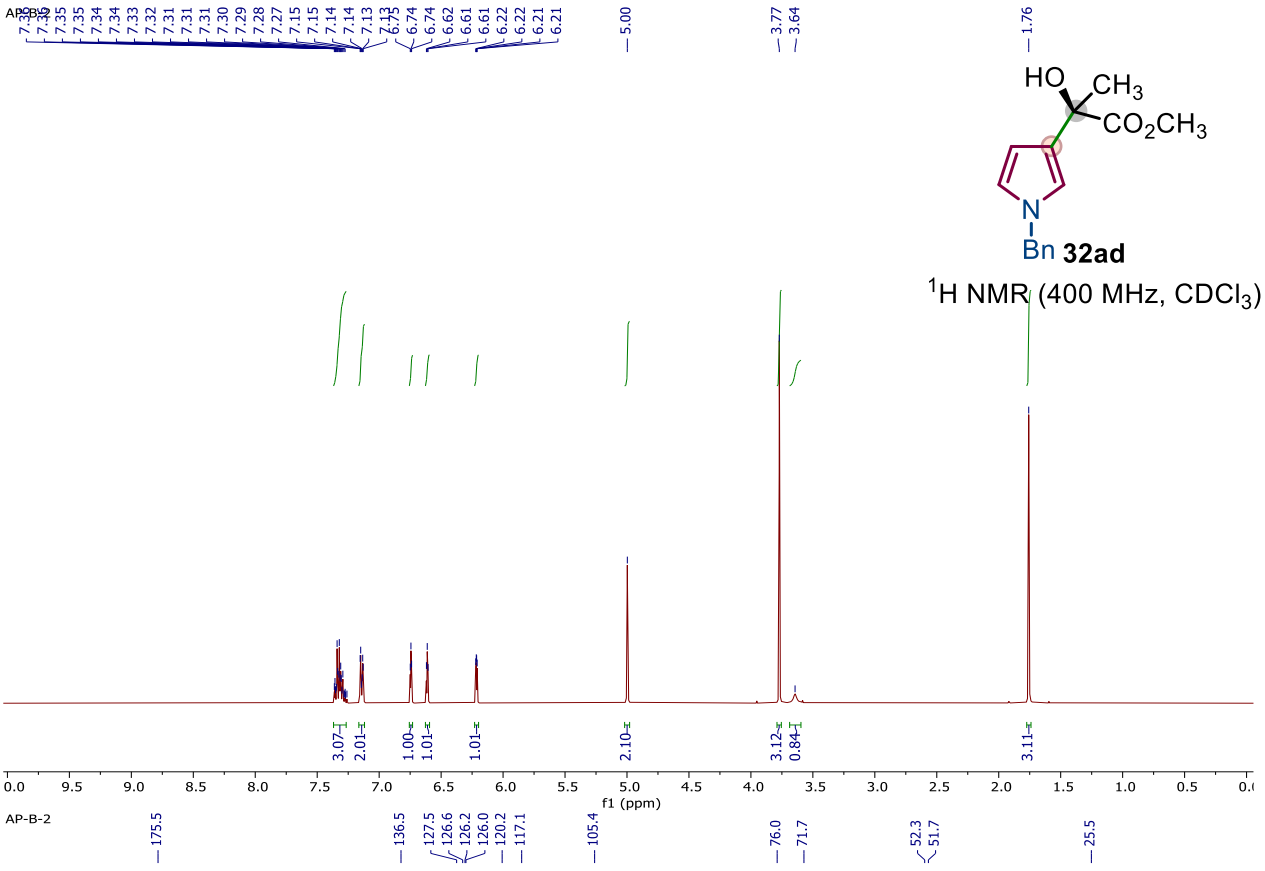
	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 263.3 nm	5.464	48729	0.54	2791
2	PDA 263.3 nm	10.064	8953315	99.46	227051



Channel: 2998; Processed Channel: PDA 263.7 nm; Result Id: 3905; Processing Method: AP CHI 4NO2 Bn D

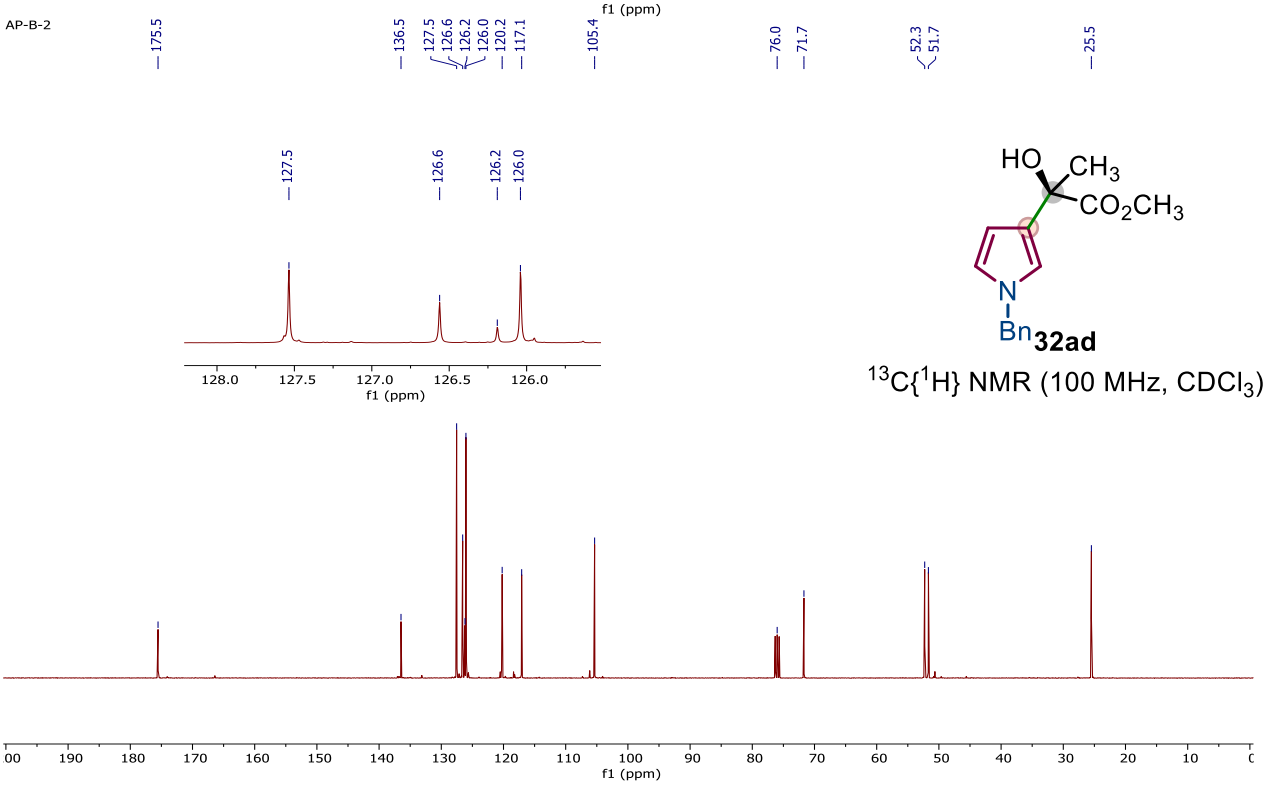
Processed Channel Descr.: PDA 263.7 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 263.7 nm	5.415	5147919	98.51	311350
2	PDA 263.7 nm	10.293	77913	1.49	3620



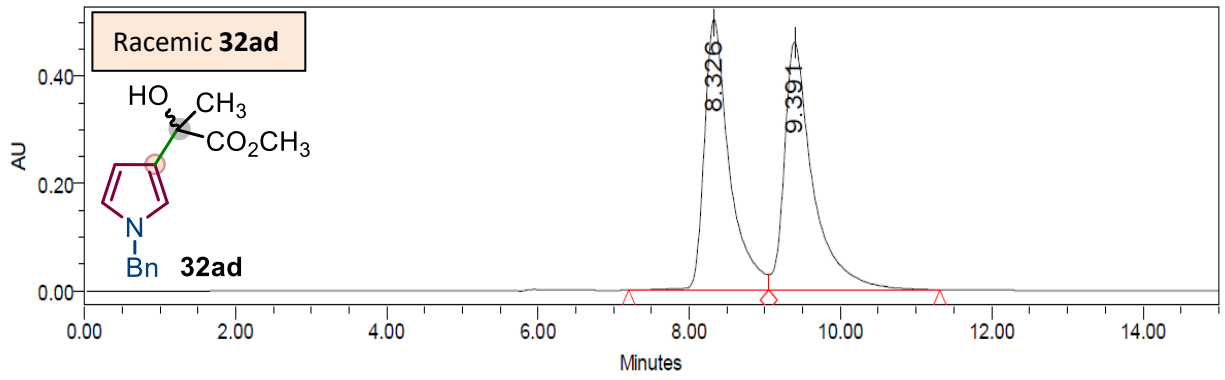
32ad

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



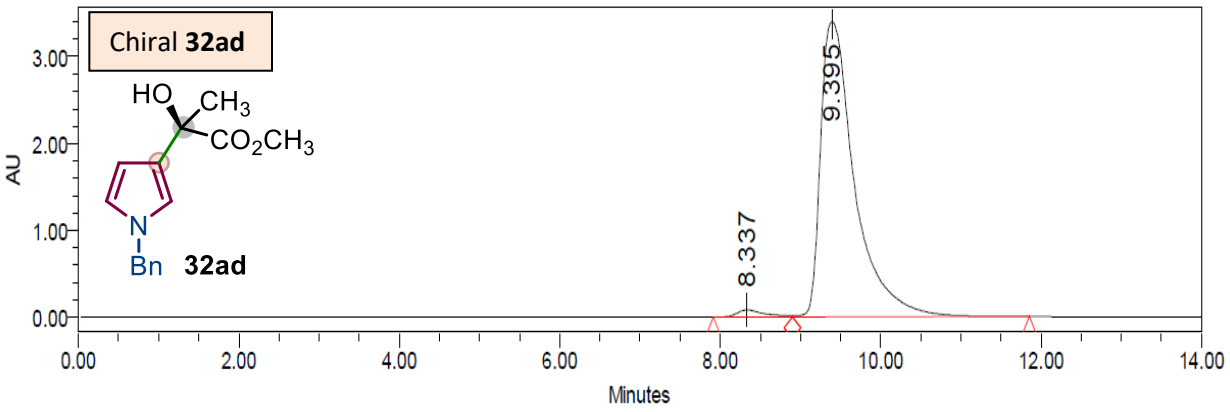
32ad

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)



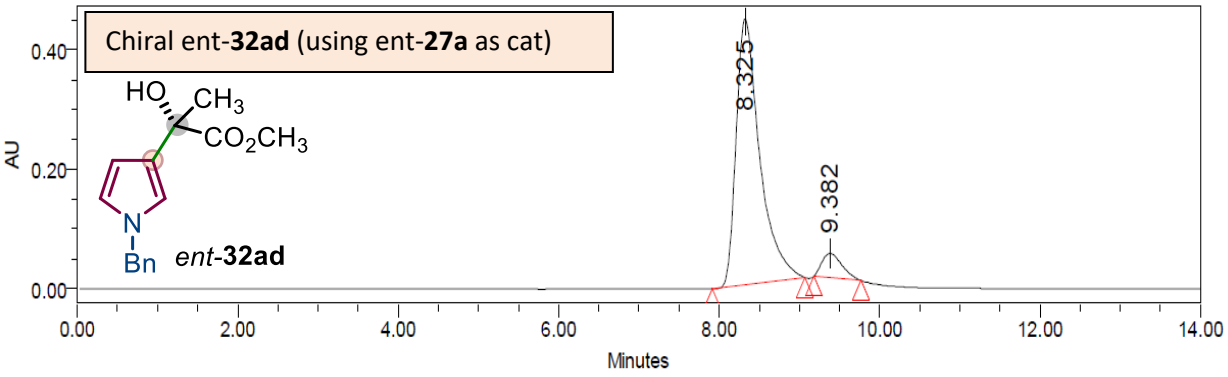
Peak Results

	SampleName	Processed Channel Descr.	RT	Area	% Area	Height
1	Rac 7aa	2998 PDA 299.3 nm (2998 (200-400)nm)	8.326	11620116	48.96	502728
2	Rac 7aa	2998 PDA 299.3 nm (2998 (200-400)nm)	9.391	12113154	51.04	462298



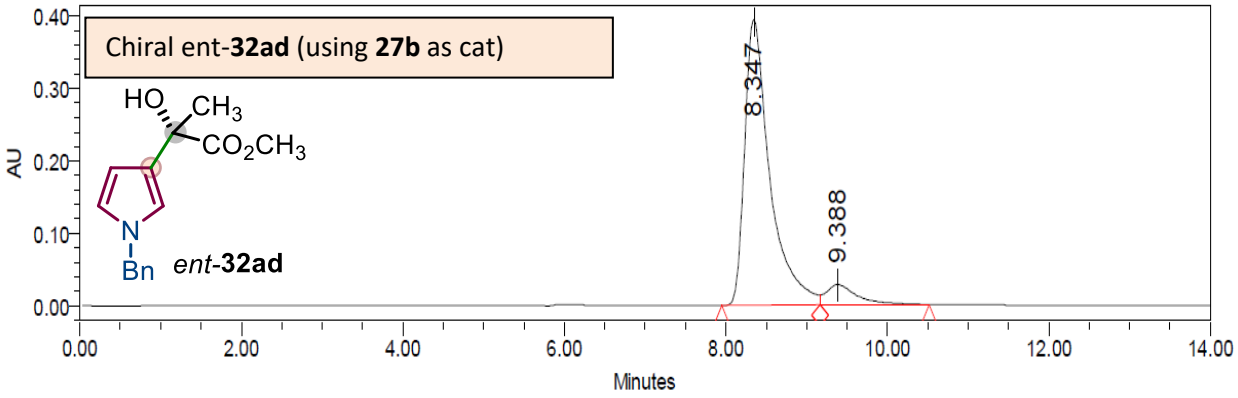
Peak Results

	SampleName	Processed Channel Descr.	RT	Area	% Area	Height
1	Chi 7aa L-pro	2998 PDA 299.0 nm (2998 (200-400)nm)	8.337	1806580	1.77	78358
2	Chi 7aa L-pro	2998 PDA 299.0 nm (2998 (200-400)nm)	9.395	100089473	98.23	3402752



Peak Results

	SampleName	Processed Channel Descr.	RT	Area	% Area	Height
1	Chi 7aa ent D-pro	2998 PDA 299.0 nm (2998 (200-400)nm)	8.325	9098913	92.86	445653
2	Chi 7aa ent D-pro	2998 PDA 299.0 nm (2998 (200-400)nm)	9.382	699953	7.14	40681



Peak Results

	SampleName	Processed Channel Descr.	RT	Area	% Area	Height
1	Chi 7aa J-H	2998 PDA 299.0 nm (2998 (200-400)nm)	8.347	8558605	91.89	394419
2	Chi 7aa J-H	2998 PDA 299.0 nm (2998 (200-400)nm)	9.388	755678	8.11	28169

4.9 References

[1] (a) Jacquot, D. E. N.; Lindel, T. *Curr. Org. Chem*., **2005**, *9*, 1551. (b) Walsh, C. T.; Garneau-Tsodikova, S.; Howard-Jones, A. R. *Nat. Prod. Rep*. **2006**, *23*, 517. (c) Rane, R.; Sahu, N.; Shah, C.; Karpoormath, R. *Curr. Top. Med. Chem*. **2014**, *14*, 253.

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Chapter – 5

Catalyst-free Direct Synthesis of C3-Arylated/Alkenylated Pyrroles

5.1 Introduction

Pyrroles are widely distributed in bioactive natural products, synthetic, medicinal agents, and drug-like compounds among nitrogen-containing heterocycles.[1] The easy availability of suitably substituted and functionalized pyrrole derivatives is widespread. It is the critical structural fragment of many important bioactive molecules, such as pentabromopseudodiline and pioluteorine, isolated from bacterial sources that are prominent in marine natural products.[2] In that particular aryl pyrroles, Fludioxonil is a contact broad-spectrum fungicide structurally related to pyrrolnitrin.[3] Fused-nitrogen heterocycles are found in numerous natural products with engaging biological activities and broad applications.

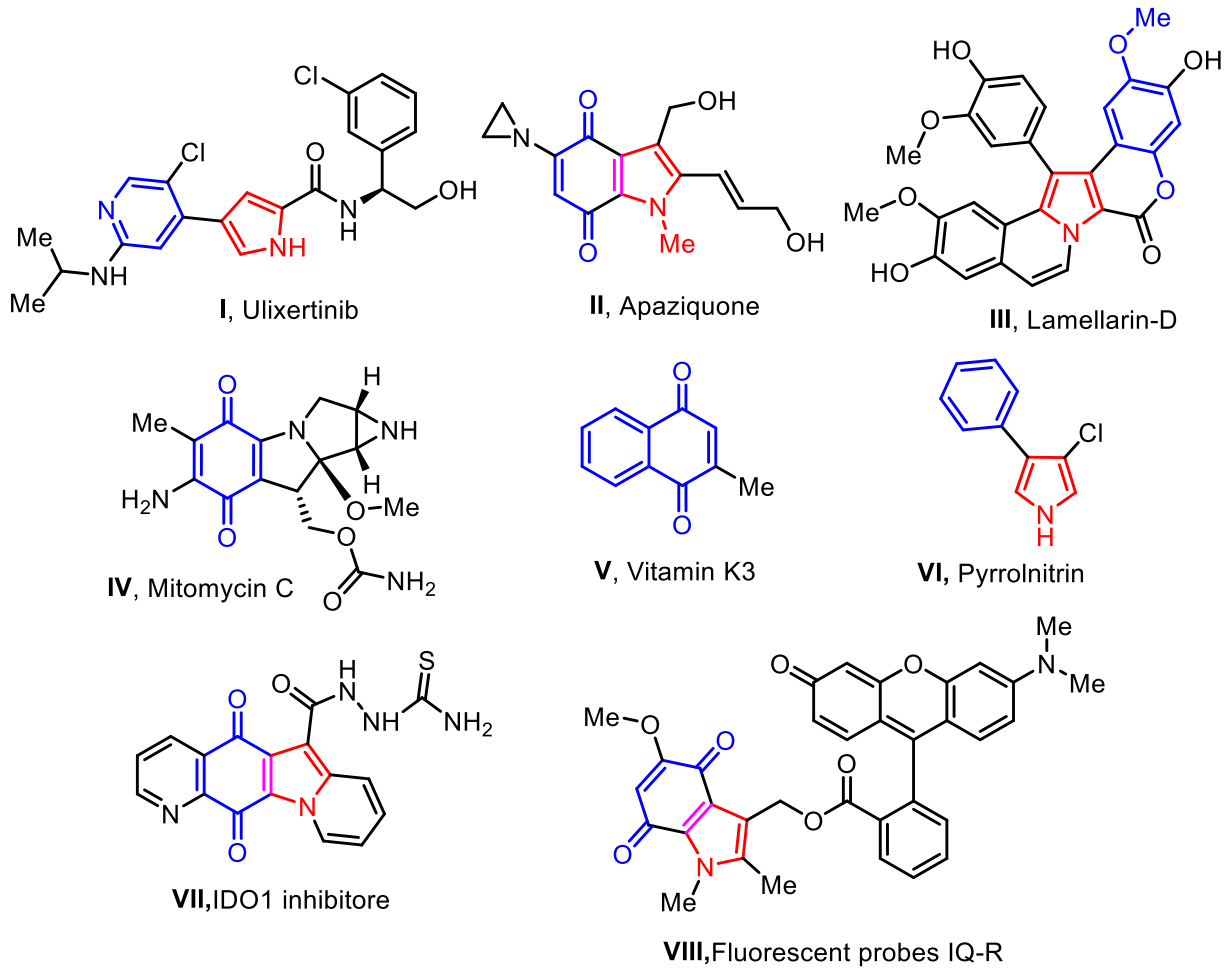


Figure 5.1 Selected pyrrole fused quinone and related derivatives.

1,4-Quinone motifs[4] were found in various biologically active natural compounds like Vitamin K-1,2,3 and Mitomycin C (Figure 5.1). Pyrrole and its derivatives are pharmacologically

necessary functional scaffolds with almost all pharmacological activities. This unit presents in various pharmacological agents of diverse therapeutic categories. The 1,4-quinone and pyrrole hybrid molecules,[5] such as Neolamellarin-A, show antitumor activity.[6] Novel hypoxia cancer cells sensitive fluorescent probes IQ-R and IDO-1 show good antibacterial and anticancer activities.[7] C3-heteroaromatic bonded pyrrole motif like Ulixertinib used to inhibit extracellular signal-regulated kinase (ERK) 1 and 2 in cancer treatment[8] and Lamellirin-D and pyrrolnitrin derivatives as an antifungal agent. Apaziquone, an indolequinone moiety act as a bioreductive prodrug, like older chemotherapeutic mitomycin-C.[9, 10]

5.2 General methods of arylation or alkenylation on pyrrole

After studying the existing literature, we found that *β*–Arylation/*β*–Olefination on pyrroles is challenging.[11] The C2-position of pyrrole is well explored, whereas the C3-position of pyrrole is less explored because of its more reactive site and stable resonating intermediate. The synthesis of C2-arylated[12a] and C2-alkenenated[12b] pyrrole is well known for using Metal catalyzed coupling reactions, nucleophilic aromatic substitution reactions,[13] free radical processes, which include various photolytic conditions, C-H activation, and using oxidant strategy.[14] To achieve the C3-Substitution on pyrrole, the nitrogen should be protected with electron-withdrawing or bulky groups.

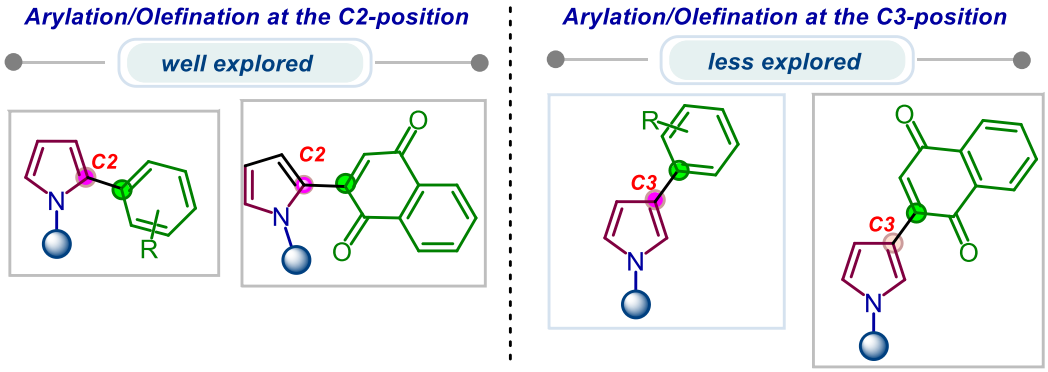
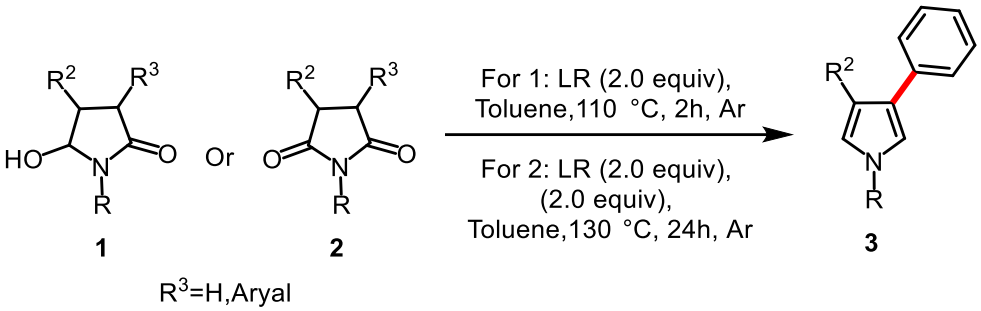


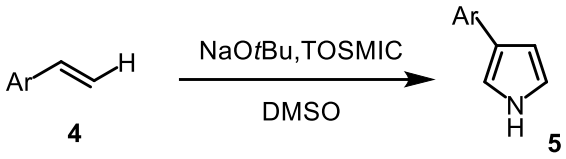
Figure 5.2 General methods of Arylation and Olefination.

Recently, a new method was developed using Lawesson's reagent to synthesize C3-arylated pyrroles **3** through deoxygenating γ-hydroxypyrrolidones **1** or succinimides **2** with good yields (Scheme 5.1).[15]



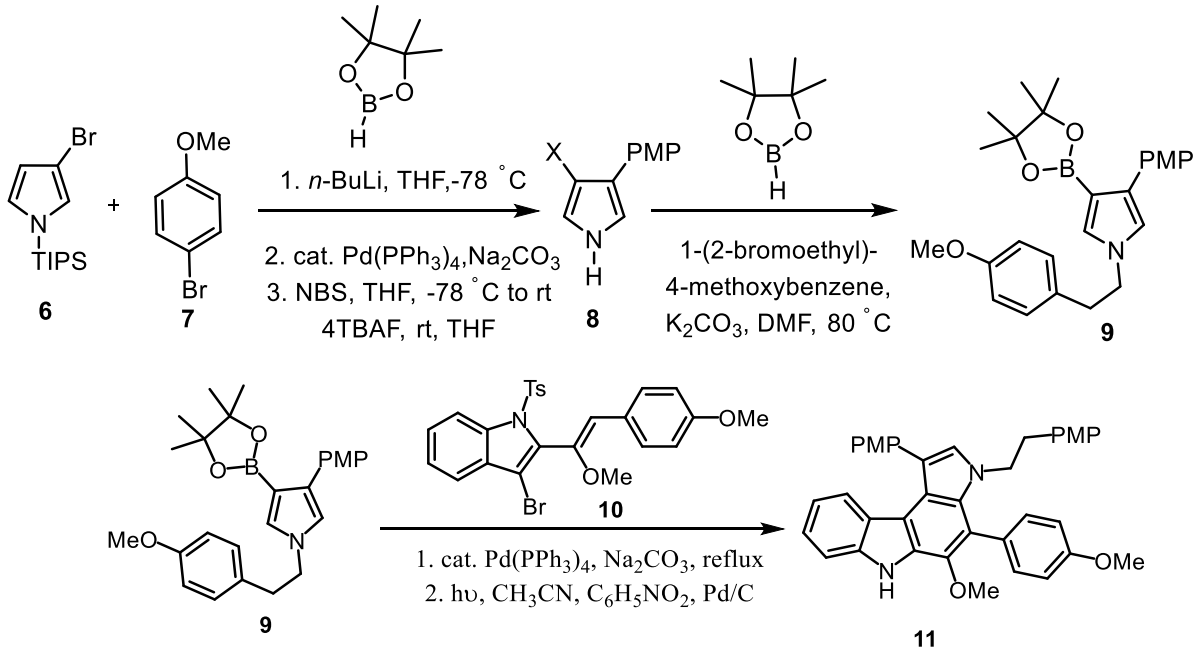
Scheme 5.1 Lawson's reagent-promoted synthesis of C3-aryl pyrroles.

In 2002, Smith and co-workers reported the utilization of vinyl arenes **4** with Leusen's TOSMIC ester reagent to synthesize free-NH 3-aryl pyrroles **5** (Scheme 5.2).[16]



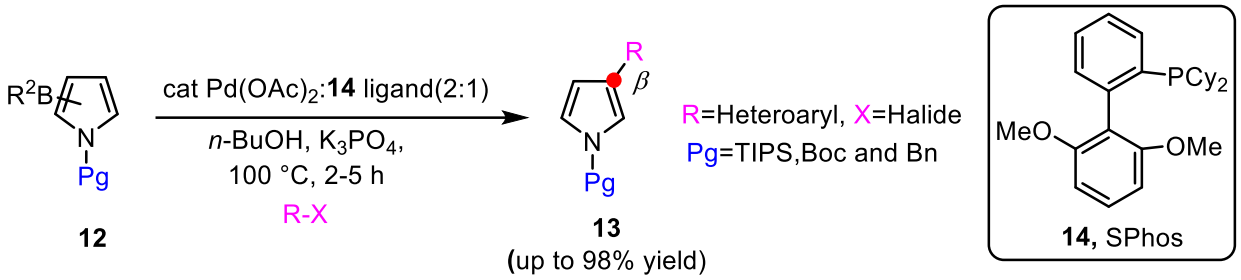
Scheme 5.2 Cross-coupling reaction to synthesis of *β*–aryl pyrroles.

In 2009, Mercedes and co-workers synthesized pyrrolo[2,3-*c*]carbazole **11**, the common core of the marine alkaloids known as the dictyodendrins. The sequence is based on a Suzuki cross-coupling reaction between the pyrrole fragment **9** and the indole fragment **10**, followed by tandem photochemical 6π-electrocyclization/aromatization (Scheme 5.3).[17]



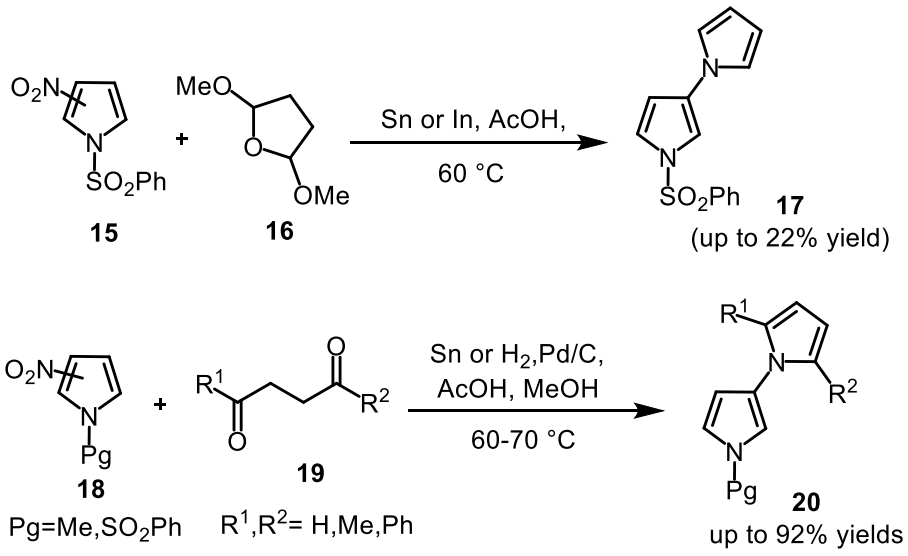
Scheme 5.3 Heck coupling reaction to synthesize pyrrolo[2,3-*c*]carbazole **11.**

In 2007, Buchwald and co-workers synthesized C3-substituted pyrroles **13** using palladium-catalyzed Suzuki-Miyaura cross-coupling between *N*-protected pyrrole boronate ester **12** and heteroaryl halides to furnish C3-functionalized pyrroles with excellent yields (Scheme 5.4).[18]



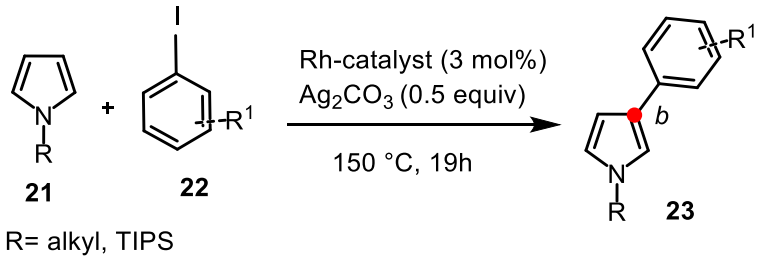
Scheme 5.4 Synthesis of C3-heteroaryl pyrroles using Suzuki-Miyaura coupling reaction.

Gribble and co-workers developed the synthesis of C3-heteroarylpyrrole **17** from 3-nitro-1-(phenylsulfonyl)pyrrole **15** through initial reduction followed by treatment with 2,5-dimethoxy tetrahydrofuran **16** in acetic acid at 60 °C as Paal-Knorr product. Similarly, exploring 1-methyl-3-nitropyrrole/3-nitro-1-(phenylsulfonyl)pyrrole **18** for in-situ reduction to amine followed by reaction with 1,4-dicarbonyl **19** under acidic conditions furnished the desired 1,3-bispyrrole **20** (Scheme 5.5).[19]



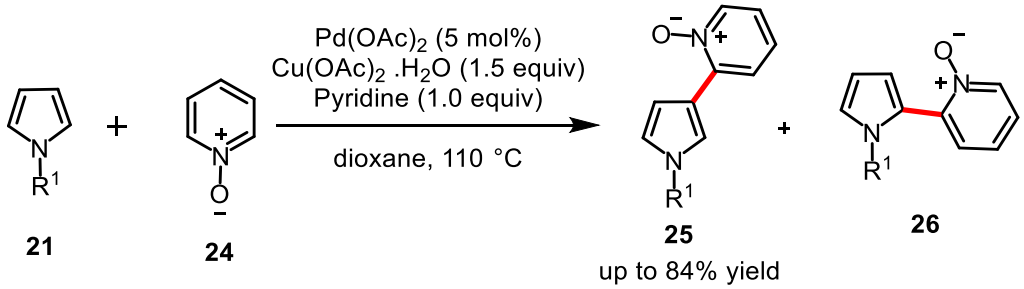
Scheme 5.5 Synthesis of 1,3-bispyrrole *via* Paal-Knorr method.

In 2014, Yamaguchi and co-workers developed the first general C3-selective C−H arylation of pyrroles **23** using a rhodium catalyst. *N*-substituted pyrrole **21** undergoes selective C−H arylation with various aromatic/heteroaromatic halides **22** in the presence of Rhodium (3 mol%) and base at 150 °C to furnish *β*-arylated pyrroles **23** (Scheme 5.6).[20]



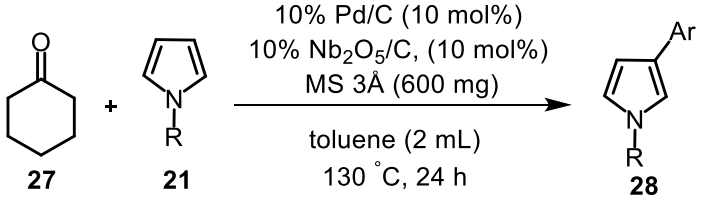
Scheme 5.6 Rh-catalyzed *β*−C−H activation of pyrrole.

In 2016, Tzschucke and co-workers developed a cross-dehydrogenative reaction between N-alkyl pyrrole **21** and pyridine *N*-oxides **24** using palladium (II) as a catalyst. Coupling at the *β*-position was facilitated by using $Cu(OAc)_2 \cdot H_2O$ as a co-catalyst and acts as the terminal oxidant to furnish C3-substituted pyrrole **25** (Scheme 5.7).[21]



Scheme 5.7 Pd- and Cu-catalyzed Cross-dehydrogenative coupling reaction.

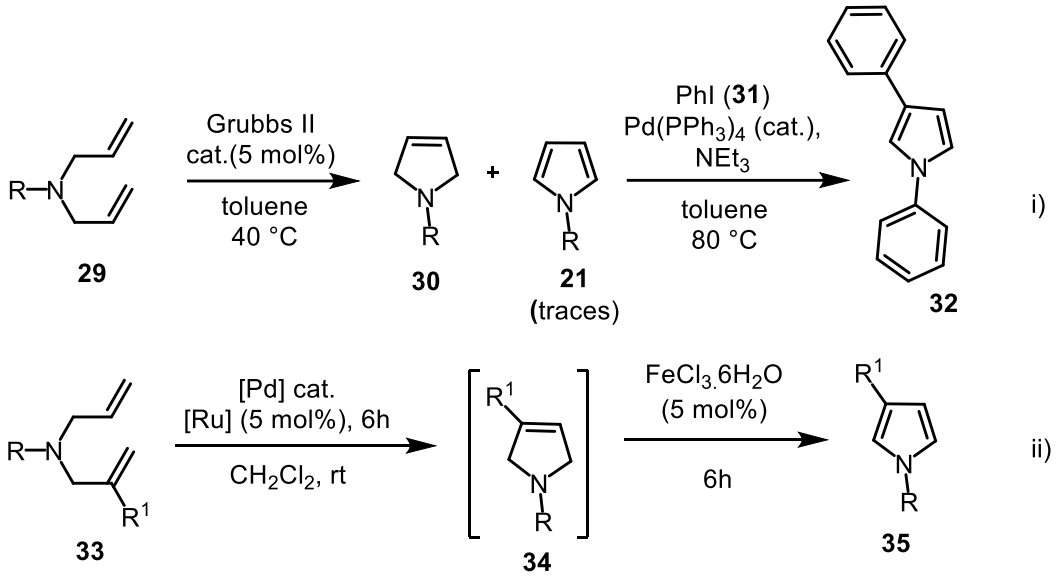
In 2020, Sawama and co-workers developed a method to furnish the regioselective aromatized pyrrole/indole to get C3-aromatic products. Pyrrole **21** reacted with cyclohexanone **27** in the presence of Pd/C to give C3-tethered-aromatic pyrrole, water, and hydrogen as by-products (Scheme 5.8).[22]



Scheme 5.8 Regioselective C3-aromatization on pyrrole.

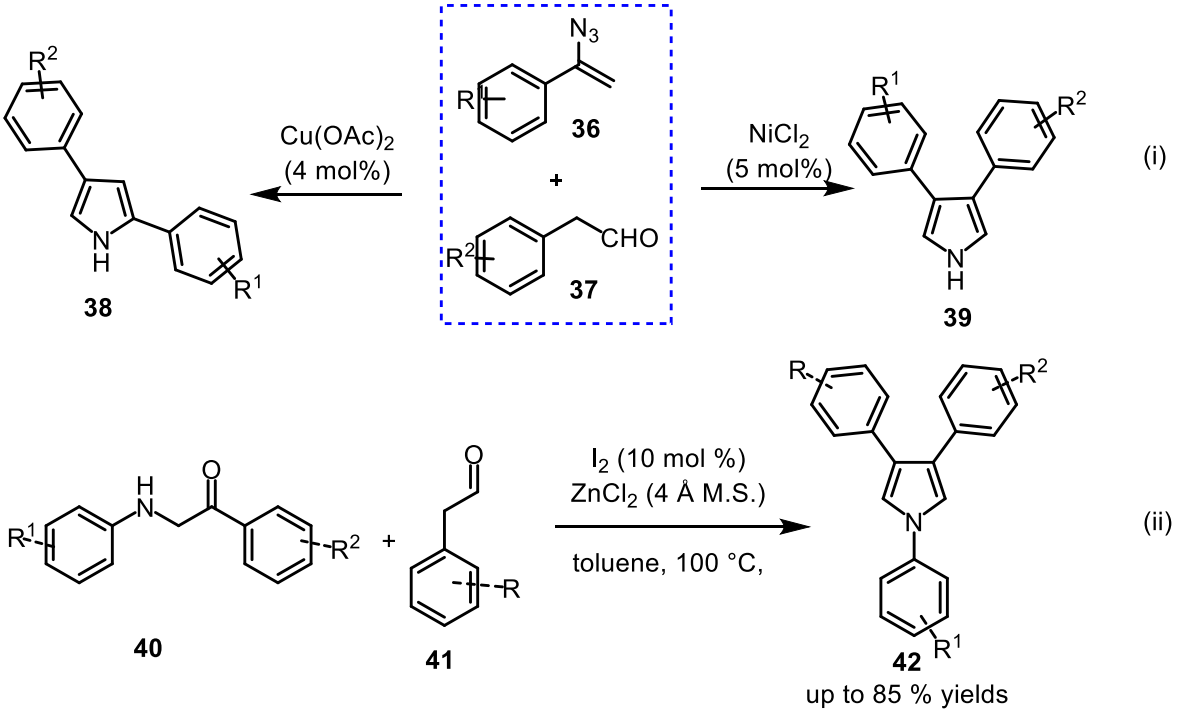
In 2011, Wirth and co-workers used micro flow techniques for the synthesis of 1,3-di-substituted pyrroles **32** followed by Ru-catalyzed ring-closing metathesis (Grubbs II as a catalyst (5 mol%)) and Pd-catalysed Heck coupling reaction (scheme 5.9 i). The pyrrole derivative was the only product observed in this reaction sequence.[23]

In 2016, Samec and co-workers developed a multistep and pot-economic route to give *β*-substituted pyrroles using amines and allylic alcohols. This method includes two steps, Pd catalyzed cross-coupling reaction followed by Ru-catalyzed ring-closing metathesis to obtain **34** as an intermediate and finally, aromatization to furnish C3-Substituted pyrrole **35** (Scheme 5.9 ii).[24]



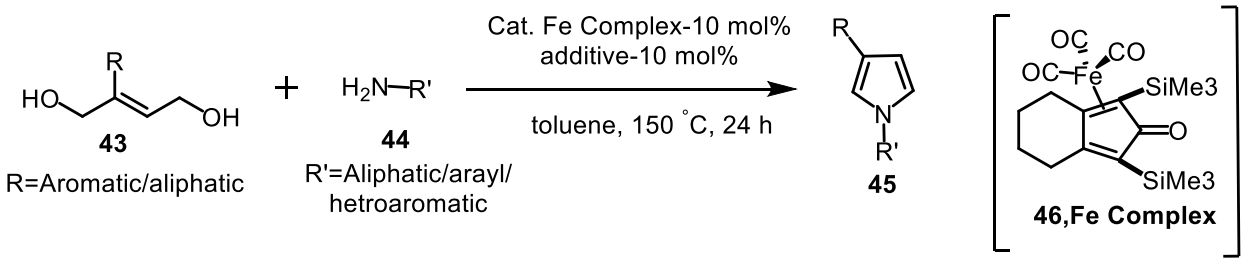
Scheme 5.9 Multistep synthesis of 1,3-di-substituted pyrrole using metathesis reaction.

In 2012, Ning Jiao and co-workers developed a method to synthesize 3,4-diaryl **38** and 3,4-diaryl **39** substituted pyrroles using vinyl azides **36** with aryl acetaldehydes **37** under copper or nickel-catalyzed condition (Scheme 5.10 i).[25] In 2014, a direct method was achieved for synthesizing 1,3,4-triarylpyrroles **42** through the cyclization of α-amino carbonyl compounds and aldehydes catalyzed by I_2. Various substituted groups can be employed, with moderate to good yields (Scheme 5.10 ii).[26-28]



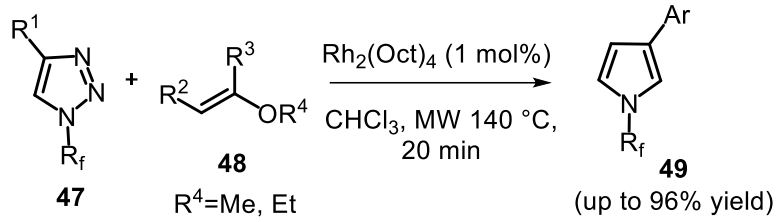
Scheme 5.10 Metal catalyzed reaction on aryl acetaldehydes.

In 2016, B. Sundaraju and co-workers investigated a method to access C3 and *N*-substituted pyrrole using (*E*)-2-phenylbut-2-ene-1,4-diol **43** and benzylamine **44** as a model substrate along with the catalytic amount of [Fe]-catalyst. This iron-catalyzed straightforward method to furnish substituted pyrroles covers a broad scope of amine and alcohol with excellent yields (Scheme 5.11).[29]



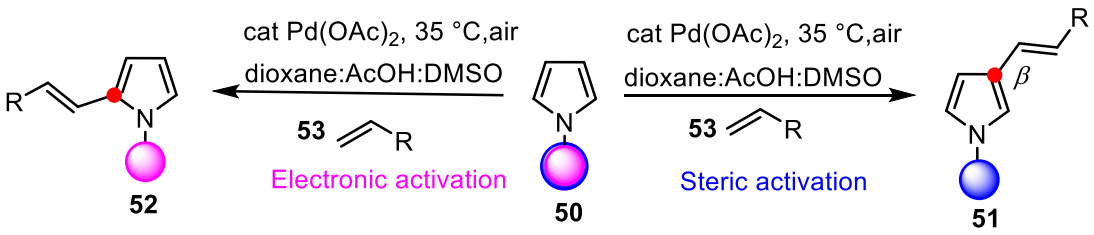
Scheme 5.11 Iron-catalyzed 1,3-substituted pyrrole synthesis.

In 2018, Beier and co-workers reported a rhodium-catalyzed trans-annulation via ring-opening of substituted 1,2,3-triazoles **47** followed by cycloaddition with different vinyl ethers **48** under microwave heating provided a highly efficient route to access C3-substituted pyrrole **49** with good yields (Scheme 5.12).[30]



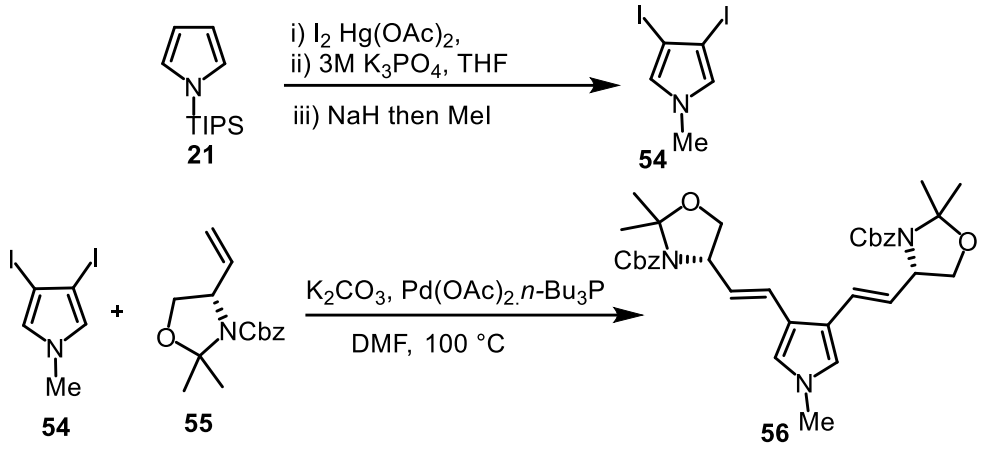
Scheme 5.12 Using triazole and vinyl ether to the synthesis of C3-substituted pyrrole.

In 2006, Gaunt and co-workers utilized mild aerobic oxidative palladium (II) catalyzed C-H bond functionalization systems to produce C2- and C3- alkylated pyrrole (**52** and **51**). This method can generate a range of functionalized and annulated pyrrole architectures directly, and it is possible to control the position of C-H bond functionalization *via* simple steric and electronically tuned *N*-pyrrole protecting groups to form products with either C2- or C3-substitution (Scheme 5.13).[31]



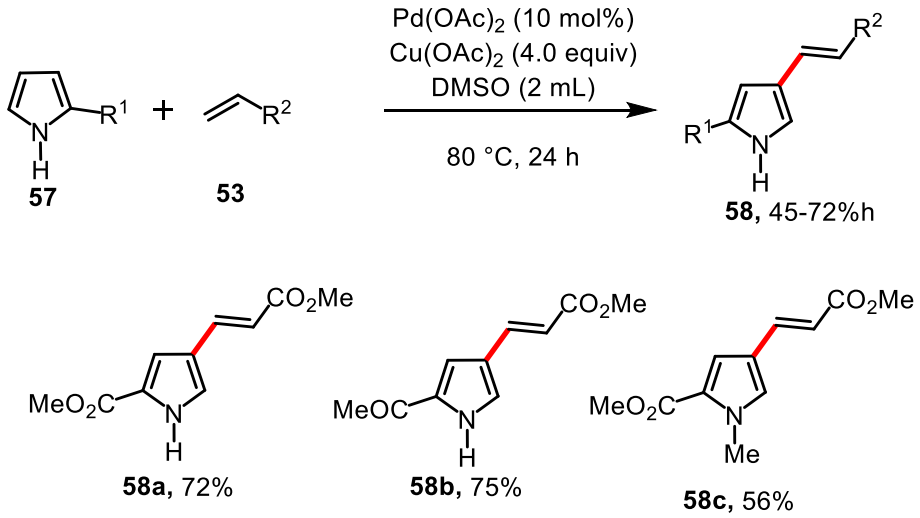
Scheme 5.13 Pd-catalyzed regioselective C–H functionalization.

In 2002, Collier and co-workers produced pyrrolidine and deoxypyrrolidine analogs using a Heck coupling with in situ generated 3,4-diiodopyrroles **54** and amino acid enclosing olefin **55** as a coupling partner using Hg/Pd-catalyst for substitution of aromatic compounds. These reaction conditions can also use with protecting and deprotecting strategies on pyrroles with bulky groups (Scheme 5.14).[32a]



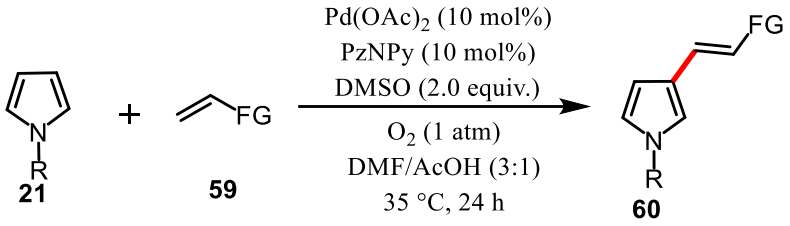
Scheme 5.14 Heck reaction to synthesis of 3,4-disubstituted pyrroles.

In 2017, Laha and co-workers confirmed a regioselective C4- alkenylation of free-(NH) pyrrole. The reaction is controlled by a C2- substituent on free (NH) or *N*-protected pyrroles for the regioselective outcome (Scheme 5.15).[32b]



Scheme 5.15 Dual Pd and Cu C(sp2) – C(sp2) coupling reaction.

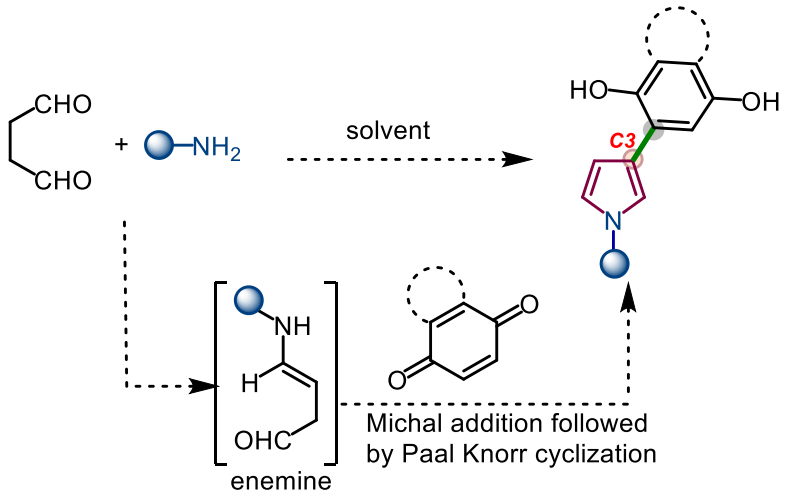
In 2021, Joo and co-workers reported sterically controlled C–H alkenylations of *N*-substituted pyrroles using pyrazolonaphthyridine [Pz(N)Py] ligands, which led to steric demand for alkenylation at the less hindered position of pyrrole. The steric demand and stable bidentate binding mode of the pyrazolonaphthyridine ligand are key to the success of these sterically controlled alkenylations using oxygen as an oxidant to furnish C3- substituted pyrroles.[32c]



Scheme 5.16 C–H alkenylation of pyrroles and thiophenes.

5.3 Hypothesis to present work for the direct synthesis of C3 arylation pyrroles

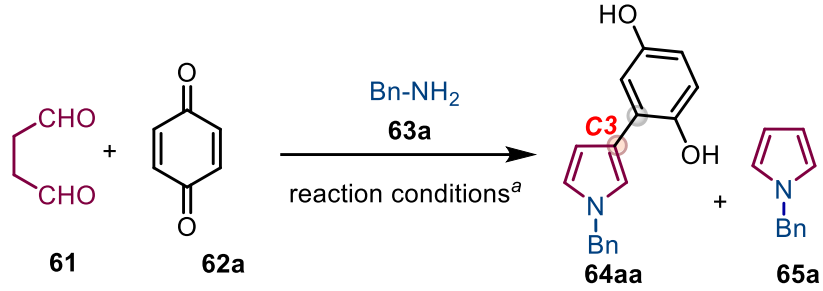
The reported strategies required harsh Metal catalyzed conditions, strong Oxidants, radical initiators, or unique functionalized starting material for the reaction. Most of this functionalization has been studied with protected pyrroles.[33] Besides, the use of metals, limited substrate scope, and regioselectivity are significant issues of concern. To address these challenging issues, consider the importance of the C3–arylation of pyrroles motifs in bioactive molecules. We decided to design a new strategy for synthesizing C3-tethered aryl–pyrrole products using commercially available starting material. To fulfill this task based on our continuing efforts in developing *β*–functionalized pyrroles with the help of the previous report[34]. To achieve the multicomponent *β*–functionalized pyrroles under catalyst-free conditions via direct Michal type reaction followed by Paal Knorr reaction. We hypothesized the reaction of succinaldehyde and amine to the formation of an enamine intermediate. That enamine intermediate gives Michal an addition reaction with 1,4-quinone followed by the Paal Knorr reaction cyclization access C3-substituted pyrrole.



5.4 Results and discussion

We initiated our study after the hypothesis and previous literature to investigate 1,4–Benzoquinone **62a** aqueous succinaldehyde **61**, and benzylamine **6**3**a** the primary condition; we obtained minor product **64aa** (35%) and a primary product accompanied by pyrrole **65a** (52%) as a significant product by just mixing the substrates in DCM: EtOH (1:1) at room temperature (entry 1, Table 5.1). We observed less yield **64aa** (25%) when the reaction was carried out in CH_2Cl_2 at reflux temperature (entry 2, Table 5.1). Subordinately decreasing the temperature from room temperature to 5 ^oC a slight improvement was shown in yield **64aa** (50%) (entry 3, Table 5.1). Additional variations of solvents like DCE, $CHCl_3$, CH_3CN, and hexane less yield decreases (entries 4–7, Table 5.1). Gratifyingly, an improvement was seen in the protocol using non-protic as well as non-polar solvents like Et_2O; after 10 h, the yield of **64aa** (66% yield) increased was obtained along with **65a** (10% yield) (entry 8, Table 5.1). In the same solvent changing the temperature from 5 ^oC to 0 ^oC resulted **64aa** in 72% yield (entry 9, Table 5.1). Further changes in the reaction conditions, either adding acetic acid as an acid-additive condition or lowering the temperature to –10 ^oC, do not refine the desired product yields (entries 10 & 11, Table 5.1). Also, screened different polar protic solvent EtOH (entry 12, Table 5.1), and a mixture of solvent Et_2O: EtOH (1:1) (entry 13, Table 5.1), and the varying solvents like 1,4-dioxane and THF (entries 14-15, Table 5.1), did not improve the outcome. Thus, we preferred to operate the reaction under optimized condition (entry 9, Table 5.1).

Table 5.1 Optimization of Reaction Conditions[a]



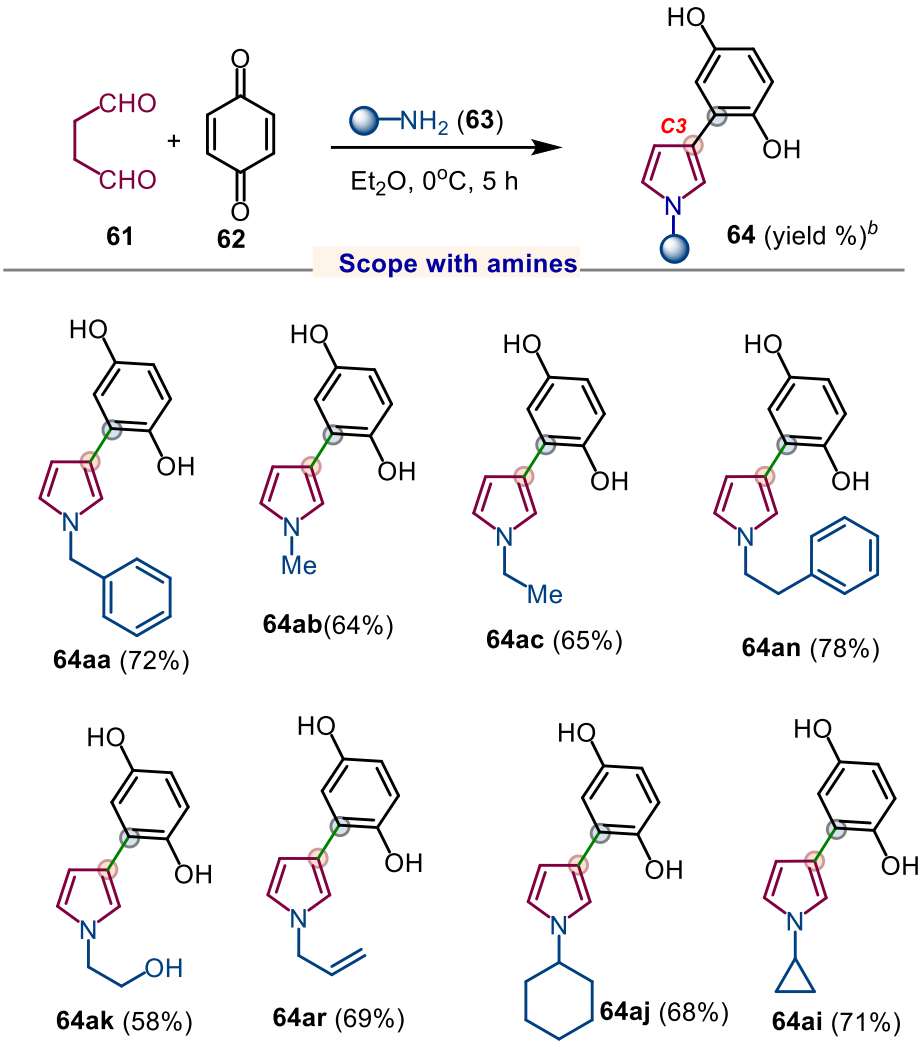
61 **62a** **64aa** **65a**

entry	reaction conditions[a]	yield **64aa/65a** (%)[b]
1	CH_2Cl_2: EtOH,(1:1), rt,24h	45/52
2	CH_2Cl_2, refluxe, 24 h	25/60
3	CH_2Cl_2, 5 ^oC, 20 h	50/28
4	$C_2H_4Cl_2$, 5 ^oC , 20 h	35/30
5	$CHCl_3$, 5 ^oC, 24 h	46/36
6	CH_3CN, 5 ^oC, 14 h	21/64
7	Hexane, 5 ^oC, 24 h	50/32
8	Et_2O , 5 ^oC,10 h	66/10
9	**Et_2O , 0 ^oC, 5 h**	**72/10**
10	Et_2O , CH_3CO_2H (10 mol%), 0 ^oC, 5 h	45/38
11	Et_2O , -10 ^oC, 10 h	60/10
12	EtOH, 0 ^oC, 24 h	35/25
13	Et_2O:EtOH (1:1), 0 ^oC, 24 h	30/28
14	1,4-dioxane, 0 ^oC, 24 h	55/10
15	THF, 0 ^oC, 24 h	42/15

[a]Unless otherwise indicated, the reaction was carried out with succinaldehyde **61** (3.0 M sol, 0.6 mmol, 2.0 equiv.), 1,4-Benzoquinone **62a** (0.3 mmol, 1.0 equiv.), benzylamine **63a** (0.45 mmol, 1.5 equiv.), Solvent (3.0 mL), 0 ^oC. [b]Isolated yield of **64aa**/**65a** refers to **62a**.

After establishing the optimal condition, we explored the reaction scope using 1,4-Benzoquinone **62a,** succinaldehyde **61** as a substrate for the reaction and a variety of *N*–alkyl amines **63** for the synthesis of *β*–arylation on pyrroles as illustrated in Table 5.2.

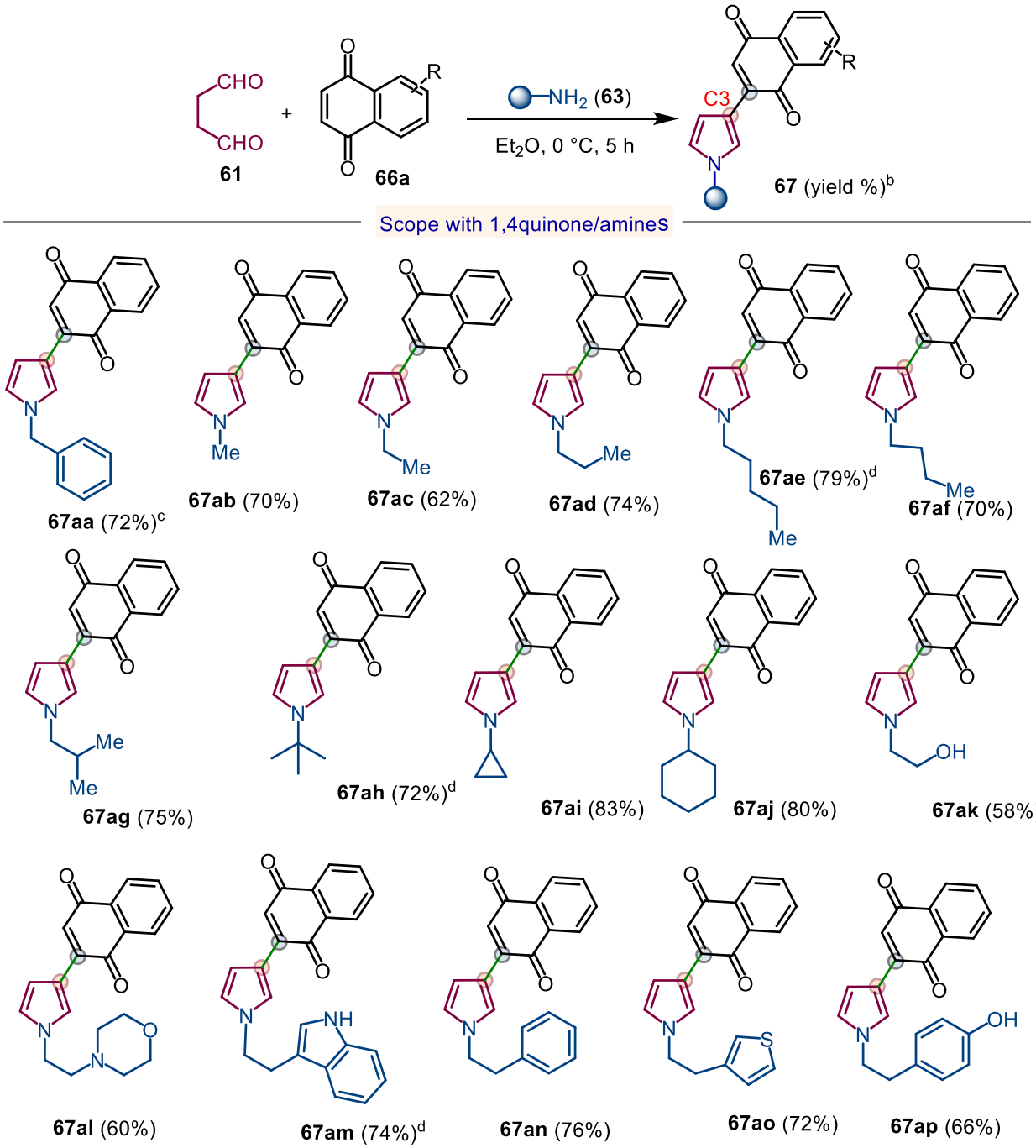
Table 5.2 Substrate scopes with 1,4-benzoquiones **62** and amines **63**



[a]Unless otherwise indicated, the reaction was carried out with succinaldehyde **61** (3.0 M sol, 0.6 mmol, 2.0 equiv.), 1,4-benzoquinones **62** (0.3 mmol, 1.0 equiv.), Amines **63** (0.45 mmol, 1.5 equiv.), Solvent (3.0 mL), 0 °C. [b]Isolated yield of **64** refers to **62.**

Under the optimized condition, the reaction scope with various aliphatic amines **63a-d** (–methyl, –ethyl, and 2-phenylethylamine) was checked to afford **64a-d** up to 78% yields. With cyclic amines, such as cyclopropyl amine **63i** and cyclohexyl amine **63j**, related products **64ai** and **64aj** were obtained with good yield (up to 71%).

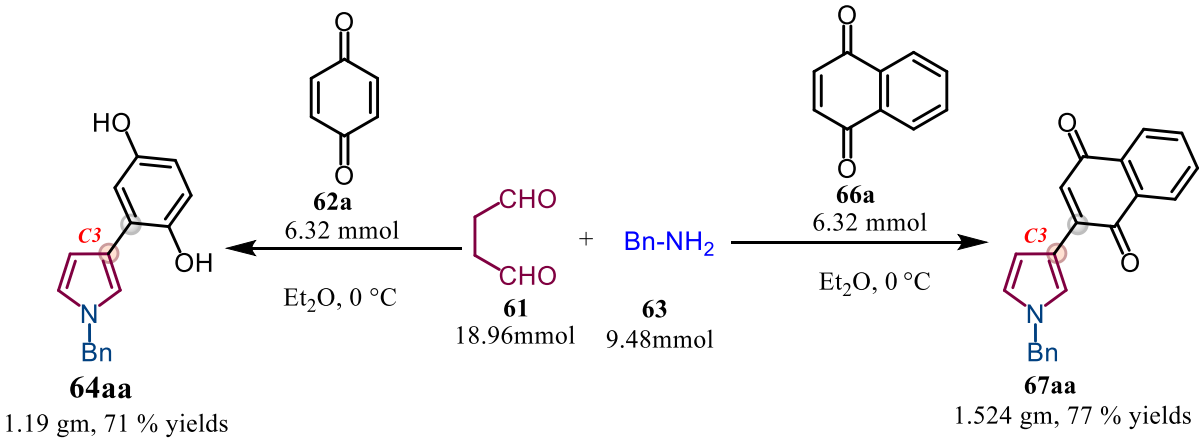
Table 5.3 Substrate scope with 1,4-Napthaquinone **66** and amines **63**



[a]Unless otherwise indicated, the reaction was carried out with succinaldehyde **61** (3.0 M sol, 0.6 mmol, 2.0 equiv.), 1,4-Napthaquinone **66a** (0.3 mmol, 1.0 equiv.), Amines **63** (0.45 mmol, 1.5 equiv.), Solvent (3.0 mL), 0 °C. [b]Isolated yield of **67** refers to **66**,[c] Time 30 min, [d] Time 50 min.

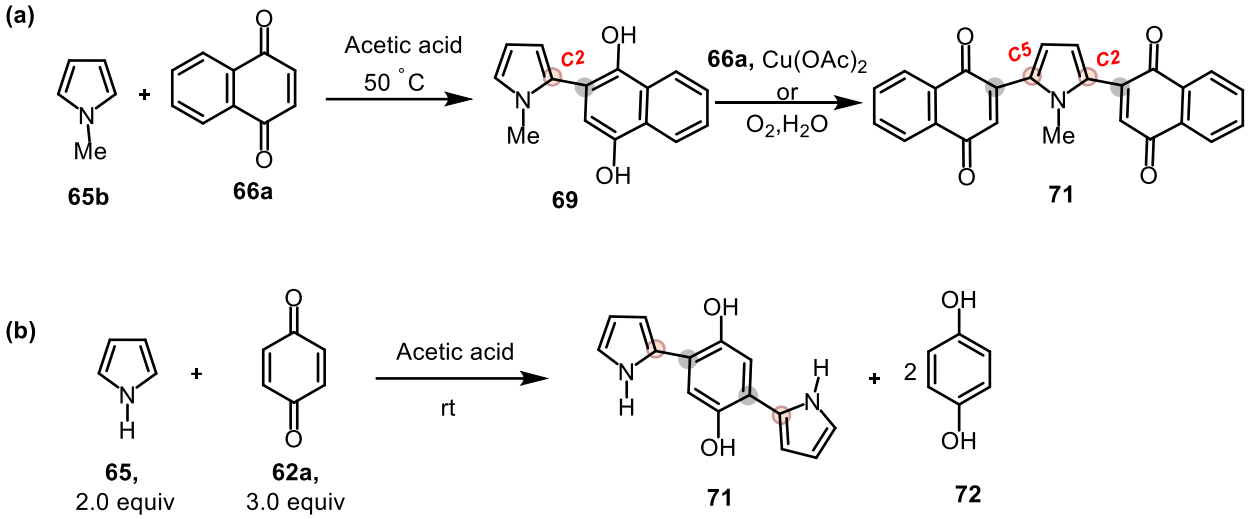
Further, the synthetic utility of this method was investigated by using *N*–substituted alkyl amines **63** and 1,4-Napthoquinone **66** as a substrate for the synthesis of *β*–arylation on pyrroles with succinaldehyde **61**. Surprisingly, oxidized product **67aa** was obtained with **a** 72% yield rather than the expected hydroquinone product. As shown in Table 5.3, a series of *N*-substituted alkyl amines **63b-63h** (-methyl, –ethyl, –cyclopropyl, –pentyl, -butyl, -*iso*-butyl, and -*tert*-butyl) utilized as a competent reactant for this reaction, which gives the products **67ab-67ah** with high yields (up to 79%). With cyclic amines such as cyclopropyl amine **63i** and cyclohexyl amine **63j**, obtained products **6ai** and **67aj** with yield (up to 80%). More importantly, substituents based on the biological active amine **63k-63p** like 2–ethanol amine, morpholine–2–ethyl amine, Tryptamine, phenyl ethyl amine, Thiophene–2–ethyl amine, and Tryptophan furnished the corresponding products **67ak-67ap** with good yield (up to 76%) (Table 5.3).

Additional transformations were performed to showcase the utility of our protocol at the gram-scale synthesis of product **67aa** (1.524 gm, 77% yield) from 1,4-naphthoquinone **66a** (6.32 mmol) and the compound **64aa** (1.190 gm, 71% yield) from 1,4-benzoquinone **62a** (6.32 mmol) under standard optimized conditions (Scheme 5.17).

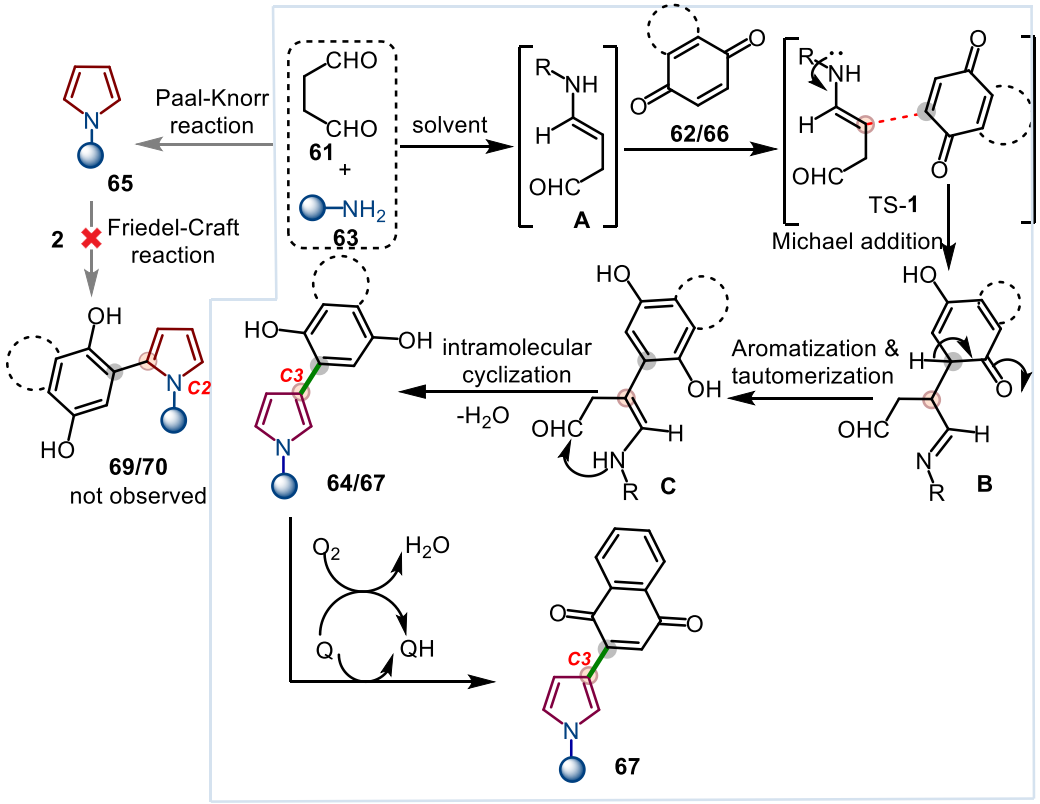


Scheme 5.17 Scale up reaction condition.

To better understand the reaction process [36-37], the control experiment was performed as shown in Scheme 5.18. The reaction of 1-methyl pyrrole **65b** and 1,4-naphthoquinone **66a** in the presence of acid at 50 °C affords the product and again gets oxidative dimers as C2/C5 product **71** as shown in Scheme 5.18(a). The same condition with pyrrole **65** (2 equiv.) and 1,4-benzoquinone **62a** (3 equiv.) in the presence of acid gives C2-arylated pyrrole (2,5-bispyrrole benzene-1,4-diol) product **71** as displayed in Scheme 5.18(b).



Scheme 5.18 Control experiments.



Scheme 5.19: The plausible reaction mechanism.

A Michael addition reaction between enamine-**A** as Michael donor and 1,4-quinone **62/66,** which acts as Michael acceptor via TS-1, resulted in the formation of intermediate-**B**, which further on aromatization, tautomerization, and finally cyclization sequence as an overall Paal-Knorr

reaction to furnish C3-substituted pyrrole **64/67**. While the construction of C2-substituted pyrrole **69/70** was not observed, which was expected through the Friedel-Craft response of pyrrole **65** with 1,4-quinone **62**.

5.5 Conclusion

In summary, we have developed a direct Michael reaction to synthesize *β*-arylated/olefinated pyrroles under open-flask catalyst-free condition. The suitable electrophilic substrate, such as 1,4-quinone units, was used as a Michael acceptor, and *in-situ* generated enamine from succinaldehyde and amines as a Michael donor. A wide range of substrate scope with readily available and inexpensive 1,4-quinone and amines as starting material to obtain direct C3-substituted pyrroles with moderate to good yields. We highlighted our method and synthetic utility in conjugated addition/Paal-Knorr reaction to get a C-C coupling cascade reaction.

5.6 General experimental methods

Unless otherwise stated, all commercially available compounds were used as received without further purification. All solvents employed in the reactions were distilled from appropriate drying agents. Aqueous succinaldehyde **61** (3M solution) was prepared using the reported procedure.[35] The reactions under the standard conditions were monitored by thin-layer chromatography (TLC) on Merck silica gel 60 F254 pre-coated plates (0.25 mm). Column chromatographic purification was performed on silica gel (100–200 mesh) using a petroleum ether/EtOAc mixture. Chemical yields refer to pure, isolated substances. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solution on a BRUKER-AV400 spectrometer. High-resolution mass spectra were recorded on Agilent 6545 Q-TOF LC/MS. Melting points were determined by EZ–Melt Automated Melting Point Apparatus and are incorrect.

5.6.1 General procedure for the preparation of C3-substituted pyrrole (64/67)

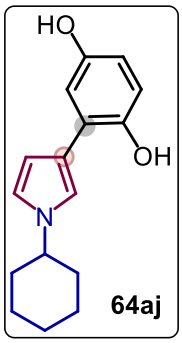
An oven-dried Schlenk tube (25 mL) was charged with aqueous succinaldehyde **61** (3.0 M sol, 0.6 mmol, 2.0 equiv.), 1,4-quinones **62** (0.3 mmol, 1.0 equiv.) and amine **63** (0.3 mmol, 1.0 equiv.) in diethyl ether (3.0 mL) at 0 °C. The combined reaction mixture was stirred at the same temperature and monitored as the reaction progressed by TLC. Upon completion, the solvent was removed under reduced pressure, and the reaction was stirred between diethyl ether (5.0 mL) and water (5.0 mL) for five minutes. The organic layer was separated, dried over anhydrous Na_2SO_4,

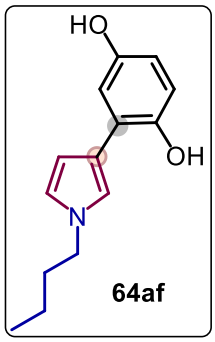
and concentrated under reduced pressure. The product **64/6**7 (up to 81% yield) was obtained by passing through a silica-gel column by eluting with petroleum ether/EtOAc.

5.6.2 Spectral data for compounds

2-(1-benzyl-1*H*-pyrrol-3-yl) benzene-1,4-diol (64aa). The general procedure was followed with 1, 4-benzaquinone (**66a**, 65 mg, 0.6 mmol), succinaldehyde (**61**, 600 µl, 3.0 M sol, 1.8 mmol), benzylamine (**63a**, 96 mg, 0.9 mmol) to furnish **64aa** after purification using petroleum ether/ EtOAc (8/2) as eluent; Orange solid (158 mg, 72% yield); **^{1}H NMR (400 MHz, CDCl$_3$)** δ7.32 – 7.24 (m, 3H), 7.13 – 7.10 (m, 2H), 6.89 (t, *J* = 2.0 Hz, 1H), 6.76 (d, *J* = 3.1 Hz, 1H), 6.75 – 6.70 (m, 2H), 6.65 (s, 1H), 6.55 (dd, *J* = 8.5, 3.0 Hz, 1H), 6.31 (dd, *J* = 2.8, 1.8 Hz, 1H), 5.17 (s, 1H), 5.03 (s, 2H).**^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)** δ 149.1, 146.5, 122.8, 120.0, 119.2, 116.2, 116.0, 115.4, 113.9, 107.7, 50.5, **HRMS (ESI-TOF)** *m/z*: [M + H] $^+$ Calcd for $C_{17}H_{16}NO_2$ 266.1176; found 266.1179.

2-(1-cyclohexyl-1*H*-pyrrol-3-yl)benzene-1,4-diol (64aj). The general procedure was followed with 1, 4-benzaquinone (**66a**, 65 mg, 0.6 mmol), succinaldehyde (**61**, 600 µl, 3.0 M sol, 1.8 mmol), cyclohexylamine (**63j**, 89 mg, 0.9 mmol) to furnish **64aj** after purification using petroleum ether/ EtOAc (8/2) as eluent; Orange solid (105 mg, 68% yield);**^{1}H NMR (400 MHz, CDCl$_3$)** δ 6.96 (t, *J* = 2.02, 2.02 Hz, 1H), 6.82 (m, 2H), 6.79 (s, 1H), 6.61 (dd, *J* = 8.61, 3.05 Hz, 1H), 6.31 (dd, *J* = 2.75, 1.82 Hz, 1H), 3.83 (m, 1H), 2.14 (m, 2H), 1.91 (m, 2H), 1.69 (m, 2H), 1.42 (m, 2H), 1.26 (m, 1H).**^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)** δ 149.1, 146.6, 123.8, 120.0, 118.7, 117.2, 115.9, 115.4, 113.8, 107.2, 59.0, 34.6(2C), 25.6(2C), 25.4.**HRMS (ESI-TOF)** *m/z*: [M + H] $^+$ Calcd for $C_{16}H_{20}NO_2$ 258.1489; found 258.1494.

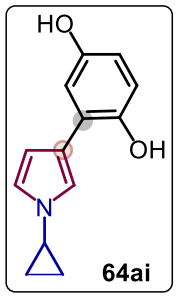




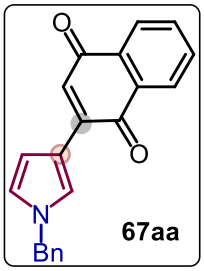
2-(1-butyl-1*H*-pyrrol-3-yl)benzene-1,4-diol (64af). The general procedure was followed with 1, 4-benzaquinone (**66a**, 65 mg, 0.6 mmol), succinaldehyde (**61**, 600 µl, 3.0 M sol, 1.8 mmol),1-butylamine (**63f**, 66 mg, 0.9 mmol) to furnish **64af** after purification using petroleum ether/ EtOAc (8/2) as eluent; Orange solid (90 mg, 65% yield); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 6.90 (t, *J* = 1.96, 1.96 Hz, 1H), 6.83 (d, *J* = 2.95 Hz, 1H), 6.79 (d, *J* = 8.63 Hz, 1H), 6.73 (t, *J* = 2.46, 2.46 Hz, 1H), 6.70 (s, 0H), 6.61 (dd, *J* = 8.65, 3.00 Hz, 1H), 6.31 (t, *J* = 2.27, 2.27 Hz, 1H), 3.88 (t, *J* = 7.15, 7.15 Hz, 2H), 1.84 – 1.60 (m, 2H), 1.34 (q, *J* = 7.45, 7.45, 7.43 Hz, 2H), 0.94 (t, *J* = 7.31, 7.31 Hz, 4H).**^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)** δ 149.2,

146.4, 123.7, 121.9, 119.3, 119.1, 116.0, 115.4, 113.8, 107.5, 49.6, 33.4, 19.9, 13.6.**HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{18}NO_2$ 232.1332; found 232.1335.

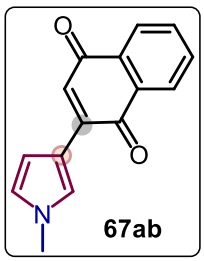
2-(1-cyclopropyl-1*H*-pyrrol-3-yl)benzene-1,4-diol (64ai). The general procedure was followed with 1, 4-benzaquinone (**66a**, 65 mg, 0.6 mmol), succinaldehyde (**61**, 600 µl, 3.0 M sol, 1.8 mmol), Cyclopropyl amine (**63i**, 51 mg, 0.9 mmol) to furnish **64ai** after purification using petroleum ether/ EtOAc (8/2) as eluent; Orange solid (89 mg, 69% yield) **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.99 (t, *J* = 2.03, 2.03 Hz, 1H), 6.83 (t, *J* = 2.53, 2.53 Hz, 1H), 6.79 (m, 2H), 6.71 (s, 1H), 6.61 (dd, *J* = 8.65, 3.01 Hz, 1H), 6.27 (t, *J* = 2.37, 2.37 Hz, 1H), 5.26 (s, 1H), 4.72 (s, 1H), 3.39 (m, 1H), 0.98 (m, 2H), 0.94 (m, 2H).**^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 149.1, 146.5, 122.8, 120.0, 119.2, 116.2, 116.0, 115.4, 113.9, 107.7, 30.2, 6.3(2C).**HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{14}NO_2$ 216.1019; found 216.1024.



2-(1-benzyl-1H-pyrrol-3-yl)naphthalene-1,4-dione (67aa). The general procedure was followed with 1, 4-benzaquinone (**62a**, 91 mg, 0.6 mmol), succinaldehyde (**61**, 600 µl, 3.0 M sol, 1.8 mmol), benzylamine (**63a**, 95 mg, 0.9 mmol) to furnish **67aa** after purification using petroleum ether/ EtOAc (8/2) as eluent; Orange solid (135 mg, 72% yield); **^{1}H NMR (400 MHz, $CDCl_3$)** δ8.11 – 8.02 (m, 2H), 7.83 (t, *J* = 2.0 Hz, 1H), 7.72 – 7.67 (m, 2H), 7.16 – 7.11 (m, 2H), 7.03 (s, 1H), 6.89 – 6.85 (m, 2H), 6.70 – 6.67 (m, 1H), 6.57 (dd, *J* = 3.0, 1.7 Hz, 1H), 5.02 (s, 2H), 3.79 (s, 3H).**^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 185.7, 185.3, 142.0, 137.7, 133.5, 133.1, 132.9, 132.2, 128.7(2C), 128.6(2C), 127.5, 126.8, 126.6, 126.3, 125.6, 122.3, 116.2, 107.8, 51.7. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{16}NO_2$ 314.1176; found 314.1181.

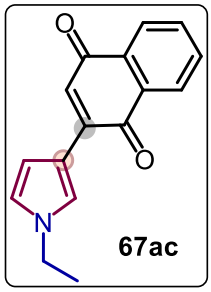


2-(1-methyl-1H-pyrrol-3-yl) naphthalene-1,4-dione (67ab). The general procedure was followed with 1, 4-benzoquinone (**62a**, 95 mg, 0.6 mmol), succinaldehyde (**61**, 600 µl, 3.0 M sol, 1.8 mmol), *n*-methylamine [**63c**, 28 mg (70 µl, 40% in water), 0.9 mmol] to furnish **67ab** after purification using petroleum ether/ EtOAc (8/2) as eluent; Orange solid (88 mg, 62% yield) **^{1}H NMR (400 MHz, $CDCl_3$)** δ8.13 – 8.04 (m, 2H), 7.73 (t, *J* = 2.0 Hz, 1H), 7.72 – 7.68 (m, 2H), 7.04 (s, 1H), 6.65 (dd, *J* = 3.0, 2.2 Hz, 1H), 6.55 (dd, *J*= 3.0, 1.8 Hz, 1H), 3.72 (s, 3H).**^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 185.7, 185.3, 142.1, 133.5, 133.2, 133.0, 127.6, 127.4, 126.7, 125.7,

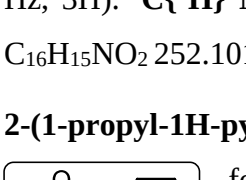


123.4 (2C), 123.3, 108.1, 36.6.**HRMS (ESI-TOF)** *m/z*: [M + H] $^{+}$ Calcd for $C_{15}H_{12}NO_2$ 208.0863; found 208.0869.

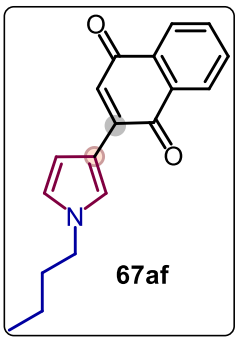
2-(1-ethyl-1H-pyrrol-3-yl)naphthalene-1,4-dione (67ac). The general procedure was followed with 1, 4-benzoquinone (**62a**, 95 mg, 0.6 mmol), succinaldehyde (**61**, 600 µl, 3.0 M sol, 1.8 mmol), *n*-ethylamine (**63c**, 41 mg, 0.9 mmol) to furnish **67ac** after purification using petroleum ether/ EtOAc (8/2) as eluent; Orange solid (112 mg, 74% yield); **^{1}H NMR (400 MHz, CDCl$_3$)** δ8.14 – 8.07 (m, 2H), 7.81 (t, *J* = 2.0 Hz, 1H), 7.73 – 7.71 (m, 2H), 7.06 (s, 1H), 6.72 (dd, *J* = 3.0, 2.1 Hz, 1H), 6.58 (dd, *J* = 3.0, 1.8 Hz, 1H), 4.00 (q, *J* = 7.3 Hz, 2H), 1.49 (t, *J* = 7.3 Hz, 3H).**^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)** δ. **HRMS (ESI-TOF)** *m/z*: [M + H] $^{+}$ Calcd for $C_{16}H_{15}NO_2$ 252.1019 ; found 252.1025.



2-(1-propyl-1H-pyrrol-3-yl) naphthalene-1,4-dione (67ad). The general procedure was followed with 1, 4-benzaquinone (**62a**, 95 mg, 0.6 mmol), succinaldehyde (**61**, 600 µl, 3.0 M sol, 1.8 mmol), *n*-propylamine (**63d**, 53 mg, 0.9 mmol) to furnish **67ad** after purification using petroleum ether/ EtOAc (8/2) as eluent; Orange solid (118 mg, 69% yield); **^{1}H NMR (400 MHz, CDCl$_3$)** δ8.16 – 8.01 (m, 2H), 7.79 (d, *J* = 2.0 Hz, 1H), 7.75 – 7.65 (m, 2H), 7.05 (s, 1H), 6.68 (t, *J* = 2.6 Hz, 1H), 6.56 (dd, *J* = 2.9, 1.7 Hz, 1H), 3.88 (t, *J* = 7.1 Hz, 2H), 1.83 (p, *J* = 7.3 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).**^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)** δ 185.7, 185.3, 142.1, 133.5, 133.1, 132.9, 132.2, 127.4, 126.6, 126.5, 125.6, 122.2, 116.1, 107.7, 51.9, 24.5, 11.2.**HRMS (ESI-TOF)** *m/z*: [M + H] $^{+}$ Calcd for $C_{17}H_{16}NO_2$ 266.1176; found 266.1179.

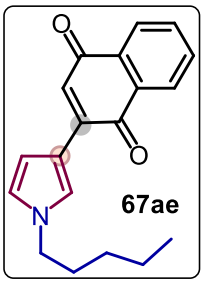


2-(1-butyl-1H-pyrrol-3-yl) naphthalene-1,4-dione (67af). The general procedure was followed with 1, 4-benzaquinone (**62a**, 95 mg, 0.6 mmol), succinaldehyde (**61**, 600 µl, 3.0 M sol, 1.8mmol), *n*-butylamine (**63f**, 66 mg, 0.9 mmol) to furnish **67af** after purification using petroleum ether/ EtOAc (8/2) as eluent; Orange solid (117 mg, 70% yield); **^{1}H NMR (400 MHz, CDCl$_3$)** δ8.12 – 8.03 (m, 2H), 7.76 (t, *J* = 1.8 Hz, 1H), 7.72 – 7.67 (m, 2H), 7.04 (s, 1H), 6.66 – 6.63 (m, 1H), 6.54 (dd, *J* = 2.9, 1.7 Hz, 1H), 3.69 (s, 2H), 2.07 (dp, *J* = 13.7, 6.8 Hz, 1H), 0.93 (d, *J* = 6.7 Hz, 6H).**^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)** δ 185.7, 185.3, 142.1, 133.4, 133.1, 132.9, 132.2, 127.4, 126.9, 126.6, 125.6, 122.7, 116.0, 107.6,

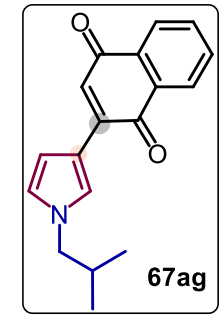


57.9, 30.4, 19.9 (2C). **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$ Calcd for $C_{18}H_{18}NO_2$ 280.1332; found 280.1339.

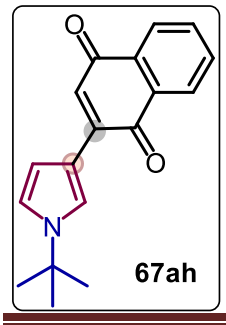
2-(1-pentyl-1H-pyrrol-3-yl) naphthalene-1,4-dione (67ae). The general procedure was followed with 1, 4-benzaquinone (**62a**, 95 mg, 0.6 mmol), succinaldehyde (**61**, 600 µl, 3.0 M sol, 1.8 mmol), *n*-butylamine (**63e**, 78 mg, 0.9 mmol) to furnish **67ae** after purification using petroleum ether/ EtOAc (8/2) as eluent; Orange solid (139 mg, 79% yield); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.16 – 8.11 (m, 1H), 8.11 – 8.06 (m, 1H), 7.80 (t, *J* = 2.0 Hz, 1H), 7.76 – 7.68 (m, 2H), 7.06 (s, 1H), 6.70 (dd, *J* = 3.0, 2.1 Hz, 1H), 6.58 (dd, *J* = 3.0, 1.7 Hz, 1H), 3.93 (t, *J* = 7.2 Hz, 2H), 1.84 (p, *J* = 7.4 Hz, 2H), 1.43 – 1.27 (m, 4H), 0.93 (t, *J* = 7.0 Hz, 3H).**^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 185.7, 185.3, 142.1, 133.5, 133.1, 132.9, 132.2, 127.4, 126.6, 126.5, 125.6, 122.2, 116.1, 107.7, 50.2, 30.9, 28.8, 22.2, 13.9. **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$ Calcd for $C_{19}H_{20}NO_2$ 294.1489; found 294.1496.



2-(1-isobutyl-1H-pyrrol-3-yl)naphthalene-1,4-dione (67ag). The general procedure was followed with 1, 4-benzaquinone (**62a**, 95 mg, 0.6 mmol), succinaldehyde (**61**, 600 µl, 3.0 M sol, 1.8 mmol), *iso*-butylamine (**63g,** 66 mg, 0.9 mmol) to furnish **67ag** after purification using petroleum ether/ EtOAc (8/2) as eluent; Orange solid (126 mg, 75% yield); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.11 – 8.04 (m, 2H), 7.76 (td, *J* = 2.4, 1.0 Hz, 1H), 7.71 – 7.68 (m, 1H), 7.03 (s, 1H), 6.97 (s, 1H), 6.65 (dd, *J* = 3.0, 2.1 Hz, 1H), 6.54 (dd, *J* = 3.0, 1.7 Hz, 1H), 3.70 (d, *J* = 7.2 Hz, 2H), 2.06 (dt, *J* = 13.5, 6.8 Hz, 1H), 0.93 (d, *J* = 6.7 Hz, 6H).**^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 185.7, 185.3, 138.6, 133.9, 133.5, 133.1, 127.4, 126.9, 126.6, 126.4, 125.9, 125.6, 122.7, 116.0, 107.6, 57.8, 30.4, 19.9. **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$ Calcd for $C_{18}H_{18}NO_2$ 280.1332; found 280.1338.

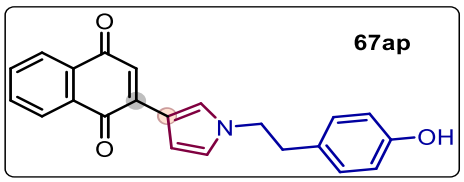


2-(1-(*tert*-butyl)-1*H*-pyrrol-3-yl) naphthalene-1, 4-diol (67ah). The general procedure was followed with 1, 4-benzoquinone (**62a**, 65 mg, 0.6 mmol), succinaldehyde (**61**, 600 µl, 3.0 M sol, 1.8 mmol), *tert*-butylamine (**63h**, 66 mg, 0.9 mmol) to furnish **67ah** after purification using petroleum ether/ EtOAc (8/2) as eluent; Orange solid (121 mg, 72% yield);**^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.23 – 8.02 (m, 1H), 7.95 (s, 1H), 7.79 – 7.51 (m, 2H), 7.05 (s, 1H), 6.89 (dd, *J* = 3.15,

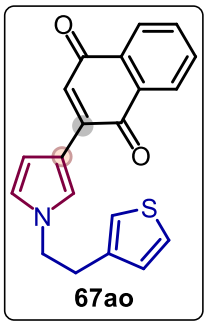


2.29 Hz, 1H), 6.58 (dd, *J* = 3.14, 1.77 Hz, 1H), 1.59 (s, 7H).**^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)** δ 185.8, 185.2, 142.2, 133.4, 133.1, 133.0, 132.3, 127.3, 126.5, 125.6, 123.7, 119.5, 115.8, 107.6, 55.7, 30.6(3C). **HRMS (ESI-TOF)** *m/z*: [M + H] $^+$ Calcd for $C_{18}H_{18}NO_2$ 280.1332; found 280.1335.

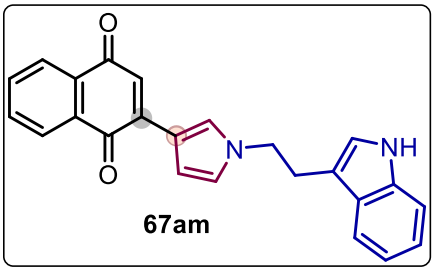
2-(1-(4-hydroxyphenethyl)-1H-pyrrol-3-yl)naphthalene-1,4-dione (67ap). The general procedure was followed with 1, 4-benzaquinone (**62a**, 95 mg, 0.6 mmol), succinaldehyde (**61**, 600 µl, 3.0 M sol, 1.8 mmol), tyramine (**63a**, 123 mg, 0.9 mmol) to furnish **67ap** after purification using petroleum ether/ EtOAc (8/2) as eluent; Orange solid (140 mg, 66% yield); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.13 – 8.09 (m, 1H), 8.09 – 8.05 (m, 1H), 7.74 – 7.69 (m, 3H), 7.03 (s, 1H), 6.96 (d, *J* = 8.5 Hz, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 6.57 (dd, *J* = 3.0, 2.1 Hz, 1H), 6.51 (dd, *J* = 3.0, 1.7 Hz, 1H), 4.92 (s, 1H), 4.10 (t, *J* = 7.3 Hz, 2H), 3.01 (t, *J* = 7.3 Hz, 2H).**^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)** δ 185.6, 185.3, 155.7, 142.1, 133.4, 133.1, 132.8, 132.1, 129.5, 128.5, 127.3, 126.6, 126.3, 125.5, 122.4, 116.1, 115.6, 108.2, 107.6, 52.0, 40.0, 37.1.**HRMS (ESI-TOF)** *m/z*: [M + H] $^+$ Calcd for $C_{22}H_{18}NO_2$ 344.1281; found 344.1285.



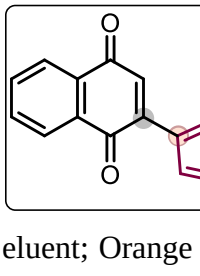
2-(1-(2-(thiophen-3-yl)ethyl)-1*H*-pyrrol-3-yl)naphthalene-1,4-dione (67ao). The general procedure was followed with 1, 4-benzaquinone (**62a**, 95 mg, 0.6 mmol), succinaldehyde (**61**, 600 µl, 3.0 M sol, 1.8 mmol), ethyl-3-thioamine (**63o**, 102 mg, 0.9 mmol) to furnish **67ao** after purification using petroleum ether/ EtOAc (8/2) as eluent; Orange solid (144 mg, 72% yield); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.15 – 8.02 (m, 2H), 7.77 (t, *J* = 1.8 Hz, 1H), 7.75 – 7.68 (m, 2H), 7.17 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.03 (s, 1H), 6.93 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.79 – 6.72 (m, 1H), 6.67 – 6.60 (m, 1H), 6.54 (dd, *J* = 2.9, 1.7 Hz, 1H), 4.18 (t, *J* = 7.2 Hz, 2H), 3.32 (t, *J* = 7.2 Hz, 2H).**^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)** δ 185.3, 141.9, 139.5, 133.5, 133.1, 132.9, 132.2, 127.7, 127.1, 126.6, 126.3, 125.8, 125.6, 124.3, 122.2, 116.4, 107.9, 77.0, 51.6, 32.0. **HRMS (ESI-TOF)** *m/z*: [M + H] $^+$ Calcd for $C_{18}H_{20}NO_2S$ 334.0896; found 334.0899.



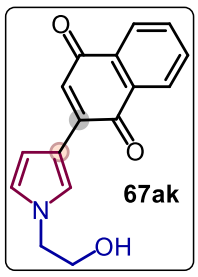
2-(1-(2-(1*H*-indol-3-yl)ethyl)-1*H*-pyrrol-3-yl)naphthalene-1,4-dione (67am). The general procedure was followed with 1, 4-benzaquinone (**62a**, 95 mg, 0.6 mmol), succinaldehyde (**61**, 600 µl, 3.0 M sol, 1.8mmol), tryptamine (**63m**, 144 mg, 0.9 mmol) to furnish **67am** after purification using petroleum ether/ EtOAc (8/2) as eluent; Orange solid (163 mg, 74% yield); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.13 – 8.04 (m, 3H), 7.78 (t, *J* = 1.9 Hz, 1H), 7.74 – 7.68 (m, 2H), 7.58 (dq, *J* = 7.8, 1.0 Hz, 1H), 7.38 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.22 (m, 1H), 7.15 (m, 1H), 7.03 (s, 1H), 6.86 (d, *J* = 2.3 Hz, 1H), 6.62 (dd, *J* = 3.0, 2.1 Hz, 1H), 6.52 (dd, *J* = 3.0, 1.7 Hz, 1H), 4.22 (t, *J* = 7.3 Hz, 2H), 3.26 (td, *J* = 7.3, 0.8 Hz, 2H).**^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 185.7, 185.3, 142.1, 136.2, 133.5, 133.1, 132.9, 132.2, 127.4, 127.0, 126.6, 126.4, 125.6, 122.4, 122.3, 122.2, 119.6, 118.3, 116.2, 111.9, 111.3, 107.7, 50.7, 27.6. **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$ Calcd for $C_{24}H_{19}N_2O_2$ 367.1441; found 367.1446.



2-(1-phenethyl-1*H*-pyrrol-3-yl)naphthalene-1,4-dione (67an). The general procedure was followed with 1, 4-benzaquinone (**62a**, 95 mg, 0.6 mmol), succinaldehyde (**61**, 600 µl, 3.0 M sol, 1.8 mmol), phynylethyl-2-amine (**63n**, 109 mg, 0.9 mmol) to furnish **67an** after purification using petroleum ether/ EtOAc (8/2) as eluent; Orange solid (149 mg, 76% yield); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.11 – 8.06 (m, 1H), 8.06 – 8.02 (m, 1H), 7.73 (t, *J* = 1.9 Hz, 1H), 7.71 – 7.66 (m, 2H), 7.31 – 7.20 (m, 3H), 7.12 – 7.07 (m, 2H), 7.00 (s, 1H), 6.56 (dd, *J* = 3.0, 2.1 Hz, 1H), 6.50 (dd, *J* = 3.0, 1.7 Hz, 1H), 4.12 (dd, *J* = 8.0, 6.8 Hz, 2H), 3.07 (t, *J* = 7.4 Hz, 2H).**^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 185.7, 185.3, 142.0, 137.7, 133.5, 133.1, 132.9, 132.2, 128.7(2C), 128.6(2C), 127.5, 126.8, 126.6, 126.3, 125.6, 122.3, 116.2, 107.8, 51.7, 38.0. **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$ Calcd for $C_{22}H_{18}NO_2$ 328.1332; found 328.1336.

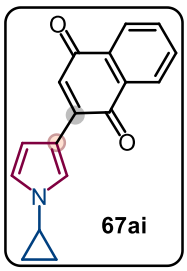


2-(1-(2-hydroxyethyl)-1*H*-pyrrol-3-yl)naphthalene-1,4-dione (67ak). The general procedure was followed with 1, 4-benzaquinone (**62a**, 95 mg, 0.6 mmol), succinaldehyde (**61**, 600 µl, 3.0 M sol, 1.8 mmol), 2-aminoethanol (**63k**, 55 mg, 0.9 mmol) to furnish **67ak** after purification using petroleum ether/ EtOAc (8/2) as eluent; Orange solid (93 mg, 58% yield); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.09 – 8.02

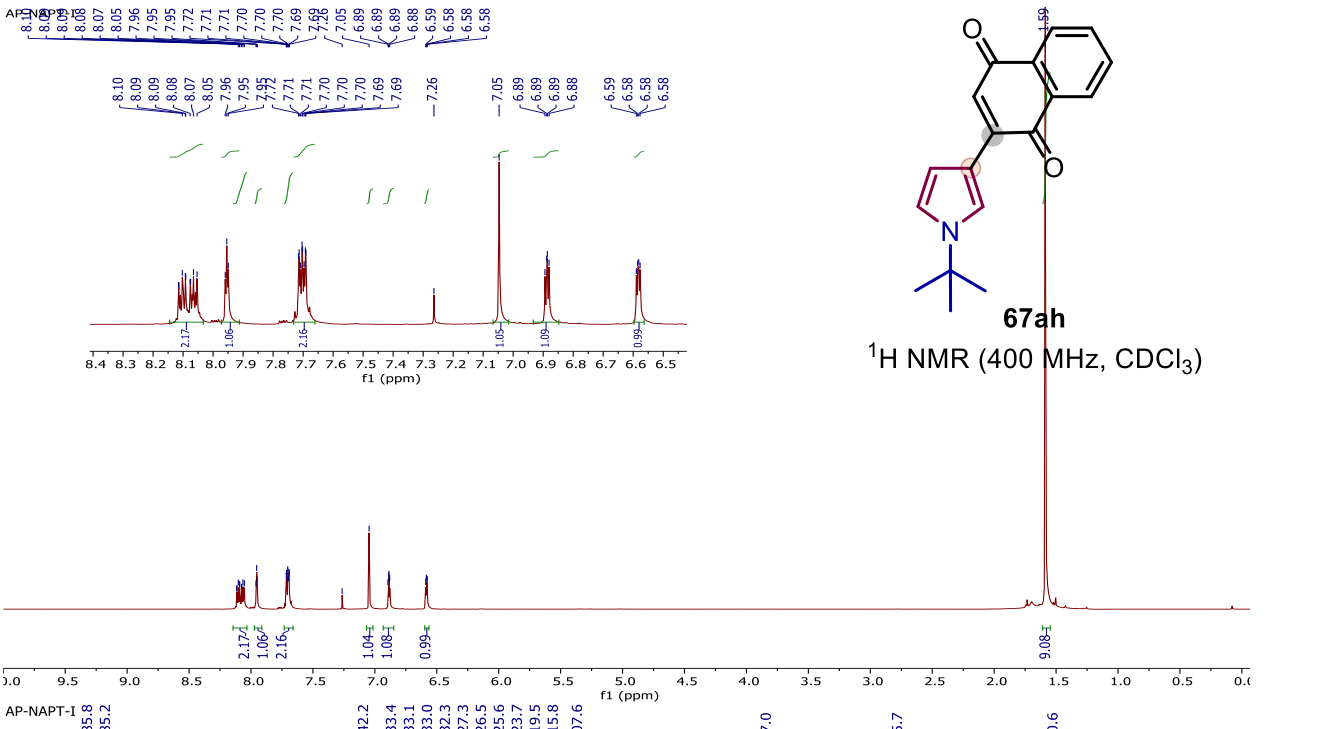


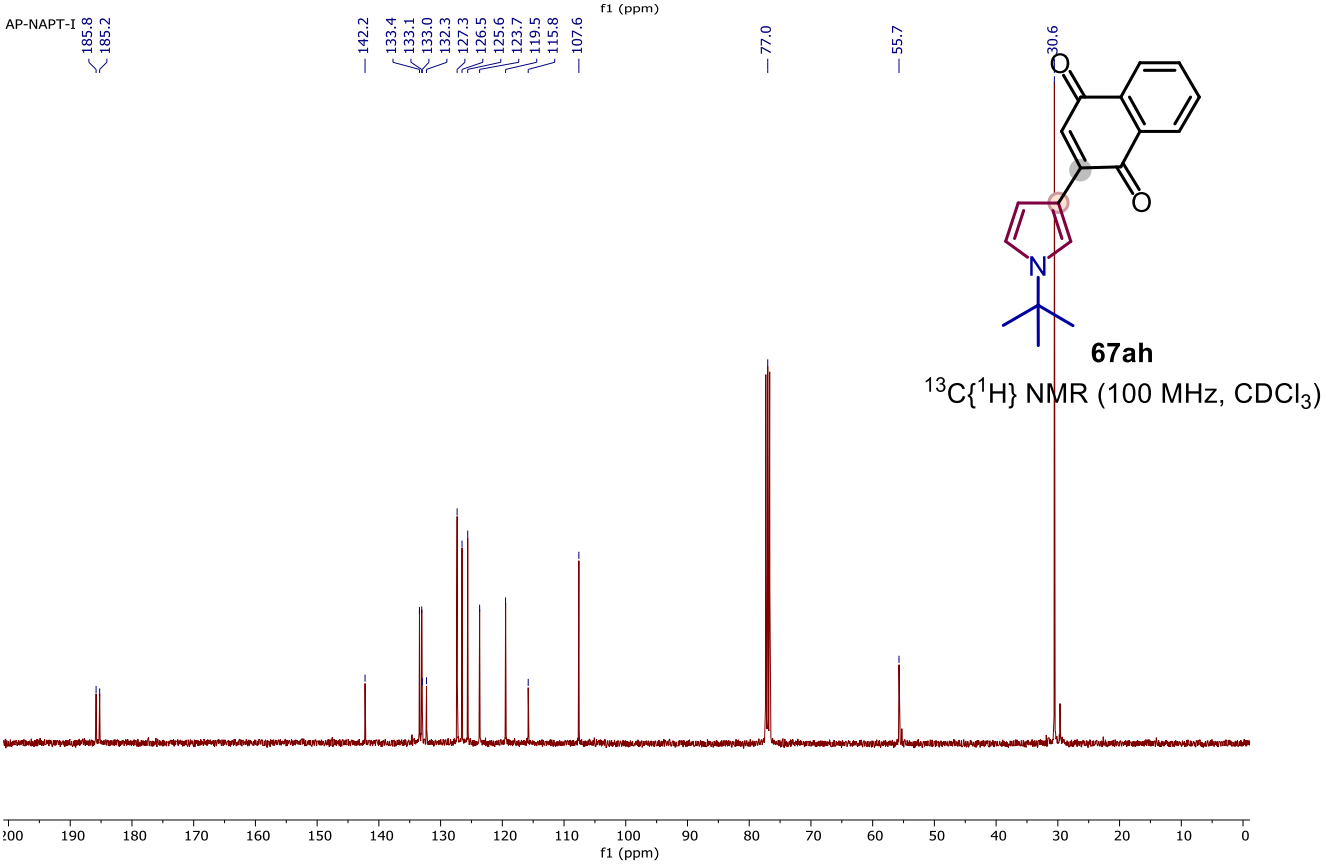
(m, 2H), 7.80 (t, *J* = 1.9 Hz, 1H), 7.71 – 7.68 (m, 2H), 7.00 (s, 1H), 6.74 (dd, *J* = 3.0, 2.1 Hz, 1H), 6.55 (dd, *J* = 3.0, 1.7 Hz, 1H), 4.70 (t, *J* = 5.1 Hz, 1H), 4.07 (dd, *J* = 5.7, 4.6 Hz, 2H), 3.94 (dd, *J* = 5.8, 4.5 Hz, 2H).**^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)** δ 185.6, 185.3, 142.0, 133.6, 133.2, 132.8, 132.2, 127.8, 126.7, 126.6, 125.7, 122.7, 116.6, 108.2, 62.6, 52.4.**HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{14}NO_3$ 268.0968; found 268.0974.

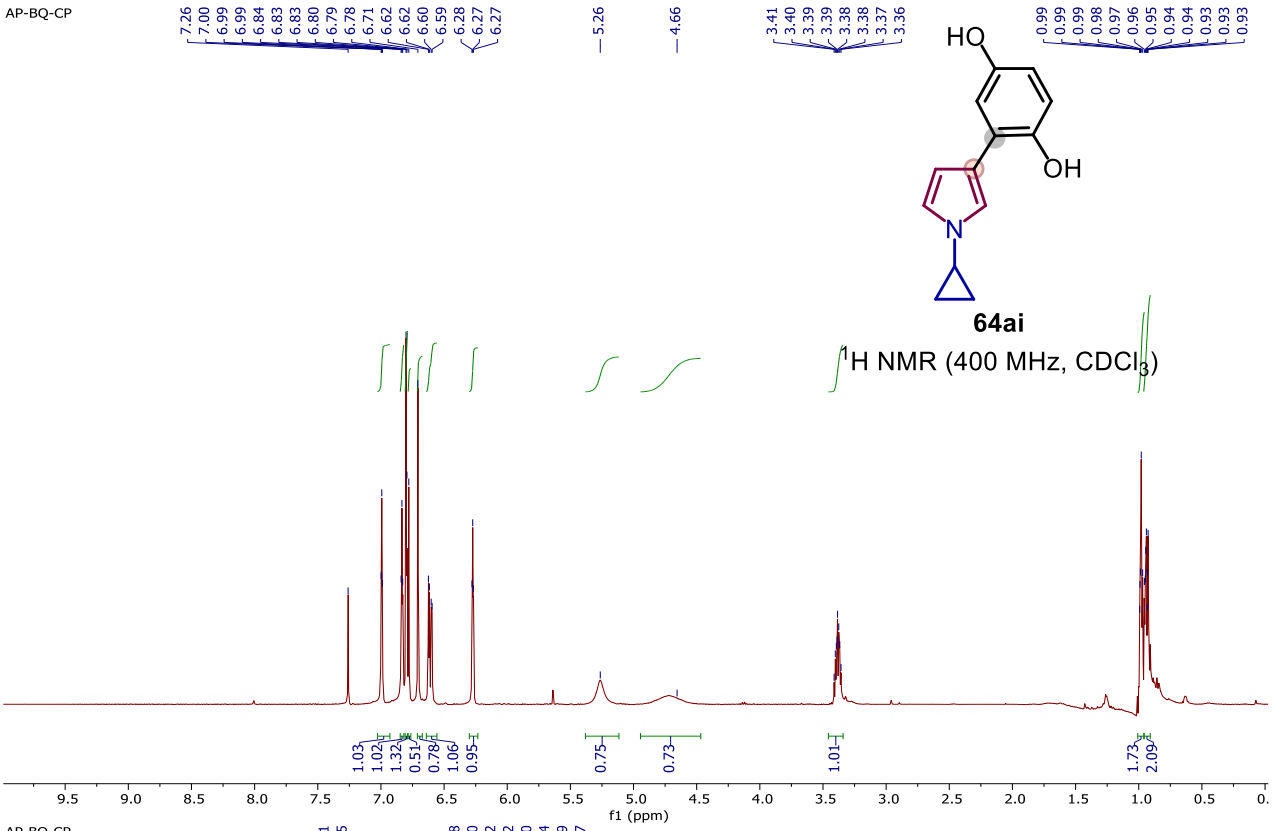
2-(1-cyclopropyl-1*H*-pyrrol-3-yl)naphthalene-1,4-dione (67ai). The general procedure was followed with 1, 4-benzaquinone (**62a**, 95 mg, 0.6 mmol), succinaldehyde (**61**, 600 µl, 3.0 M sol, 1.8 mmol), cyclopropylamine (**63i**, 51 mg, 0.9 mmol) to furnish **67ai** after purification using petroleum ether/ EtOAc (8/2) as eluent; Orange solid (131 mg, 83% yield) **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.15 – 8.08 (m, 1H), 8.09 – 8.03 (m, 1H), 7.85 (t, *J* = 1.9 Hz, 1H), 7.74 – 7.69 (m, 2H), 7.03 (s, 1H), 6.78 (dd, *J* = 3.1, 2.1 Hz, 1H), 6.51 (dd, *J* = 3.1, 1.8 Hz, 1H), 3.46 – 3.34 (m, 1H), 1.03 – 0.95 (m, 4H).**^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)** δ 185.6, 185.3, 142.0, 133.5, 133.2, 132.9, 132.2, 127.8, 127.1, 126.6, 125.7, 123.0, 116.2, 107.7, 30.5, 29.7, 6.40.**HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{14}NO_2$ 264.1019; found 264.1025.



5.7 Spectral Information

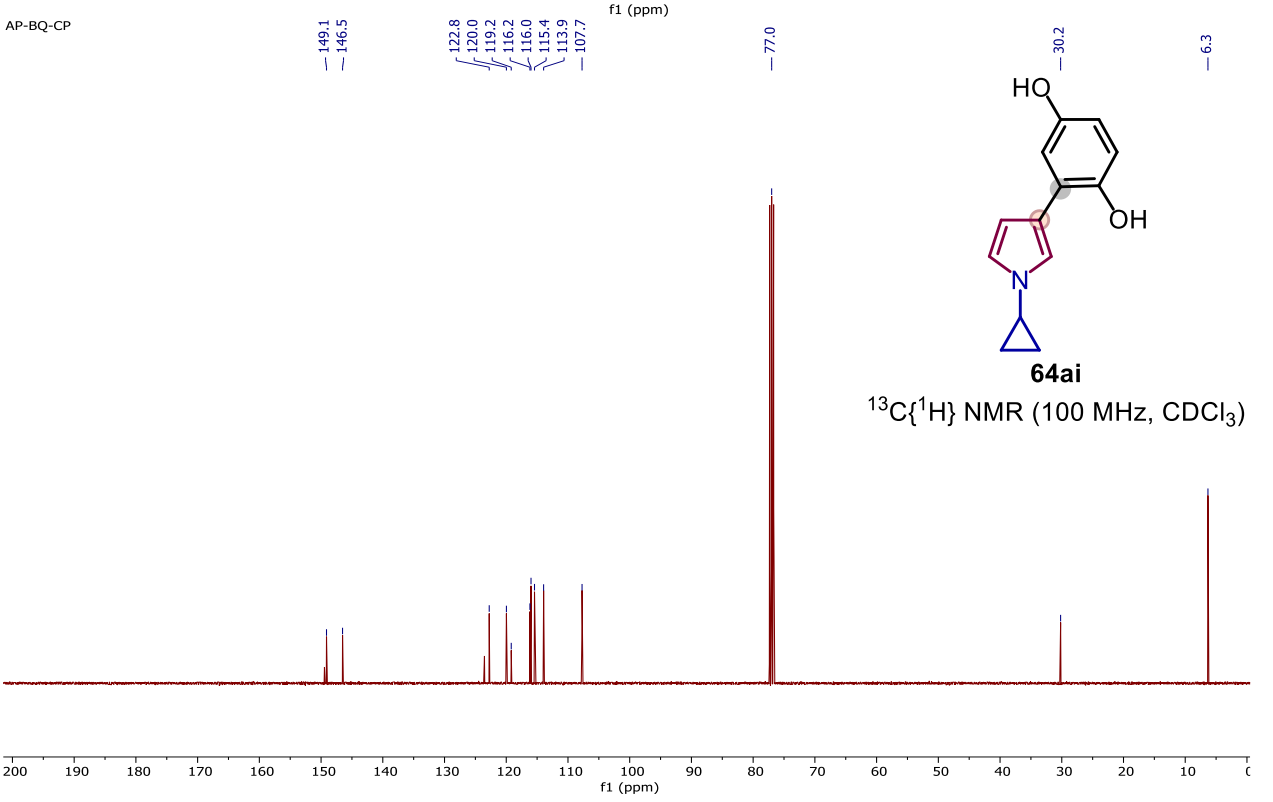






64ai

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



64ai

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)

5.8 Single-crystal X-ray Diffraction Experiment and Analysis

Single Crystal XRD Experiments for 67ae: The single crystal XRD data collection and reduction were performed using CrysAlis PRO on a single crystal Rigaku Oxford XtaLab Pro Kappa dual home/near diffractometer. The crystals were kept at 93(2) K during data collection using CuKα (λ = 1.54184 Å) radiation. Using Olex2[37], the structure was solved with the ShelXT[38] structure solution program using Intrinsic Phasing and refined with the ShelXL[39] refinement package using Least Squares minimization.

Single Crystal structure, Cell parameters, and structure data of compound.

Table 1 Crystal data and structure refinement for exp_1272_IK-AP-NqP-01_20221116.

Identification code	exp_1272_IK-AP-NqP-01_20221116
Empirical formula	$C_{19}H_{19}NO_2$
Formula weight	293.35
Temperature/K	133(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	4.72400(10)
b/Å	23.9337(3)
c/Å	13.2586(2)
α/°	90
β/°	92.5940(10)
γ/°	90
Volume/Å^3	1497.52(4)
Z	4
ρ_{calc}g/cm^3	1.301
μ/mm^{-1}	0.668
F(000)	624.0
Crystal size/mm^3	0.2 × 0.11 × 0.05
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	9.962 to 159.152

Index ranges	$-4 \leq h \leq 5, -30 \leq k \leq 29, -16 \leq l \leq 16$
Reflections collected	7523
Independent reflections	3138 [R_{int} = 0.0224, R_{sigma} = 0.0284]
Data/restraints/parameters	3138/0/200
Goodness-of-fit on F^2	1.074
Final R indexes [I>=2σ (I)]	R_1 = 0.0370, wR_2 = 0.0950
Final R indexes [all data]	R_1 = 0.0400, wR_2 = 0.0969
Largest diff. peak/hole / e $Å^{-3}$	0.29/-0.20

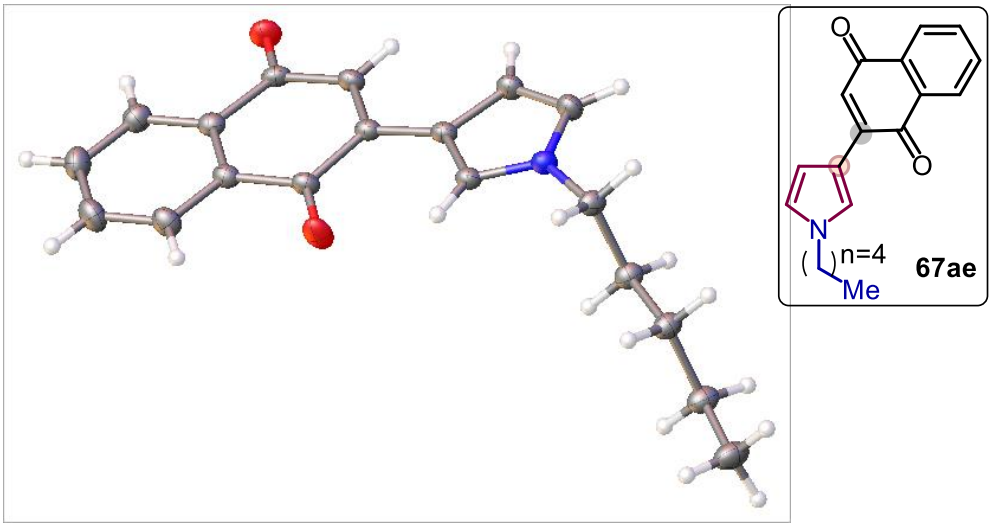


Figure 5.3 Single Crystal X-ray analysis for **67ae**

Experimental

Single crystals of $C_{19}H_{19}NO_2$ **[exp_1272_IK-AP-NqP-01_20221116]** a suitable crystal was selected and analyzed on an **XtaLAB AFC12 (RINC): Kappa dual home/near** diffractometer. The crystal was kept at 133(2) K during data collection. Using Olex2, the structure was solved with the SHELXT structure solution program using Intrinsic Phasing and refined with the SHELXL refinement package using Least Squares minimization.

Crystal structure determination of [exp_1272_IK-AP-NqP-01_20221116]

Crystal Data for $C_{19}H_{19}NO_2$ (*M* =293.35 g/mol): monoclinic, space group $P2_1/c$ (no. 14), *a* = 4.72400(10) Å, *b* = 23.9337(3) Å, *c* = 13.2586(2) Å, *β* = 92.5940(10)°, *V* = 1497.52(4) $Å^3$, *Z* = 4, *T* = 133(2) K, μ(Cu Kα) = 0.668 mm^{-1}, *Dcalc* = 1.301 g/cm^3, 7523 reflections measured

($9.962° \leq 2\Theta \leq 159.152°$), 3138 unique ($R_{int}$ = 0.0224, R_{sigma} = 0.0284) which were used in all calculations. The final R_1 was 0.0370 ($I > 2\sigma(I)$), and wR_2 was 0.0969 (all data).

5.9 References

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Chapter – 6

Overall Conclusion

and

Future Scope

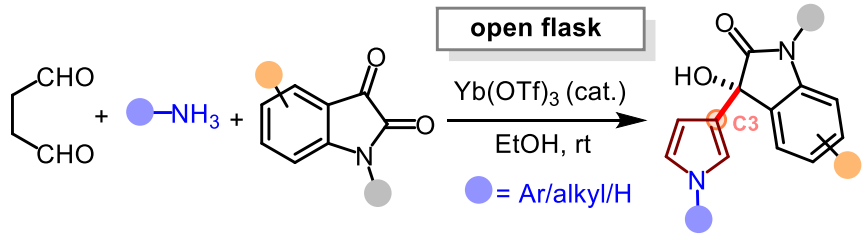
6.1 General Conclusion

The work discussed in this thesis entitled "**Development of Methods for the Direct Synthesis of C3-Functionalized Pyrroles"** provides a brief description of the development of the new method for synthesizing C3-substituted pyrrole form 1,4-dicarbonyls. The developed way is a multicomponent one-pot, domino/ cascade reaction sequence between succinaldehyde and amine and suitable electrophile using mild catalysis or catalyst-free conditions to access pyrrole. The developed strategy utilizes commercially available inexpensive starting substrates such as succinaldehyde, primary amines, and various electrophiles. The central theme of the thesis work relay on the trapping of the enamine intermediate, generated from primary amine and succinaldehyde, with electrophiles before it underwent Paal-Knorr cyclization to furnish C3-substituted pyrrole. The present study provides a complimentary addition to the Paal-Knorr reaction by which C3-substituted pyrrole can be accessed in a non-asymmetric and asymmetric fashion.

6.2 Specific Conclusions

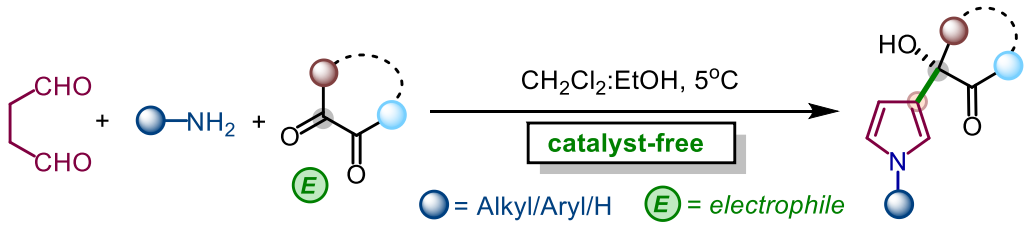
Chapter One briefly discussed amine catalysis and its applications for developing enamine and various transformations, such as direct Aldol reaction, Michael, and cascade reactions. In addition, discussions on the utilization of succinaldehyde for amine-catalyzed conversions to access various carbo-, and heterocyclic compounds have been briefly discussed. Moreover, a literature survey on the existing methods for synthesizing C3-substituted from the selective functionalization of pyrrole or directly from pyrrolidine is also disclosed.

Chapter Two described the mild Lewis acid-catalyzed direct access to C3-functionalized pyrroles with succinaldehyde, isatin, and amine, followed by a Paal Knorr reaction. The developed method has been applied to synthesize C3-substituted pyrrole in gram-scale synthesis. A tentative reaction mechanism has been proposed and is well supported by the DFT calculation.



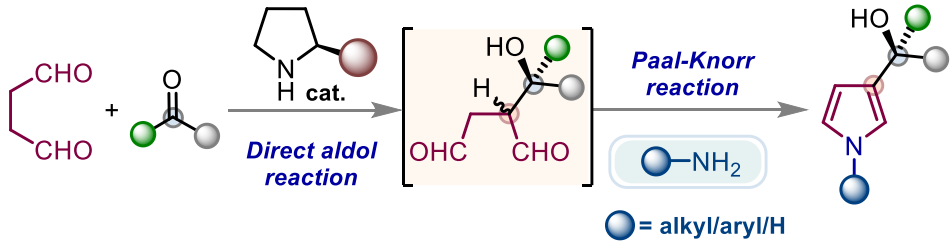
Scheme 6.1 Metal catalyzed direct access to C3-functionalized pyrroles.

Chapter Three revealed the integration of novel Synthetic methods put forward to prepare a direct catalyst-free method for synthesizing *β*-functionalized pyrroles under open-flask conditions. With readily available and inexpensive starting materials such as reactive carbonyls and amines just before the Paal-Knorr reaction was a crucial parameter for developing C3-substituted pyrroles with moderate to good yields. This transformation was further probed computationally and well-supported with close energy profiles, and late-stage modifications on pyrrole were established.



Scheme 6.2 Direct aldol reaction to synthesis catalyst-free *β*-functionalized pyrroles

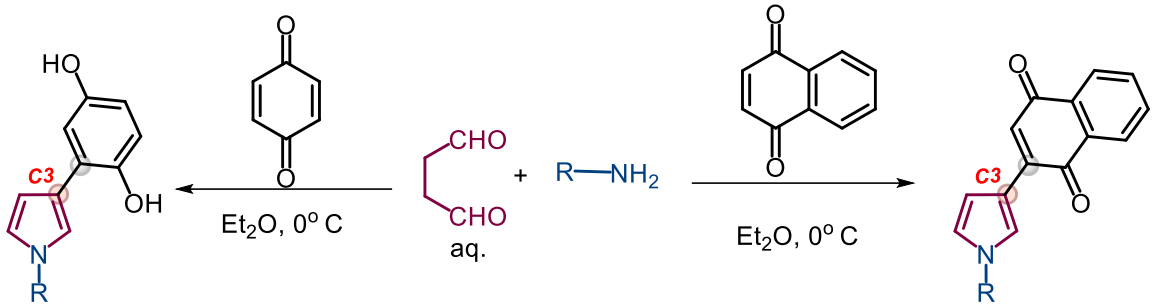
Chapter Four describes the first organocatalytic asymmetric synthesis of pyrrole having a chiral center at the C3-position. In this work, we have utilized the enamine generated from succinaldehyde and chiral amine catalyst for direct aldol reaction to develop the functionalized 1,4-dicarbonyl, which further reacts with a primary amine to furnish C3-substituted pyrroles asymmetrically. The practical utility of the developed protocol was also shown for the gram-scale synthesis of both enantiomers. These synthetic strategies have the potential for the synthesis of novel bioactive compounds and natural products.



Scheme 6.3 Direct-aldol reactions to achieve asymmetric C3-substituted pyrroles synthesis

Chapter Fifth describes a direct method to synthesize *β*-arylated/olefination pyrroles under open-flask catalyst-free conditions. In this method, a direct Michael reaction of in situ generated enamine took place with alkene dienophile, afterword the Paal-Knorr with primary amine furnish C3-arylated/olefination pyrroles. The suitability of α,β–unsaturated 1,4-quinone units has been tested as a Michael acceptor under the developed conditions. Interestingly, C3-arylated pyrrole was obtained when benzoquinones were used as Michael acceptor, while C3-alkenylated pyrrole was

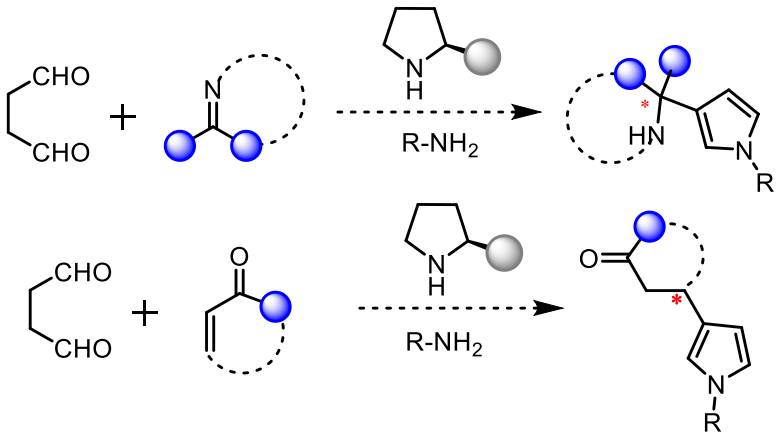
obtained when naphthoquinone was employed under standard conditions. Several C3-arylated/alkenylated pyrroles were obtained with moderate to good yields.



Scheme 6.4 Michal-type addition of quinone to synthesis *β*-functionalized pyrroles

6.3 Future Scope of the Research Work

It is clear from the above discussion that the research work carried out is exciting and showcases new methods for synthesizing C3-substituted pyrrole. Some of the synthesized C3-substituted pyrroles may find exciting applications in medicinal chemistry. The developed method can bring other functionality at C3-position of pyrrole in asymmetric and non-asymmetric fashion. The developed protocol utilizes readily available starting materials to create functionality at position C3 of pyrrole. Now, the future scope of this work is quite clear. We intend to utilize other cyclic and acyclic aldimines/ketamine and use different α, β-substituted carbonyl compounds to create functionality at position C3 of pyrrole (Scheme 6.5).



Scheme 6.5 Amine catalyzed direct synthesis of *β*-functionalized pyrroles.

Appendices

11. A survey on the synthesis of C3-substituted pyrrole: **Amol P. Pawar**, J. Yadav, Manuscript Under preparation (**2022**)
10. Electrochemical Oxidative Addition of Nucleophiles on 2-Arylindoles: Synthesis of C2-Heteroquaternary Indolin-3-ones. Y. K. Nagare, I. A. Shah, J. Yadav, **Amol P. Pawar**, K. Rangan, R. Choudhary, E. Iype, Indresh Kumar, ***J. Org. Chem.*, 2022, *87*, 15771-15782.**
9. Enantioselective Direct Synthesis of C3-Hydroxyalkylated Pyrrole via an Amine-Catalyzed Aldol/Paal–Knorr Reaction Sequence. **Amol P. Pawar**, J. Yadav, A. J. Dolas, Y. K. Nagare, E. Iype, K. Rangan, I. Kumar, ***Org. Lett.*, 2021, *24*, 7549–7554**.
8. Catalyst-free direct regiospecific multicomponent synthesis of C3-functionalized pyrroles, Manuscript under preparation, **Amol P. Pawar**, J. Yadav, A. J. Dolas, E. Iype, K. Rangan, Indresh Kumar, ***Org. Biomol. Chem.*, 2022, *20*, 5747-5758.**
7. Two-pot synthesis and photophysical studies of 1,6-disubstituted 5-aza-indoles from succinaldehyde and N-aryl propargylic-imines; S. Vanaparthi, Mamta, J. Yadav, **Amol P. Pawar**, E. Iype, K. Rangan, S. Rana, I. Kumar; ***Org. Biomol. Chem.*, 2021, *19*, 10601-10610**.
6. Electrochemical Oxidative Coupling between Benzylic C(sp^3)-H and N-H of Secondary Amines: Rapid Synthesis of α-Amino α-Aryl Esters. Y. K. Nagare, I. A. Shah, J. Yadav, **Amol P. Pawar**, R. Choudhary, P. Chauhan, I. Kumar. ***J. Org. Chem.*, 2021, *86*, 9682-9691.**
5. Direct catalytic synthesis of β-(C3)-substituted pyrroles: A complementary addition to the Paal-Knorr reaction. **Amol P. Pawar**, J. Yadav, N. A Mir, E. Iype, K. Rangan, S. Anthal, R. Kant, I. Kumar, ***Chem. Commun.*, 2021**, *57*, **251-254**.
4. Direct Amine-Catalyzed Enantioselective Synthesis of Pentacyclic Dibenzo[*b*,*f*][1,4]oxazepine /Thiazepine-Fused Isoquinuclidines along with DFT Calculations. J. Yadav, **Amol P. Pawar**, Y. K. Nagare, E. Iype, K. Rangan, J. Ohshita, D. Kumar, I. Kumar, ***J. Org. Chem.*, 2020, *85*, 14094-14108.**
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2. Enantio- And Diastereoselective Two-Pot Synthesis of Isoquinuclidines from Glutaraldehyde and N-Aryl Imines with DFT Calculations. P. Ramaraju, **Amol P. Pawar**, E. Iype, N. A. Mir, S. Choudhary, D. K. Sharma, R. Kant, I. Kumar, ***J. Org. Chem.*, 2019, *84*, 12408-12419.**
1. One-Pot Synthesis of Chiral Tetracyclic Dibenzo[*b*,*f*][1,4]oxazepine-Fused 1,2-Dihydropyridines (DHPs) under Metal-Free Conditions. S. Choudhary, **Amol P. Pawar**, J. Yadav, D. K. Sharma, R. Kant, I. Kumar, ***J. Org. Chem.*, 2018, *83*, 9231-9239.**

1. **Amol Prakash Pawar,** I. Kumar, "Organocatalytic enantioselective synthesis of Fused 1,2-Dihydropyridines via formal [4+2] cycloaddition between aq. Glutaraldehyde and Dibenzo[*b*,*f*][1,4]oxazepine imines" at 25th **ISCBC-2019**, ISCB, Lucknow, India, January 12-14, 2019. (Poster presentation)
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4. **Amol Prakash Pawar,** I. Kumar, "Enantio- and Diastereoselective Two-Pot Synthesis of Isoquinuclidines from Glutaraldehyde and *N*-Aryl Imines with DFT Calculations" at 26th **ISCBC**-NIPiCON-**20**20, Nirma University, Ahmadabad, India, January 22-24, 2020. (Oral presentation)
5. **Amol Prakash Pawar,** I. Kumar, "Lewis-Acid Catalyzed Direct Synthesis of β–Substituted Pyrroles: A Complementary Addition to the Paal-Knorr Reaction" **One-day MINI-SYMPOSIUM,** Department of Chemistry, BITS Pilani, Pilani (Rajasthan), India February 28, 2022. (Poster presentation).
6. **Amol Prakash Pawar,** I. Kumar, "Lewis-Acid Catalyzed Direct Synthesis of β–Substituted Pyrroles: A Complementary Addition to the Paal-Knorr Reaction" # **RSC Poster-2022**, Twitter Web, Online Mode, March 01, 2022. (Poster presentation)

Brief biography of the candidate A-3

Amol Prakash Pawar was born on 30th July 1991 in Hatnoor, Tq. Kannad, Dist. Aurangabad, Maharashtra (India). He completed his master's degree from the Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University Aurangabad Maharashtra, in 2014. In June 2016, he was awarded UGC-LS in chemical sciences (A. I. Rank =18) by UGC-New Delhi, Govt. of India. In May 2017, he joined the Department of Chemistry, BITS Pilani, for a Ph.D. under Prof. Indresh Kumar guidance. In March 2019, he was awarded DST-SERB-SRF in chemical sciences by UGC-New Delhi, Govt. of India. He has published ten research articles in international journals; some are being communicated, and a few others are being prepared for the manuscript. He presented his papers at many national/international conferences/symposiums. His research interest lies in developing a new methodology to synthesize non-asymmetric asymmetric and bioactive heterocyclic-based pyrroles and their biological activity.

Brief biography of the supervisor [A4]

Prof. Indresh Kumar is an Professor of Chemistry at the Birla Institute of Technology and Science Pilani, Pilani campus (Rajasthan). Dr. Kumar did his B.Sc. (Chemistry) and M.Sc. (Organic Chemistry) from Ch. Charan Singh University, Meerut (U.P), India. He completed his Ph.D. in Organic Chemistry from National Chemical Laboratory (CSIR), Pune, with Dr. C. V. Rode (Scientist-F) from 2007-08. He did his Post-doctoral research work with Prof. Yujiro Hayashi at the Tokyo University of Sciences, Tokyo. He joined Shri Mata Vaishno Devi University, Katra (J&K), India, as Assistant Professor in Chemistry in 2009 and continued till January 2012.

Prof. Kumar is the recipient of "Professor D.K. Banerjee Memorial Lecture Award-2016" from the Department of Organic Chemistry, IISc., Bangalore., award of "Outstanding Potential for Excellence in Research and Academics (OPERA)" during 2014-15 from BITS Pilani, ISCB Young Scientist award in Chemical Sciences from Indian Society of Chemists and Biologists, Lucknow for 2016. He has 14 years of research experience and 12 years of teaching experience. He has authored 51 research papers in peer-reviewed journals, and his work has been widely recognized and cited by the scientific community. He has participated in several national and international symposia/conferences and delivered more than 45 invited lectures. Four (04) students (as sole supervisor) and two (02) students (as co-supervisor) have already obtained Ph.D. degrees; seven (07) students are currently pursuing research for their Ph.D. research under his guidance. Dr. Kumar has completed five research projects as Principal Investigator sponsored by UGC, DST-SERB New Delhi, and BITS Pilani. Currently, he has one major project from DST-SERB New Delhi and another continued industry project sponsored by Praveen Labs Pvt. Ltd. (Surat). He has also served as a reviewer for several journals. He is a lifetime member of the Indian Society of Chemists and Biologists, Lucknow, and the Chemical Research Society of India, Bangalore. Prof. Kumar has authored a book entitled "Dienamine Catalysis for Organic Synthesis" published by RSC-London. His main research interests are asymmetric organocatalysis, the development of new synthetic methodology, and the total synthesis of biologically active compounds.

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One-Pot Synthesis of Chiral Tetracyclic Dibenzo[*b*,*f*][1,4]oxazepine-Fused 1,2-Dihydropyridines (DHPs) under Metal-Free Conditions

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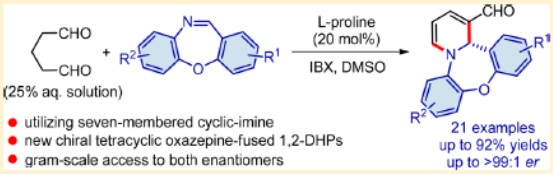
Supporting Information

ABSTRACT: An efficient protocol for the catalytic asymmetric synthesis of new dibenzo[*b*,*f*][1,4]-oxazepine-fused 1,2-dihydropyridines (DHPs) has been described under metal-free conditions. This reaction proceeds through proline-catalyzed direct Mannich/cyclization between seven-membered dibenzo[*b*,*f*][1,4]-oxazepine-imines and aqueous glutaraldehyde, followed by IBX-mediated site-selective dehydrogenative oxidation in one-pot operation with high yields (up to 92%) and excellent enantioselectivity (up to >99:1 er).



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Enantio- and Diastereoselective Two-Pot Synthesis of Isoquinuclidines from Glutaraldehyde and *N*-Aryl Imines with DFT Calculations

Panduga Ramaraju,[†] Amol Prakash Pawar,[†] Eldhose Iype,[‡] Nisar A. Mir,[†] Sachin Choudhary,[†] Devinder Kumar Sharma,[§] Rajni Kant,[§] and Indresh Kumar*[,†]

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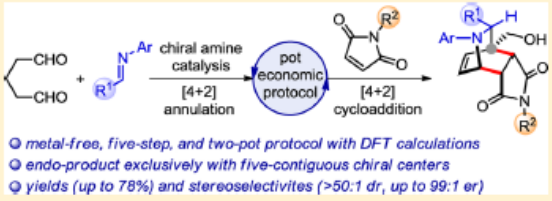
Supporting Information

ABSTRACT: A pot-economic method for the enantio- and diastereoselective synthesis of a [2.2.2] azabicyclic isoquinuclidine system is developed. This protocol involves the proline-catalyzed direct Mannich reaction-cyclization/IBX-mediated site-selective oxidation/$NaBH_4$-reduction sequence between glutaraldehyde and imines to generate in situ chiral 1,2-DHPs, followed by the diastereoselective Diels−Alder reaction with *N*-aryl maleimides furnishing isoquinuclidines in overall five steps. A variety of isoquinuclidines having five-contiguous chiral centers, including an all-carbon quaternary, were prepared with high yields (up to 78%) and excellent stereoselectivity (>50:1 dr, and up to >99:1 er). DFT calculations support the observed high stereoselective reaction outcome.



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Sequential multicomponent site-selective synthesis of 4-iodo and 5-iodopyrrole-3-carboxaldehydes from a common set of starting materials by tuning the conditions†

Sachin Choudhary,[a] Jyothi Yadav,[a] Mamta,[a] Amol Prakash Pawar,[a] Satheeshvarma Vanaparthi,[a] Nisar A. Mir,[a] Eldhose Iype,[b] Ratika Sharma,[c] Rajni Kant[c] and Indresh Kumar *[a]

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A simple and straightforward method for the synthesis of 4-iodo and 5-iodopyrrole-3-carboxaldehydes is developed from a common set of starting materials by tuning the reaction conditions. This sequential multicomponent protocol involves I_2-mediated regioselective C4-iodination and aromatization of intermediate dihydropyrrole, generated through proline-catalyzed direct Mannich reaction-cyclization sequence between succinaldehyde and imines, to access 4-iodopyrroles. While aerobic oxidative aromatization of dihydropyrrole to pyrrole followed by NIS-mediated regioselective iodination furnished 5-iodopyrroles in a two-pot fashion. A series of site-selective C4/C5-iodopyrroles have been synthesized in good to high yields (up to 78%) and DFT calculations of these compounds were also performed.

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Direct Amine-Catalyzed Enantioselective Synthesis of Pentacyclic Dibenzo[*b*,*f*][1,4]oxazepine/Thiazepine-Fused Isoquinuclidines along with DFT Calculations

Jyothi Yadav, Amol Prakash Pawar, Yadav Kacharu Nagare, Eldhose Iype, Krishnan Rangan, Joji Ohshita, Dalip Kumar, and Indresh Kumar*

Cite This: *J. Org. Chem.* 2020, 85, 14094–14108 Read Online

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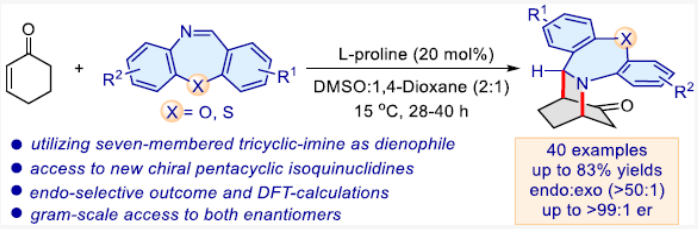

ABSTRACT: A direct protocol for the asymmetric synthesis of dibenzoxazepine/thiazepine-fused [2.2.2] isoquinuclidines is developed. The reaction proceeds through a proline-catalyzed direct Mannich reaction followed by an intramolecular aza-Michael cascade sequence between 2-cyclohexene-1-one and various tricyclic imines, like dibenzoxazepines/thiazepines, as an overall [4 + 2] aza-Diels–Alder reaction. A series of pentacyclic isoquinuclidines have been prepared, with complete endo-selectivity, in good to high yields and excellent enantioselectivity (>99:1). Density functional theory (DFT) calculations further support the observed high stereochemical outcome of the reaction.

ChemComm

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Direct catalytic synthesis of β-(C3)-substituted pyrroles: a complementary addition to the Paal–Knorr reaction†

Amol Prakash Pawar,[a] Jyothi Yadav,[a] Nisar Ahmad Mir,[a] Eldhose Iype,[b] Krishnan Rangan,[c] Sumati Anthal,[d] Rajni Kant[d] and Indresh Kumar *[a]

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Electrochemical Oxidative Coupling Between Benzylic C(sp^3)–H and N–H of Secondary Amines: Rapid Synthesis of α-Amino α-Aryl Esters

Yadav Kacharu Nagare, Imtiyaz Ahmad Shah, Jyothi Yadav, Amol Prakash Pawar, Rahul Choudhary, Pankaj Chauhan, and Indresh Kumar*

Cite This: *J. Org. Chem.* 2021, 86, 9682–9691

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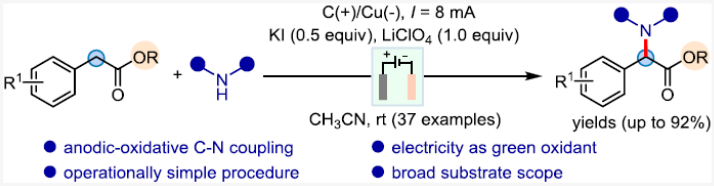

ABSTRACT: An intermolecular electrochemical coupling between the benzylic C(sp^3)–H bond and various secondary amines is reported. The electronic behavior of two electronically rich units viz the α-position of α-aryl acetates and amines was engineered electrochemically, thus facilitating their reactivity for the direct access of α-amino esters. A series of acyclic/cyclic secondary amines and α-aryl acetates were tested to furnish the corresponding α-amino esters with high yields (up to 92%) under mild conditions.

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Cite this: *Org. Biomol. Chem.*, 2021, **19**, 10601

Two-pot synthesis and photophysical studies of 1,6-disubstituted 5-aza-indoles from succinaldehyde and *N*-aryl propargylic-imines†

Satheeshvarma Vanaparthi, *[a] Mamta,[a] Jyothi Yadav,[a] Amol Prakash Pawar,[a] Eldhose Iype,[b] Sravendra Rana [c] and Indresh Kumar *[a]

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Accepted 17th November 2021

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rsc.li/obc

A two-pot synthesis of 5-aza-indoles has been developed from aqueous succinaldehyde and *N*-aryl propargylic-imines. This overall protocol involves: (i) the metal-free [3 + 2] annulation of aqueous succinaldehyde and *N*-aryl propargylic-imines to access 2-alkynyl-pyrrole-3-aldehydes and (ii) Ag-catalyzed 6-*endo*-*dig*-cyclization to obtain substituted 5-aza-indoles in the second pot. The 5-aza-indoles showed engaging photophysical activities, and the practicality of this pot-economic gram-scale synthesis has been demonstrated.

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Cite this: *Org. Biomol. Chem.*, 2022, **20**, 5747

Catalyst-free direct regiospecific multicomponent synthesis of C3-functionalized pyrroles†

Amol Prakash Pawar,[a] Jyothi Yadav,[a] Atul Jankiram Dolas,[a] Eldhose Iype, [b] Krishnan Rangan[c] and Indresh Kumar *[a]

Received 20th May 2022,
Accepted 23rd June 2022

DOI: 10.1039/d2ob00961g

rsc.li/obc

An operationally simple catalyst-free protocol for the direct regiospecific synthesis of β-(C3)-substituted pyrroles has been developed. The enamine intermediate, *in situ* generated from succinaldehyde and a primary amine, was trapped with activated carbonyls before the Paal–Knorr reaction in a direct multicomponent "just-mix" fashion to furnish pyrroles with overall good yields. Several C3-substituted *N*-alkyl/aryl/H pyrroles have been produced under open-flask conditions with high atom economy and avoiding protection–deprotection chemistry.

OL | Organic Letters

pubs.acs.org/OrgLett Letter

Enantioselective Direct Synthesis of C3-Hydroxyalkylated Pyrrole via an Amine-Catalyzed Aldol/Paal–Knorr Reaction Sequence

Amol Prakash Pawar, Jyothi Yadav, Atul Jankiram Dolas, Yadav Kacharu Nagare, Eldhose Iype, Krishnan Rangan, and Indresh Kumar*

Cite This: https://doi.org/10.1021/acs.orglett.2c02922 Read Online

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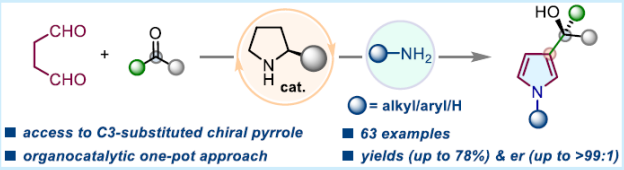

ABSTRACT: Creating functionality with chirality at position C3 of pyrrole is challenging. An operationally simple organocatalytic method has been developed to generate functionality with a chiral tertiary/quaternary stereocenter at position C3 of pyrrole. The process proceeds through an amine-catalyzed direct aldol reaction of succinaldehyde with various acceptor carbonyls, followed by a Paal–Knorr reaction with a primary amine in the same pot. A series of chiral C3-hydroxyalkylated *N*-alkyl/Ar/H-pyrroles have been synthesized for the first time with good to high yields and excellent enantioselectivity.

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Electrochemical Oxidative Addition of Nucleophiles on 2-Arylindoles: Synthesis of C2-Heteroquaternary Indolin-3-ones

Yadav Kacharu Nagare, Imtiyaz Ahmad Shah, Jyothi Yadav, Amol Prakash Pawar, Krishnan Rangan, Rahul Choudhary, Eldhose Iype, and Indresh Kumar*

Cite This: https://doi.org/10.1021/acs.joc.2c01734 Read Online

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ABSTRACT: An electrochemical method has been developed to synthesize 2,2-disubstituted indolin-3-ones under mild conditions. A series of nucleophiles have been added to the 2-arylindole-3-ones, generated in situ under metal-free electrochemical oxidative dearomatization of 2-arylindoles, to afford 2,2-disubstituted 3-carbonyl indoles with heteroquaternary centers in 57–79% yields.