Max-Planck-Institut für
molekulare Physiologie

Technische Universität
Dortmund

Development of Efficient Methods for the Syntheses of Heterocycles *via* Direct C–H Bonds Functionalization

Dissertation

zur Erlangung des akademischen Grades eines

Doktors der Naturwissenschaften

(Dr. rer. nat.)

von der Fakultät Chemie und Chemische Biologie

der Technischen Universität Dortmund

vorgelegt von

M. Sc. **Zengqiang Song**

aus Tianshui

Dekan: Prof. Dr. Insa Melle
1. Gutachter: Prof. Dr. Herbert Waldmann
2. Gutachter: Prof. Dr. Guido Clever

Eingereicht am: 25.07.2016
Datum der mündlichen Prüfung: 08.09.2016

Die vorliegende Arbeit entstand im Zeitraum von September 2012 bis Juni 2016 unter Anleitung von Prof. Dr. Herbert Waldmann und Dr. Andrey P. Antonchick an der Fakultät für Chemie und Chemische Biologie der Technischen Universität Dortmund und dem Max-Planck-Institut für molekulare Physiologie, Dortmund.

This thesis was prepared between September 2012 and June 2016 under the supervision of Prof. Dr. Herbert Waldmann and Dr. Andrey P. Antonchick at the Department of Chemistry and Chemical Biology of the Technical University of Dortmund and the Max Planck Institute of Molecular Physiology, Dortmund.

Teile dieser Arbeit wurden bereits in folgender Publikation veröffentlicht:

Part of the work was published in the following papers:

1. **Rhodium(III)-Catalyzed Direct Regioselective Synthesis of 7-Substituted Indoles**

   Zengqiang Song, Rajarshi Samanta, Andrey P. Antonchick

   Org. Lett. **2013**, *15*, 5662–5665

2. **Iridium(III)-Catalyzed Regioselective C7-Sulfonamidation of Indoles**

   Zengqiang Song, Andrey P. Antonchick

   Org. Biomol. Chem. **2016**, *14*, 4804–4808

3. **Cataching *α*-Aminoalky Radicals: Cyclization between Tertiary Alkylanilines and Alkenes**

   Zengqiang Song, Andrey P. Antonchick

   Tetrahedron, **2016**, *72*, DOI:10.1016/j.tet.2016.04.052

For My Family

Table of Contents

Abstract

Heterocyclic compounds are extensively present in natural products and bioactive compounds, the synthesis of these compounds attracts attention from synthetic chemists. Although various methods have been established to prepare heterocyclic compounds, limited functional group tolerance and the requirement for a prefunctionalized starting material weaken the synthetic value of those methods. Therefore, new approaches for the straightforward synthesis and functionalization of these compounds are highly desirable.

Based on transition-metal catalysis, two novel reaction methodologies for the synthesis of C7-substituted indoles were developed. The first method was conducted *via* rhodium(III)-catalyzed regioselective alkenylation and subsequent oxidation in a one-pot fashion; the second method was accomplished by iridium(III)-catalyzed regioselective amination using sulfonyl azides as a nitrogen source. Both protocols feature excellent regioselectivity, high efficiency and good tolerance with different functional groups. Subsequently, two novel approaches to construct nitrogen-containing heterocycles were achieved through direct functionalization of $C(sp^3)$–H bond at *a*-position of tertiary amines. Cyclizations between tertiary arylamines and electron-deficient alkenes *via* *α*-aminoalkyl radicals, which were generated by TBAI/TBHP, laid the groundwork for the described transformation. Tertiary arylamines even with strong electron-withdrawing groups yielded the desired products under this newly developed reaction condition. The other described approach was the construction of imidazo[4,5-*b*]pyridines through iminium ion intermediates, which were *in situ* formed by oxidation of electron-deficient amines. 3-Amino pyridines with dialkyl amino groups at the C2-postion rapidly delivered the desired products using $T^+BF_4^-$ as oxidant at ambient temperature.

A series of compounds were synthesized by these novel strategies. All of them were subjected to various cell-based assays to investigate potential modulation of important biological pathways.

Kurzfassung

Indole und dessen Derivate sind ein häufiger Bestandteil von Naturstoffen und bioaktiven Verbindungen. Auch wenn bereits erfolgreich Methoden zur Synthese heterocyclischer Verbindungen etabliert wurden, ist deren synthetischer Nutzen häufig durch ein limitiertes Substratspektrum oder das Erfordernis eines prefunktionalisierten Startmaterials begrenzt. Aus diesem Grund sind neue und zielgerichtete Methoden zur Synthese und Funktionalisierung dieser Verbindungen von hohem Interesse.

Basierend auf Übergangsmetallkatalyse wurden zwei neue Reaktionsmethoden zur Synthese von C7-substutierten Indolen entwickelt. Die erste Methode wurde mittels Rhodium(III)-katalysierter Alkenylierung mit anschließender Oxidation im Ein-Topf-Verfahren durchgeführt. Die zweite Methode basierte auf einer Iridium(III)-katalysierten regioselektiven Aminierung, wobei Sulfonylazide als Stickstoffquelle verwendet wurden. Beide Protokolle erzielten exzellente Regioselektivität, hohe Atomeffizienz und gute Toleranz gegenüber verschiedenen funktionellen Gruppen.

Zwei neue Ansätze zur Konstruktion Stickstoff-haltiger Heterocyclen, durch die direkte Funktionalisierung einer C(sp^3)-H Bindung, in Nachbarschaft zu einem Stickstoffatom, wurden im Folgenden etabliert. Cyclisierung eines tertiären Arylamines und elektron-armen Alkenen, durch die Bildung eines α-Aminoalkylradikals mit TBAI/TBHP, stellte die Grundlage für die entwickelte Transformation dar. Tertiäre Arylamine, sogar mit stark elektronen-ziehenden Gruppen, bildeten die gewünschten Produkte mit Hilfe der neuentwickelten Reaktionsbedingungen. Der zweite Ansatz erzielte die Konstruktion von Imidazo[4,5-*b*]pyridinen durch die *in situ* Generierung eines Iminiumions, durch die Oxidation von elektronenarmen Aminen. 3-Aminopyridine ausgestattet mit Dialkylaminogruppen an der C2-Position lieferten die Zielverbindungen bei Raumtemperatur unter Verwendung von $T^+BF_4^-$ als Oxidationsmittel in kurzer Reaktionszeit.

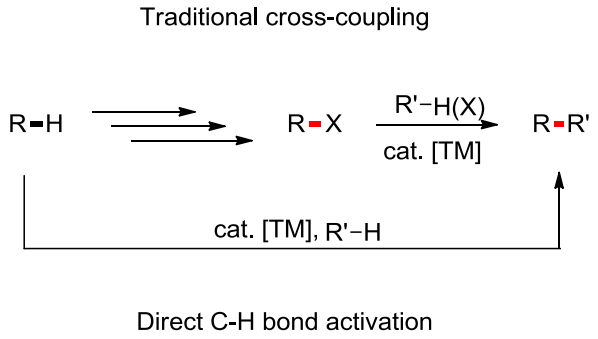
Eine Vielzahl an interessanten Verbindungen wurde mit Hilfe dieser neuen Strategien

synthetisiert. Alle Verbindungen wurden auf potentielle Modulierung von wichtigen biologischen Signalwegen in verschiedenen Zell-basierten Assays getestet.

1. Introduction

1.1 Transition-Metal-Catalyzed C–H Bond Activation

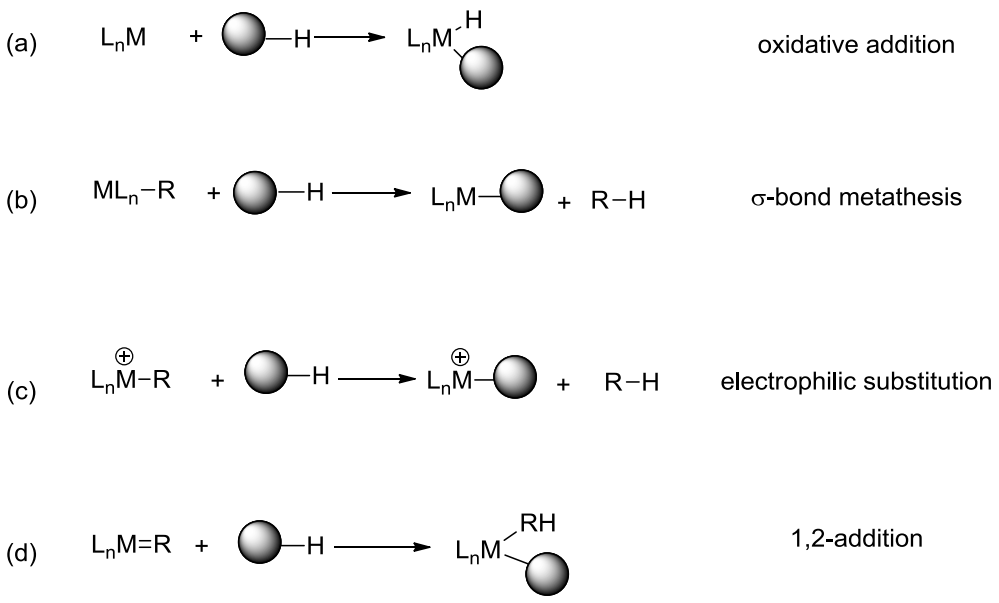
As an efficient synthetic tool, transition-metal-catalyzed cross-coupling[1] is frequently used to the synthesis and functionalization of heterocyclic compounds which are widely present in natural products and bioactive compounds.[2] This strategy requires prefunctionalized starting materials for the reactivity and selectivity of reactions. The extra steps for the functionalization of starting materials usually limit their applicability, increasing the number of reaction steps and produce waste. In contrast to it, transition-metal-catalyzed C–H bond activation[3] allows the use of starting materials without prefunctionalization in the reactions (Scheme 1.1). This new strategy not only improves the efficiency of multistep reactions, but also enlarges the substrate scope of reactions.



Scheme 1.1 Comparison between traditional cross-coupling and direct C–H bond activation.

In 1960s, methods for activation of inert C–H bond using stoichiometric amounts of transition-metal complexes were developed.[4] After 20 years, catalytic amounts of transition-metal complexes were used to the reactions of C–H bond cleavage.[5] Since then, substantial methods *via* catalytic C–H bond functionalization to form C–C and C–heteroatom bonds were reported.[5–7] Accordingly, numerous pharmaceutically

active compounds and natural products had been synthesized on the basis of this strategy.[6] The mechanism of C–H bond metalation has various pathways, depending on the nature of the metal, ligand and other parameters.[3,5–7] Four different routes are frequently used for the C–H bond insertion of metals (Scheme 1.2): a) oxidative addition for electron rich late transition metals;[7a] b) σ-bond metathesis for early transition metals;[7f] c) electrophilic activation for late or post transition metals;[7b] d) 1,2-addition for early to middle transition metals with unsaturated M=X bond.[7c]

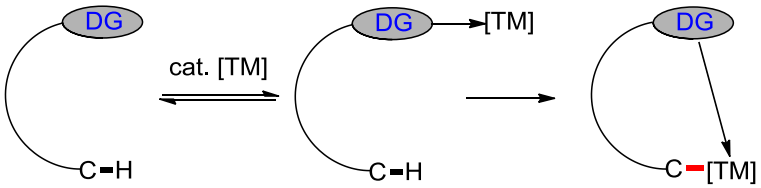


Scheme 1.2 Simplified presentation of different mechanisms for C–H bond metalation.[3,5,6,7]

There are two main challenges should be overcome before the transition-metal-catalyzed C–H bond functionalization becomes a feasible tool in synthetic chemistry. The first one is the reactivity of C–H bond, as most of them are inert. In recent years, numerous remarkable results of the inert C–H bond activation were obtained using late transition metals, such as copper,[8] palladium,[8,9] ruthenium,[10] rhodium,[11] iridium[12] and so on.[13] Iron, cobalt, nickel as earth-abundant transition metals were also successful in these transformations.[14]

The other challenge is the site selectivity which includes regio- and stereoselectivity.

It is very difficult to be controlled due to the ubiquity and inertness of C–H bond. Of all strategies addressing this problem, the use of DG (directing group) was demonstrated as an efficient way to control it. The [C–H···M] σ-complex, which formed after the initial coordination of a DG and a transition metal, activated the proper site (Scheme 1.3).[15] Numerous regioselective reactions were developed using various functional groups as directing groups.[16] Transition-metal-catalyzed C–H bond activation also showed high potential in controlling stereoselectivity and enantioselectivity.[17]



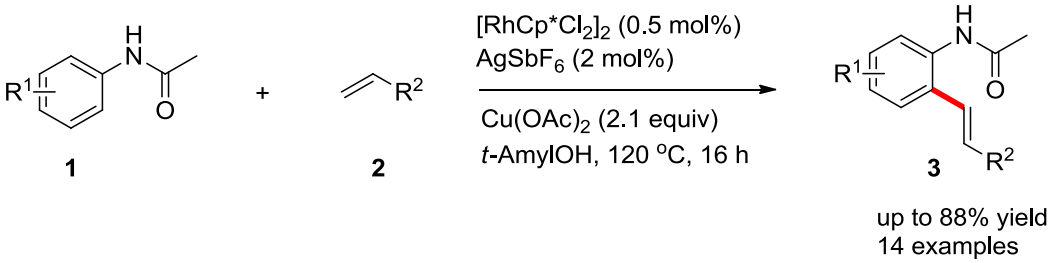
Scheme 1.3 Site selectivity controlled by the assistance of directing groups.[15]

1.1.1 Rh(III)-Catalyzed Direct C(sp^2)–H Bond Oxidative Alkenylation

Rhodium(III) catalysis, which includes the Rh(III)/Rh(I) redox cycle, is broadly used in the functionalization of C–H bond.[18] Although rhodium complexes are relatively expensive compared to the palladium and ruthenium catalysts, the rhodium catalysts have high demand in C–H bond functionalization due to their capability to activate substrates.[18c] Substantial reactions of C–H bond functionalization with rhodium(III) catalysts, especially Cp*Rh(III) (Cp*=pentamethylcyclopentadienyl) catalysts have been developed in recent years.[18b] The remarkable reactivity of Cp*Rh(III) catalysts is because of the following reasons: (1) coordination of Rh(III) complexes with unsaturated compounds is able to activate the related bonds; (2) organorhodium intermediates are stabilized by coordination with electron-rich Cp* moiety; (3) the appropriate size of Cp* helps the elimination or insertion of organorhodium(III)

complexes; (4) Cp*Rh(III)Ar species is octahedral, and only one position can be coordinated. Thus no additional ligand is needed. Among all of Cp*Rh(III) catalysts, $[RhCp^*Cl_2]_2$ complex is often used for the C–H bond activation. In 2007, Miura and Satoh reported the first example of $[RhCp^*Cl_2]_2$-catalyzed C−H bond activation with arenes.[19] Since then, significant achievements were gained in this field. Various C(sp^2)–H bond oxidative alkenylation reactions were developed using the $[RhCp^*Cl_2]_2$ complex.

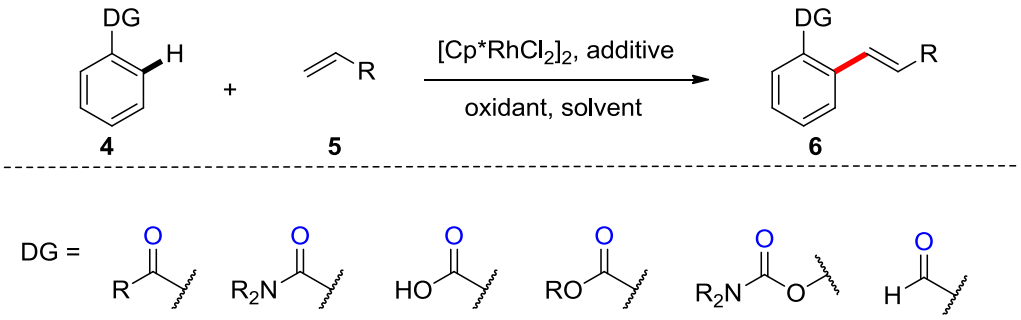
In 2010, Glorious et al. reported reactions of olefins **2** with various acetanilides **1** (Scheme 1.4).[20] The reactions proceeded smoothly, and alkenes with different substituents were tolerated in this transformation. The corresponding alkenylated products **3** were provided with moderated to good yields.



Scheme 1.4 Rh(III)-catalyzed alkenylation of unactivated acetanilides.[20]

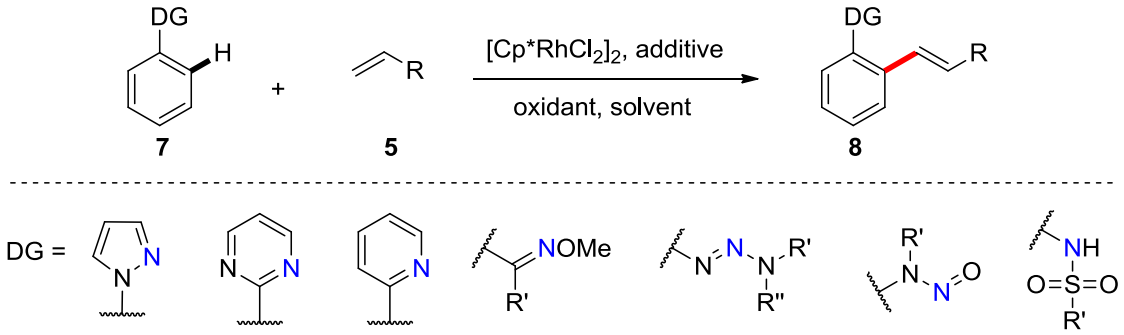
Using ketones and amides as directing groups, Glorious et al. successfully developed a selective rhodium(III)-catalyzed alkenylation reaction with different acetophenones and benzamides.[21] The reactions proceeded successfully with both styrenes and acrylate esters, and no dialkenylation product was detected. As a removable directing group, carboxylic acids were also successfully applied in alkenylation reactions. After the reactions completed, carboxylic groups can be retained or removed depending on the desired products.[22] Chang's group[23] and other groups[24] reported alkenylation reactions using esters as directing group. Results showed that esters either from acids or from aryl phenols behaved well in reactions. Aldehydes were rarely used as directing groups due to their weak coordination ability. Impressively, Chang's group

achieved the alkenylation of benzaldehydes, although isolated yields were low, and decarbonylation products were observed under the oxidative condition (Scheme 1.5).[23]



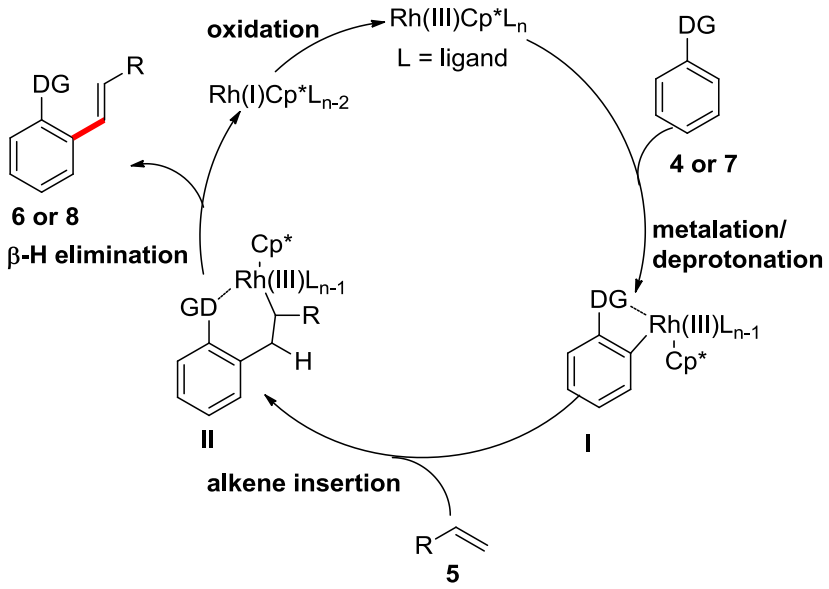
Scheme 1.5 Carbonyl-based directing groups in C(sp^2)–H bond alkenylation.[21-24]

Nitrogen-heterocycles,[25] oximes,[26] triazenes[27] and nitroso[28] were also reported as directing groups in alkenylation reactions by different research groups (Scheme 1.6). Interestingly, Shi and co-workers accomplished the alkenylation of 2-arylpyridines under a competition between C–H and C–C bonds activation. The C–C bond activation occurred with high selectivity.[29] Li et al. demonstrated *peri* oxidative olefination of *N*-(1-naphthyl)sulfonamide using $[RhCp^*Cl_2]_2$ as catalyst and $Cu(OAc)_2$ as oxidant. In this transformation, the directing group was sulfonamide which was rare in Rh(III) complexes catalyzed reactions (Scheme 1.6).[30]



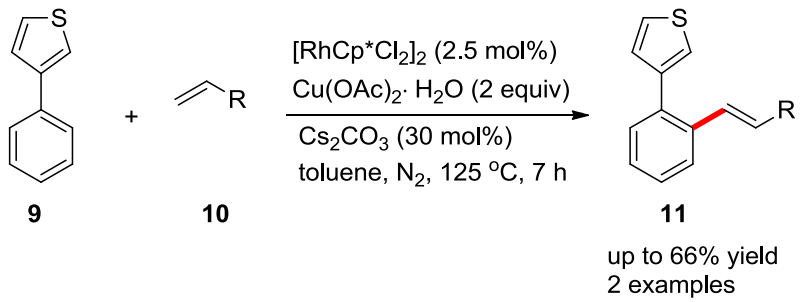
Scheme 1.6 Nitrogen-containing directing groups in C(sp^2)–H bond alkenylation.[25–30]

The mechanism of these rhodium(III)-catalyzed oxidative alkenylation reactions includes metalation/deprotonation, alkene insertion, β-hydrogen elimination and the regeneration of the catalyst (Scheme 1.7).[21–30]



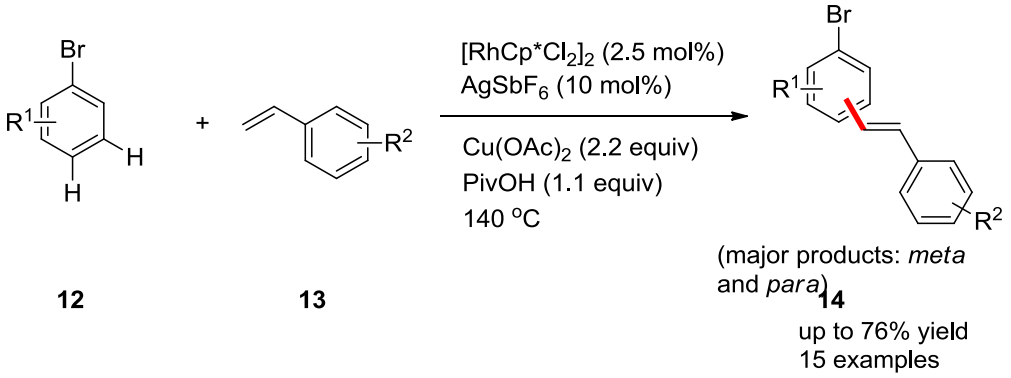
Scheme 1.7 Catalytic cycle of rhodium(III)-catalyzed oxidative alkenylation.[21–30]

Recently, C–H bond functionalization has been studied using π-coordinating functional groups as directing groups. In comparison to the σ-bond coordination, π-bonding electron pairs offer weak coordination with metals due to their lower energy. In 2014, Miura et al. reported a heterocyclic π-bond assisted C–H bond alkenylation reaction. The thiophene π-bond functioned as the directing group in this transformation (Scheme 1.8).[31]



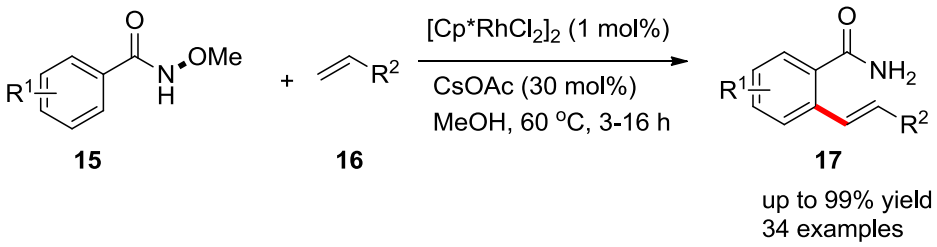
Scheme 1.8 Rhodium(III)-catalyzed C–H bond alkenylation with assistance of thiophene.[31]

An olefination reaction, which did not have directing groups, was developed by Glorious and co-workers. The formation of desired products was proposed by the interaction between the easily accessible C–H bond and the rhodium catalyst (Scheme 1.9).[32]



Scheme 1.9 C–H alkenylation without chelation assistance.[32]

In contrast to the majority of reports on Rh(III) complexes catalyzed alkenylation with external oxidants, reports about the use of directing groups as internal oxidants in reactions were rare. In 2011, Glorious et al. reported a Rh(III)-catalyzed *ortho* C–H bond olefination of aromatic benzamides **15** under mild reaction condition. It was demonstrated that the cleavage of the N–O bond of benzamide **15** oxidized Rh(I) species to Rh(III) species (Scheme 1.10).[33] Later, You and co-workers achieved the alkenylation of tertiary aniline *N*-oxides. In this reaction, the N–O bond was identified to act as an internal oxidant.[34]

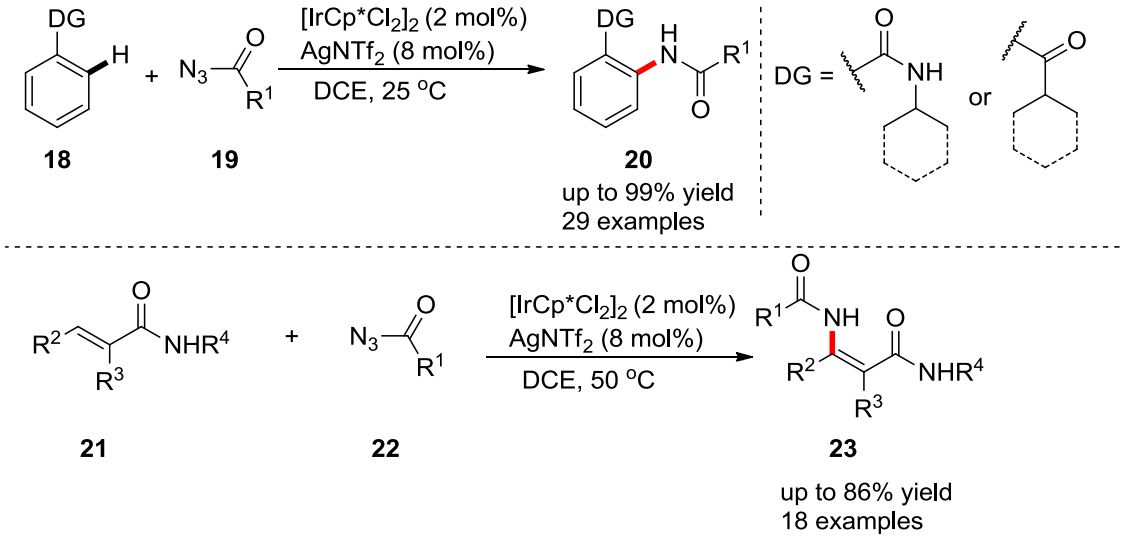


Scheme 1.10 Directing groups act as internal oxidants in C–H bond alkenylation.[33]

1.1.2 Iridium(III)-Catalyzed C–N Bond Formation

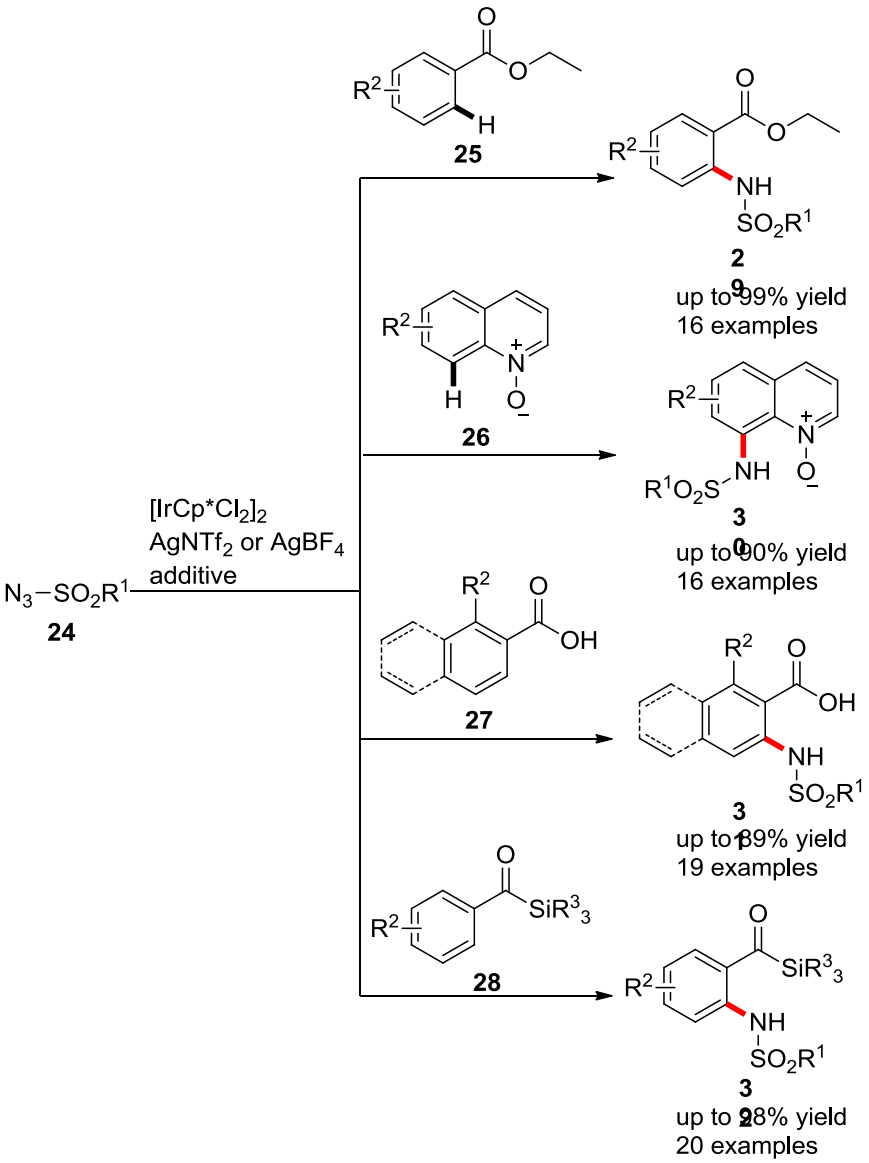
C–N bond formation is one of the most important transformation of organic synthesis,[35,36] the development of efficient and convenient methodologies for this transformation is highly interesting. Due to the broad application of transition-metal catalysis in organic synthesis, the generation of C–N bond is also widely explored with this strategy. Early results of this exploration were based on the use of prefunctionalized starting materials, such as Ullmann's and Goldberg's methods of *N*-arylations with stoichiometric copper,[37] Buchwald's and Hartwig's methods of palladium- and copper-catalyzed *N*-arylation reactions,[38] Chan-Lam coupling reaction.[39] Consequently, straightforward approaches for the generation of C–N bond with non-prefunctionalized starting materials were in high demand.

In recent years, various transition metals were used for the investigation of C–H bond amination. Elegant methods for the direct C–N bond formation were developed using azides as a nitrogen source, which only released dinitrogen as byproduct.[40–43] Early development in this area was provided by Chang et al.[44,45] They successfully achieved the Ir(III)-catalyzed C−H bond amidation of arenes **18** and alkenes **21** using acyl azides **19** and **22** as nitrogen sources (Scheme 1.11).[45] The reactions smoothly proceeded when $[IrCp^*Cl_2]_2$ was employed as catalyst along with $AgNTf_2$, and no external oxidants were required.



Scheme 1.11 Ir(III)-catalyzed amidation with acyl azides.[45]

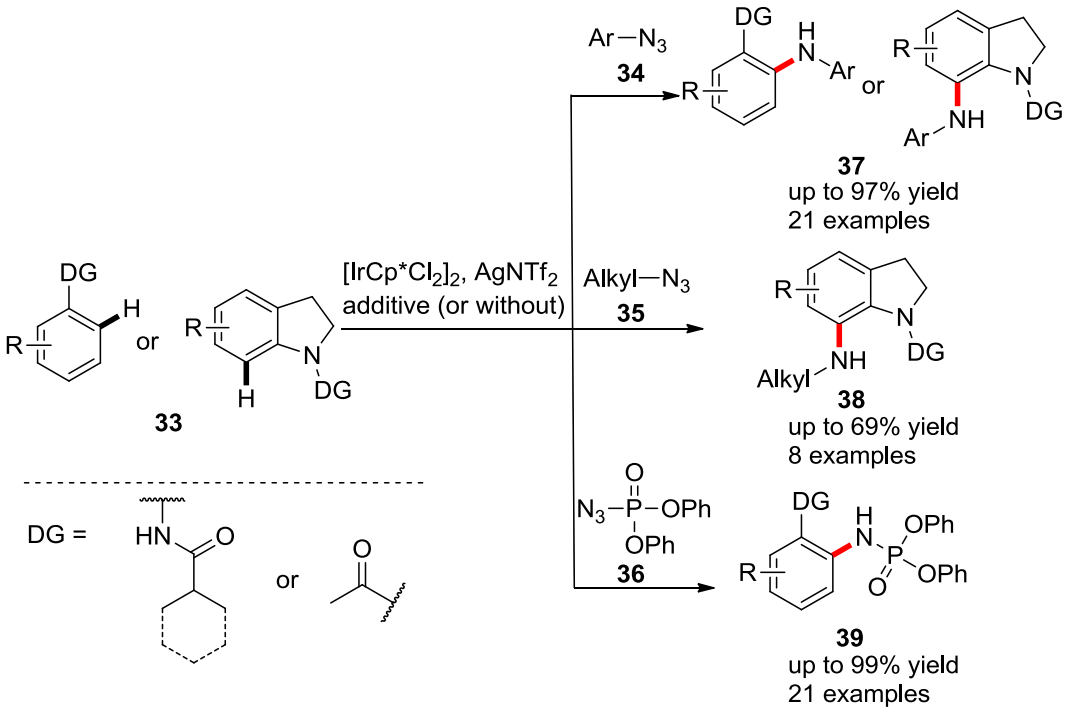
Subsequently, amidation of diverse substrates, like ethyl benzoates **25**,[46a] quinoline *N*-oxides **26**,[46b] benzoic acids **27**,[47a] phenyl(trialkylsilyl)methanone **28**[47b] with tosyl azides were developed by $[IrCp^*Cl_2]_2$ catalysis (Scheme 1.12). It was found that additives played a very important role in these reactions. In the absence of additives, these reactions did not proceed or just produce little amounts of desired products. Very recently, Bolm and co-workers performed the amidation of benzamides with sulfonyl azides in a ball mill without solvents.[48]



Scheme 1.12 Ir(III)-Catalyzed amidation of tosyl azides with various substrates.[46,47]

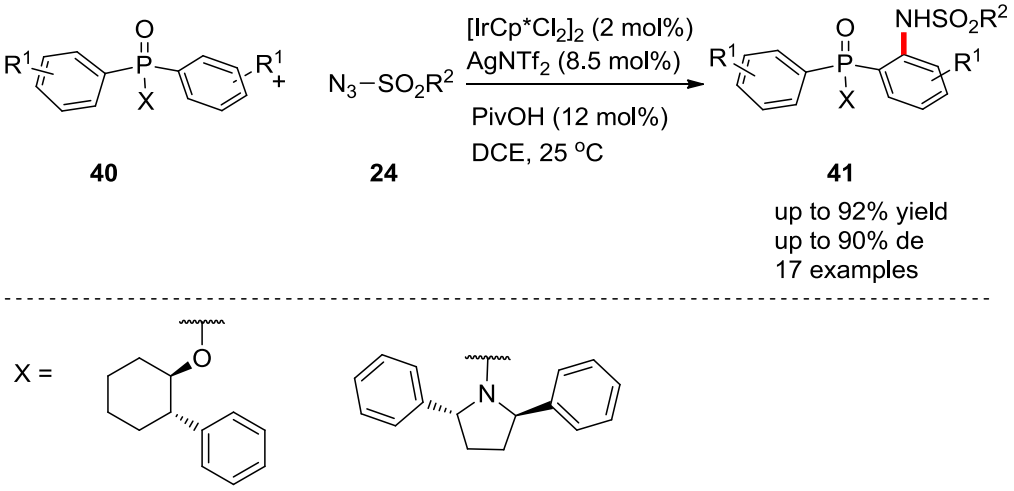
Aryl azides **34**, alkyl azides **35** and phosphoryl azides **36** as efficient amino sources

were also employed in different reactions. The corresponding products were obtained in good yields with diverse functional groups (Scheme 1.13).[49]



Scheme 1.13 Ir(III)-Catalyzed amidation of different azides.[49]

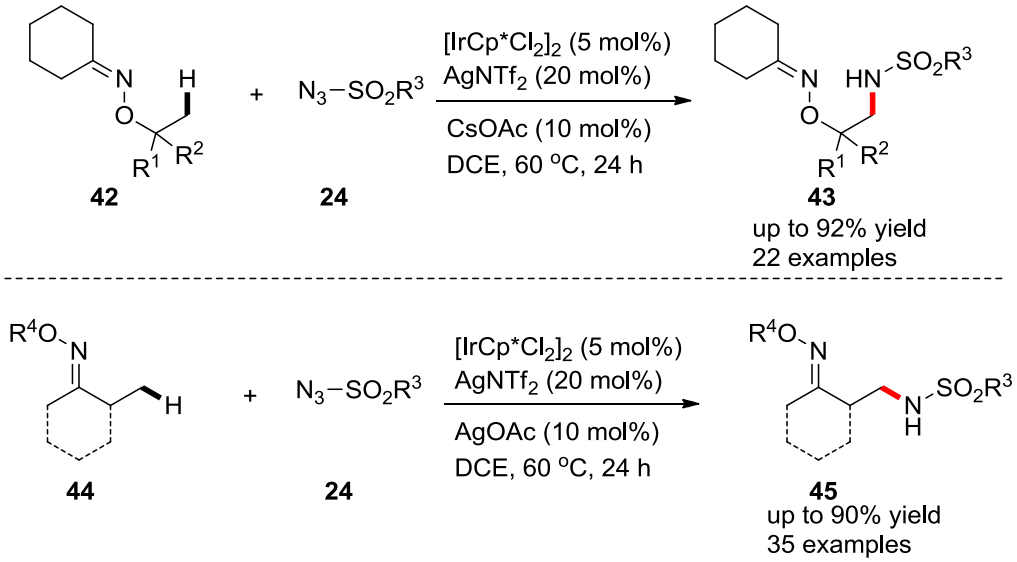
Chang et al. developed asymmetric C–H bond amidation of diarylphosphoryl compounds **40**. Experimental results and mechanistic studies suggested that the formation of an iridacycle was the diastereo-determining step. It was assumed that the *pseudo*-diastereomeric environment of the substrate controlled the stereoselectivity of this transformation (Scheme 1.14).[50]



Scheme 1.14 Ir(III)-Catalyzed asymmetric C–H bond amidation of diarylphosphoryl

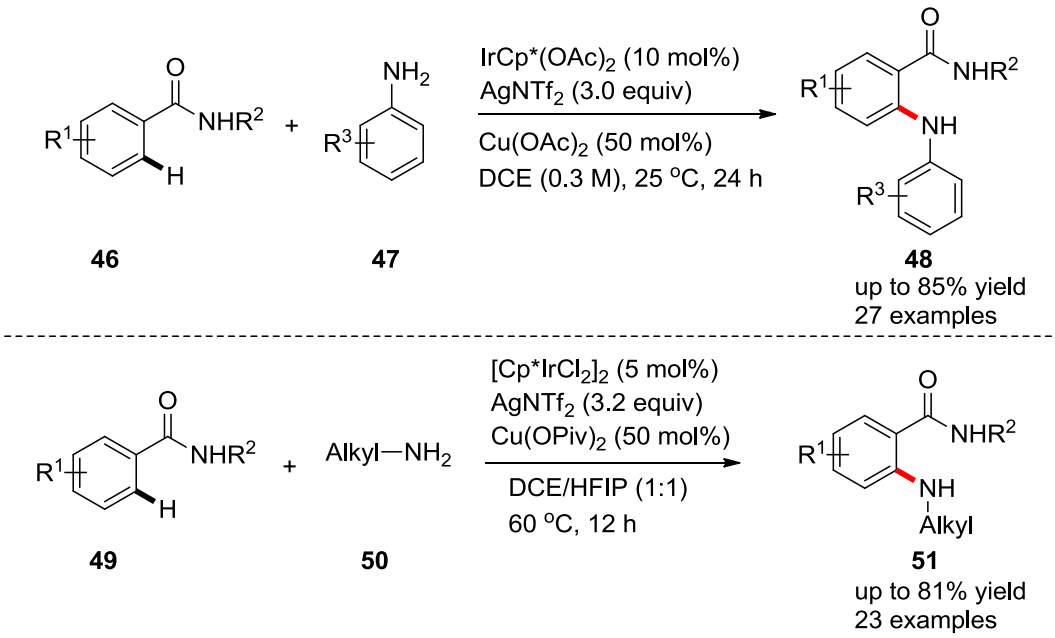
compounds.[50]

Iridium(III) catalysts were not only used for the amidation of aromatic compounds, but also used for unreactive C(sp^3)–H bond amidation. Chang et al. developed direct amidation of methyl C(sp^3)–H bond using $[IrCp^*Cl_2]_2$ as catalyst. Reactions proceeded smoothly under mild reaction conditions, providing desired products with diverse functional groups in good to excellent yields. These results further demonstrated the high applicability of Ir(III) catalysis in organic synthesis (Scheme 1.15).[51]



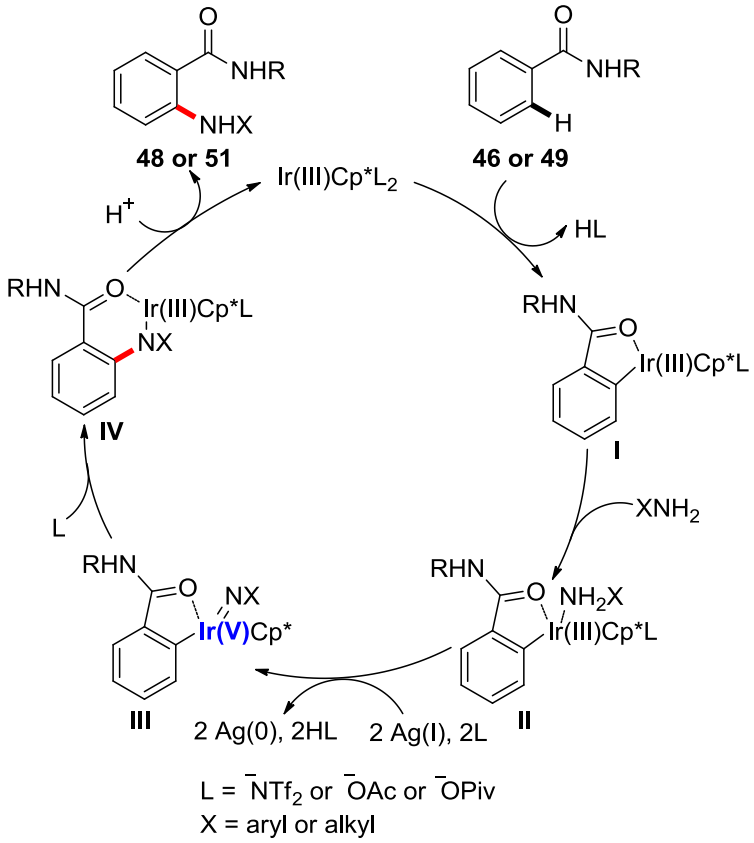
Scheme 1.15 Ir(III)-catalyzed C(sp^3)–H bond amidation.[51]

The use of anilines as a nitrogen source for direct C–H bond amination by cross-dehydrogenative coupling (CDC) is highly desirable due to their availability. However, the biggest issue in this process is the lower activity of the employed catalytic system in the presence of aniline, mostly because of its high nucleophilicity.[52] In 2014, Chang and co-workers reported the first example of Ir(III)-catalyzed C–H bond amination with anilines **47** at room temperature (Scheme 1.16).[53] Later, amination with alkylamines **50** was also demonstrated by the same group using Ir(III) catalyst and external oxidant under mild reaction condition (Scheme 1.16).[54]



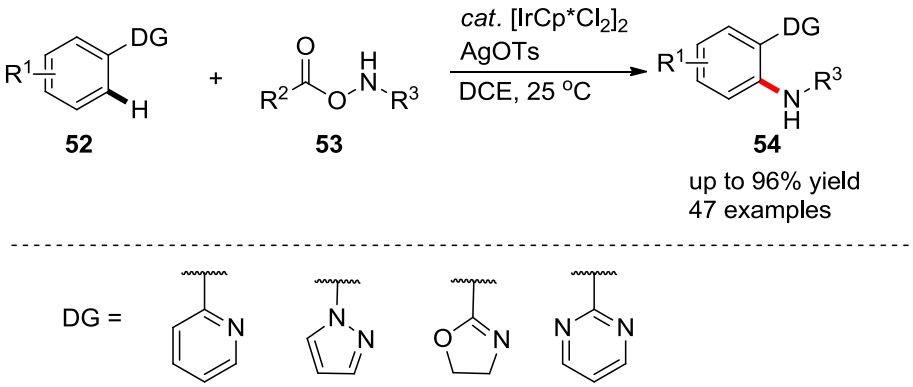
Scheme 1.16 Ir(III)-catalyzed amination with anilines and alkylamines.[53,54]

In both reactions, Ir(III) catalytic systems were well compatible with external oxidants. Mechanistic studies suggested that the catalytic cycle involved Ir(V) species **III** (Scheme 1.17).[53,54]



Scheme 1.17 Ir(III)-catalyzed amination with anilines and alkylamines.[53,54]

N-Substituted hydroxylamines were also successfully applied in the Ir(III)-catalyzed direct C–H bond amination of arenes as an alternative nitrogen source. The reactions of hydroxyamines with different substituents on nitrogen, such as Boc (*tert*-butyloxycarbonyl), Cbz (carboxybenzyl), Troc (trichloroethyl carbamate), Bz (benzoyl), Ts (*para*-toluenesulfonyl) and Ac (acetyl), were developed at ambient temperature, and the corresponding products were obtained in good to excellent yields (Scheme 1.18).[55]

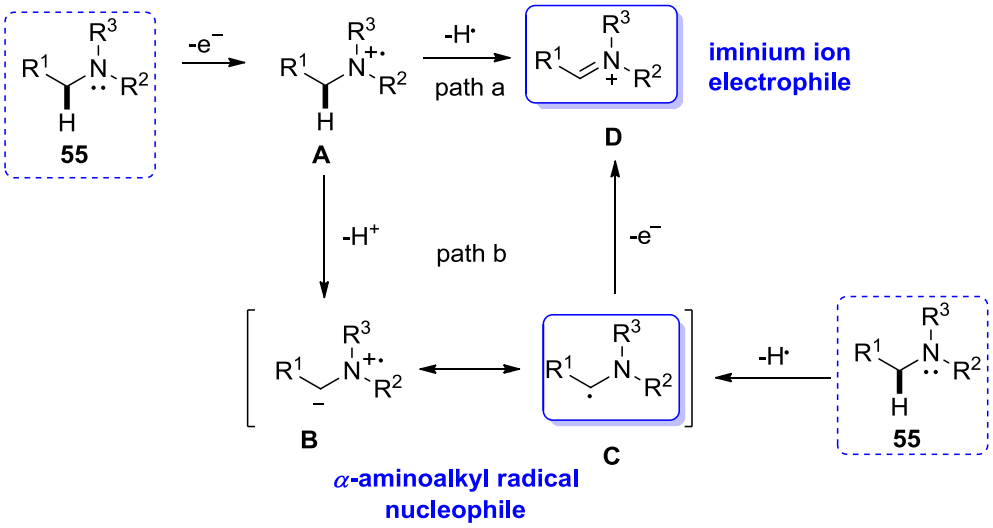


Scheme 1.18 Ir(III)-catalyzed amination with *N*-substituted hydroxylamines.[55]

1.2 Direct Functionalization of C(sp^3)–H Bond at *a*-Position of Tertiary Amines

Direct functionalization of C(sp^3)−H bond at *a*-position of tertiary amines, which has two possible transformation pathways, has been considered as a straightforward strategy to synthesize nitrogen-containing compounds in recent years (Scheme 1.19).[56] The one involves the formation of α-aminoalkyl radical **C**[56d] through one electron oxidation/deprotonation or hydrogen abstraction of amine **55**. The formed α-aminoalkyl radical **C** as a nucleophile reacts with different electrophiles to produce the related nitrogen-containing heterocycles. The other one involves the formation of iminium ion **D**[56c] through single electron transfer and hydrogen abstraction of amine or further one electron oxidation of α-aminoalkyl radical **C**. The formed iminium ion **D** as an electrophile reacts with various nucleophiles to afford the corresponding

nitrogen-containing heterocycles.

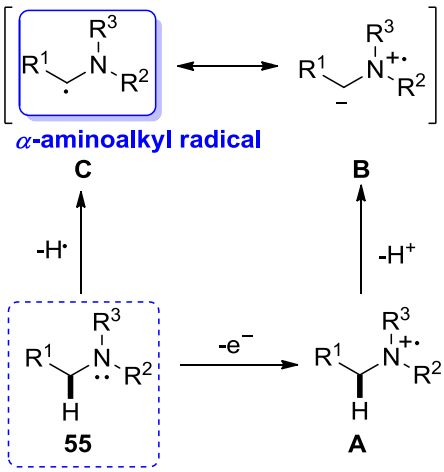


Scheme 1.19 Formation of *α*-aminoalkyl radicals and iminium ions from tertiary amines.[56b–56d]

Based on this strategy, numerous methods were developed to generate *α*-aminoalkyl radicals and iminium ions from tertiary amines under different reaction conditions, and they were successfully applied in the construction of nitrogen-containing compounds.[56b–56d]

1.2.1 Formation and Application of *α*-Aminoalkyl Radicals in Synthetic Chemistry

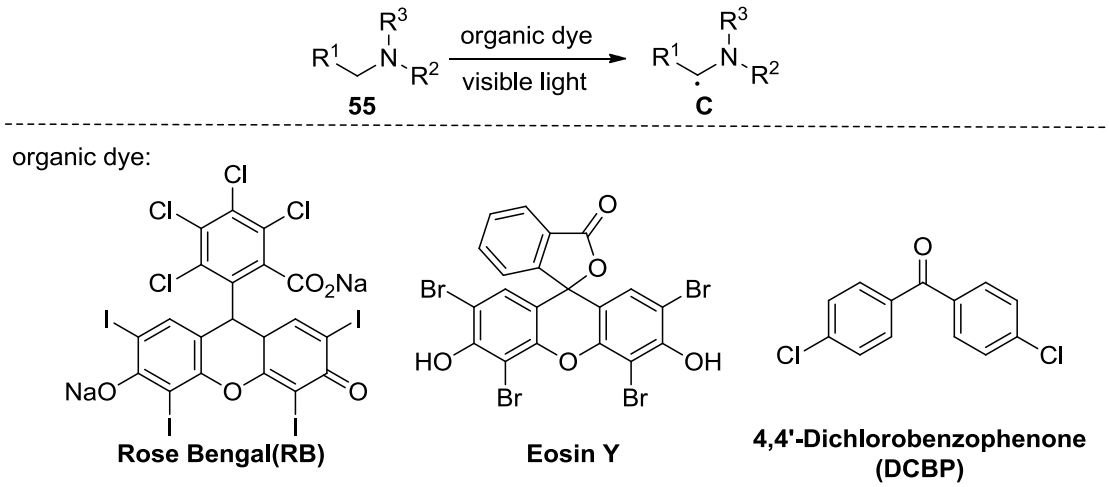
α-Aminoalkyl radicals can be formed from tertiary amines by single electron transfer/deprotonation or hydrogen abstraction (Scheme 1.20).[57–67] Generally, the former pathway is common in the photochemical reactions,[57–66] the latter pathway is present in the thermal reactions.[67]



Scheme 1.20 Formation of *α*-Aminoalkyl radicals from tertiary amines.[57–67]

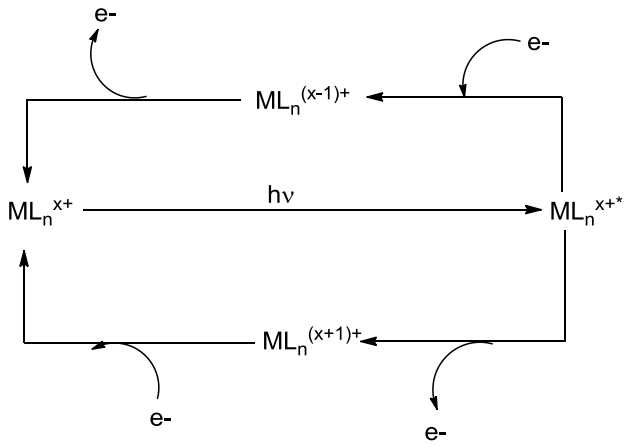
Transformation of amines to *α*-aminoalkyl radicals *via* single electron transfer has been extensively studied with visible-light-induced photoredox catalysis in recent decades. The formation of *α*-aminoalkyl radicals by direct irradiation with visible light has limited application in organic photochemical reactions, because most of the organic compounds do not tend to absorb photons between 400 nm to 800 nm.[57] Therefore, photocatalysts, which can convert sunlight to electrochemical potential by visible light irradiation, are usually required in such processes.

Photoredox catalysts contain organic compounds and inorganic compounds. Organic photoredox catalysts are organic compounds which have aromatic ring or conjugated unsaturated bonds (like double bonds, triple bonds) in their structures. Energy can be stored by means of quantum vibration. Normally, organic photoredox catalysts are strongly colored. In 2010, Tan and co-workers reported a visible-light-mediated Aza-Henry reaction. The *α*-aminoalkyl radical **C** was formed using Rose Bengal (RB) which is an organic photoredox catalyst (Scheme 1.21).[58] Later, Zhang's group[59] and Itoh's group[60] achieved the related reactions with Eosin Y and 4,4′-dichlorobenzophenone (DCBP) (Scheme 1.21).



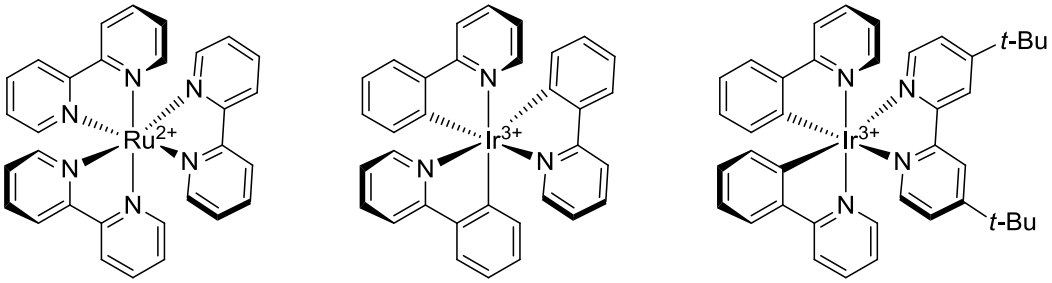
Scheme 1.21 Formation of α-aminoalkyl radicals by organic photoredox catalysts and visible light.[58–60]

Metal-ligand complexes as one kind of inorganic photoredox catalysts are used in numerous reactions for producing α-aminoalkyl radicals. The photoredox process is initiated by excitation of metal-ligand. Subsequently, one electron moves between metals and substrates. During the movement, the electron will reduce electron-deficient substrates or oxidize electron-rich substrates. Accordingly, two different pathways are introduced to describe the mechanism of this process. The former one is called photoreductive quenching, the latter one is called photooxidative quenching (Scheme 1.22).[61]



Scheme 1.22 Metal-ligand photocatalysts in photoredox reactions.[61]

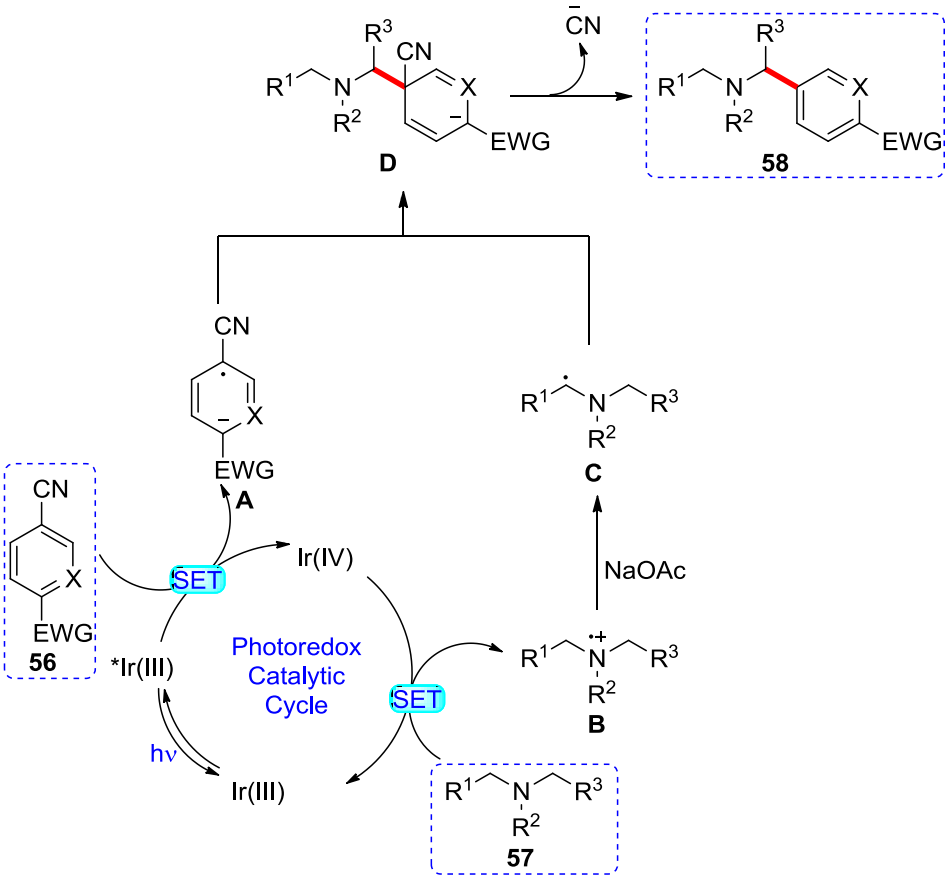
So far, various metal-ligand photocatalysts were applied in the reactions with the formation of α-aminoalkyl radicals. The majority of these catalysts are ruthenium and iridium complexes (Scheme 1.23).[61] A series of nitrogen-containing heterocycles were constructed from the reactions of *α*-aminoalkyl radicals with diverse electron-deficient alkenes using these catalysts.[61]



$Ru(bpy)_3^{2+}$ $Ir(ppy)_3$ $Ir(ppy)_2(dtb\text{-}bpy)^+$

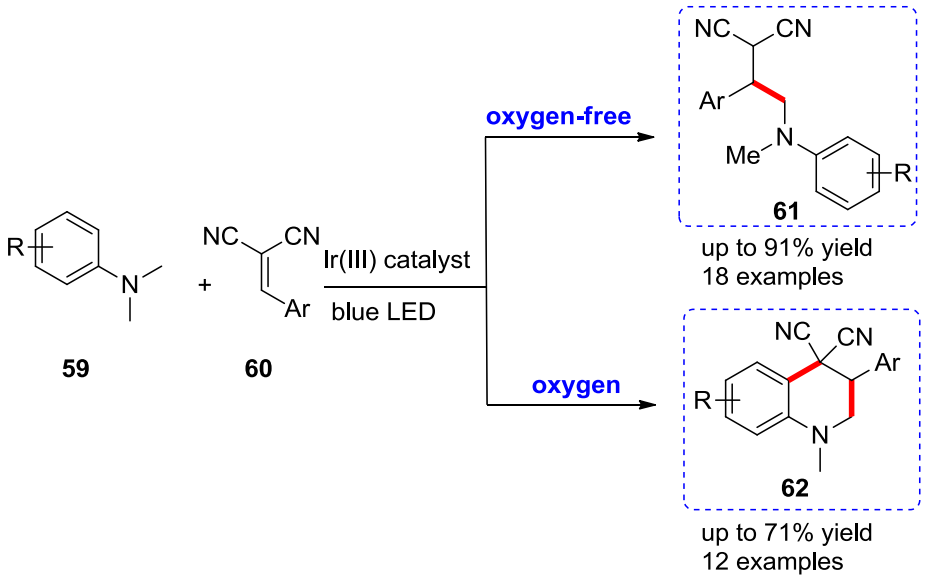
Scheme 1.23 Metal-ligand photocatalysts.[61]

In 2011, MacMillan and co-workers reported an impressive way to construct benzylic amines **58** from electron-deficient cyanoarenes **56** and tertiary amines **57** by a photocatalyst and visible light (Scheme 1.24).[62] According to the mechanism of this process, a radical anion **A** and an *α*-amino radical **C** were initially produced with the recycle of the photocatalyst. The coupling of the **A** and **C** delivered an intermediate anion **D** which followed by elimination of CN-, leading to the product **58**. Later, the use of the similar reaction condition, they achieved *α*-vinylation of *N*-aryl tertiary amines with vinyl sulfones.[63] In 2015, Xiao et al. accomplished *α*-allylation of tertiary amines by the use of a palladium catalyst and a visible-light photoredox catalyst. In this transformation, the photoredox catalyst was regenerated by the formation of *α*-amino radicals and allyl radicals.[64]



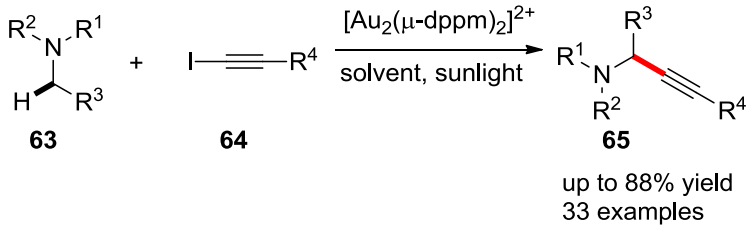
Scheme 1.24 C–H Bond arylation using visible-light photoredox catalysis.[62]

In 2013, Rueping et al. reported an intriguing C–H bond functionalization of tertiary amines **59** with visible-light photoredox catalysis. It was found that in the absence of oxygen, inter-molecular addition reactions occurred between *α*-aminoalkyl radicals and electron-deficient alkenes **60**. In contrast, in the presence of oxygen, inter- and intra-molecular reactions through addition/cyclization sequences occurred and afforded the corresponding tetrahydroquinoline derivatives **62** (Scheme 1.25).[65]



Scheme 1.25 Photoredox-catalyzed radical addition and addition/cyclization reactions.[65]

Very recently, Hashmi and co-workers developed an efficient alkynylation reaction of tertiary amines **63** with 1-iodoalkynes **64** using $[Au_2(\mu\text{-dppm})_2]^{2+}$ as photoredox catalyst. The coupling of alkynyl and α-aminoalkyl radicals, which were generated by the gold catalyst, delivered the desired products **65** (Scheme 1.26).[66]

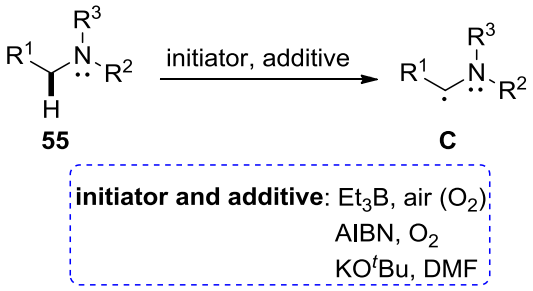


Scheme 1.26 α-C(sp^3)–H Alkynylation of tertiary amines by gold-catalyzed photoredox catalysis.[66]

Comparing to the reports of α-aminoalkyl radicals formation by one electron oxidation/deprotonation with photoredox catalysis, reports about the generation of α-aminoalkyl radicals through hydrogen abstraction are relatively rare. For such

reactions, special reagents are required as initiators. They react with additives and provide corresponding radicals. The formed radicals abstract hydrogen at the α-position of nitrogen and produce α-aminoalkyl radicals which attacked to electrophiles, providing the desired products.

Nagaoka et al. developed a method to form α-aminoalkyl radicals using Et_3B and air (oxygen), reactions of these radicals with aldehydes and isocyanates afforded the desired products in good yields (Scheme 1.27).[67a,67b] AIBN (azobisisobutyronitrile) and oxygen, KO^{t}Bu and DMF were also successfully applied in the formation of α-aminoalkyl radicals from tertiary amines by different research groups (Scheme 1.27).[67c,67d]



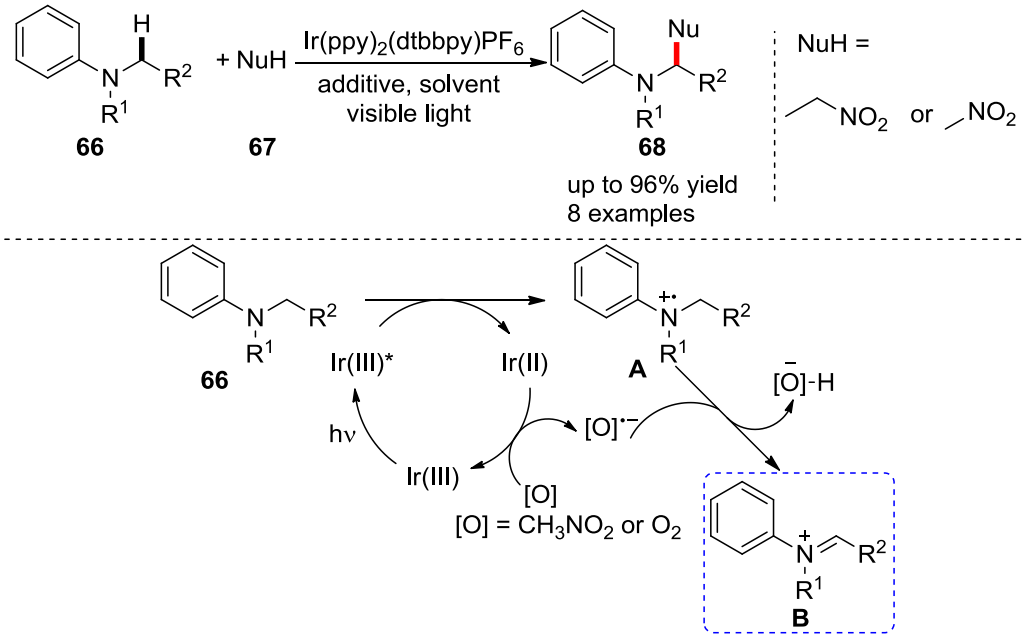
Scheme 1.27 Formation of α-aminoalkyl radicals through hydrogen abstraction pathway.[67]

1.2.2 Formation and Application of Iminium Ions in Synthetic Chemistry

The formation of iminium ions involves single electron transfer and hydrogen abstraction sequences. According to different reaction conditions and substrates, the order of the pathway is either single electron transfer/hydrogen abstraction or hydrogen abstraction/single electron transfer.

Iminium ions, which are involved in photochemical reactions, frequently undergo

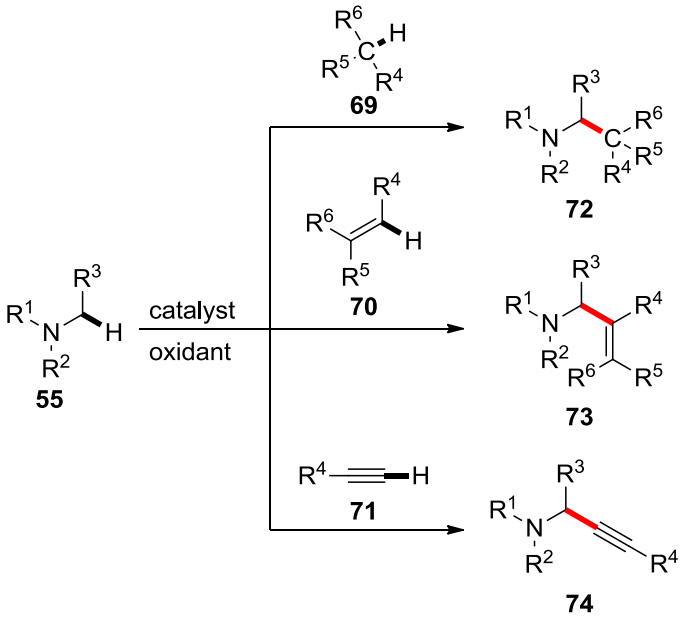
single electron transfer/hydrogen abstraction pathway. In 2010, Stephenson et al. developed visible-light-mediated oxidative coupling of nitroalkanes **67** with tertiary *N*-arylamines **66** *via* α-aminoalkyl radicals (Scheme 1.28).[68] According to the plausible mechanism of this process, a radical cation **A** was initially formed by single electron transfer from excited photoredox catalyst to **66**. Subsequent hydrogen abstraction at the α-position of the radical cation **A** by $[O]^{\bullet-}$ led to an iminium ion **B**. Nucleophilic attack of **67** to **B** delivered the desired products **68**.



Scheme 1.28 Aza-Henry reaction *via* iminium ions using visible-light photoredox catalysis.[68]

Recently, CCl_4 and $BrCCl_3$ were also applied in the formation of iminium ions in photochemical reactions as initiators.[69] The formed $\cdot CCl_3$ radicals accomplished hydrogen abstraction in the transformations. Using this strategy, several inter- and intra-molecular reactions were successfully developed to synthesize interesting compounds by different research groups.[69] Zeitler et al. reported a novel method to form iminium ions using $CBrCl_3$ and visible light, and no photocatalyst was required in this reaction.[70]

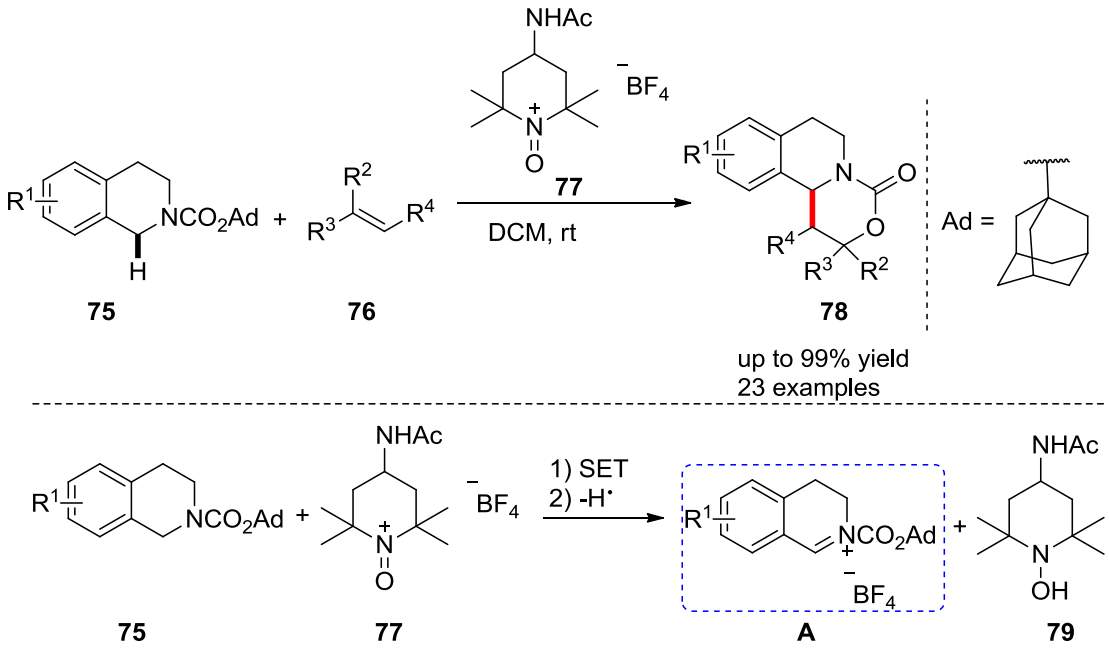
Actually, most of the reported reactions, which included the formation of iminium ion intermediates from tertiary amines or amides, were accomplished under thermal reaction conditions. Li and others reported numerous reactions for the construction of nitrogen-containing heterocycles.[71] The transformation underwent the CDC (cross-dehydrogenative coupling) process with iminium ion intermediates. The related reactions were achieved by coupling with C(sp)–H bond, C(sp^2)–H bond and C(sp^3)–H bond. Different catalysts (copper salts, iron salts, I_2, iodide reagents and so on) and different oxidants (air or oxygen, DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), peroxides and so on) were employed in these reactions (Scheme 1.29).[71]



Scheme **1.29** Cross-dehydrogenative coupling of tertiary amines *via* iminium ions.[71]

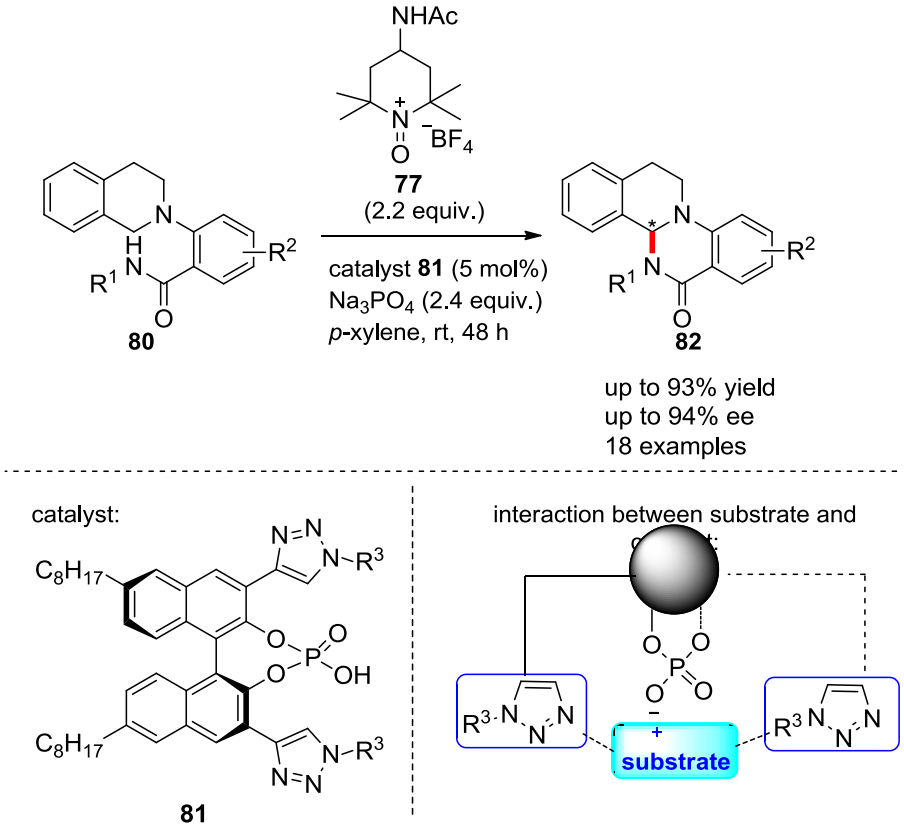
In 2012, Mancheño and co-workers developed an interesting method to construct heterocycles *via* iminium ions. Various polycyclic tetrahydro-1,3-oxazin-2-one derivatives **78** were synthesized in the presence of oxidant $NHAcT^+BF_4^-$ (4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammoniumtetrafluoro borate) **77** at room temperature. It was assumed that the iminium ion **A** was formed through SET

and hydrogen abstraction of **75** by the oxidation of **77**. The hydrogen abstraction step was proposed to be the rate-determining step (Scheme 1.30).[72]



Scheme **1.30** Cyclization between *N*-benzyl carbamates and alkenes *via* iminium ions.[72]

Asymmetric C–C bond formation *via* iminium ions were also explored by different research groups. Several chiral heterocycles were successfully obtained using various catalysts and chiral ligands.[73] The chirality was induced through the interaction between iminium ions and chiral ligands. An elegant asymmetric intra-molecular cross-dehydrogenative coupling reaction was reported by Toste et al. in 2013. In this transformation, the enantioselectivity was obtained with a chiral catalyst **81** which bearing 1,2,3-triazoles at the 3 and 3′ positions. It was found that conventional PAs (phosphoric acid) was not able to provide the enantioselectivity under the same reaction condition. Consequently, it was assumed that the chirality was induced under the organization of triazoles (Scheme 1.31).[74]

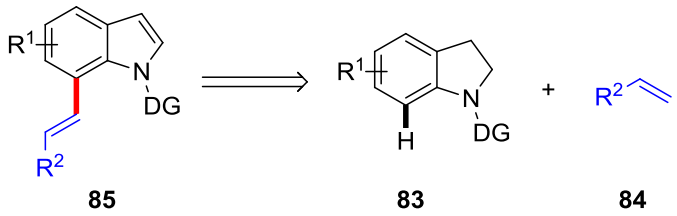


Scheme 1.31 Formation of asymmetric C–C bond *via* iminium ions using chiral phosphoric acids.[74]

2. Objectives

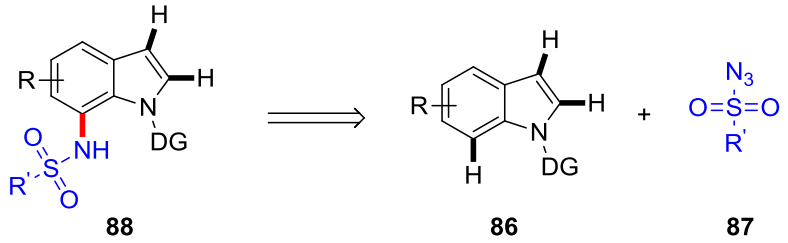
Transition-metal-catalyzed C–H bond functionalization has been applied in the organic synthesis as an efficient and robust tool. In the last few decades, significant achievements had been obtained in this area. Numerous natural products and bioactive compounds were successfully constructed under this strategy.

Indole scaffolds as a core structure are ubiquitously present in natural products and biologically active compounds. Substantial methods have been developed to construct substituted indoles *via* transition-metal catalysis by different research groups in these decades. Comparing to the functionalization of indoles at other positions, reports about the functionalization at the C7-position of indoles are rare. In this context, we devised a novel approach for the efficient synthesis of 7-substituted indoles **85** (Scheme 2.1). It included transition-metal-catalyzed regioselective olefination of indolines **83** and subsequent oxidation. The prime challenges of this methodology were the control of regioselectivity and combination of these two steps reaction in a one-pot fashion.



Scheme 2.1 Synthesis of 7-substituted indoles *via* olefination/oxidation.

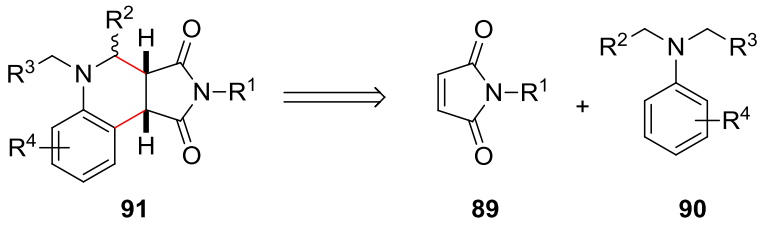
Next, a new approach for the direct regioselective sulfonamidation of indoles **86** at the C7-position by transition-metal catalysis was proposed. The biggest challenge of this strategy was the regioselective functionalization, as three positions were likely to be functionalized in this case. This methodology was possible to be applied for the synthesis of bioactive compounds (Scheme 2.2).



Scheme 2.2 Regioselective sulfonamidation of indoles at the C7-position.

As an efficient synthetic strategy, the direct functionalization of C(sp^3)–H bond at *α*-position of tertiary amines has been extensively studied in recent years. Abundant reactions involving *α*-aminoalkyl radicals, that were formed by direct functionalization of tertiary amines, were reported. Nevertheless, the application of *α*-aminoalkyl radicals in synthetic chemistry is limited due to their easy oxidation to iminium ions. This issue is special for *α*-aminoalkyl radicals which are formed from electron-poor amines, as strong oxidants are required in the transformation. Hence, novel approaches to produce *α*-aminoalkyl radicals are highly expected.

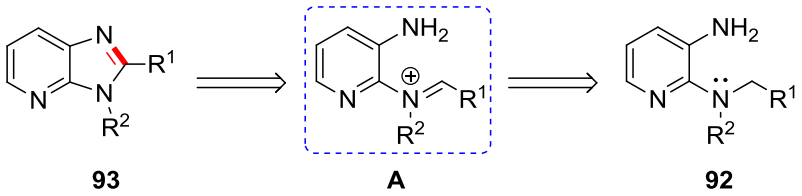
During our study, it was found that *α*-aminoalkyl radicals could be formed by KI and TBHP, which was frequently used to generate iminium ions. Compared to the addition reactions with *α*-aminoalkyl radicals, annulation reactions with *α*-aminoalkyl radicals were less studied. It was wonder if this new approach could be applied in radical reactions, especially in radical annulation reactions. Thus an annulation reaction between tertiary amines **90** and electron-deficient alkenes **89** was proposed to synthesize polycyclic compounds **91** using iodides as catalyst and peroxides as oxidant (Scheme 2.3).



Scheme 2.3 Iodide/Peroxide catalyzed annulation between tertiary amines and

electron-deficient alkenes *via* α-aminoalkyl radicals.

Imidazo[4,5-*b*]pyridine derivatives are extensively present in natural products and bioactive compounds. However, reported synthetic methods for these compounds need long synthetic steps, harsh reaction conditions and have limited substrate scopes. Therefore, practical and efficient approaches to prepare such compounds are highly desirable. Based on the strategy of direct functionalization of C(sp^3)–H bond at *a*-position of tertiary amines, a novel route to synthesize imidazo[4,5-*b*]pyridine derivatives **93** *via* iminium ions **A** was devised (Scheme 2.4). The biggest challenge of this method was the formation of the radical cation by single electron transfer at the initial step. This is due to the nitrogen, which is at the C2-position of pyridines, is electron-deficient, and it is difficult to be oxidized to the corresponding iminium ion.



Scheme 2.4 Synthesis of imidazo[4,5-*b*]pyridine derivatives *via* iminium ions.

Compounds, which synthesized by these newly developed methods, are contained in natural products and bioactive compounds as a key part, thus the bioactivity of these compounds would be investigated in different cell-based assays.

III Results and Discussion

3.1 Regioselective Synthesis of 7-Substituted Indoles

3.1.1 Synthesis of 7-Substituted Indoles by Rhodium(III)-Catalyzed Regioselective Alkenylation

The following chapter is related to:

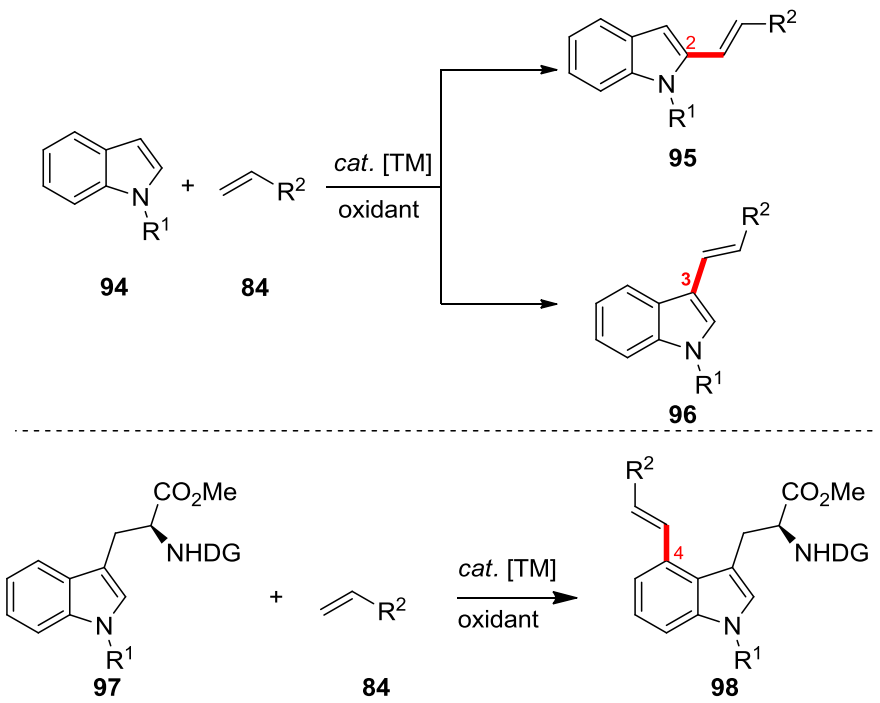
Rhodium(III)-Catalyzed Direct Regioselective Synthesis of 7-Substituted Indoles

Zengqiang Song, Rajarshi Samanta, Andrey P. Antonchick

Org. Lett. **2013**, *15*, 5662–5665

3.1.1.1 Introduction for the Regioselective Alkenylation of Indoles

Indole and its derivatives as privileged scaffolds are substantially present in natural products and pharmaceutical compounds.[75] The preparation of substituted indole derivatives draws intensive attention from organic chemists. Numerous methodologies about the construction of diverse indole derivatives have been reported.[75e,75h] However, the methods for efficiently and rapidly constructing various indole derivatives, through direct regioselective functionalization of indoles are highly expected. In the past decades, numerous reactions regarding transition-metal-catalyzed C–H bond activation of indoles at the C2-[76] and C3-positions[77] have been studied. 2- or 3-Alkenylated indole derivatives **95** or **96** were successfully prepared from indoles **94** and alkenes **84** through inter-molecular oxidative coupling reactions.[78,79] A method to access 4-substituted indole derivatives **98** was also successfully developed using a transition-metal catalyst (Scheme 3.1).[80]



Scheme 3.1 Regioselective Alkenylation of Indoles.[78–80]

Compared to the other substituted indole derivatives, 7-substituted indole derivatives are especially important due to their wide presence in natural products and pharmaceutical compounds (Figure 3.1).[81] Nevertheless, reports about the direct preparation of 7-substituted indoles through regioselective oxidative functionalization of indoles at the C7-position are rare.[82]

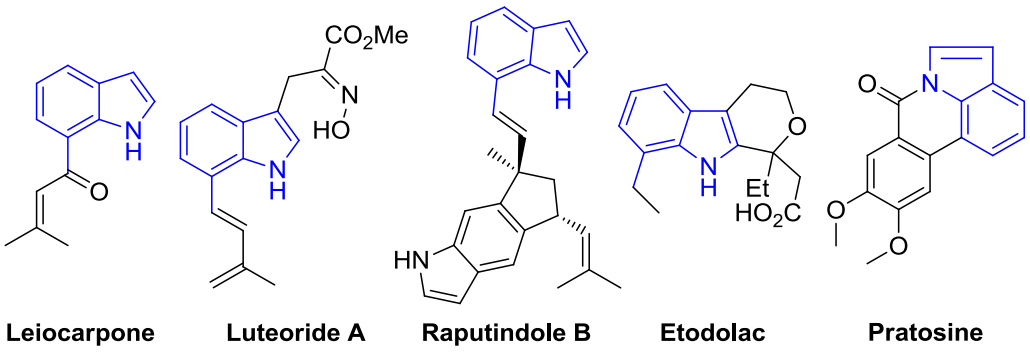


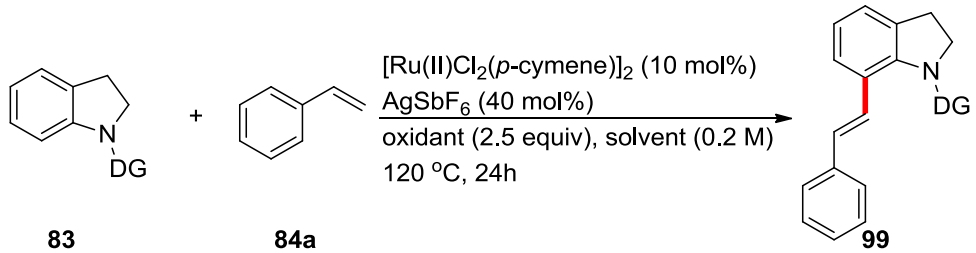
Figure 3.1 Representative natural products and bioactive compounds containing 7-substituted indoles.[81]

Due to the importance of 7-substituted indoles, an efficient method for the preparation of these compounds was explored using transition-metal catalysis.

3.1.1.2 Optimization Studies for the Synthesis of 7-Alkenylated Indoles

Initially, we examined the coupling reaction of *N*-acetylindoline **83** with styrene **84a** in DCE (1,2-dicholoroethane) at 120 °C, using $[RuCl_2(p\text{-cymene})]_2$ as catalyst and anhydrous $Cu(OAc)_2$ as oxidant.[10] Gratifyingly, the desired product **99a** was obtained in 24% isolated yield after 24 h (Table 3.1, entry 1). Subsequently, different solvents were screened, but none of them improved the yield of the desired product (Table 3.1, entries 2–12). Further screening was conducted with different oxidants. However, the desired product was obtained with trace amounts in most cases. No desired product was formed when CsOAc was used as oxidant (Table 3.1, entries 13–16). Indoles with different directing groups were also subjected to this reaction. To our delight, *N*,*N*-diethylcarbamoyl protected indoline **83d** afforded the desired product **99d** in 53% yield (Table 3.1, entry 19). Indolines with other protecting groups, such as pivaloyl **83b**, 2-pyridylcarbonyl **83c** and 2-pyridylsulfonyl **83e**, did not provide any desired products (Table 3.1, entries 17, 18 and 20).

Table 3.1 Optimization of conditions for the Ru(II)-catalyzed alkenylation of indolines at the C7-position.[a]



83 **84a** **99**

Entry	Indoline (DG)	Oxidant	Solvent	Product (DG)	Yield (%)[b]
1	Ac (**83a**)	$Cu(OAc)_2$	DCE	Ac (**99a**)	24
2	Ac (**83a**)	$Cu(OAc)_2$	EtOAc	Ac (**99a**)	trace
3	Ac (**83a**)	$Cu(OAc)_2$	1,4-dioxane	Ac (**99a**)	trace

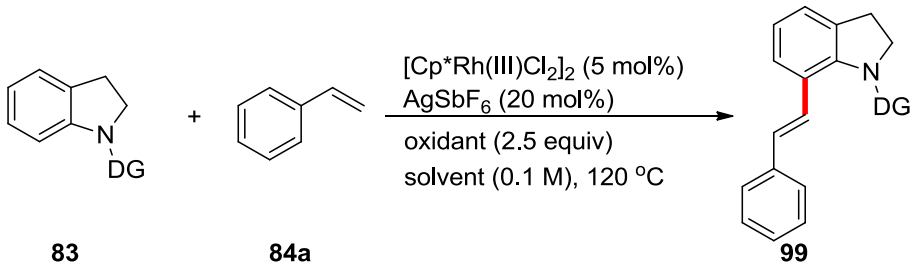
4	Ac (**83a**)	$Cu(OAc)_2$	*t*-AmOH	Ac (**99a**)	14
5	Ac (**83a**)	$Cu(OAc)_2$	CH_3CN	Ac (**99a**)	trace
6	Ac (**83a**)	$Cu(OAc)_2$	toluene	Ac (**99a**)	trace
7	Ac (**83a**)	$Cu(OAc)_2$	fluorobenzene	Ac (**99a**)	trace
8	Ac (**83a**)	$Cu(OAc)_2$	DMF	Ac (**99a**)	20
9	Ac (**83a**)	$Cu(OAc)_2$	DMSO	Ac (**99a**)	n.d.[c]
10	Ac (**83a**)	$Cu(OAc)_2$	AcOH	Ac (**99a**)	n.d.[c]
11	Ac (**83a**)	$Cu(OAc)_2$	1,1,2,2-tetrachloroethane	Ac (**99a**)	trace
12	Ac (**83a**)	$Cu(OAc)_2$	*t*-butanol	Ac (**99a**)	n.d.[c]
13	Ac (**83a**)	BQ	DCE	Ac (**99a**)	trace
14	Ac (**83a**)	CsOAc	DCE	Ac (**99a**)	n.d.[c]
15	Ac (**83a**)	AgOAc	DCE	Ac (**99a**)	trace
16	Ac (**83a**)	CuI	DCE	Ac (**99a**)	trace
17	Piv (**83b**)	$Cu(OAc)_2$	DCE	Piv (**99b**)	n.d.[c]
18	CO-2Py (**83c**)	$Cu(OAc)_2$	DCE	CO-2Py (**99c**)	n.d.[c]
19	**$CONEt_2$ (83d)**	**$Cu(OAc)_2$**	**DCE**	**$CONEt_2$ (99d)**	**53**
20	SO_2-2Py (**83e**)	$Cu(OAc)_2$	DCE	SO_2-2Py (**99e**)	n.d.[c]

[a] Reaction conditions: **83** (0.2 mmol), **84a** (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (10 mol %), $AgSbF_6$ (40 mol %), oxidant (2.5 equiv), 0.2 M at 120 °C (the internal temperature of vial was 105 °C) in a 12 mL screw-capped tube. [b] Isolated yield. [c] The formation of product was not detected. BQ = 1,4-benzoquinone.

After a series of exploration with $[RuCl_2(p\text{-cymene})]_2$, the catalyst was changed to $[Cp^*Rh(III)Cl_2]_2$ to further examine this transformation. Impressively, initial attempt with styrene **84a** and *N*,*N*-diethylcarbamoyl protected indoline **83d** in DCE delivered the desired product **99d** in 96% yield after 36 h (Table 3.2, entry 1). Subsequently, reactions were performed in different solvents (Table 3.2, entries 2–5). It was found that 1,4-dioxane or toluene did not improve the yield of the desired product (Table 3.2,

entries 2 and 3). The use of DMF as a solvent, only trace amounts of the desired product was detected (Table 3.2, entry 5). Delightedly, the desired product was obtained in 90% yield using *t*-AmOH as solvent after 8 h (Table 3.2, entry 4). Compared to DCE, the reaction proceeded more efficiently in *t*-AmOH (Table 3.2, entries 1 and 4). Screening of oxidants in *t*-AmOH did not further improve the yield of the desired product. Moderate yields were obtained when Ag_2CO_3 or Ag_2O were used as oxidants. Nevertheless, $PhI(OAc)_2$ or NFSI (*N*-fluorobenzenesulfonimide) provided desired products with trace amounts (Table 3.2, entries 6–9). Using acetyl protected indoline **83a** as substrate, the desired product was gained with an almost quantitative yield in DCE after 36 h (Table 3.2, entry 10).

Table 3.2 Optimization of conditions for the Rh(III)-catalyzed alkenylation of indolines at the C7-position.[a]

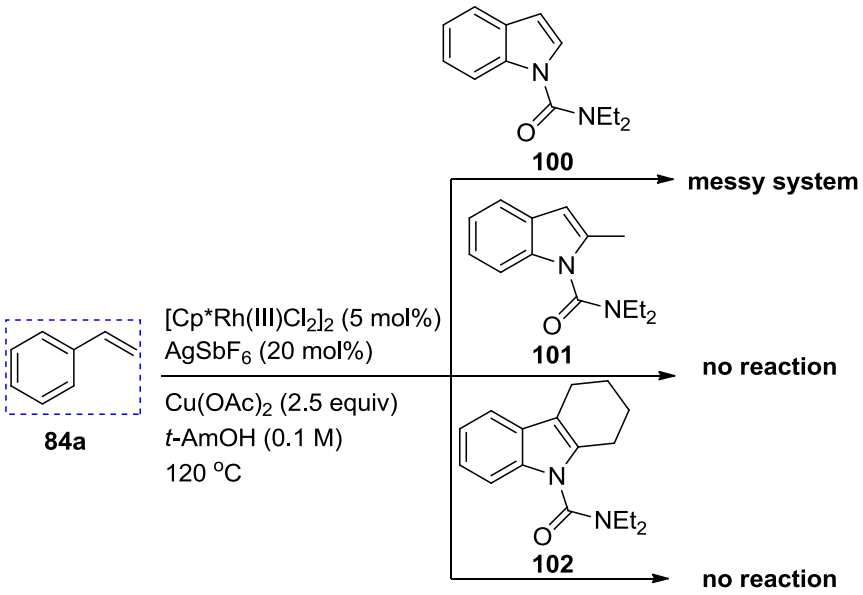


83 **84a** **99**

Entry	Indoline (DG)	Oxidant	Solvent	Product (DG)	Yield (%)[b]
1	**$CONEt_2$ (83d)**	**$Cu(OAc)_2$**	**DCE**	**$CONEt_2$ (99d)**	**96**
2	$CONEt_2$ (**83d**)	$Cu(OAc)_2$	1,4-dioxane	$CONEt_2$ (**99d**)	51
3	$CONEt_2$ (**83d**)	$Cu(OAc)_2$	toluene	$CONEt_2$ (**99d**)	31
4	$CONEt_2$ (**83d**)	$Cu(OAc)_2$	*t*-AmOH	$CONEt_2$ (**99d**)	90
5	$CONEt_2$ (**83d**)	$Cu(OAc)_2$	DMF	$CONEt_2$ (**99d**)	trace
6	$CONEt_2$ (**83d**)	Ag_2CO_3	*t*-AmOH	$CONEt_2$ (**99d**)	45
7	$CONEt_2$ (**83d**)	Ag_2O	*t*-AmOH	$CONEt_2$ (**99d**)	28
8	$CONEt_2$ (**83d**)	PIDA	*t*-AmOH	$CONEt_2$ (**99d**)	<5
9	$CONEt_2$ (**83d**)	NFSI	*t*-AmOH	$CONEt_2$ (**99d**)	trace
10	**Ac (83a)**	**$Cu(OAc)_2$**	**DCE**	**Ac (99a)**	**99**

[a] Reaction conditions: **83** (0.1 mmol), **84a** (0.5 mmol), $[Cp^*Rh(III)Cl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), oxidant (2.5 equiv), 0.1M at 120 °C, 36 h (16 h for entry 2, 48 h for entries 3 and 5, 8 h for entry 6). [b] Isolated yield.

After the alkenylation condition of indolines was established, it was wonder if this condition could be directly used for the alkenylation of indoles, and the transformations with different indoles were tested (Scheme 3.2). Firstly, styrene **84a** and *N*,*N*-diethylcarbamoyl protected indole **100** were subjected to this coupling reaction. After 1.5 h, starting materials got consumed. However, the desired product was detected with trace amounts, and the reaction was messy. *N*,*N*-Diethylcarbamoyl protected 2-methylindole **101** and 2,3,4,9-tetrahydro-1*H*-carbazole **102** were also examined in the presence of styrene **84a** under the same reaction conditions. Unfortunately, almost no reactions occurred in both cases.

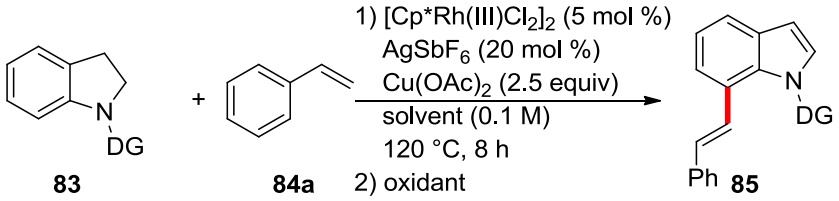


Scheme 3.2 Exploration of alkenylation with indoles.

Next, the condition for a one-pot reaction *via* the coupling and oxidation to regioselectively synthesize 7-functionalized indoles was explored. Initially, acetyl protected indoline **83a** was used as a substrate. The regioselective olefination step

completed after 36 h. The followed oxidation step did not afford the desired product **85a** with a good yield, although different oxidants were tested (Table 3.3, entries 1–3).[83] Intriguingly, replacing the protecting group of acetyl by *N*,*N*-diethylcarbamoyl, the yield of the product **85d** was dramatically improved under the oxidation of MnO_2 (Table 3.3, entries 4 and 5). The reaction time of the oxidation step became shorter, when the reaction was performed in *t*-AmOH. It afforded the product **85d** in 80% yield. Notably, the reaction could be easily scaled up to 10 folds under this reaction condition, and the product was obtained in 86% isolated yield. No improvement in the yield was observed when DDQ, $Mn(OAc)_3{\cdot}2H_2O$, TBHP (*tert*-butyl hydroperoxide) or chloranil were used as oxidants (Table 3.3, entries 6–9).

Table 3.3 Optimization of conditions for the synthesis of 7-substituted indoles in a one-pot fashion.[a]



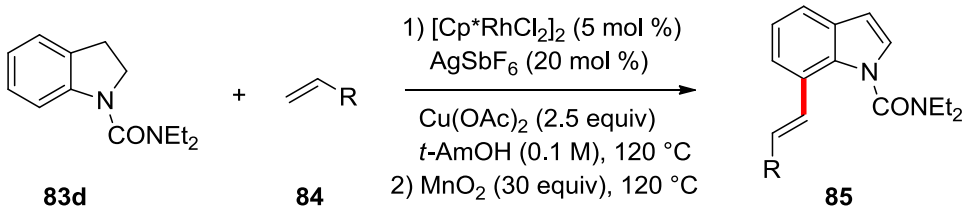
Entry	Indoline (DG)	Oxidant (equiv)	Time (h)	Product (DG)	Yield (%)[b]
1[c]	Ac (**83a**)	MnO_2 (20)	24	Ac (**85a**)	38
2[c]	Ac (**83a**)	DDQ (3)	24	Ac (**85a**)	11
3[c,d]	Ac (**83a**)	TBHP (4)	24	Ac (**85a**)	trace
4[c]	$CONEt_2$ (**83d**)	MnO_2 (20)	24	$CONEt_2$ (**85d**)	76
5	**$CONEt_2$ (83d)**	**MnO_2 (20)**	**8**	**$CONEt_2$ (85d)**	**80**
6	$CONEt_2$ (**83d**)	DDQ (3)	4	$CONEt_2$ (**85d**)	57
7	$CONEt_2$ (**83d**)	$Mn(OAc)_3{\cdot}2H_2O$ (1.5)	24	$CONEt_2$ (**85d**)	22
8[d]	$CONEt_2$ (**83d**)	TBHP (4)	24	$CONEt_2$ (**85d**)	trace
9	$CONEt_2$ (**83d**)	chloranil (3)	24	$CONEt_2$ (**85d**)	36

[a] Reaction conditions: **83** (0.1 mmol), **84a** (0.5 mmol), $[Cp^*Rh(III)Cl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), anhydrous $Cu(OAc)_2$ (2.5 equiv), solvent (0.1 M, entries 1–4 are DCE, entries 5–9 are *t*-AmOH) at 120 °C (the internal temperature of vial is 105 °C), after **99** completely disappeared (8 h), oxidant was added to the reaction system, continued stirring at 120 °C. The reaction time in table is oxidation step time. [b] Isolated yield. [c] After 36 h, **83** completely disappeared. [d] TBHP 5.5 M in decane.

3.1.1.3 Substrate Scope Evaluation for the Synthesis of 7-Alkenylated Indoles

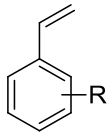
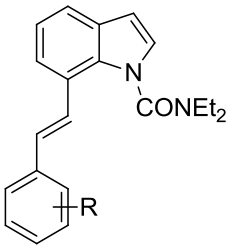
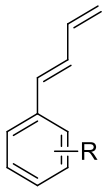
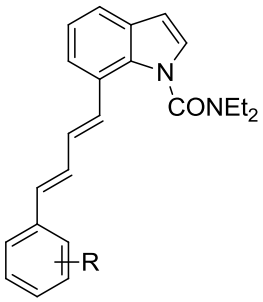
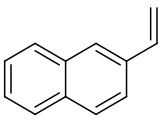
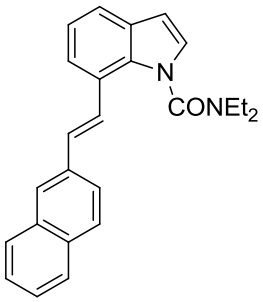
After the establishment of the optimal condition, the substrate scope of this reaction was evaluated. Initially, reactions with different alkenes **84** were explored. Delightedly, the reaction of methyl acrylate **84b** afforded the desired product **85e** in 54% yield after 9 h (Table 3.4, entry 1). Subsequently, styrenes with diverse substituents at different positions were subjected to this transformation. It was found that halogen substituted styrene **84c**–**84g** afforded corresponding products **85f**–**85j** in moderate to good yields (Table 3.4, entries 2–6). Styrene with a methoxyl group **84h** gave the desired product **85k** in moderate yield (Table 3.4, entry 7). *Ortho*-methyl substituted styrene **84i** offered the desired product **85l** in 74% isolated yield (Table 3.4, entry 8). Coupling with phenyl-1,3-butadiene derivatives **84j**, **84k** provided corresponding products **85m**, **85n** with good regioselectivity and yields (Table 3.4, entries 9 and 10). 2-Vinyl naphthalene **84l** and 1-vinyl naphthalene **84m** were also examined under this reaction condition. Reactions of both substrates proceeded smoothly and provided desired products in good yields (Table 3.4, entries 11 and 12).

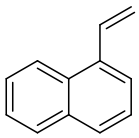
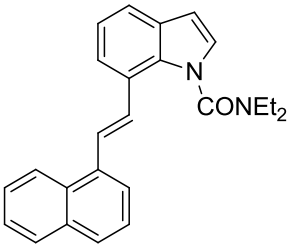
Table 3.4 Synthesis of 7-alkenylated indoles with different substituted alkenes.[a]



83d **84** **85**

Entry	Alkene	Time (h)	Product	Yield (%)[b]

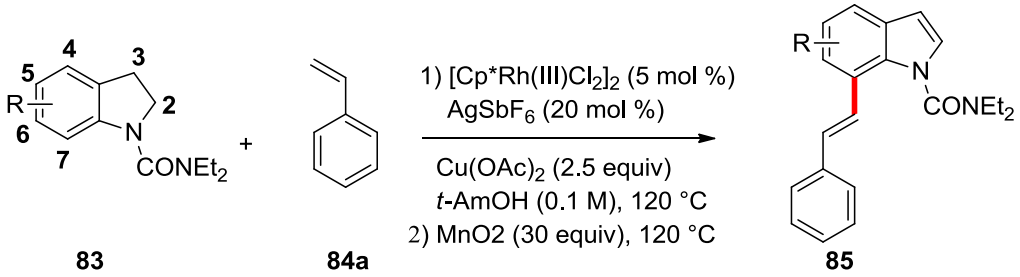
1[c]	R = CO_2Me (**84b**)	9	R = CO_2Me (**85e**)	54
				
2	R = 4-F (**84c**)	26	R = 4-F (**85f**)	66
3	R = 3-F (**84d**)	16	R = 3-F (**85g**)	57
4	R = 2-F (**84e**)	26	R = 2-F (**85h**)	64
5	R = 4-Br (**84f**)	16	R = 4-Br (**85i**)	83
6[c]	R = 3-Br, 4-F (**84g**)	16	R = 3-Br, 4-F (**85j**)	65
7[d]	R = 4-OMe (**84h**)	16	R = 4-OMe (**85k**)	50
8	R = 2-Me (**84i**)	26	R = 2-Me (**85l**)	74
				
9	R = 4-NO_2 (**84j**)	16	R = 4-NO_2 (**85m**)	58
10	R = H (**84k**)	26	R = H (**85n**)	59
11[d]	 (**84l**)	26	 (**85o**)	68

12[c]	 (**84m**)	26	 (**85p**)	96

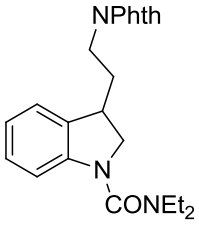
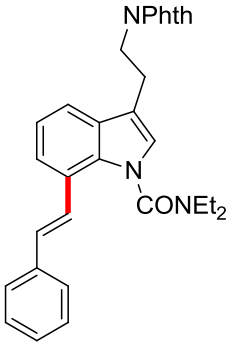
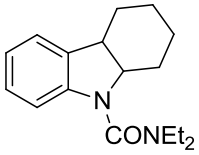
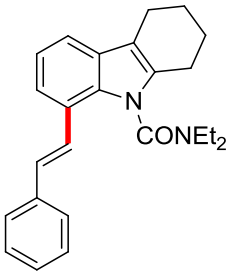
[a] Reaction conditions: **83d** (0.1 mmol), **84** (0.5 mmol), $[Cp^*Rh(III)Cl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), anhydrous $Cu(OAc)_2$ (2.5 equiv) with *t*-AmOH (0.1M) at 120 °C (the internal temperature of vial is 105 °C), after indolines completely disappeared, MnO_2 was added (30 equiv) to reaction system, continue stirring at 120 °C for 8 hours. The reaction time in table is the whole reaction time. [b] Isolated yield. [c] Use 40 equiv MnO_2. [d] Use 20 equiv MnO_2.

Subsequently, we explored the generality of this transformation with different indolines **83 (**compounds **83f–83m** were prepared by Prof. Dr. Rajashi Samanta**)**. It was found that reactions of indolines, which have diverse electron-rich or -poor substituents proceeded successfully (Table 3.5, entries 1–5). Substrates possessing halogen groups **83f–83h** were compatible with this newly developed reaction condition, and the related 7-substituted indoles **85q–85s** were obtained with moderate to good yields (Table 3.5, entries 1–3). Reactions of 5-methoxyl indoline **83i** and 2-methyl indoline **83j** gave desired products **85t**, **85u** with moderate yields after 16 h (Table 3.5, entries 4 and 5). Indolines with substituents at the C6-position was also examined. However, when 6-chloroindoline **83k** was used as a substrate, only trace amounts of the desired product **85v** was formed (Table 3.5, entry 6). It was assumed that the chlorine at the C6-position hampered the reaction of the indoline at the C7-position due to the steric effect or electronic effect. 3-Substituted indoline **83l** was also employed. Most of the starting materials were remained, and only trace amounts of the desired product **85w** were detected after 26 h (Table 3.5, entry 7). The reaction of tetrahydrocarbazole **83m** gave a messy reaction system. According to the proton NMR and GC-MS of products, except the desired product **85x**, the fully oxidized **85x**, the partially oxidized **83m** and the fully oxidized **83m** were all produced (Table 3.5, entry 8).

Table 3.5 Synthesis of 7-alkenylated indoles with different substituted indolines.[a]



83 **84a** **85**

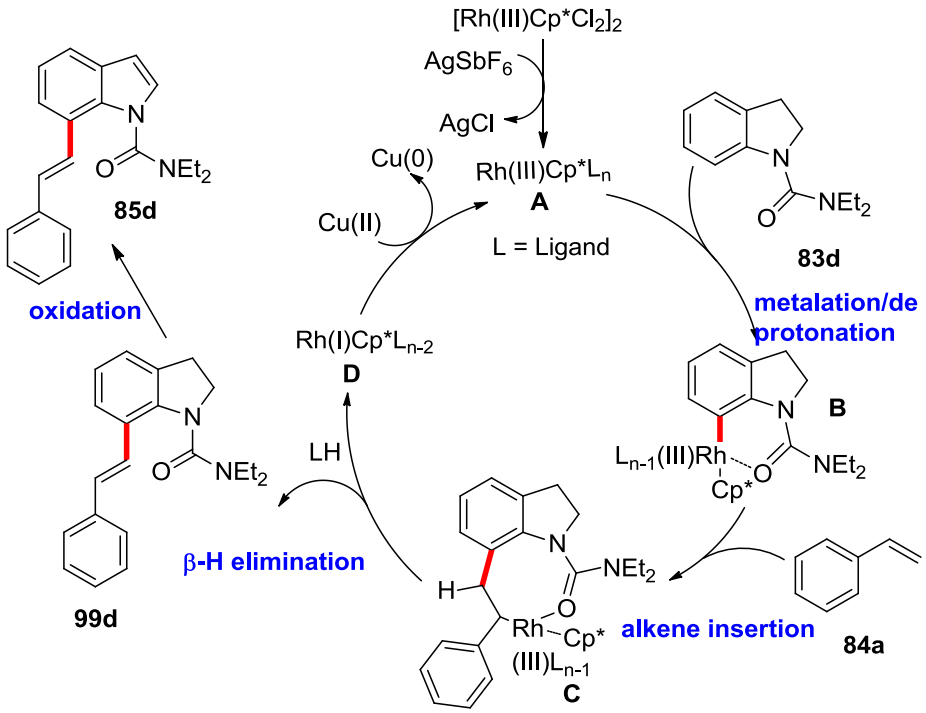
Entry	Indoline	Time (h)	Product	Yield (%)[b]
1[c]	R = 4-Br (**83f**)	26	R = 4-Br (**85q**)	55
2[d]	R = 5-F (**83g**)	26	R = 5-F (**85r**)	77
3[c]	R = 5-Br (**83h**)	16	R = 5-Br (**85s**)	64
4[c]	R = 5-OMe (**83i**)	16	R = 5-OMe (**85t**)	50
5	R = 2-Me (**83j**)	16	R = 2-Me (**85u**)	54
6	R = 6-Cl (**83k**)	26	R = 6-Cl (**85v**)	<5
7	 (**83l**)	26	 (**85w**)	<5
8	 (**83m**)	26	 (**85x**)	<5

[a] Reaction conditions: indolines **83** (0.1 mmol), alkene **84a** (0.5 mmol), $[Cp^*Rh(III)Cl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), anhydrous $Cu(OAc)_2$ (2.5 equiv) with *t*-AmOH (0.1M) at 120 °C (the internal temperature of vial is 105 °C), after indolines completely disappeared (for entries 6–8, indolines did not completely disappeared). MnO_2 was added (30 equiv) to the

reaction system, continued stirring at 120 °C for 8 hours. The reaction time in table is the whole reaction time. [b] Isolated yield. [c] Use 40 equiv MnO_2. [d] Use 20 equiv MnO_2.

3.1.1.4 Proposed Mechanism for the Synthesis of 7-Alkenylated Indoles

The mechanism for the preparation of 7-substituted indoles through regioselective alkenylation and followed oxidation was proposed (see Scheme 3.3).[21–30] Initially, the reaction of $[Rh(III)Cp^*Cl_2]_2$ and $AgSbF_6$ delivers the species **A**, in which except the pentamethylcyclopentadienyl (Cp*) ligand, acetate[84] or solvent also can be incorporated as ligands. Coordination between the rhodium species and the carbonyl oxygen of the diethyl carbamoyl group, followed by concerted metalation/deprotonation of $C(sp^2)$–H bond leads to a six membered rhodacycle **B**. Subsequently, the attack of olefin to the carbon-rhodium bond of **B** delivers an eight membered rhodacycle **C**. The intermediate **C** undergoes *β*-H elimination, offering the 7-substituted indoline **99d** and a rhodium (I) species **D**. The oxidation of **99d** by MnO_2 provides the desired product **85d**. The catalyst is regenerated under the transformation of Rh(I) species to Rh(III) species by $Cu(OAc)_2$.

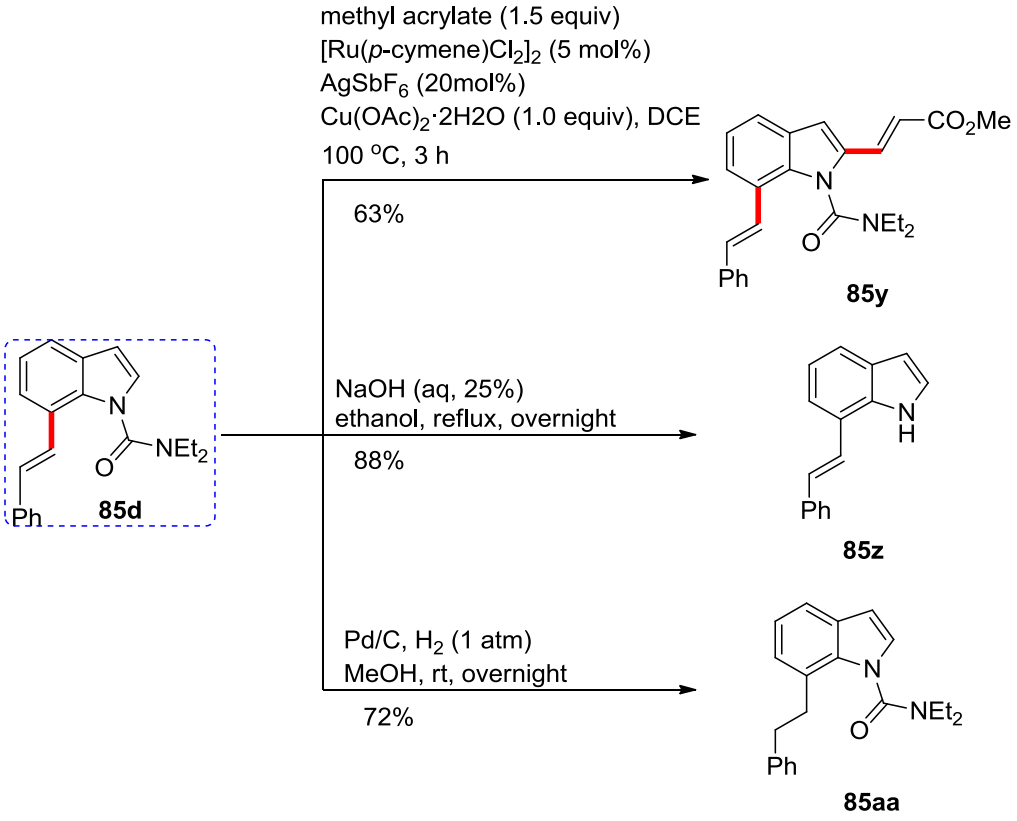


Scheme 3.3 Plausible mechanistic pathway for the synthesis of 7-substituted

indoles.[21–30]

3.1.1.5 Transformation of 7-Alkenylated Indoles

To demonstrate the utility of 7-substituted indoles in synthetic chemistry, we explored the transformation of these compounds (Scheme 3.4). Further alkenylation at the C2-position of 7-substituted indole **85d** was tried according to the reported method (Scheme 3.4).[85] Using [Ru(*p*-cymene)Cl_2]$_2$ as catalyst, the desired product **85y** was obtained in 63% yield after 3 h. This transformation provided an efficient way to synthesize 2- and 7-alkenylated indole derivatives. Additionally, the directing group of the product could be easily removed in ethanol with NaOH (25% aq.) under refluxing, and 7-substituted indole **85z** was obtained in an excellent yield after 12 h. 7-Alkenylated indoles **85d** also could be readily transformed to 7-alkylated indole **85aa** by hydrogenation over palladium/charcoal at ambient temperature. The desired product **85aa** was obtained in 72% isolated yield. This transformation offered a novel approach for the preparation of 7-alkylated indoles.



Scheme 3.4 Transformation of synthesized 7-substituted indoles.[85]

3.1.1.6 Biological Results of 7-Alkenylated Indoles

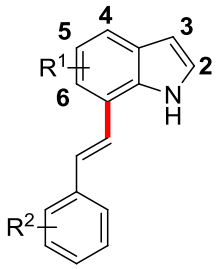
All synthesized 7-amino indoles **88** were submitted to COMAS (Compound Management and Screening Center) in Dortmund to investigate whether they exhibit biological activities against a number of targeted biological pathways in cell-based assays. Among the different assays in which the compounds were screened, it was revealed that one compound **85z** inhibited the hedgehog signaling pathway in the low micromolar range (Table 3.6).

Compared to the other submitted 7-substituted indoles, **85z** is the only compound without *N*,*N*-diethylcarbamoyl group on the nitrogen of the indole. We then decided to remove the *N*,*N*-diethylcarbamoyl group of the other compounds and subjected these compounds to different cell-based assays again. Delightedly, several compounds showed inhibitions of the hedgehog signaling pathway in the low micromolar range (Table 3.6). These results indicated that the *N*,*N*-diethylcarbamoyl group has big influence for inhibitory activity in hedgehog signaling pathway.

The details of the hedgehog cell-based assay are as follows: mouse embryonic mesoderm fibroblast C3H10T1/2 cells were used for assaying the modulation of hedgehog signaling pathway. These multipotent mesenchymal progenitor cells can differentiate into osteoblasts upon treatment with the SMO agonist purmorphamine. During differentiation, osteoblast specific genes such as alkaline phosphatase, which play a crucial role in bone formation, are strongly expressed. The activity of alkaline phosphatase can be directly monitored by following substrate hydrolysis, yielding a highly luminescent product. Inhibition of the hedgehog pathway results in a reduction in luminescence. Hits showed reduction in the luminescent signal without altering the cell viability. Dose-response analysis was performed for hit compounds.

Table 3.6 Representative results of hedgehog-pathway inhibition.

Entry	Product	IC_{50} [µM]	Viability[a] [µM]



1	R^1 = H, R^2 = H (**85z**)	2.19 ± 0.12	inactive
2	R^1 = H, R^2 = 2-Me (**85ab**)	2.67 ± 0.22	inactive
3	R^1 = 5-F, R^2 = H (**85ac**)	2.07 ± 0.06	inactive
4	R^1 = H, R^2 = 3-Br, 4-F (**85ad**)	2.03 ± 0.35	inactive
5	R^1 = H, R^2 = 4-F (**85ae**)	4.27 ± 0.37	inactive
6	R^1 = H, R^2 = 2-F (**85af**)	2.91 ± 0.12	inactive

[a] Compounds referred to as "inactive" showed more than 80% cell viability at 10 µM.

3.1.2 Synthesis of 7-Substituted Indoles by Iridium(III)-Catalyzed Regioselective Sulfonamidation

The following chapter is related to:

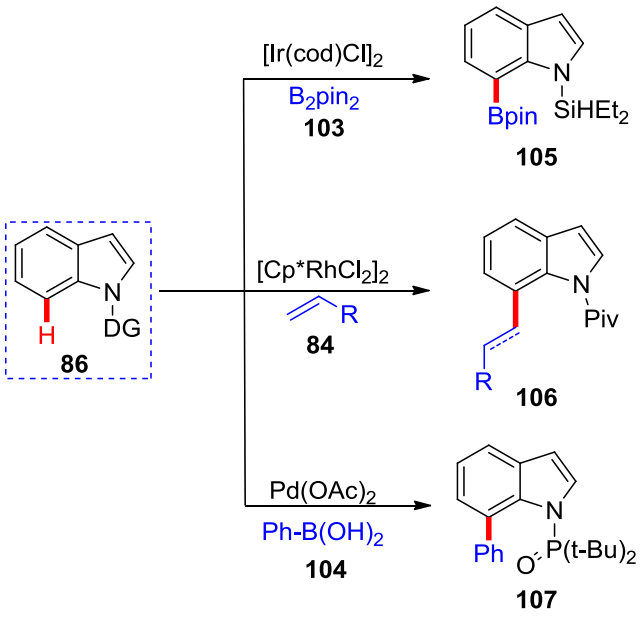
Iridium(III)-catalyzed regioselective C7-sulfonamidation of indoles

Zengqiang Song, Andrey P. Antonchick

Org. Biomol. Chem., **2016**, *14*, 4804–4808

3.1.2.1 Introduction for the Direct C7-Functionalization of Indoles and Synthesis of 7-Amino Indoles

7-Substituted indoles are frequently prepared by the functionalization of 2-substituted indoles[86] or indolines,[87] methods for the synthesis of them by direct functionalization at the C7-position of indoles are rare. The first method for direct regioselective functionalization of indoles at the C7-position was reported by Hartwig and co-workers in 2010. They successfully synthesized 7-borylated indoles with good regioselectivity when diethylsilyl was used as a directing group.[88] Very recently, Ma's group and Shi's group reported Rh(III)-catalyzed olefination[89] and Pd(II)-catalyzed arylation[90] of indoles at the C7-position, respectively (Scheme 3.5). Undoubtedly, new approaches for direct functionalization of indoles at the C7-position are highly desirable.



Scheme 3.5 Reported methods for direct functionalization of indoles at the C7-position.[88–90]

7-Amino indole derivatives as important compounds are abundantly present in natural products and bioactive compounds (Figure 3.2).[91] However, so far there is no report about the direct formation of C–N bond by C–H bond functionalization of indoles at the C7-position.[92] Hence, methods for the direct formation of C–N bond at the C7-position of indoles are in high demand.

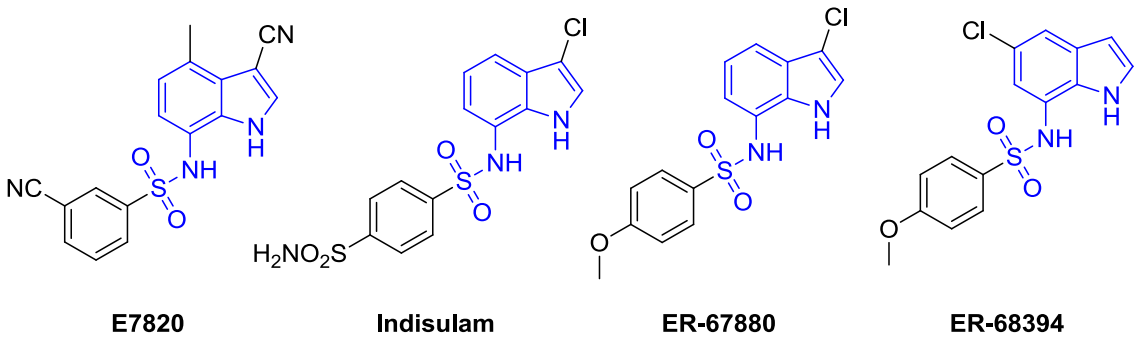
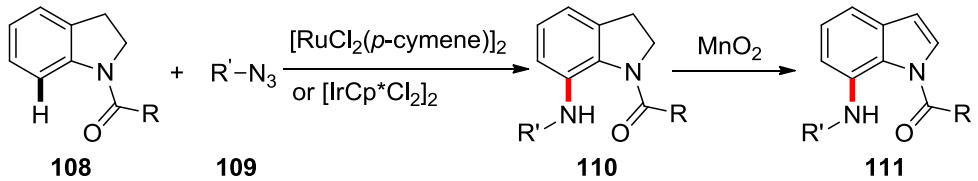


Figure 3.2 Representative bioactive compounds containing 7-amino indole structural motif.[91]

In 2014, the first example of the C7-amidation of indolines was reported by Zhu et al. with Ru(II) catalysis (Scheme 3.6).[93] Later, using Ir(III) catalysts, the same reaction was accomplished by Chang's group[49c] and Li's group.[49d] These 7-substituted indolines were transformed to 7-substituted indoles when MnO_2 was used as an external oxidant (Scheme 3.6). However, as far as we know, there are no reports about direct regioselective C–H bond amidation at the C7-position of indoles.[92] The main challenge of this methodology is regioselective functionalization of indoles at the C7-position among the C2-, C3- and C7-positions.

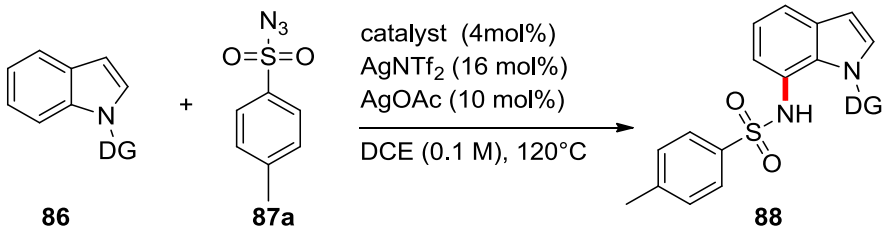


Scheme 3.6 Reported methods for the synthesis of 7-amino indoles from indolines.[49c,49d,93]

3.1.2.2 Optimization Studies for the Synthesis of 7-Amino Indoles

In the initial studies, the reaction of indole **86** and tosyl azide **87a** was examined using $[Cp^*IrCl_2]_2$ as catalyst, $AgNTf_2$ and AgOAc as additives in DCE at 120°C.[45,94] Unfortunately, no desired product was detected after 24 h (Table 3.7, entry 1). Subsequently, indoles with various directing groups were tested (Table 3.7, entries 2–8). It was found that a mixture of regioisomers at the C7- and C2-positions of indoles was formed when benzoyl was used as a directing group (Table 3.7, entry 2). Acetyl protected indole **86e** provided a complex regioisomers mixture (Table 3.7, entry 5). Intriguingly, changing the directing group from acetyl to pivaloyl led to the regioselective formation of C7-functionalized product **88f** in 58% yield (Table 3.7, entry 6). The use of other directing groups, no desired product was formed (Table 3.7, entries 3, 4, 7 and 8). Reactions with different transition-metal catalysts, like the Rh(III) complex, the Ru(II) complex and the Pd(II) complex were also tested. Unfortunately, almost no desired product was formed in all cases (Table 3.7, entries 9–11). Delightedly, the desired product was obtained in 93% yield after 1 h when the amount of tosyl azide was increased to 2.2 equiv (Table 3.7, entry 12).

Table 3.7 Exploration of reactions with different directing groups and catalysts.[a]



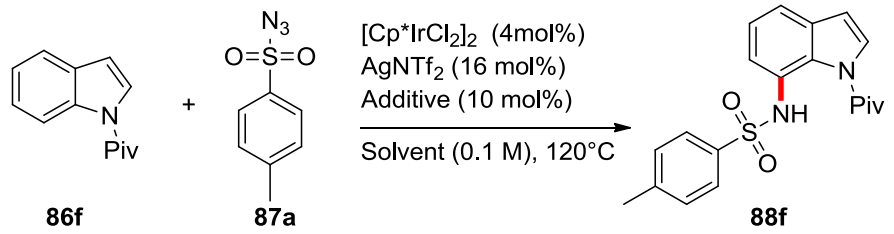
Entry	Indole (DG)	Catalyst	Product (DG)	Yield (%)[b]
1	H (**86a**)	$[Cp^*IrCl_2]_2$	H (**88a**)	n.d.
2	Benzoyl (**86b**)	$[Cp^*IrCl_2]_2$	Benzoyl (**88b**)	29[c]
3	Picolinyl (**86c**)	$[Cp^*IrCl_2]_2$	Picolinyl (**88c**)	n.d.

4	Tosyl (**86d**)	$[Cp^*IrCl_2]_2$	Tosyl (**88d**)	n.d.
5	Acetyl (**86e**)	$[Cp^*IrCl_2]_2$	Acetyl (**88e**)	n.d.[d]
6	Pivaloyl (**86f**)	$[Cp^*IrCl_2]_2$	Pivaloyl (**88f**)	58
7	Dimethyl Carbamoyl (**86g**)	$[Cp^*IrCl_2]_2$	Dimethyl Carbamoyl (**88g**)	n.d.
8	Boc (**86h**)	$[Cp^*IrCl_2]_2$	Boc (**88h**)	n.d.
9	Pivaloyl (**86f**)	$[RhCp^*Cl_2]_2$	Pivaloyl (**88f**)	<5
10	Pivaloyl (**86f**)	$[Ru(p\text{-cymene})Cl_2]_2$	Pivaloyl (**88f**)	n.d.
11	Pivaloyl (**86f**)	$Pd(OAc)_2$	Pivaloyl (**88f**)	n.d.
12	**Pivaloyl (86f)**	**$[Cp^*IrCl_2]_2$**	**Pivaloyl (88f)**	**93**

[a] Reaction conditions: **86** (0.1 mmol), **87a** (0.11 mmol for entries 1–11) or **87a** (0.22 mmol; for entry 12), catalyst (4 mol%), $AgNTf_2$ (16 mol%), AgOAc (10 mol%), DCE (0.1 M), 120 ^oC, 24 h (2 h for entry 7; 1 h for entry 12) in a 12 mL screw-capped tube. [b] Yield refers to isolated products after column chromatography. [c] C2 isomer in 12% yield and C7-isomer in 17% yield. [d] Complex regioisomer mixture. n.d. = the desired product was not detected.

After the development of method to synthesize 7-amino indoles, we did reaction condition studies of this transformation. Screening of solvents did not improve the yield of the desired product (Table 3.8, entries 1–7). Reducing the amounts of tosyl azide from 2.2 equiv to 1.6 equiv, the yield of the product dropped from 93% to 86% (Table 3.6, entry 8). Different additives were also tested for this transformation (Table 3.6, entries 9–13). Without the additive, the desired product was obtained only in 18% isolated yield after 24 h (Table 3.6, entry 9). Intriguingly, when LiOAc was used as an additive, the reaction provided the desired product in 98% yield after 1 h (Table 3.6, entry 12). It was also found that decreasing the amounts of the catalyst or lowering reaction temperature led to a decrease in the yield of the desired product (Table 3.6, entries 14 and 15).

Table 3.8 Optimization of conditions for the sulfonamidation of indoles at the C7-position.[a]



Entry	Additive	Solvent	Time (h)	Yield (%)[b]
1	AgOAc	Chloroform	1	69
2	AgOAc	1,4-Dioxane	24	12
3	AgOAc	Toluene	24	n.d.
4	AgOAc	Chlorobenzene	4	79
5	AgOAc	*tert*-Amyl alcohol	24	n.d.
6	AgOAc	DMF	24	n.r.
7	AgOAc	DMSO	24	n.r.
8[c]	AgOAc	DCE	1	86
9	—	DCE	24	18
10[d]	$Cu(OAc)_2$	DCE	1	61
11[d]	NaOAc	DCE	24	21
12[d]	**LiOAc**	**DCE**	1	**98**
13[d]	PivOH	DCE	24	34
14[d,e]	LiOAc	DCE	24	56
15[d,f]	LiOAc	DCE	1	84

[a] Reaction conditions: **86f** (0.1 mmol), **87a** (0.22 mmol), $[Cp^*IrCl_2]_2$ (4 mol%), $AgNTf_2$ (16 mol%), additive (10 mol%), solvent (0.1 M), 120 °C in a 12 mL screw-capped tube. [b] Yield refers to isolated products after column chromatography. [c] 1.6 equiv **87a** was used. [d] 40 mol% additive was used. [e] 2 mol% $[Cp^*IrCl_2]_2$, 8 mol% $AgNTf_2$ were used. [f] The reaction was performed at 80 °C. n.d. = the desired product was not detected. n.r. = no reaction occured.

The structure of the desired product **88f** was confirmed by X-ray crystal structural analysis (Figure 3.3).

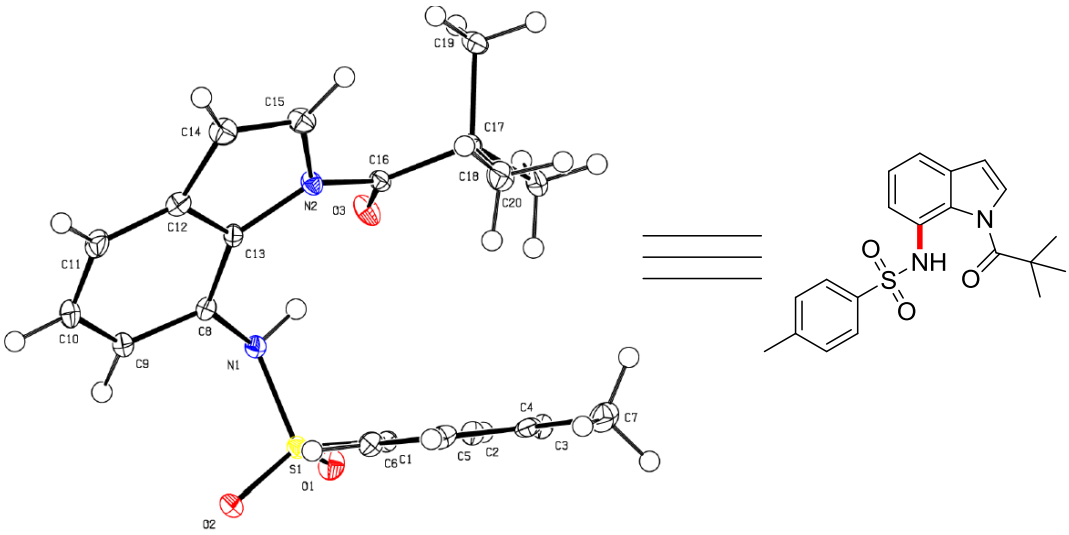
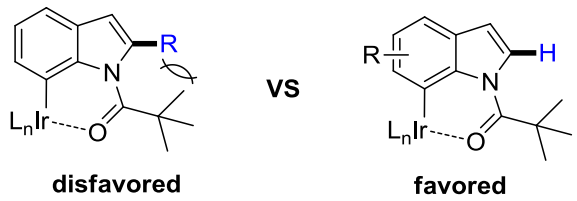


Figure 3.3 Crystal structure of product **88f**. X-Ray structure analysis was performed by Christopher Golz (TU Dortmund).

3.1.2.3 Substrate Scope Evaluation for the Synthesis of 7-Amino Indoles

With the optimal condition in hand, the scope of this novel transformation was explored. Initially, the generality of the indole part was examined. Indoles with diverse substituents at different positions were tested with tosyl azides. It was found that reactions of indoles with electron-donating or -withdrawing groups at the C4- or C5-positions proceeded well. The corresponding products **88i–88q** were rapidly provided with good yields (Table 3.9, entries 1–9). Notably, halogens and formyl groups were tolerated under this reaction condition. Surprisingly, indole with a 6-methoxy group gave the desired product **88r** in 78% yield after 1 h (Table 3.9, entry 10). In most cases, substituents at the C6-position of indoles will hamper the C–H bond functionalization of indoles at the C7-position because of steric effect, and the related product is very difficult to be formed. Using 6-chloro indole **86s** as substrate, the desired product **88s** was obtained in 34% isolated yield after 12 h (Table 3.9, entry 11).

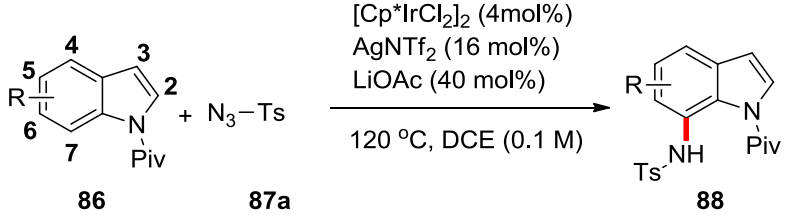
These results indicated that under this newly developed reaction condition, electronic effect is more important than steric effect to control the formation of 7-substituted indoles from 6-substituted indoles. Investigations on 3-substituted indoles gave corresponding products in good to excellent yields (Table 3.9, entries 12–15). Delightedly, reactions with tryptamine derivative **86v** and tryptophan derivative **86w** proceeded smoothly, and the corresponding products **88v** and **88w** were provided in 90% and 80% yields (Table 3.9, entries 14 and 15). 2-Substituted indoles were also examined. However, when 2-methylindole **86x** was used as a substrate, no desired product **88x** was detected after 12 h (Table 3.9, entry 16). It was assumed that a possible interaction between 2-methyl group and pivaloyl group led to an unfavored coordination between the metal catalyst and the substrate. Hence, no desired product was formed in this case (Scheme 3.7).



Scheme 3.7 Interaction between catalyst and indoles.

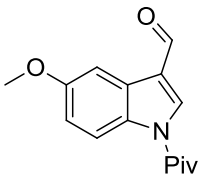
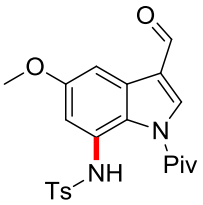
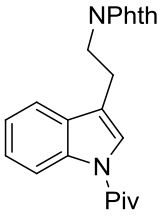
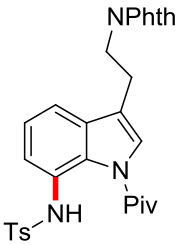
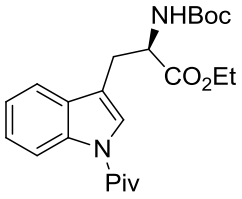
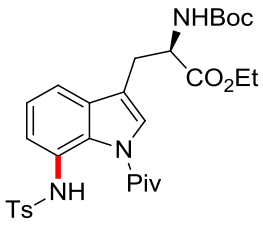
The same result was obtained using tetrahydrocarbazole as substrate (Table 3.9, entry 17).

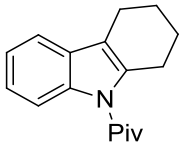
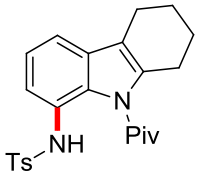
Table 3.9 Synthesis of 7-amino indoles with various substituted indoles.[a]



86 87a 88

Entry	Indole	Time (h)	Product	Yield (%)[b]

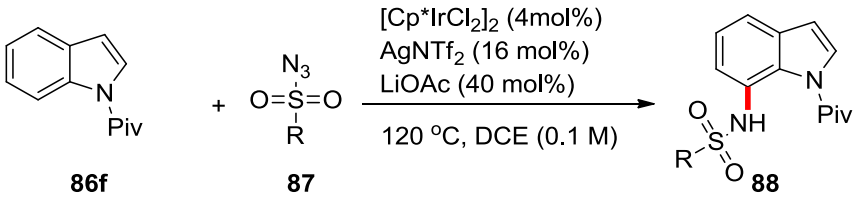
1	R = 4-Ph (**86i**)	1	R = 4-Ph (**88i**)	87
2	R = 4-Br (**86j**)	2	R = 4-Br (**88j**)	69
3	R = 4-Cl (**86k**)	1	R = 4-Cl (**88k**)	76
4	R = 4-CHO (**86l**)	1	R = 4-CHO (**88l**)	92
5	R = 5-OMe (**86m**)	2	R = 5-OMe (**88m**)	72
6	R = 5-Ph (**86n**)	1	R = 5-Ph (**88n**)	88
7	R = 5-F (**86o**)	2	R = 5-F (**88o**)	73
8	R = 5-Cl (**86p**)	2	R = 5-Cl (**88p**)	66
9	R = 5-Br (**86q**)	2	R = 5-Br (**88q**)	80
10	R = 6-OMe (**86r**)	1	R = 6-OMe (**88r**)	78
11	R = 6-Cl (**86s**)	12	R = 6-Cl (**88s**)	34
12	R = 3-Me (**86t**)	2	R = 3-Me (**88t**)	79
13	 **(86u)**	1	 (**88u**)	75
14	 **(86v)**	1	 (**88v**)	90
15	 **(86w)**	2	 (**88w**)	80
16	R = 2-Me (**86x**)	12	R = 2-Me (**88x**)	n.d.

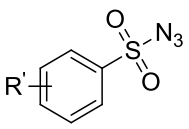
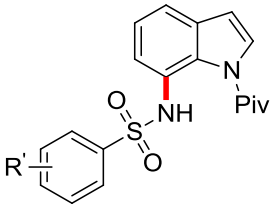
17	 (**86y**)	12	 (**88y**)	n.d.

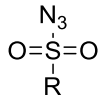
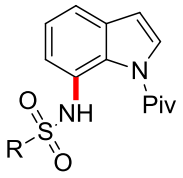
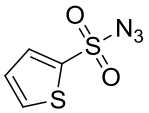
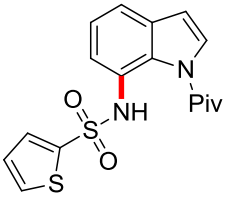
[a] Reaction conditions: **86** (0.1 mmol), **87a** (0.22 mmol), $[Cp^*IrCl_2]_2$ (4 mol%), $AgNTf_2$ (16 mol%), LiOAc (40 mol%) in DCE (0.1 M) at 120 °C. [b] Yield refers to isolated products after column chromatography.

The scope of the reaction with different azides was also explored. Firstly, reactions with various sulfonyl azides were examined. It was found that aryl sulfonyl azides with diverse groups at different positions of phenyl ring provided related products **88z**–**88ad** in moderate to excellent yields (Table 3.10, entries 1–5). The reactions of alkyl azides, such as methyl azide **87g**, heptyl azide **87h**, proceeded smoothly and provided corresponding products **88ae** and **88af** in 94% and 80% yields (Table 3.10, entries 6 and 7). Interestingly, using thiophene-2-sulfonyl azide **87i** as substrate, the desired product **88ah** was obtained in 83% yield after 1 h (Table 3.10, entry 8).

Table 3.10 Synthesis of 7-amino indoles with various substituted tosyl azides.[a]

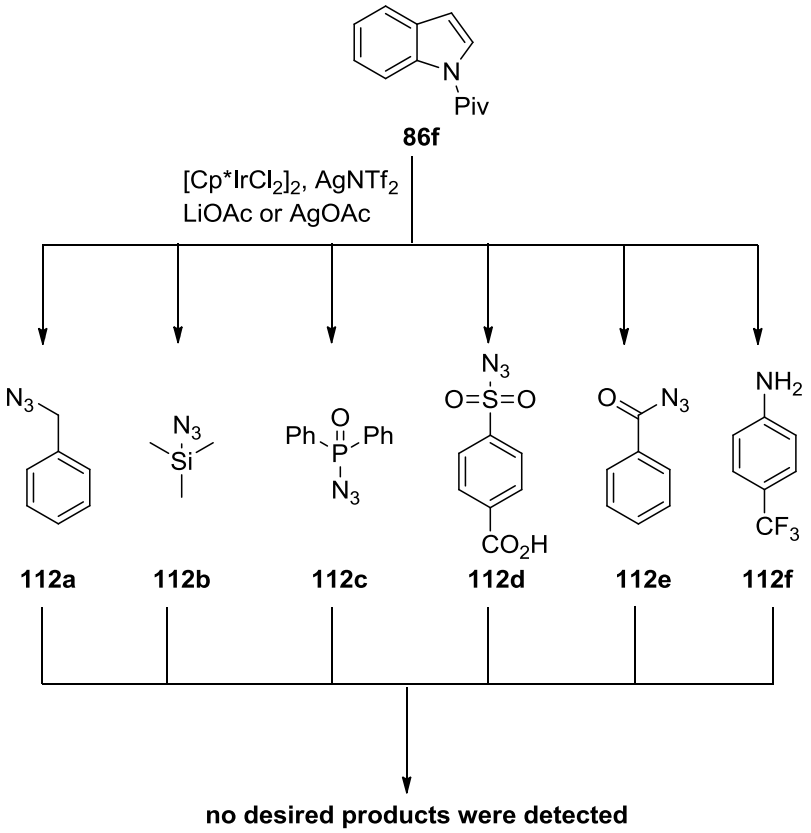


Entry	Tosyl azide	Time (h)	Product	Yield (%)[b]
				
1	R' = H (**87b**)	1	R' = H (**88z**)	86
2	R' = 4-Ac (**87c**)	1	R' = 4-Ac (**88aa**)	77

3	R' = 3-F (**87d**)	1	R' = 3-F (**88ab**)	88
4	R' = 3-CN (**87e**)	12	R' = 3-CN (**88ac**)	52
5	R' = 2-NO_2 (**87f**)	1	R' = 2-NO_2 (**88ad**)	93
				
6	R = CH_3 (**87g**)	1	R = CH_3 (**88ae**)	94
7	R = C_7H_{15} (**87h**)	3	R = C_7H_{15} (**88af**)	80
8	 (**87i**)	1	 (**88ah**)	83

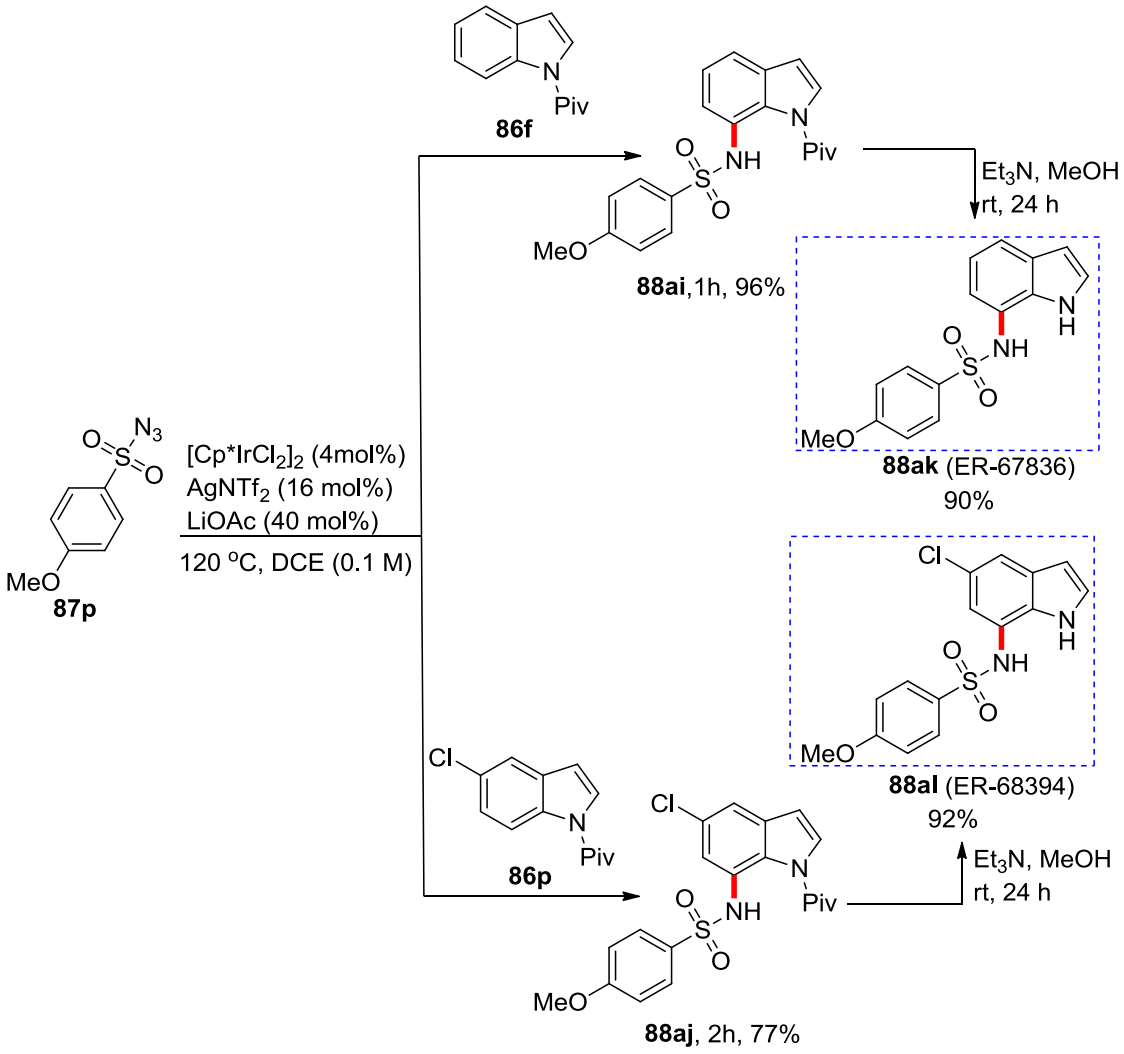
[a] Reaction conditions: **86f** (0.1 mmol), **87** (0.22 mmol), $[Cp^*IrCl_2]_2$ (4 mol%), $AgNTf_2$ (16 mol%), LiOAc (40 mol%) in DCE (0.1 M) at 120°C. [b] Yield refers to isolated products after column chromatography.

The reactions of other azides **112**, like benzyl azide **112a**, TMS (trimethylsilyl) azide **112b**, diphenylphosphoryl azide **112c** and 4-carboxybenzenesulfonazide **112d** were also tested. However, none of them produced desired products. Reactions with benzoyl azide **112e** were performed at different temperatures (at 25 °C, 60 °C, 120 °C), but no desired product was observed. Using amines instead of azides as nitrogen source, the reactions of 4-(trifluoromethyl)aniline **112f**, which was often used as a substrate in similar reactions,[53] were examined. Unfortunately, no desired product appeared using neither LiOAc nor AgOAc as oxidants (Scheme 3.8).



Scheme 3.8 Synthesis of C7-amino indoles with different nitrogen sources.

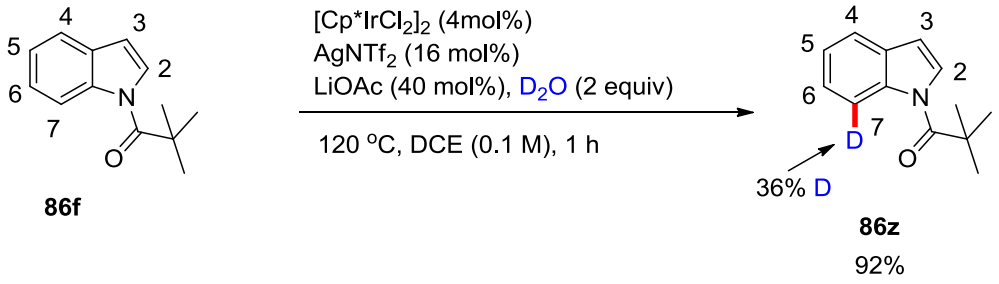
Gratifyingly, this newly developed method could be efficiently used to synthesize bioactive compounds. The reaction of azide **87p** and indole **86f** afforded the desired product **88ai** in 96% yield after 1 h under the standard reaction condition. Deprotection of **88ai** in methanol with Et_3N provided the bioactive compound **88ak** (ER-67836) with an excellent yield (Scheme 3.9).[95] It was reported that the proliferation of HeLa cell was inhibited by ER-67836 with half-maximal inhibitory concentrations ranging from 6 to 17 μM. The other bioactive compound **88al** (ER-68394) was also readily prepared by the same procedures (Scheme 3.9).[95b,96]



Scheme 3.9 Synthesis of bioactive 7-amino indoles.[95,96]

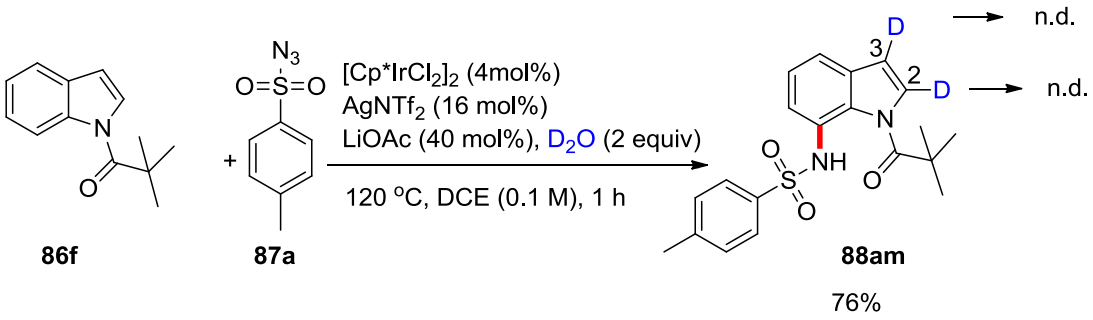
3.1.2.4 Mechanistic Studies for the Synthesis of 7-Amino Indoles

To gain the evidence into the mechanism and regioselectivity of this novel transformation, deuterium labelling experiments were carried out. Initially, the reaction of **86f** with 2 equiv of D_2O was tested under the standard reaction condition. After 1 h, the reaction was stopped, and **86z** was obtained in 92% isolated yield. The proton NMR revealed that **86z** contained 36% D at the C7-position (Scheme 3.10).



Scheme 3.10 Deuterium labelling experiment with *N*-pivaloyl indole.

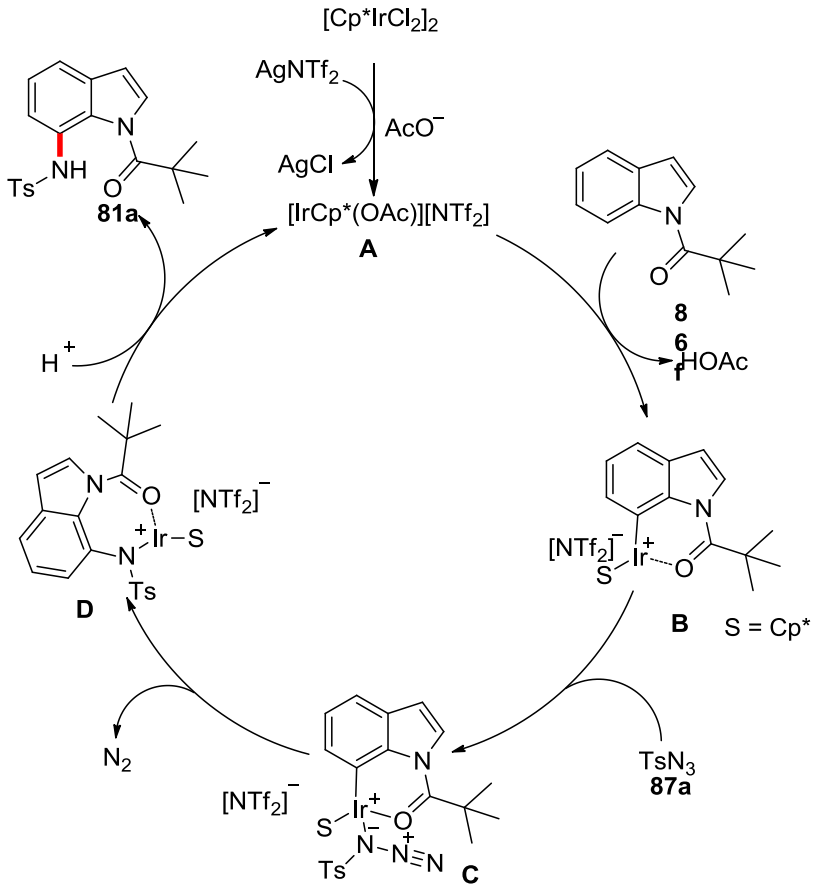
Subsequently, the same reaction in the presence of 2.2 equiv of **87a** was performed. **88am** was obtained in 76% yield after 1h. In the proton NMR of **88am**, no deuterium on the indole ring was observed (Scheme 3.11). This result indicated that C–H bond activation exclusively occurred at the C7-position of the indole under the described reaction condition.



Scheme 3.11 Deuterium labelling experiment with *N*-pivaloyl indole and tosyl azide.

Based on the experimental results and literature reports,[40,44a,97,98] a mechanism for the sulfonamidation of indoles at the C7-position using Ir(III) catalysis was proposed (Scheme 3.12). Initially, the reaction of $[Cp^*IrCl_2]_2$ with $AgNTf_2$ and acetate anion delivers an active cationic species **A**.[46a] The coordination of the species **A** to the oxygen of the pivaloyl group and subsequent C(sp^2)–H bond activation provides a metallocycle **B**. The attack of TsN_3 to the iridium species **B** leads to the intermediate **C**, which give the intermediate **D** and releases N_2 by sulfonyl amido group migratory insertion. A stepwise nitrenoid pathway also will be possible for this sulfonyl amido group transfer process.[40] Finally, a

proto-demetalation of **D** delivers the desired product **88a** with the regeneration of the iridium complex **A**.



Scheme 3.12 Proposed mechanism for the amidation of indoles at the C7-position.[40,44a,46a,97,98]

3.1.2.5 Biological Results of 7-Amino Indoles

All synthesized 7-amino indoles **88** were submitted to COMAS (Compound Management and Screening Center) in Dortmund to investigate whether they exhibit biological activities against a number of targeted biological pathways in cell-based assays. Among the different assays in which the compounds were screened, it was revealed that three compounds **88k**, **88p** and **88q** showed inhibition of the autophagy signaling pathway (Figure 3.4), and one compound **88aj** showed inhibition of the Wnt

signaling pathway (Figure 3.5).

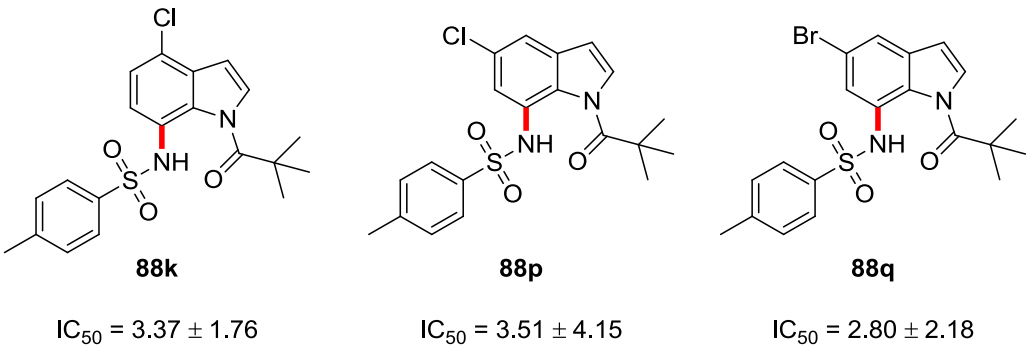
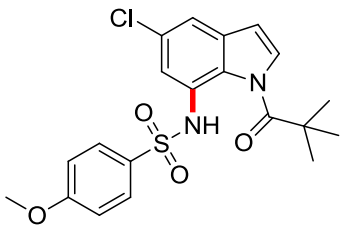


Figure 3.4 Results of autophagy-pathway inhibition.

The details of the autophagy cell-based assay are as follows: MCF7-LC3 (4000 cells/well) cells were seeded in 384 well plates (Greiner). The next day cells were washed three times with 1x PBS using plate washer ELX405 (Biotek). After that, 10 µM of compound was added using Echo dispenser (Labcyte) along with EBSS (starvation medium) and Chloroquine (50 µM) or Rapamycin (100 nM) and Chloroquine (50 µM). Three hours after incubation at 37°C cells were fixed by addition of 25 µl formaldehyde in 1 x PBS (4.6% final concentration) and simultaneously staining the nucleus with 1:500 Hoechst (Stock 1 mg/ml) for 20 min at ambient temperature. Fixed cells were washed thrice with 1x PBS using plate washer ELX405 (Biotek). For visualization 4 pictures/well were acquired using ImageXpress Micro XL (Molecular Devices) at 20x and analysed with the granularity algorithm of MetaXpress Software (Molecular Devices).

Dose-response analysis was carried out starting from 10 µM using a three-fold dilution curve over eight steps. IC_{50} calculations were done using Quattro Workflow software (Quattro Research GmbH).



88aj

IC_{50} = 15.67 ± 1.52
viability: inactive

Figure 3.5 Result of Wnt-pathway inhibition. Compounds referred to as "inactive" showed no inhibition of luciferase activity at 30 µM.

The details of the Wnt cell-based assay is as follows: compounds were screened at a concentration of 30 µM in a cell-based reporter gene assay using HEK293 cell line stably transfected with SuperTopFlash (STF) reporter plasmid. In addition, the cells were also stably transfected with multiple copies of Frizzled receptor (the binding partner of Wnt3a ligands to activate the pathway) to increase the sensitivity of the pathway activity for stimulation by Wnt3a proteins (approx. 10–20 fold higher induction of wnt-driven luciferase reporter compared with wild type HEK293 cells). Only the compounds that displayed cell viability above 80% were subjected to this assay. Furthermore, the compounds were also tested parallelly in HEK293 cells constitutively expressing renilla luiferase reporter plasmid to rule out false positives arising due to general transcription, translation and luciferase protein inhibition itself.

3.2 Synthesis of Nitrogen-Containing Heterocycles by Direct Functionalization of C(sp^3)–H Bond at *a*-Position of Tertiary Amines

3.2.1 Cyclization Between Tertiary Alkylanilines and Alkenes by Peroxide and Iodide

The following chapter is related to:

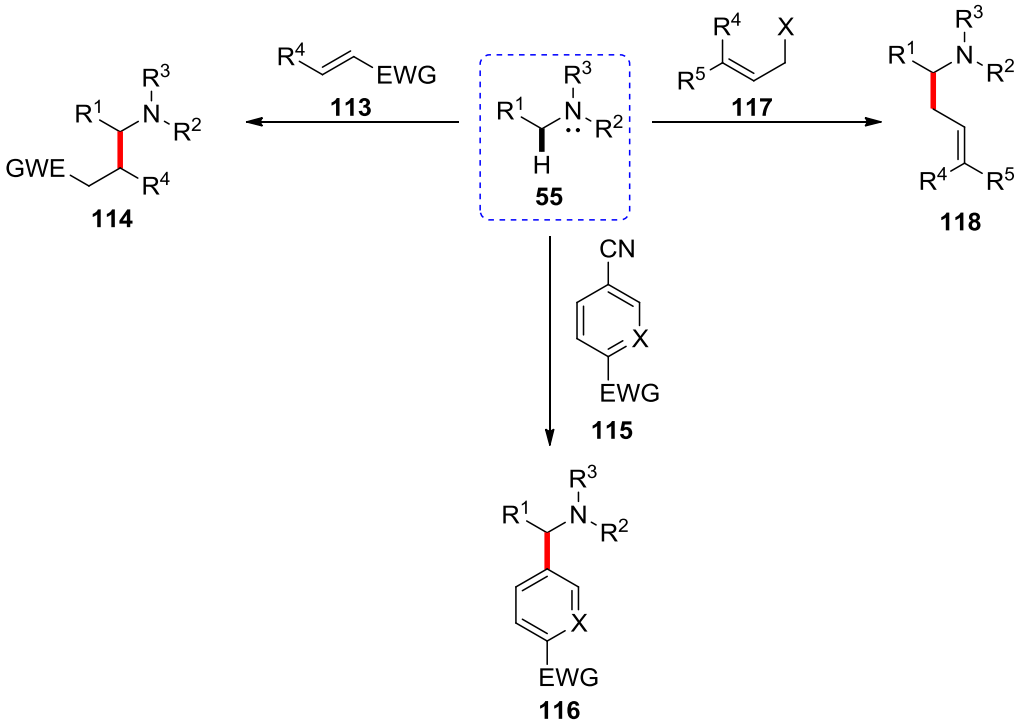
Catching a-aminoalkyl radicals: cyclization between tertiaryalkylanilines and alkenes

Zengqiang Song, Andrey P. Antonchick

Tetrahedron, **2016**, DOI:10.1016/j.tet.2016.04.052

3.2.1.1 Introduction for the Synthesis of Nitrogen-Containing Heterocycles *via* α-Aminoalkyl Radicals

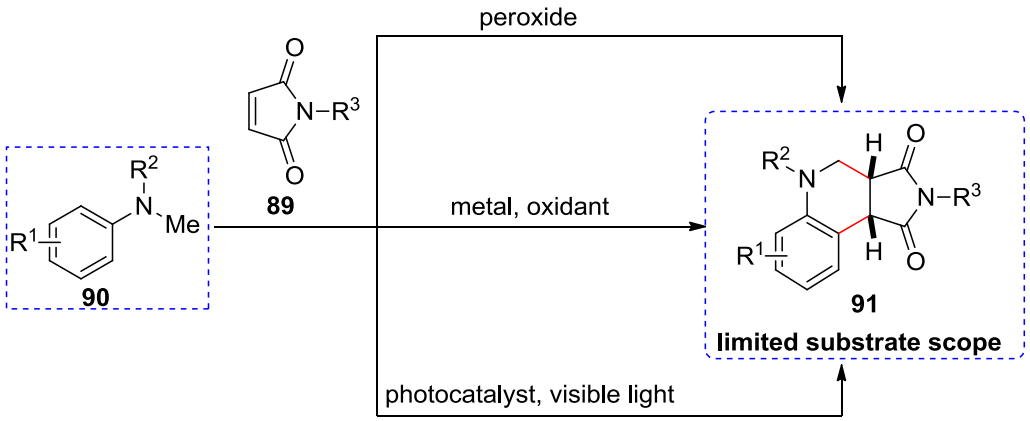
The development of new approaches to construct nitrogen-containing heterocycles attracts intensive attention in synthetic chemistry. Reactions involving *α*-aminoalkyl radicals, which are formed by direct functionalization of C(sp^3)–H bond at *a*-position of tertiary amines, are one of the efficient tool to synthesize these compounds. In recent years, abundant of these reactions have been developed by different research groups under visible light photoredox catalysis, and diverse compounds were prepared through the addition or coupling of *α*-aminoalkyl radicals with electron deficient alkenes, arenes or allylic esters (Scheme 3.13).[62,65,99]



Scheme 3.13 Reactions with *α*-aminoalkyl radicals by photoredox catalysis.[62,65,99]

Compared to the addition reactions, annulation reactions involving *α*-aminoalkyl radical intermediates for the preparation of nitrogen-containing heterocycles were less studied.[65,100] In 1969, using benzoyl peroxide as catalyst, Swan and Roy discovered a cyclization reaction of tertiary anilines **90** with *N*-phenyl maleimides **89** *via* α-aminoalkyl radicals at low temperature (Scheme 3.14).[101] Later, the same reaction was accomplished by Miura and co-workers. They used $Mn(NO_3)_2$[102] or $CuCl_2$[103] as oxidants to transfer single electron (Scheme 3.14). Bian's group completed this reaction under visible light when iridium or ruthenium complexes were used as catalysts (Scheme 3.14).[104] Very recently, Shen's group[105] and Zhang's group[59] reported the same transformation using nickel(II) oxide surface-modified titanium dioxide and Eosin Y as photoredox catalysts, respectively (Scheme 3.14). Although methods regarding this transformation were reported, the reactions still suffer from the limited substrate scope. Especially, in the case of strong electron-deficient tertiary alkylamines, for which the nitrogen has weak electron donating capability, are difficult to be oxidized to *α*-aminoalkyl radicals. Therefore, it is still an unsolved

challenge to broadly use this kind of reactions in the synthesis of nitrogen-containing heterocycles.



Scheme 3.14 Annulation reactions *via* α-aminoalkyl radicals.[59,102–105]

Pyrrolo[3,4-*c*]quinolone scaffolds are widely present in natural products and bioactive compounds (Figure 3.6).[106] The development of efficient methods to prepare this kind of compounds is highly interesting. During our studies on reactions involving *α*-aminoalkyl radical intermediates, it was found that KI and TBHP (*tert*-butyl hydroperoxide) were able to produce *α*-aminoalkyl radicals of tertiary alkyl amines. Mostly, in the presence of peroxides and iodides, tertiary alkyl amines are initially transformed to α-aminoalkyl radicals by hydrogen abstraction or radical cations through single electron transfer, either α-aminoalkyl radicals or radical cations can be easily converted to iminium ions by one electron oxidation or deprotonation under this condition.[107] Therefore, this discovery was of interest, and it was wonder if this new approach could be applied in the radical reactions. To demonstrate the utility of this novel way in synthetic chemistry, an annulation reaction between tertiary alkyl amines and electron-deficient alkenes *via* *α*-aminoalkyl radicals was explored with peroxides and iodides.

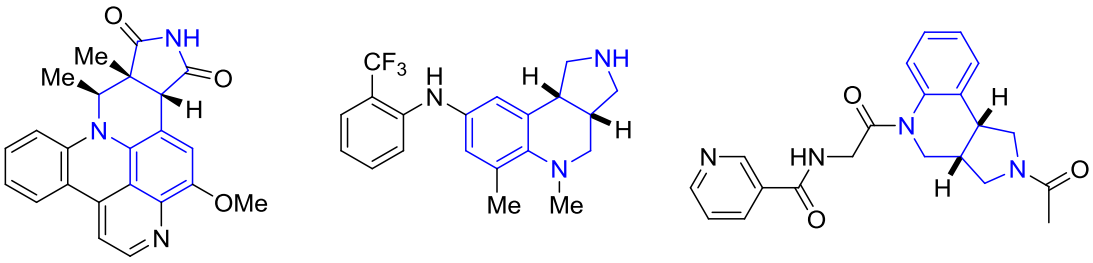


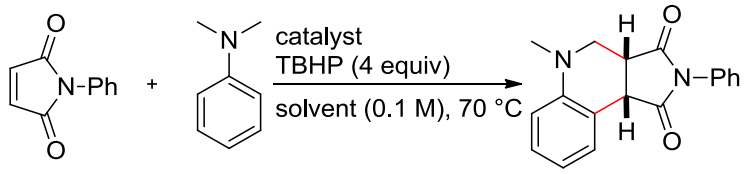
Figure 3.6 Representative natural product and bioactive compounds containing pyrrolo[3,4-*c*]quinolone scaffold.[106]

3.2.1.2 Optimization Studies for the Annulation by Peroxide and Iodide

Initially, the reaction of *N*-phenyl maleimide **89a** and *N*,*N*-dimethyl aniline **90a** was examined using KI (20 mol%) as catalyst and TBHP (70% in H_2O, 4 equiv) as oxidant at 70 °C in MeCN (Table 3.11, entry 1). Delightedly, the desired product was obtained in 62% isolated yield after 1 h. Next, different reaction conditions were employed to improve the yield of the desired product **91a**. Firstly, several iodide reagents were tested (Table 3.11, entries 1–4). It was found that KI and TBAI (tetrabutylammonium iodide) were the most efficient catalysts for this transformation. Using I_2 or NIS (*N*-Iodosuccinimide) as catalysts, the desired product was rapidly formed, but the yield was dropped. Further screening was conducted with different solvents (Table 3.11, entries 5–11). DCE was found the best solvent, and it provided the desired product in 90% yield after 2 h (Table 3.11, entry 10). When methanol was used as a solvent, the reaction completed after 0.5 h, but it gave a messy system (Table 3.11, entry 7). Other solvent did not improve the yield of the desired product, although in some solvents, like dioxane and EtOAc, reactions accomplished fast (Table 3.11, entries 5, 6, 8, 9 and 11). When the amounts of TBHP were decreased to 2 equiv, the desired product was obtained with a decreased yield after 8 h (Table 3.11, entry 12). Changing the loading amounts of KI from 20 mol% to 5 mol%, the yield of the desired product remained, but the reaction time was prolonged (Table 3.11, entries 10, 13 and 14). Gratifyingly, when TBAI was used as a catalyst, the desired product was

obtained with an excellent yield (Table 3.11, entry 15). In the absence of the iodide, the reaction provided the desired product in 72% yield after 12 h (Table 3.11, entry 16). This result further demonstrated that the peroxide is crucial for this transformation.

Table 3.11 Optimization of conditions for the annulation between *N*-phenyl maleimides and *N*,*N*-dimethyl anilines.[a]



89a **90a** **91a**

Entry	Solvent	Catalyst (mol%)	Time (h)	Yield (%)[b]
1	MeCN	KI (20)	1	62
2	MeCN	TBAI (20)	1	59
3	MeCN	I_2 (20)	1	56
4	MeCN	NIS (20)	1	50
5	THF	KI (20)	12	52
6	Dioxane	KI (20)	0.5	67
7	MeOH	KI (20)	0.5	messy
8	$CHCl_3$	KI (20)	12	80
9	Toluene	KI (20)	12	63
10	DCE	KI (20)	2	90
11	EtOAc	KI (20)	0.5	69
12[c]	DCE	KI (20)	8	84
13	DCE	KI (10)	2	89
14	DCE	KI (5)	3	87
15	**DCE**	**TBAI (10)**	**2**	**91**
16	DCE	—	12	72

[a] Reaction conditions: **89a** (0.1 mmol), **90a** (0.2 mmol), TBHP (70 % in H_2O, 4 equiv), catalyst (mol%) in solvent (0.1 M) at 70°C. [b] Yield refers to isolated products after column chromatography. [c] TBHP (70%, in H_2O) 2 equiv was used.

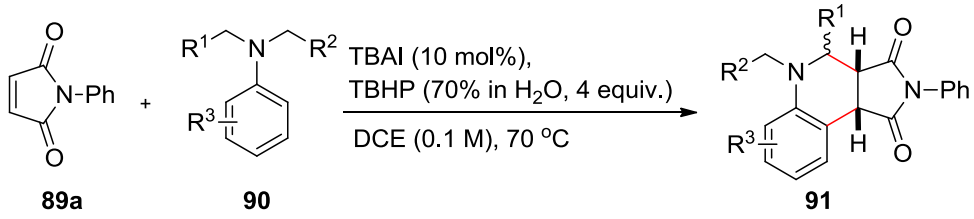
3.2.1.3 Substrate Scope Evaluation for the Annulation by Peroxide and Iodide

Having the optimized condition in hand, the substrate scope and generality of this transformation were explored. Initially, *N*,*N*-dimethyl anilines with different electron-rich and electron-poor substituents were tested. To our delight, all of them provided related products through radical annulations (Table 3.12, entries 1–13). Halogens at the *para*-position of *N*,*N*-dimethylaniline were tolerated, and the formed products could be readily transformed to other compounds by coupling reactions (Table 3.12, entries 3–5). Reactions of 3-methoxy or 3-acetyl substituted *N*,*N*-dimethylanilines afforded a mixture of regioisomers, in both cases the congested regioisomers **A** were favored. This result indicated that radicals at the *ortho*-position of substituents are more stable in these reactions (Table 3.12, entries 7 and 8). The desired products regarding *ortho*-substituted *N*,*N*-dimethylanilines were afforded with moderate to good yields, only 2 equiv of TBHP were used for the reaction of benzyl substituted *N*,*N*-dimethylaniline **89j** (Table 3.12, entries 9–11). Using trimethoxy substituted *N*,*N*-dimethylaniline **89m** as substrate, the desired product **91m** was obtained in 93% yield after 6 h (Table 3.12, entry 12). Intriguingly, *N*,*N*-dimethylaniline even with a strong electron-withdrawing group, such as a ditrifluoromethyl group, still offered the desired product **91n** in an acceptable yield (Table 3.12, entry 13). This indicated that under our newly developed reaction condition, strong electron-deficient *N*,*N*-dimethylanilines can be oxidized to the corresponding α-aminoalkyl radicals and provide the desired products. In most cases, iminium ions will be generated, and no desired products will be formed under this reaction condition.

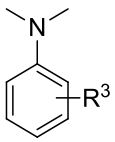
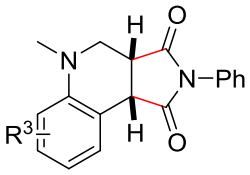
The nitrogen of anilines with various aromatic as well as aliphatic substituents were also subjected to this reaction (Table 3.12, entries 14–19). Delightedly, the reaction of *N*-methyl-*N*-phenyl aniline **89o** proceeded smoothly and furnished the desired product

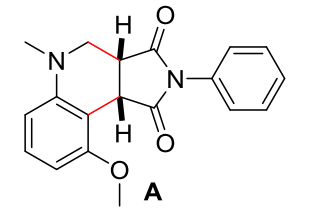
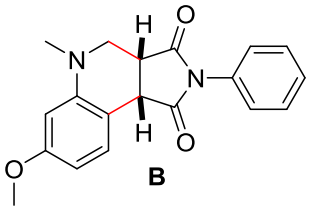
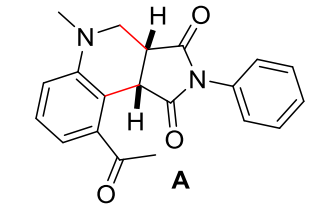
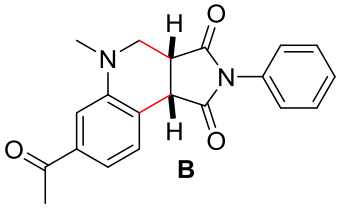
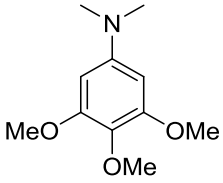
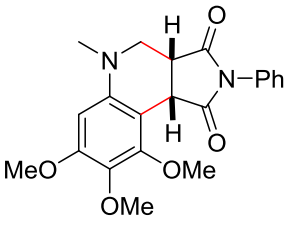
91o in 67% after 12 h (Table 3.12, entry 14). Impressively, only **91p** was obtained when *N*-benzyl-*N*-methyl aniline **89p** was used as a substrate. The product was formed by the reaction with the methyl group of **89p**, and the benzyl group of **89p** was tolerated in this transformation (Table 3.12, entry 15). The reaction of *N*-butyl-*N*-methylaniline **89q** gave the same selectivity with the reaction of **89p** (Table 3.12, entry 16). It was assumed that this result was because of the steric effect. Although the benzyl and butyl radicals are more stable than the methyl radicals for these compounds, the methyl is less steric hindered than the benzyl and butyl. Thus the methyl radical was selectively formed by TBHP/TBAI in this novel transformation. Additionally, anilines, such as *N*-diethylaniline **89r**, 1-phenylpyrrolidine **89s** and 1-phenylpiperidine **89t**, which have two same aliphatic groups on nitrogen, offered desired products in good to excellent yields. Nevertheless, all of them consisted of two diastereomers, and it seemed the stereoselectivity of these reactions were random (Table 3.12, entries 17–19).

Table 3.12 Annulation with different tertiary amines.[a]

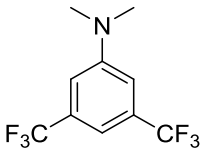
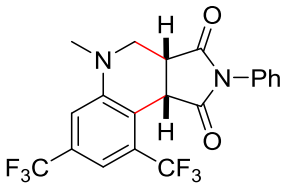
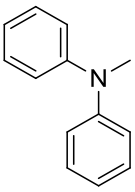
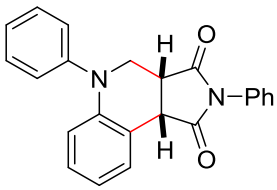
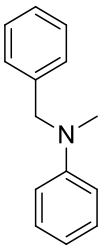
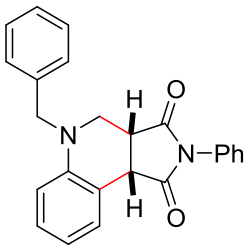
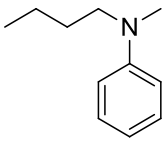
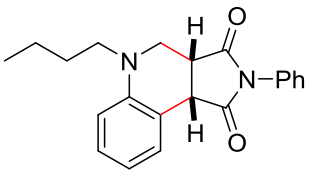
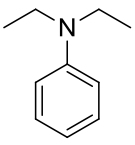
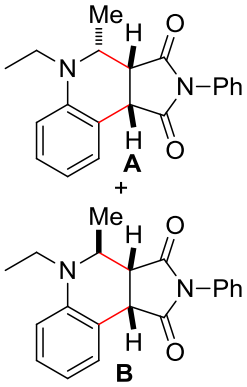


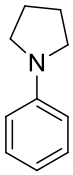
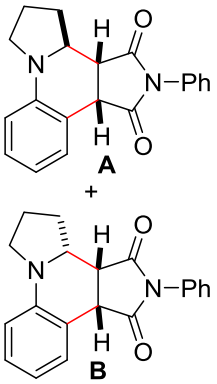
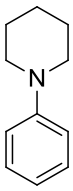
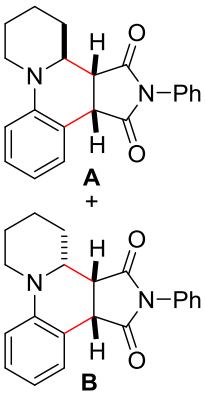
89a 90 91

Entry	Tertiary Amine	Time (h)	Product	Yield (%)[b]
				
1	R^3 = 4-Me (**89b**)	2	R^3 = 4-Me (**91b**)	94
2	R^3 = 4-Et (**89c**)	1	R^3 = 4-Et (**91c**)	79
3	R^3 = 4-F (**89d**)	3	R^3 = 4-F (**91d**)	81
4	R^3 = 4-Br (**89e**)	6	R^3 = 4-Br (**91e**)	86

5	R^3 = 4-I (**89f**)	6	R^3 = 4-I (**91f**)	77
6	R^3 = 4-CO_2Me (**89g**)	6	R^3 = 4-CO_2Me (**91g**)	45
7	R^3 = 3-OMe (**89h**)	6	 A +  B **(91h)**	91 (8:5)
8	R^3 = 3-$COCH_3$ (**89i**)	6	 A +  B **91i**	76 (9:5)
9[c]	R^3 = 2-Bn (**89j**)	10	R^3 = 2-Bn (**91j**)	51
10	R^3 = 2-Ph (**89k**)	4	R^3 = 2-Ph (**91k**)	63
11	R^3 = 2-Bz (**89l**)	12	R^3 = 2-Bz (**91l**)	45
12	 (**89m**)	6		93

(91m)

13	 **(89n)**	24	 **(91n)**	40
14	 **(89o)**	12	 **(91o)**	67
15[c]	 **(89p)**	12	 **(91p)**	46
16	 **(89q)**	24	 **(91q)**	65
17	 **(89r)**	1	 **(91r)**	63 (3:7)

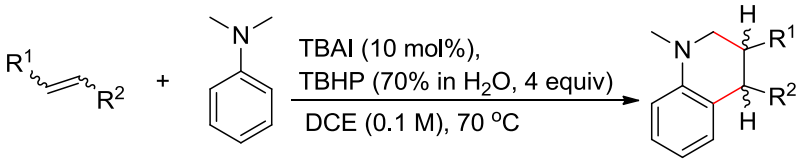
18	 (**89s**)	3	 **(91s)**	78 (1:2)
19	 (**89t**)	12	 **(91t)**	73 (5:3)

[a] Reaction conditions: **89a** (0.1 mmol), **90** (0.2 mmol), TBAI (10 mol%), TBHP (70 % in H_2O, 4 equiv) in DCE (0.1 M) at 70°C. [b] Yield refers to isolated products after column chromatography. [c] TBHP (70 %, in H_2O, 2 equiv) used.

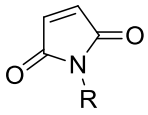
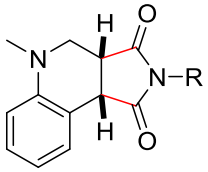
Reactions with various electron-deficient alkenes were also explored. Initially, maleimides with different substituents were examined (Table 3.13, entries 1–5). Aliphatic as well as aromatic groups on the nitrogen of maleimides were compatible with this transformation, and corresponding products were rapidly obtained with good yields (Table 3.13, entries 1–4). Using 3-methyl-*N*-phenylmaleimide **89f** as substrate, the desired product **91y** was formed in an acceptable yield with 1 : 3 ratio of regioisomers (Table 3.13, entry 5). This result indicated that the formed radical preferably attacked to the small steric hindrance part of maleimide in the reaction. Interestingly, the reaction of maleimide without substituent on nitrogen proceeded

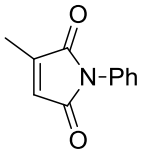
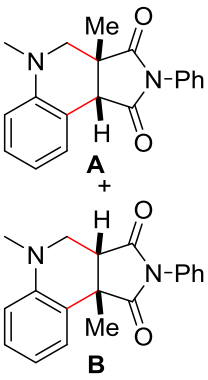
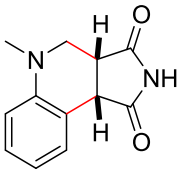
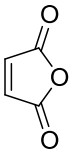
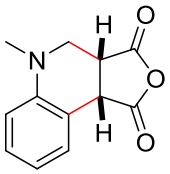
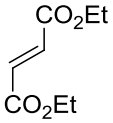
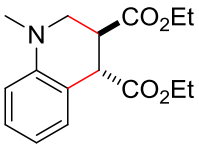
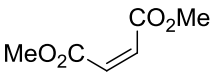
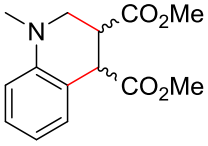
successfully. The desired product **91z** was obtained in 78% isolated yield after 30 min (Table 3.13, entry 6). This suggested that substituents on the nitrogen of maleimides had less effect on this reaction. Maleic anhydride **89h** was also examined and the reaction completed after 1.5 h (Table 3.13, entry 7). Unfortunately, only trace amounts of the desired product **91aa** was detected in this case. It was assumed that the weak stability of formed intermediates leading to this result. Gratifyingly, tetrahydroquinoline **91ab** was diastereoselectively formed when diethyl fumarate **89i** was used as a substrate (Table 3.13, entry 8). The reaction of dimethyl maleate **89j** was also tested. However, the desired product **91ac** was obtained with trace amounts after 12 h (Table 3.13, entry 9). This result indicated that the *trans* configuration of acyclic alkenes is favored for this transformation.

Table 3.13 Annulation with different alkenes.[a]



89 **90a** **91**

Entry	Alkene	Time (h)	Product	Yield (%)[b]
				
1	R = Me (**89b**)	0.5	R = Me (**91u**)	62
2	R = Propyl (**89c**)	0.5	R = propyl (**91v**)	66
3	R = cyclohexyl (**89d**)	0.5	R = cyclohexyl (**91w**)	87
4	R = 4-bromophenyl (**89e**)	2.5	R = 4-bromophenyl (**91x**)	68

5	 (**89f**)	2.5	 (**91y**)	45 (1:3)
6	R = H (**89g**)	0.5	 (**91z**)	78
7	 (**89h**)	1.5	 (**91aa**)	trace
8	 (**89i**)	12	 (**91ab**)	60
9	 (**89j**)	12	 (**91ac**)	trace

[a] Reaction conditions: **89** (0.1 mmol), **90a** (0.2 mmol), TBAI (10 mol%), TBHP (70 % in H_2O, 4 equiv) in DCE (0.1 M) at 70°C. [b] Yield refers to isolated products after column chromatography.

3.2.1.4 Identification of Diastereomers

Product **91r** consisted of two diastereomers **A** and **B**. To identify them, NOE experiments were conducted regarding both of isomers (spectra see: Figures 7.2 and 7.3 in part 7.6).

According to the NOE spectra of **91r** (**A**), there was no correlation between methyl **4** and proton **1**. This indicated that methyl **4** and proton **1** were in *trans* configuration with each other (Figure 3.7).

According to the NOE spectra of **91r** (**B**), there was a correlation between methyl **4** and proton **1**. This indicated that methyl **4** and proton **1** were in *cis* configuration with each other (Figure 3.7).

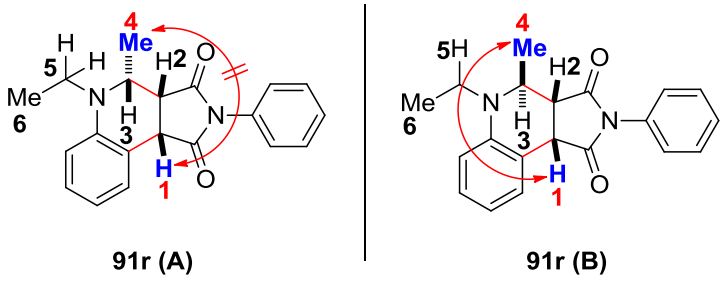


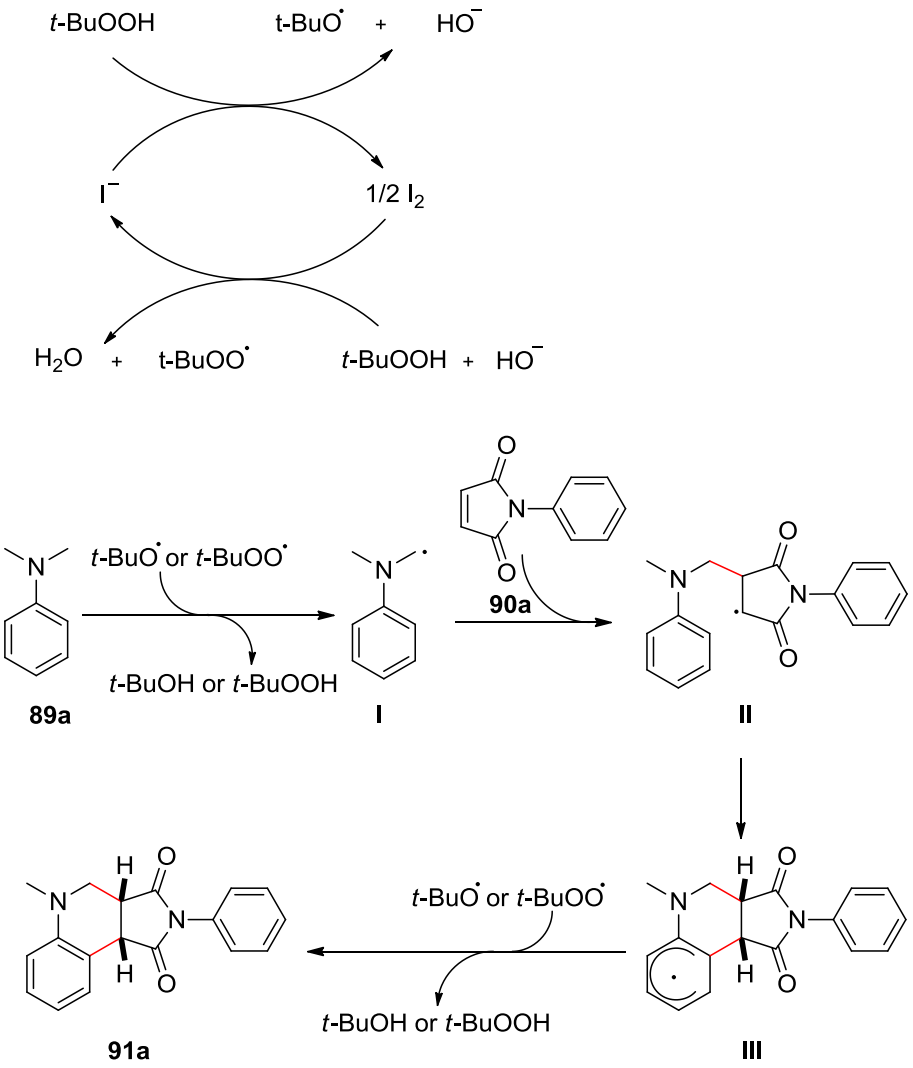
Figure 3.7 Identification of diastereomers of **91r** by NOE experiments.

The diastereomers of **91s** and **91t** were also identified according to the above procedures (spectra see: Figures 7.4–7.7 in part 7.6).

3.2.1.5 Proposed Mechanism for the Annulation by Peroxide and Iodide

Based on the experimental results and literature reports, a plausible mechanism for this radical annulation reaction between *N*,*N*-dimethylanilines and alkenes was proposed (Scheme 3.15).[59,101-105,108] Initially, reaction between *tert*-butyl hydroperoxide and iodide ion provides *tert*-butoxyl radical, iodine and hydroxyl anion. The reaction of formed iodine and *tert*-butyl peroxide produces *tert*-butylperoxyl radical, water and regenerated the iodide ion. One electron oxidation of

N,*N*-dimethylaniline **89a** by *tert*-butoxyl or *tert*-butylperoxyl radicals and subsequent deprotonation offers a *α*-aminoalkyl radical **I**. The nucleophilic attack of **I** to alkene **90a** affords a radical intermediate **II**, which provides the intermediate **III** by following intra-molecular cyclization. Hydrogen abstraction of the intermediate **III** by *tert*-butoxyl or *tert*-butylperoxyl radicals leads to the desired product **91a**.



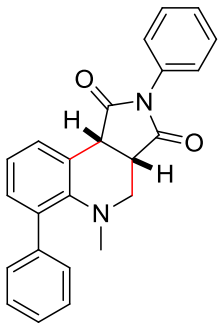
Scheme 3.15 Proposed mechanism of the annulation by TBHP/KI.[59,101–105,108]

3.2.1.6 Biological Results of pyrrolo[3,4-*c*]quinolone derivatives

All synthesized polycyclic compounds **91** were submitted to COMAS (Compound

Management and Screening Center) in Dortmund to investigate whether they exhibit biological activities against a number of targeted biological pathways in cell-based assays. Among the different assays in which the compounds were screened, it was revealed that one compound **91k**, showed inhibition of the autophagy signaling pathway (Figure 3.8). The details of the autophagy cell-based assay are as follows: MCF7-LC3 (4000 cells/ well) cells were seeded in 384 well plates (Greiner). The next day cells were washed three times with 1x PBS using plate washer ELX405 (Biotek). After that, 10 µM of compound was added using Echo dispenser (Labcyte) along with EBSS (starvation medium) and Chloroquine (50 µM) or Rapamycin (100 nM) and Chloroquine (50 µM). Three hours after incubation at 37°C cells were fixed by addition of 25 µl formaldehyde in 1 x PBS (4.6% final concentration) and simultaneously staining the nucleus with 1:500 Hoechst (Stock 1 mg/ml) for 20 min at RT. Fixed cells were washed thrice with 1x PBS using plate washer ELX405 (Biotek). For visualization 4 pictures/well were acquired using ImageXpress Micro XL (Molecular Devices) at 20x and analysed with the granularity algorithm of MetaXpress Software (Molecular Devices).

Dose-response analysis was carried out starting from 10 µM using a three-fold dilution curve over eight steps. IC50 calculations were done using Quattro Workflow software (Quattro Research GmbH).



91k

IC_{50} = 8.42 ± 1.05

Figure 3.8 Result of autophagy-pathway inhibition.

Compared to the other synthesized polycyclic compounds, **91k** is the only compound with phenyl group on *N*,*N*-dimethylaniline part. We then synthesized the analogues of **91k** (figure 3.9) and subjected these compounds to different cell-based assays again. Unfortunately, none of them has potential inhibition of various signaling pathways.

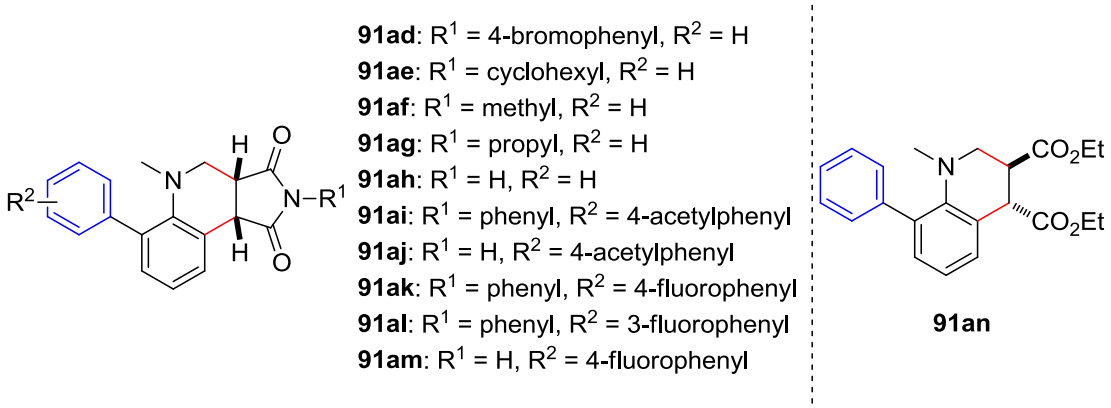


Figure 3.9 Synthesized analogues of **91k**.

3.2.2 Synthesis of Imidazo[4,5-*b*]pyridine Derivatives by C(sp^3)–H Bond Amination

3.2.2.1 Introduction for the Synthesis of Imidazo[4,5-*b*]pyridine Derivatives

Imidazo[4,5-*b*]pyridine derivatives as a key core extensively exist in natural products and bioactive compounds (Figure 3.10).[109] Traditional methods were frequently used to synthesize these compounds.[110] However, the disadvantages of these methods, such as long reaction sequences, harsh reaction conditions, low yields and limited substrate scope, diminish the synthetic efficiency of imidazo[4,5-*b*]pyridine derivatives.

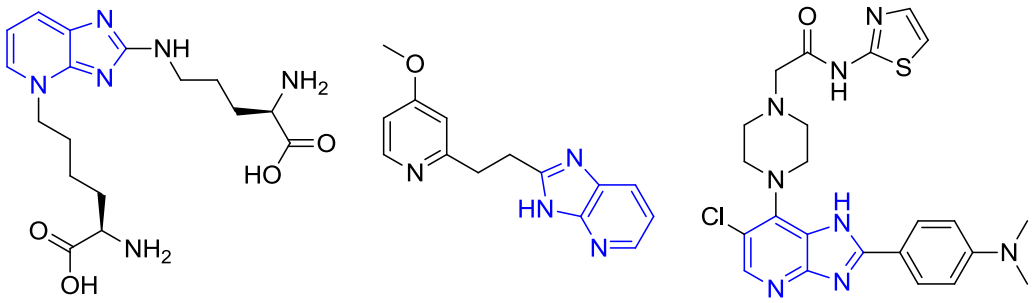
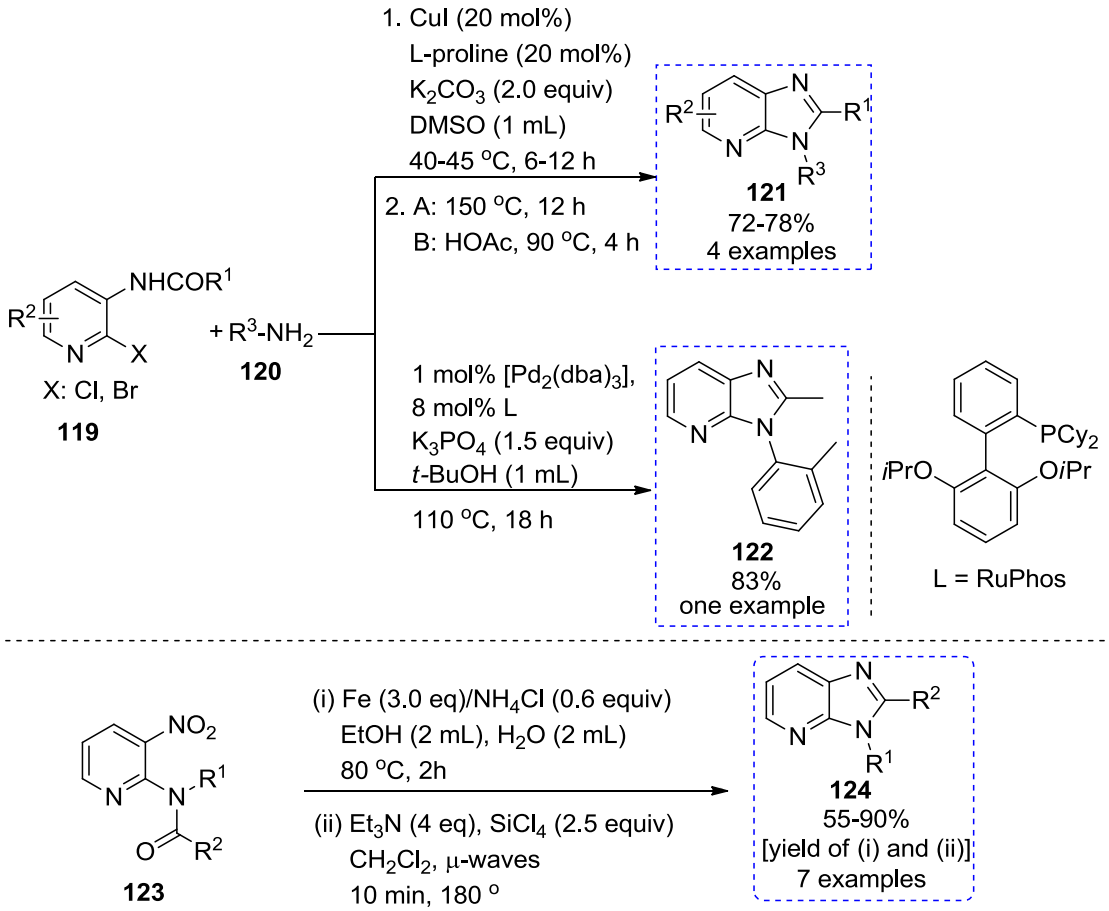


Figure 3.10 Representative natural product and bioactive compounds based on imidazo[4,5-*b*]pyridines.[109]

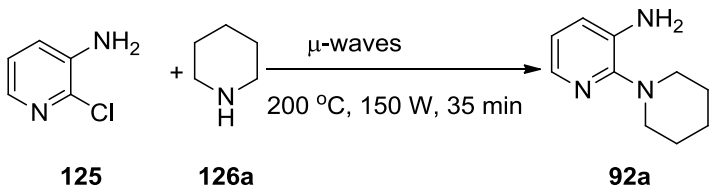
In recent years, several new approaches to access these compounds have been developed by different research groups (Scheme 3.16).[111] Ma et al. reported a novel method to synthesize 1,2-disubstituted benzimidazoles by a copper catalyst with two steps, and four imidazo[4,5-*b*]pyridine derivatives **121** were prepared by this newly developed method (Scheme 3.16).[111a] Using palladium as a catalyst, a new approach for the construction of *N*-aryl benzimidazoles was discovered by Buchwald and co-workers, it provided imidazo[4,5-*b*]pyridine **122** by the reaction of **119** and **120** (Scheme 3.16).[111b] In 2009, a rapid way to synthesize imidazo[4,5-*b*]pyridine derivatives **124** was developed by Schmitt and co-workers (Scheme 3.16).[111c] This method contained two steps, and second step was performed by µ-waves at 180 ^{o}C. Unfortunately, harsh reaction conditions and expensive transition metals are still required in these novel methods, and some of them have long reaction sequences. Therefore, efficient methods for the synthesis of imidazo[4,5-*b*]pyridine derivatives are in high demand.



Scheme 3.16 Newly developed approaches to access imidazo[4,5-*b*]pyridine derivatives.[111]

3.2.2.2 Preliminary Exploration and Results of Imidazo[4,5-*b*]pyridine Derivatives Synthesis

Inspired by the applications of direct functionalization of C(sp^3)–H bond at *a*-position of tertiary amines in the construction of nitrogen-containing compounds,[56d,67-70,71h] a new route to synthesize imidazo[4,5-*b*]pyridine derivatives *via* iminium ion intermediates was designed. To check the possibility of it, starting material **92a** was prepared according to the literature report.[112] However, after 72 h refluxing in piperidine, the desired product **92a** was obtained with only around 30% yield. Delightedly, when the reaction was performed in microwave, it completed after 35 min and provided the desired product **92a** in 75% isolated yield (Scheme 3.17).

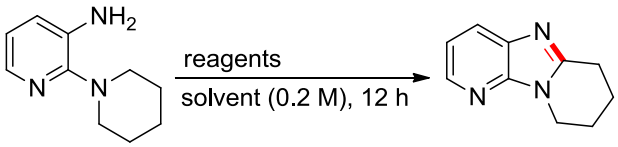


Scheme 3.17 Synthesis of starting materials by using microwave.

With synthesized starting materials **92a** in hand, we started to explore this novel approach under different reaction conditions. Initially, reactions were tested using metals as catalysts and peroxides as oxidants (Table 3.12, entries 1–12).[71] Iminium ions will be formed under this reaction condition, and subsequent intra-molecular cyclization with amino groups will afford the desired products. Unfortunately, when TBHP was used as an oxidant, no desired product was detected using neither CuBr nor $Cu(OAc)_2$ as catalysts at 120 ^oC in DCE (Table 3.12, entries 1 and 2). Reactions with different iron salts like $FeCl_3$ and $FeCl_2$ were examined (Table 3.12, entries 3–6). It was found that the desired product with trace amounts was observed when DTBP (di-*tert*-butyl peroxide) was used as an oxidant, other oxidants like TBHP, TBPB (*tert*-butyl peroxybenzoate) did not afford any desired product. Then, different catalysts, such as $CuF_2 \cdot H_2O$, CuO and Cu_2O, and different oxidants, such as DCP (dicumyl peroxide), TBHP, DTBP (di-*tert*-butyl peroxide) and TBPB, were employed in this transformation (Table 3.12, entries 7–12). However, almost no desired product was formed in all cases. Starting materials completely disappeared in all reactions with metal catalysts and peroxides, but none of them produced the desired product (Table 3.12, entries 1–12). This result suggested that **92a** was difficult to be oxidized to the iminium ion under these conditions, and the formation of byproducts consumed the starting materials. Reactions with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), PIDA [(diacetoxyiodo)benzene] and NaN_3, which are used to generate radicals, were also tried (Table 3.12, entries 13 and 14).[71h] Starting materials were completed, but no desired product was formed in both cases. To our delight, when $T^+BF_4^-$ (2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoro borate) salt[72,74,113] was used as an oxidant, the desired product was

obtained in 70% yield after 15 min at rt (Table 3.12, entry 15). Commercial available 4-NHAcT$^+$BF$_4^-$ (4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoro borate) salt,[72,74] which has similar reactivity with T$^+$BF$_4^-$, was also examined. The reaction completed after 15 min; however, the isolation of the desired product was difficult, since it has similar polarity with reduced 4-NHAcT$^+$BF$_4^-$ salt.

Table 3.12 Optimization of conditions for the synthesis of imidazo[4,5-*b*]pyridine derivatives *via* iminium ions.[a]



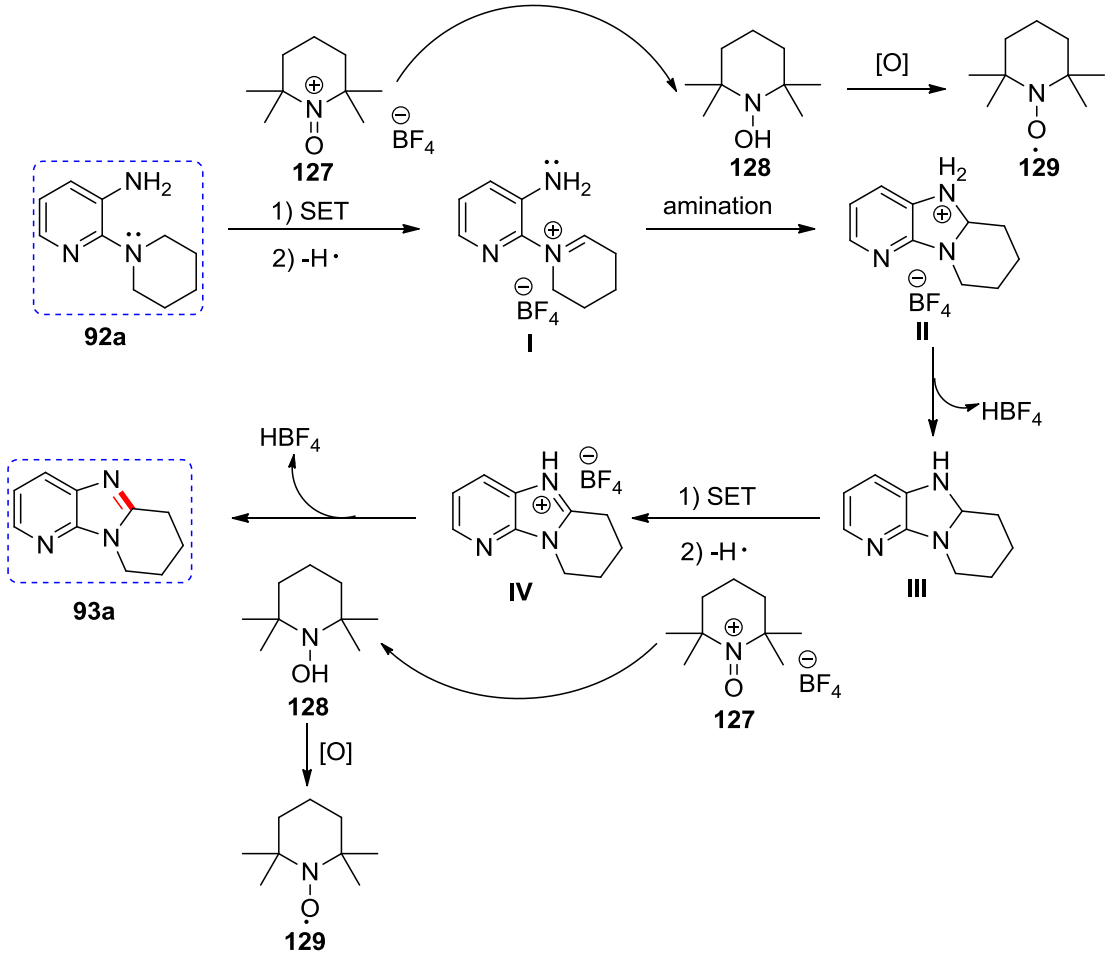
92a **93a**

Entry	Reagent	Solvent	T (^{o}C)	Yield (%)[b]
1	CuBr (10 mol%), TBHP (1.2 equiv, 70 wt% in water)	DCE	120	n.d.
2	Cu(OAc)$_2$·H$_2$O (10 mol%), TBHP (1.2 equiv, 70 wt% in water)	DCE	120	n.d.
3	FeCl$_3$ (10 mol%), TBHP (1.2 equiv, 70 wt% in water)	DCE	120	n.d.
4	FeCl$_3$ (3 mol%), TBPB (4.0 equiv)	DCE	120	n.d.
5	FeCl$_3$ (3 mol%), DTBP (4.0 equiv)	DCE	120	trace
6	FeCl$_2$ (20 mol%), TBPB (4.0 equiv)	DCE	120	n.d.
7	FeCl$_2$ (20 mol%), DTBP (4.0 equiv)	DCE	120	trace
8	CuF$_2$·H$_2$O (5 mol%), DCP (3.0 equiv)	DCE	120	n.d.
9	CuF$_2$·H$_2$O (10 mol%), TBHP (4.0 equiv, 70 wt% in H$_2$O)	DCE	120	n.d.
10	CuO (20 mol%), DTBP (4.0 equiv)	DCE	120	trace
11	Cu$_2$O (5 mol%), DCP (3.0 equiv)	DCE	120	n.d.
12	Cu$_2$O (5 mol%), TBPB (2.0 equiv)	benzene	120	trace

13	DDQ (1.2 equiv)	DCE	120	n.d.
14	PIDA (4 equiv), NaN_3 (4 equiv)	DCE	25	n.d.
15[c]	**$T^+BF_4^-$ (3 equiv)**	**DCE**	**25**	**70**

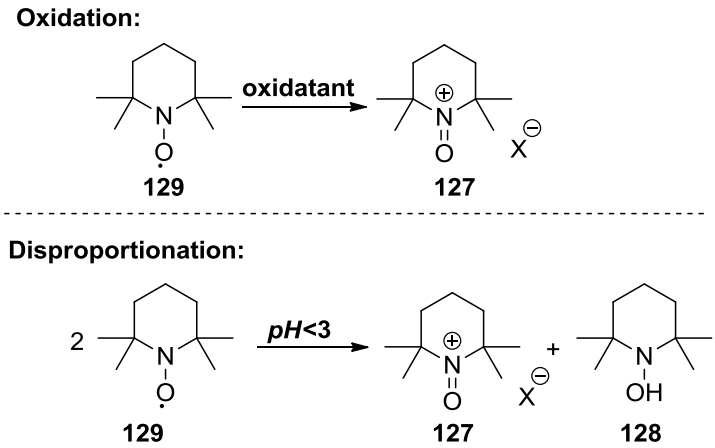
[a] Reaction conditions: **92a** (0.2 mmol) with reagents in solvent (0.2 M). [b] Yield refers to isolated products after column chromatography. [c] 30 min. n.d. = the desired product was not detected.

Based on the literature reports and experimental results,[72,74,113] a mechanism for the synthesis of imidazo[4,5-*b*]pyridine **93a** by $T^+BF_4^-$ **100** was proposed (Scheme 3.18). Initially, single electron transfer from the nitrogen of tertiary amine **92a** to $T^+BF_4^-$ **127** and subsequent hydrogen abstraction affords the iminium ion **I**. Amination of **I**, followed by deprotonation leads to the intermediate **III**, which provides the intermediate **IV** through one electron oxidation and hydrogen abstraction by **127**. Deprotonation of the intermediate **IV** delivers the desired product **93a**.



Scheme 3.18 Proposed mechanism for the synthesis of imidazo[4,5-*b*]pyridine derivatives *via* iminium ions.[72,74,113]

In this newly developed method, $T^+BF_4^-$ (Fw: 243) were used as an oxidant with 3 equiv amounts. It was wonder if the amounts of $T^+BF_4^-$ could be reduced to further improve the efficiency of this transformation. We then checked literatures. Only a few reactions were achieved using $T^+BF_4^-$ as oxidant, and all of them used stoichiometric amounts of this oxidant.[72,74,113] According to the plausible mechanism (Scheme 3.18), $T^+BF_4^-$ was firstly reduced to TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy)-hydroxylamine **128**, then **128** was oxidized to TEMPO **129**. Therefore, if $T^+BF_4^-$ can be regenerated by oxidizing the formed TEMPO **129**, the amounts of $T^+BF_4^-$ will be reduced. In principle, there are two pathways to transform TEMPO to TEMPO oxoammonium salts.[114,115] One way is oxidation, the other way is disproportionation under acidic conditions (Scheme 3.19).

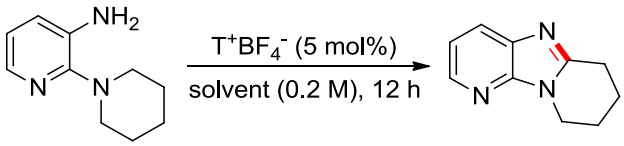


Scheme 3.19 Transformation of TEMPO to TEMPO oxoammonium salt.[114,115]

Based on the above strategies, reactions were tested under different reaction conditions. Initially, various oxidants, such as PIDA, H_2O_2, Br_2 and NaOCl, were used in the reactions.[114] Unfortunately, no desired product was obtained in all cases (Table 1.3, entries 1–4). Reactions were also examined under acidic conditions with

various acids (Table 1.3, entries 5–7).[115] However, only trace amounts of the desired product were observed when the reaction was performed with DIAD (diisopropyl azodicarboxylate) and AcOH (Table 1.3, entry 7). In other cases, no desired products were yielded (Table 1.3, entries 5 and 6). These results indicated that the use of extra oxidants or acids to reduce the amounts of TEMPO oxoammonium salt did not work in this reaction. Subsequently, the scope and generality of this reaction were examined using 3 equiv of $T^+BF_4^-$.

Table 3.13 Optimization of conditions for the synthesis of imidazo[4,5-*b*]pyridine using catalytic amounts of $T^+BF_4^-$.[a]



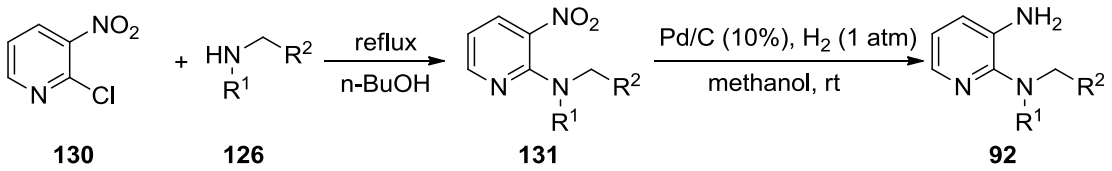
92a **93a**

Entry	Reagent	Solvent	T (^{o}C)	Yield (%)[b]
1	PIDA (1.2 equiv)	DCE	25	n.d.
2	H_2O_2 (1.1 equiv)	DCE	80	n.d.
3	Br_2 (1.5 equiv)	chloroform	25	n.d.
4	NaOCl (0.6 equiv, 11 %), KBr(5 mol %)	DCE : $NaHCO_3$ (aq. 0.4 M) (1 : 1)	80	n.d.
5	$NaNO_2$ (6.5 mol%), HCl (13 mol%, 37%)	MeCN	80	n.d.
6	HNO_3 (10 mol%, 68%), HBr (10 mol%, 48%)	MeCN : H_2O (20 :1)	80	n.d.
7	DIAD (1.2 equiv), AcOH (1.0 equiv)	DCE	80	trace

[a] Reaction conditions: **92a** (0.2 mmol), $T^+BF_4^-$ (5 mol%) with reagents in solvent (0.2 M). [b] Yield refers to isolated products after column chromatography. n.d. = the desired product was not detected.

3.2.2.3 Further Exploration and Results of Imidazo[4,5-*b*]pyridine Derivatives Synthesis

Initially, 3-amino pyridines with different tertiary and secondary amino groups at the C2-position were prepared from 3-amino-2-chloro-pyridines. Unfortunately, using the same microwave condition with the synthesis of **92a**, only trace or even no desired products were obtained for these substrates. Finally, the desired 3-amino pyridine derivatives **92** were prepared by nucleophilic substitution of amines **126** to 3-nitro-2-chloro-pyridines **130** and followed reduction of the nitro groups (Scheme 3.20).[116]

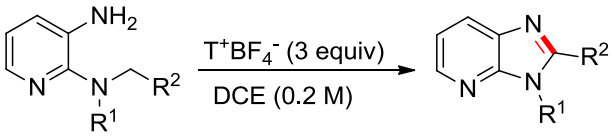


Scheme 3.20 Preparation of starting materials.[116]

After the preparation of the starting materials, reactions of 3-amino pyridines with different tertiary or secondary amino groups at the C2-position were examined (Table 3.14). To our delight, the reaction of **92b** afforded the desired product **93b** in a moderate yield after 30 min (Table 3.14, entry 1). When **92c** was used as a substrate, the reaction completed after 30 min at 25 ^{o}C, but no desired product **93c** was detected (Table 3.14, entry 2). Reducing the reaction temperature to -40 ^{o}C did not change the result of the reaction even after 1h (Table 3.14, entry 3). No desired product **93d** was provided from the reaction of **92d**, although starting materials disappeared after 30 min (Table 3.14, entry 4). Using **92e** or **92f** as substrates, the same result was obtained with the reaction of **92d** (Table 3.14, entries 4–6). These results suggested that this method can only be used for the reactions of 3-aminopyridines with dialkyl amino groups at the C2-position. 3-Aminopyridines with benzyl alkyl amino groups or alkyl amino groups at the C2-position did not provide desired products. It was assumed that this was due to the electron density difference of the nitrogen which connected to the

C2-position of the 3-amino pyridines. Only 3-amino pyridines with dialkyl amino groups were suitable for this transformation under this reaction condition. In this case, iminium ion intermediates were formed and led to the desired products. For others, side reactions happened and no desired products were yielded.

Table 3.14 Evaluation of substrate scope.[a]



92 **93**

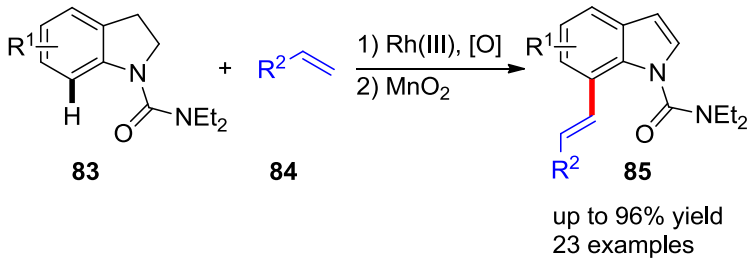
Entry	Pyridine	T (^{o}C)	T (min)	Product	Yield (%)[b]
1	R^1 = Ethyl, R^2 = Methyl (**92b**)	25	30	R^1 = Ethyl, R^2 = Methyl (**93b**)	57
2	R^1 = H, R^2 = Phenyl (**92c**)	25	30	R^1 = H, R^2 = Phenyl (**93c**)	n.d.
3	R^1 = H, R^2 = Phenyl (**92c**)	-40	60	R^1 = H, R^2 = Phenyl (**93c**)	n.d.
4	R^1 = Methyl, R^2 = phenyl (**92d**)	25	30	R^1 = Methyl, R^2 = phenyl (**93d**)	n.d.
5	R^1 = H, R^2 = Ethyl (**92e**)	25	30	R^1 = H, R^2 = Ethyl (**93e**)	n.d.
6	R^1 = H, R^2 = Pentyl (**92f**)	25	30	R^1 = H, R^2 =Pentyl (**93f**)	n.d.

[a] Reaction conditions: **92** (0.2 mmol), $T^+BF_4^-$ (3 equiv) in solvent (0.2 M). [b] Yield refers to isolated products after column chromatography. n.d. = the desired product was not detected.

IV Summary

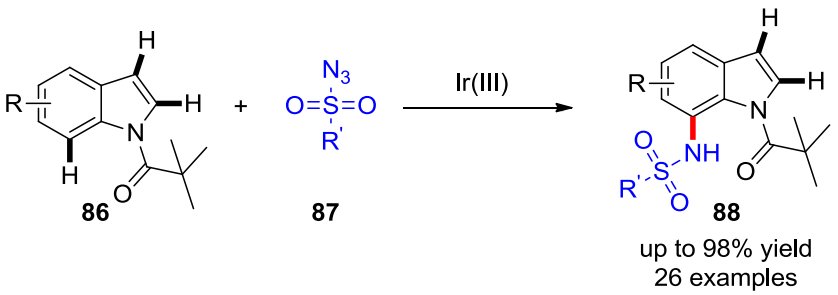
In summary, four novel methods to prepare heterocyclic compounds have been developed. Two methods are used to synthesize 7-substituted indoles with transition-metal catalysis. The other two methods deal with the construction of nitrogen-containing compounds *via* direct functionalization of C(sp^3)–H bond at *a*-position of tertiary amines.

I started my study from the synthesis of 7-substituted indoles. A new and convenient methodology for the synthesis of 7-substituted indoles was developed in a one-pot fashion. This transformation involves rhodium(III)-catalyzed regioselective alkenylation of indolines and subsequent oxidation of MnO_2 (Scheme 4.1). It features high regioselectivity and broad substrate scope. A series of 7-substituted indoles with good to excellent yields were efficiently prepared under this strategy. Additionally, the synthesized 7-substituted indoles can be further transformed to the other compounds.



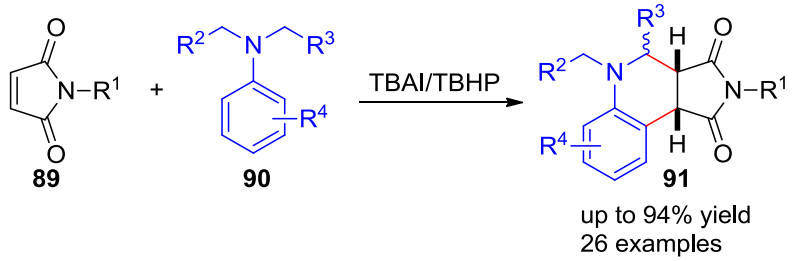
Scheme 4.1 Rhodium(III)-catalyzed direct regioselective synthesis of 7-substituted indoles.

Subsequently, a novel method for the selective sulfonamidation of indole derivatives at the C7-position was established using iridium(III) catalysis (Scheme 4.2). Substrates with diverse functional groups were tolerated in this reaction. Various 7-substituted indoles with good to excellent yields were readily synthesized by this new approach. Furthermore, this method provided an efficient way to prepare biologically active compounds. The results of the mechanistic studies explained the regioselectivity of this transformation.



Scheme 4.2 Iridium(III)-catalyzed regioselective C7-sulfonamidation of indoles.

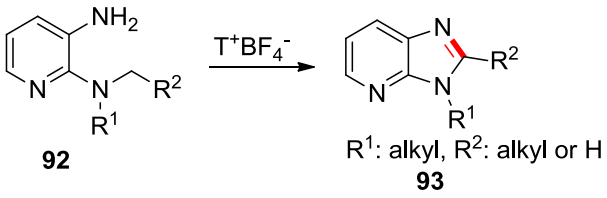
Based on the strategy of direct functionalization of C(sp^3)–H bond at *a*-position of tertiary amines, a robust and environmentally benign method to construct polycyclic heterocycles was developed. In this transformation, *α*-aminoalkyl radicals as reaction intermediates were generated using TBAI and TBHP. The cyclization between electron-deficient alkenes and tertiary alkylanilines proceeded smoothly and provided different tricyclic products in good to excellent yields (Scheme 4.3). Notably, strong electron-deficient tertiary arylamines could be transformed to corresponding *α*-aminoalkyl radicals and provided the desired products.



Scheme 4.3 Cyclization between tertiary alkylanilines and alkenes *via* α-aminoalkyl radicals.

Using $T^+BF_4^-$ as oxidant, a new route to construct imidazo[4,5-*b*]pyridines *via* iminium ions was discovered (Scheme 4.4). In this transformation, iminium ions as reaction intermediates were formed by the oxidation of electron-deficient amines. Reactions of 3-aminopyridines with dialkyl amino groups at the C2-position

proceeded smoothly under this metal-free condition at ambient temperature. The corresponding products were efficiently prepared with moderate to good yields. Unfortunately, no desired products were obtained when 3-aminopyridines with alkyl benzyl amino groups or alkyl amino groups at the C2-position were used as substrates.



Scheme 4.4 Synthesis of imidazo[4,5-*b*]pyridines *via* iminium ions.

All synthesized compounds were subjected to various cell-based assays to investigate potential modulation of important biological pathways. The results of biological studies revealed the potential inhibitors of Wnt, hedgehog and autophagy signaling pathways.

V Experimental Part

5.1 General Information

5.1.1 Materials

Unless otherwise noted, chemicals were obtained from Sigma-Aldrich, Alfa Aesar, Acros Organics and TCl were used without further purification. Solvents for chromatography were technical grade. Petroleum ether 40-60 °C was used for column chromatography and thin layer chromatography. Dry dichloromethane was purified by the Solvent Purification System M-BRAUN Glovebox Technology SPS-800. Dry tetrahydrofuran, methanol, toluene, benzene, *tert*-amyl alcohol, 1,2-dichloroethane, 1,4-dioxane, diethyl ether, ethyl acetate, acetonitrile, chloroform, dimethylformamide, dimethyl sulfoxide were purchased from Sigma-Aldrich, Alfa Aesar, Acros Organics. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel aluminium plates with F-254 indicator, visualized by irradiation with UV light. Column chromatography was performed using silica gel Merck 60 (particle size 0.040-0.063 mm). Solvent mixtures are understood as volume/volume.

5.1.2 Instrumentation

Proton and carbon nuclear magnetic resonance spectra (^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR) spectra were recorded on *Varian Mercury 200* (200 MHz*), Bruker Avance DPX-300* (300 MHz), *Varian Mercury 400* (400 MHz), *Bruker Avance DRX 500* (500 MHz), *INOVA500* (500 MHz) and *Bruker AV600* (600 MHz) spectrometer in $CDCl_3$ (δ = 7.26 ppm for ^{1}H, δ = 77.16 ppm for ^{13}C), CD_2Cl_2 (δ = 5.32 ppm for ^{1}H, δ = 54.00 ppm for ^{13}C) and CD_3CN (δ = 1.940 ppm for ^{1}H, δ = 1.320, 118.260 ppm for ^{13}C). Data are reported in the following order: chemical shift (δ) in ppm; multiplicities are indicated s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet); coupling constants (*J*) are given in Hertz (Hz).

High resolution mass spectra (HRMS) were recorded on a LTQ Orbitrap mass spectrometer coupled to an Accela HPLC-System (HPLC column: Hypersyl GOLD, 50 mm × 1 mm × 1.9 μm). Mass spectra (MS-EI, 70 eV) were collected using a **GC-MS** (GC system 7890A equipped with 5975C detector) produced by Agilent Technologies (column: HP-5MS, 30 m × 0.250 mm × 0.25μm).

Fourier transform infrared spectroscopy (FT-IR) spectra were obtained with a Bruker Tensor 27 spectrometer (ATR, neat) and are reported in terms of frequency of absorption (cm^{-1}). Chemical yields refer to pure isolated substances.

Optical rotations ($[\alpha]_D^{RT}$) were measured in a *Schmidt + Haensch Polartronic HH8* polarimeter in cuvettes with a path length of 10 cm at ambient temperature. The concentration is given as g/100 mL.

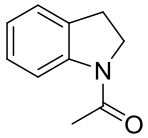
5.2 Experimental Part for 3.1.1

5.2.1 Synthesis of *N*-Protected Indolines 83a–83e

General Procedure A for the Synthesis of *N*-Protected Indolines **83a**, **83b**, **83d**:[117]

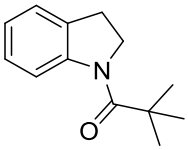
To a solution of indoline (10 mmol) in 8 mL THF was added to a suspension of NaH (60% in mineral oil, 1.2 equiv, 12 mmol) in 6 mL THF at 0 °C. The mixture was stirred for 1 h at room temperature. After recooling to 0 °C, acyl chloride (1.1 equiv, 11 mmol) was added and the mixture was stirred overnight at room temperature. Then a saturated solution of NH_4Cl was carefully added and the resulting mixture was extracted three times with Et_2O. The combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated. The product was purified by normal silica gel column with petroleum ether (40-60°C)/EtOAc mixture.

Characterization of Compounds **83a**, **83b**, **83d:**



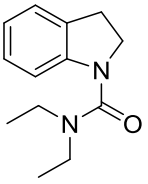
1-(Indolin-1-yl)ethan-1-one (83a):[117]

The product was prepared according to the general procedure A. Yield: 85%; Light brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.15; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.21 (d, *J* = 8.0 Hz, 1H), 7.20 – 7.16 (m, 2H), 7.00 (td, *J* = 7.5, 0.8 Hz, 1H), 4.04 (t, *J* = 8.5 Hz, 2H), 3.19 (t, *J* = 8.5 Hz, 2H), 2.22 (s, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 168.83, 142.94, 131.19, 127.60, 124.62, 123.66, 117.00, 48.83, 28.05, 24.36.



1-(Indolin-1-yl)-2,2-dimethylpropan-1-one (83b):[118]

The product was prepared according to the general procedure A. Yield: 91%; Light brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.15; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.24 – 8.22 (m, 1H), 7.20 – 7.17 (m, 2H), 7.03 – 7.00 (m, 1H), 4.23 (t, *J* = 8.2 Hz, 2H), 3.14 (t, *J* = 8.2 Hz, 2H), 1.38 (s, 9H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 176.66, 144.89, 130.90, 127.49, 124.36, 123.72, 118.54, 49.59, 40.34, 29.48, 27.88.



***N*,*N*-diethylindoline-1-carboxamide (83d):**[86a]

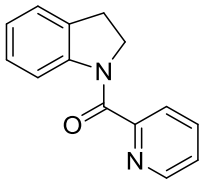
The product was prepared according to the general procedure A. Yield: 91%; Brown liquid; TLC (10% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.16 (dd, *J* = 7.4, 0.6 Hz, 1H), 7.11 (ddd, *J* = 8.0, 1.2, 0.6 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.86 (td, *J* = 7.4, 1.2 Hz, 1H), 3.89 (t, *J* = 8.3 Hz, 2H), 3.35 (q, *J* = 7.1 Hz, 4H),

3.02 (t, *J* = 8.3 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 159.74, 144.88, 131.49, 127.11, 124.93, 121.34, 112.98, 50.50, 42.03, 28.25, 13.71.

Procedure for the Synthesis of *N*-Protected Indolines **83c:**[117]

The indoline (3 mmol) were added to pyridine-2-carboxylic acid (2.7 mmol), triethylamine (0.48 mL) and TBTU (29.1 mmol) in THF(20 mL). The reaction mixture was stirred for 3 h at room temperature, diluted with EtOAc and washed with 15% potassium carbonate solution, saturated sodium chloride solution and 1 M hydrochloric acid. The organic phase was dried over $MgSO_4$ and concentrated under vacuum. The product was purified by normal silica gel column with petroleum ether (40-60°C)/EtOAc mixture.

Characterization of Compounds **83c:**



Indolin-1-yl(pyridin-2-yl)methanone (83c):[117]

Yield: 53%; Light brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.2; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.63 (d, *J* = 4.5 Hz, 1H), 8.31 (d, *J* = 7.9 Hz, 1H), 7.88 – 7.86 (m, 2H), 7.41 (m, 1H), 7.28 – 7.22 (m, 2H), 7.08 (t, *J* = 7.2 Hz, 1H), 4.35 (t, *J* = 8.3 Hz, 2H), 3.15 (t, *J* = 8.3 Hz, 2H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 166.15, 154.58, 148.07, 143.30, 137.25, 132.27, 127.49, 125.12, 124.71, 124.49, 124.27, 118.03, 50.62, 28.75.

Procedure for the Synthesis of *N*-Protected Indoline **83e**:[117]

First step:

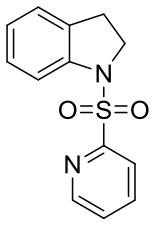
To a solution of 2-mercaptopyridine (3.6 mmol) in conc. H_2SO_4 (10 mL) was added dropwise a commercially available bleach solution (roughly 5% NaOCl, 40 mL). The

resulting mixture was stirred at 0 ºC for 15 min before extracting two times with dichloromethane. The combined organic phase was dried over Na_2SO_4 and concentrated to afford the 2-pyridylsulfonyl chloride as colorless oil.

Second step:

To a solution of indoline (2.4 mmol) and pyridine (3.6 mmol) in THF (25 mL), was slowly added 2-pyridylsulfonyl chloride (3.6 mmol) under argon at 0 ^{o}C. The resulting solution was stirred at room temperature overnight. The mixture was quenched with saturated NH_4Cl solution (10 mL) and extracted three times with EtOAc. The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated under vacuum. The product was purified by normal silica gel column with petroleum ether (40-60°C)/EtOAc mixture.

Characterization of Compounds **83e:**



1-(Pyridin-2-ylsulfonyl)indoline (83e):[117]

Yield: 65%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.61 (d, *J* = 4.6 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.83 (td, *J* = 7.8, 1.6 Hz, 1H), 7.47 – 7.41 (m, 2H), 7.12 – 7.09 (m, 2H), 6.93 (t, *J* = 7.4 Hz, 1H), 4.34 (t, *J* = 8.5 Hz, 2H), 3.06 (t, *J* = 8.5 Hz, 2H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 156.41, 150.27, 141.63, 137.83, 132.04, 127.61, 127.04, 125.22, 123.77, 123.15, 114.59, 51.47, 28.18.

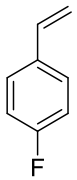
5.2.2 Synthesis of Substituted Styrenes 84

General Procedure B for the Synthesis of Substituted Styrenes **84c, 84g, 84i–84m:**[119]

To a suspension of phosphonium salt (10 mmol) in 25 mL dry diethyl ether was added

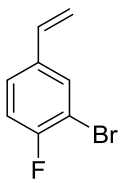
potassium *tert*-butoxide (1.8 equiv, 9 mmol) under argon at 0 ^{o}C. After stirring 15 min, it turned yellow. The solution was kept for 10 min without stirring to precipitate all the solids and get a supernatant. In another flask, aldehyde (2 equiv, 5 mmol) was dissolved in 10 mL dry ether and the solution was kept at 0 ^{o}C. The supernatant was added to the aldehyde solution and the mixture was stirred for 30 min at room temperature. The mixture was quenched with saturated NH_4Cl solution, extracted three times with ether, washed with water, brine and dried over anhydrous Na_2SO_4. The product was purified by normal silica gel column with petroleum ether (40-60°C)/EtOAc mixture.

Characterization of Compounds **84c, 84g, 84i–84m:**



1-Fluoro-4-vinylbenzene (84c):[119]

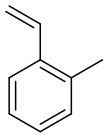
The product was prepared according to the general procedure B. Yield: 40%; Colourless liquid; TLC (in petroleum ether): R_f = 0.6; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.40 – 7.37 (m, 2H), 7.05 – 7.00 (m, 2H), 6.69 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.68 (d, *J* = 17.6 Hz, 1H), 5.23 (d, *J* = 10.9 Hz, 1H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 162.57 (d, *J* = 246.7 Hz), 135.80, 133.82 (d, *J* = 3.3 Hz), 127.86 (d, *J* = 8.0 Hz), 115.53 (d, *J* = 21.6 Hz), 113.65 (d, *J* = 2.2 Hz).



2-Bromo-1-fluoro-4-vinylbenzene (84g):[120]

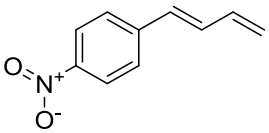
The product was prepared according to the general procedure B. Yield: 41%; Colourless liquid; TLC (in petroleum ether): R_f = 0.6; **^{1}H NMR (500 MHz, $CDCl_3$)** δ

7.59 (dd, *J* = 6.6, 2.2 Hz, 1H), 7.30 (ddd, *J* = 8.5, 4.7, 2.2 Hz, 1H), 7.08 – 7.05 (m, 1H), 6.61 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.68 (d, *J* = 17.6 Hz, 1H), 5.27 (d, *J* = 10.9 Hz, 1H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 158.73 (d, *J* = 248.0 Hz), 135.42 (d, *J* = 3.8 Hz), 134.66, 131.20, 126.82 (d, *J* = 7.2 Hz), 116.57 (d, *J* = 22.7 Hz), 115.12 (d, *J* = 2.3 Hz), 109.34 (d, *J* = 21.3 Hz).



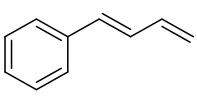
1-Methyl-2-vinylbenzene (84i):[119]

The product was prepared according to the general procedure B. Yield: 43%; Colourless liquid; TLC (in petroleum ether): R_f = 0.3; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.52 – 7.50 (m, 1H), 7.23 – 7.16 (m, 3H), 6.98 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.67 (dd, *J* = 17.4, 1.4 Hz, 1H), 5.32 (dd, *J* = 11.0, 1.4 Hz, 1H), 2.38 (s, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 136.98, 135.53, 135.00, 130.36, 127.79, 126.21, 125.50, 115.26, 19.83.



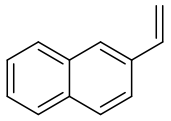
(*E*)-1-(Buta-1,3-dien-1-yl)-4-nitrobenzene (84j):[120]

The product was prepared according to the general procedure B. Yield: 75%; Yellow amorphous solid; TLC (2% EtOAc in petroleum ether): R_f = 0.3; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.53 – 7.50 (m, 2H), 6.95 – 6.90 (m, 1H), 6.62 – 6.50 (m, 2H), 5.48 (dd, *J* = 16.9, 0.5 Hz, 1H), 5.34 (dd, *J* = 10.0, 0.5 Hz, 1H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 146.94, 143.78, 136.53, 134.12, 130.52, 126.92, 124.19, 121.03.



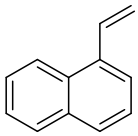
(*E*)-Buta-1,3-dien-1-ylbenzene (84k):[120]

The product was prepared according to the general procedure B. Yield: 47%; Colourless liquid; TLC (1% EtOAc in petroleum ether): R_f = 0.5; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.43 – 7.41 (m, 2H), 7.35 – 7.31 (m, 2H), 7.26 – 7.22 (m, 1H), 6.83 – 6.78 (m, 1H), 6.60 – 6.49 (m, 2H), 5.37 – 5.33 (m, 1H), 5.20 – 5.18 (m, 1H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 137.31, 137.27, 132.99, 129.76, 128.74, 127.76, 126.58, 117.74.



2-Vinylnaphthalene (84l):[121]

The product was prepared according to the general procedure B. Yield: 49%; Colourless liquid; TLC (in petroleum ether): R_f = 0.1; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.84 – 7.81 (m, 3H), 7.77 (s, 1H), 7.66 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.50 – 7.44 (m, 2H), 6.91 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.90 (d, *J* = 17.6 Hz, 1H), 5.36 (d, *J* = 10.9 Hz, 1H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 137.08, 135.16, 133.71, 133.30, 128.29, 128.18, 127.80, 126.50, 126.37, 126.05, 123.32, 114.31.



1-Vinylnaphthalene (84m):[121]

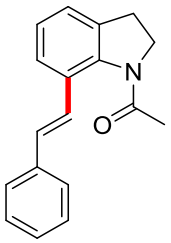
The product was prepared according to the general procedure B. Yield: 43%; Colourless liquid; TLC (in petroleum ether): R_f = 0.1; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.15 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 7.4 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.65 (d, *J* = 7.1 Hz, 1H), 7.56 – 7.47 (m, 4H), 5.82 (dd, *J* = 17.3, 1.4 Hz, 1H), 5.51 (dd, *J* = 11.0, 1.4 Hz, 1H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 135.75, 134.52, 133.73, 131.25, 128.64, 128.22, 126.18, 125.88, 125.76, 123.90, 123.76, 117.23.

5.2.3 Synthesis of 7-Alkenylated Indolines 99

General Procedure C for the Synthesis of 7-Substituted Indolines **99a, 99d:**

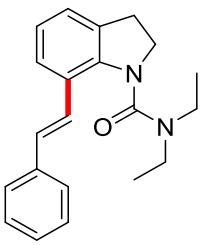
Protected indoline (0.1 mmol) was dissolved in a 12 mL screw-capped tube with 1 mL of anhydrous *t*-AmOH. Then styrene (0.5 mmol) followed by [(RhCp*Cl_2)$_2$] (5 mol %), $AgSbF_6$ (20 mol %) and anhydrous $Cu(OAc)_2$ (0.25 mmol) were added to the reaction mixture at room temperature. The reaction mixture was allowed to warm up to 120 °C and stirred for 1-16 h. After the reaction finished, the reaction mixture was directly loaded in silica gel column and purified with petroleum ether (40-60°C)/EtOAc mixture.

Characterization of Compounds **99a, 99d:**



(E)-1-(7-Styrylindolin-1-yl)ethanone (99a):

The compound was prepared according to the general procedure C. Yield: 99%; Beige amorphous solid; TLC (25% EtOAc in petroleum ether): R_f = 0.15; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.52 – 7.50 (m, 3H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.28 – 7.24 (m, 1H), 7.17 – 7.11 (m, 3H), 7.07 (br s, 1H), 4.21 (br s, 2H), 3.01 (t, *J* = 7.1 Hz, 2H), 2.21 (br s, 3H) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 128.81 (br s), 128.28, 126.69, 125.56, 124.87, 123.80 (br s), 51.41, 29.57 ppm; **FT-IR:** ṽ = 3063.54, 3019.64, 2921.25, 1943.79, 1736.43, 1583.56, 1387.37, 1328.92, 1015.38 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{18}H_{18}ON_2$: 264.13829 found: 264.13851.



(E)-*N*,*N*-Diethyl-7-styrylindoline-1-carboxamide (99d):

The compound was prepared according to the general procedure C. Yield: 96%;

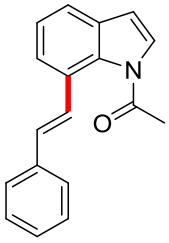
Yellow liquid; TLC (25% EtOAc in petroleum ether): R_f = 0.3; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.44 (d, *J* = 7.5 Hz, 3H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.10 (d, *J* = 7.2 Hz, 1H), 7.02 – 6.98 (m, 3H), 3.93 (t, *J* = 8.0 Hz, 2H), 3.42 (q, *J* = 7.1 Hz, 4H), 3.12 (t, *J* = 7.9 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 6H) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 161.49, 143.82, 138.01, 133.97, 128.60, 128.35, 127.35, 126.65, 126.57, 125.98, 124.56, 123.68, 123.59, 53.19, 41.53, 30.46, 13.50 ppm; **FT-IR:** ṽ = 2970.15, 2932.55, 2360.60, 2341.66, 1600.16, 1450.89, 1412.63, 1290.89, 1263.37,1153.97, 1028.18; **HRMS**: calc. for $[M+H]^+$ $C_{21}H_{25}ON_2$: 321.19614 found: 321.19650.

5.2.4 Synthesis of 7-Alkenylated Indoles 85

General Procedure D for the Synthesis of 7-substituted Indoles **85a:**

N,*N*-Diethylcarbamoyl protected indoline (0.1 mmol) was dissolved in a 12 mL screw-capped tube with 1 mL of anhydrous *t*-AmOH. Then styrene (0.5 mmol) followed by [($RhCp^*Cl_2)_2$] (5 mol %), $AgSbF_6$ (20mol %) and anhydrous $Cu(OAc)_2$ (0.25 mmol) were added to the reaction mixture at room temperature. The reaction mixture was allowed to warm up to 120 °C and stirred for 1-16 h. After *N*,*N*-diethylcarbamoyl protected indoline disappeared, 20-40 mmol MnO_2 was added to the reaction system at 120 °C and continued stirring for 8 h. After the reaction finished, the reaction mixture was directly loaded in silica gel column and purified with petroleum ether (40-60°C)/EtOAc mixture.

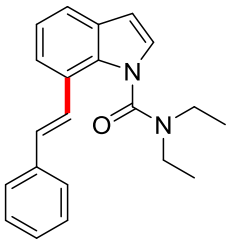
Characterization of Compounds **85a, 85d-85x:**



(*E*)-1-(7-Styryl-1*H*-indol-1-yl)ethanone (85a):

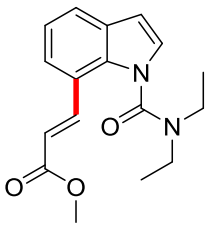
The product was prepared according to the general procedure D. Yield: 38%; Beige

amorphous solid; TLC (5% EtOAc in petroleum ether): R_f = 0.15; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.80 (d, *J* = 16.0 Hz, 1H), 7.60 – 7.56 (m, 3H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 3.8 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.26 – 7.24 (m, 1H), 6.91 (d, *J* = 16.0 Hz, 1H), 6.67 (d, *J* = 3.8 Hz, 1H), 2.68 (s, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 168.32, 138.19, 133.51, 132.53, 129.43, 128.78, 128.74, 127.49, 127.36, 127.22, 126.79, 124.51, 124.49, 120.45, 109.33, 24.98 ppm; **FT-IR:** ṽ = 3058.06, 2929.01, 2360.61, 2341.37, 1598.03, 1494.34, 1448.15, 1409.43, 1301.82, 1201.37; **MS-EI:** m/z (%) 262 (11) $[M+H]^+$, 261 (57) $[M]^{+\cdot}$, 219 (81), 218 (100), 204 (6), 189 (12).



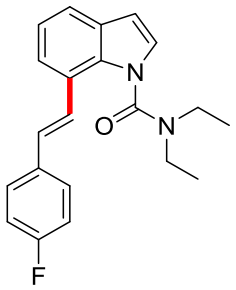
(*E*)-*N*,*N*-Diethyl-7-styryl-1*H*-indole-1-carboxamide (85d):

The product was prepared according to the general procedure D. Yield: 80%; Yellow liquid; TLC (25% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.62 (d, *J* = 7.5 Hz, 1H), 7.59 – 7.51 (m, 4H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.33 – 7.28 (m, 2H), 7.24 (d, *J* = 3.4 Hz, 1H), 7.08 (d, *J* = 15.9 Hz, 1H), 6.68 (d, *J* = 3.4 Hz, 1H), 3.34 (br s, 4H), 1.14 (br s, 6H) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 155.04, 137.62, 133.24, 130.57, 129.78, 128.75, 127.70, 126.72, 126.61, 125.04, 123.96, 121.77, 121.52, 120.78, 104.98, 42.62, 13.44 ppm; **FT-IR:** ṽ = 2974, 1683, 1541, 1457, 1418, 1230, 1033 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{21}H_{22}N_2O$: 319.18049 found: 319.18108.



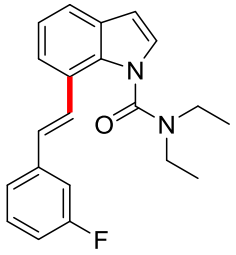
(*E*)-Methyl 3-(1-(diethylcarbamoyl)-1*H*-indol-7-yl)acrylate (85e):

The product was prepared according to the general procedure D. Yield: 54%; Yellow liquid; TLC (25% EtOAc in petroleum ether): R_f = 0.45; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.05 (d, *J* = 15.7 Hz, 1H), 7.65 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.21 – 7.18 (m, 2H), 6.63 (d, *J* = 3.4 Hz, 1H), 6.40 (d, *J* = 15.7 Hz, 1H), 3.79 (s, 3H), 3.43 (br s, 4H), 1.26 (br s, 6H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 167.23, 154.56, 141.12, 133.81, 130.43, 127.08, 123.31, 122.45, 121.82, 120.71, 118.88, 105.34, 51.68, 42.80, 13.48 ppm; **FT-IR:** ṽ = 2974, 1716, 1685, 1635, 1419, 1310, 1273, 1167 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{17}H_{20}N_2O_3$: 301.15467 found: 301.15578.



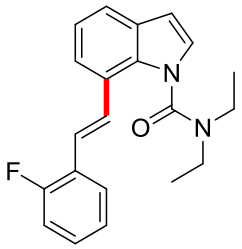
(*E*)-*N*,*N*-Diethyl-7-(4-fluorostyryl)-1*H*-indole-1-carboxamide (85f):

The product was prepared according to the general procedure D. Yield: 66%; Yellow liquid; TLC (25% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.57 (d, *J* = 7.8 Hz, 1H), 7.48 – 7.41 (m, 4H), 7.22 – 7.18 (m, 2H), 7.06 – 6.96 (m, 3H), 6.63 (d, *J* = 3.4 Hz, 1H), 3.27 (br s, 4H), 1.08 (br s, 6H) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 162.43 (d, *J* = 247.2 Hz), 155.04, 133.88 (d, *J* = 3.3 Hz), 133.24, 129.81, 129.32 , 128.18 (d, *J* = 7.9 Hz), 126.60, 124.99 (d, *J* = 2.3 Hz), 123.82, 121.78, 121.49, (d, *J* = 29.3 Hz), 120.84, 115.69 (d, *J* = 21.7 Hz), 105.03, 42.56, 13.62 ppm; **FT-IR:** ṽ = 2975, 1683, 1600, 1508, 1419, 1299, 1224 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{21}H_{21}FN_2O$: 337.17107found: 337.17162.



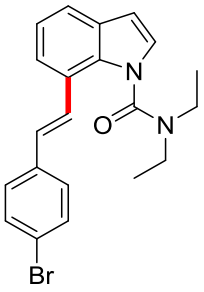
(*E*)-*N*,*N*-Diethyl-7-(3-fluorostyryl)-1*H*-indole-1-carboxamide (85g):

The product was prepared according to the general procedure D. Yield: 57%; Yellow liquid; TLC (25% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.58 (d, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 15.9 Hz, 1H), 7.46 (d, *J* = 7.4 Hz, 1H), 7.33 – 7.25 (m, 2H), 7.23 – 7.18 (m, 3H), 7.00 – 6.93 (m, 2H), 6.63 (d, *J* = 3.3 Hz, 1H), 3.31 (br s, 4H), 1.11 (br s, 6H) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.51, 155.00, 140.07 (d, *J* = 7.7 Hz), 133.31, 130.19 (d, *J* = 8.5 Hz), 129.93, 129.26 (d, *J* = 2.7 Hz), 126.64 (d, *J* = 11.9 Hz), 123.48, 122.58 (d, *J* = 2.8 Hz), 121.73 (d, *J* = 19.4 Hz), 121.15, 114.57, 114.36, 113.14, 112.93, 105.11, 42.73, 13.34 ppm; **FT-IR:** ṽ = 2974, 1684, 1541, 1419, 1033 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{21}H_{21}FN_2O$: 337.17107 found: 337.17172.



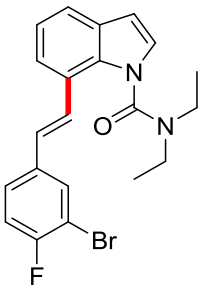
(*E*)-*N*,*N*-Diethyl-7-(2-fluorostyryl)-1*H*-indole-1-carboxamide (85h):

The product was prepared according to the general procedure D. Yield: 64%; Yellow liquid; TLC (25% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.62 – 7.54 (m, 3H), 7.50 (d, *J* = 7.4 Hz, 1H), 7.24 – 7.17 (m, 4H), 7.13 (t, *J* = 7.4 Hz, 1H), 7.09 – 7.04 (m, 1H), 6.64 (d, *J* = 3.3 Hz, 1H), 3.30 (br s, 4H), 1.10 (br s, 6H) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 160.48 (d , *J* = 249.5 Hz), 154.97, 133.29, 129.87, 128.89 (d, *J* = 8.3 Hz), 127.43, 127.42 (d, *J* = 9.2 Hz), 126.67, 125.49 (d, *J* = 12.1 Hz), 124.31 (d, *J* = 3.5 Hz), 123.85, 122.66 (d, *J* = 3.6 Hz), 121.75 (d, *J* = 13.3 Hz), 121.07, 115.85 (d, *J* = 22.1 Hz), 115.74, 105.06, 42.69, 13.42 ppm; **FT-IR:** ṽ = 2974, 1684, 1541, 1488, 1456, 1418, 1299, 1230, 1033 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{21}H_{21}FN_2O$: 337.17107 found: 337.17171.



(*E*)-7-(4-Bromostyryl)-*N*,*N*-diethyl-1*H*-indole-1-carboxamide (85i):

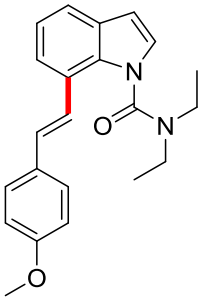
The product was prepared according to the general procedure D. Yield: 83%; Yellow liquid; TLC (25% EtOAc in petroleum ether): R_f = 0.30; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.58 (d, *J* = 7.8 Hz, 1H), 7.53 – 7.44 (m, 4H), 7.37 – 7.35 (m, 2H), 7.22 – 7.17 (m, 2H), 6.95 (d, *J* = 16.0 Hz, 1H), 6.63 (d, *J* = 3.3 Hz, 1H), 3.28 (br s, 4H), 1.09 (br s, 6H) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 155.00, 136.60, 133.20, 131.85, 129.85, 129.18, 128.16, 126.63, 125.89, 123.58, 121.80, 121.54, 121.39, 121.05, 105.06, 42.65, 13.72 ppm; **FT-IR:** ṽ = 2974, 1684, 1558, 1541, 1488, 1419, 1033, 1009 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{21}H_{21}{}^{79}BrN_2O$: 397.09100 found: 397.09029; $[M+H]^+$ $C_{21}H_{21}{}^{81}BrN_2O$: 399.08896 found:399.08729.



(*E*)-7-(3-Bromo-4-fluorostyryl)-*N*,*N*-diethyl-1*H*-indole-1-carboxamide (85j):

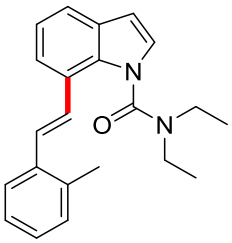
The product was prepared according to the general procedure D. Yield: 65%; Yellow liquid; TLC (25% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.90 (s, 2H), 7.74 – 7.61 (m, 3H), 7.50 (d, *J* = 7.3 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 3.4 Hz, 1H), 7.07 (d, *J* = 16.0 Hz, 1H), 6.65 (d, *J* = 3.4 Hz, 1H), 3.41 (br s, 4H), 1.17 (t, *J* = 6.6 Hz, 6H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 158.54 (d, *J* = 248.3 Hz), 155.00, 135.53 (d, *J* = 3.9 Hz), 133.35, 131.33, 130.01, 127.80 (d, *J* = 1.3 Hz), 127.08 (d, *J* = 7.1 Hz), 126.71, 126.49 (d, *J* = 2.5 Hz), 123.35, 121.86, 121.54, 121.20, 116.72 (d, *J* = 22.6 Hz), 109.48 (d, *J* = 21.3 Hz), 105.20, 42.77, 13.52 ppm;

FT-IR: $\tilde{\nu}$ = 2974, 1684, 1558, 1541, 1494, 1457, 1418, 1312, 1046 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{21}H_{20}{}^{79}BrFN_2O$: 415.08158 found: 415.08180; $C_{21}H_{20}{}^{81}BrFN_2O$: 417.07953 found: 417.07820.



(*E*)-*N*,*N*-Diethyl-7-(4-methoxystyryl)-1*H*-indole-1-carboxamide (85k):

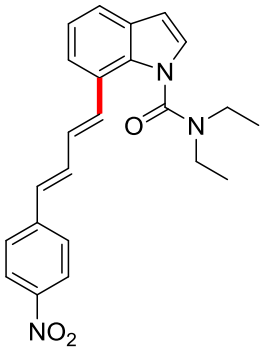
The product was prepared according to the general procedure D. Yield: 50%; Yellow liquid; TLC (25% EtOAc in petroleum ether): R_f = 0.15; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.54 (d, *J* = 7.8 Hz, 1H), 7.45 – 7.43 (m, 3H), 7.35 (d, *J* = 16.0 Hz, 1H), 7.21 – 7.17 (m, 2H), 6.97 (d, *J* = 16.0 Hz, 1H), 6.90 – 6.88 (m, 2H), 6.62 (d, *J* = 3.3 Hz, 1H), 3.83 (s, 3H), 3.28 (br s, 4H), 1.08 (br s, 6H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 159.26, 130.13, 130.00, 129.60, 127.81, 126.42, 124.18, 122.80, 121.62, 121.19, 120.28, 114.06, 113.77, 113.47, 104.78, 55.32, 42.52, 13.41 ppm; **FT-IR:** $\tilde{\nu}$ = 2930, 1683, 1606, 1509, 1418, 1249, 1175, 1033 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{22}H_{24}N_2O_2$: 349.19105 found: 349.19158.



(*E*)-*N*,*N*-Diethyl-7-(2-methylstyryl)-1*H*-indole-1-carboxamide (85l):

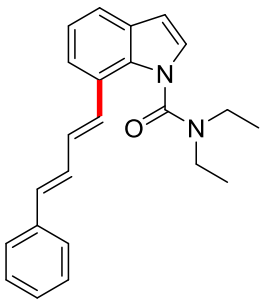
The product was prepared according to the general procedure D. Yield: 74%; Yellow liquid; TLC (25% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.59 – 7.55 (m, 2H), 7.47 (d, *J* = 7.4 Hz, 1H), 7.37 (d, *J* = 15.8 Hz, 1H), 7.26 – 7.15 (m, 6H), 6.62 (d, *J* = 3.4 Hz, 1H), 3.26 (brs, 4H), 2.41 (s, 3H), 1.05 (brs, 6H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.97, 136.59, 135.74, 133.26, 130.42, 129.80, 128.40, 127.63, 126.64, 126.30, 126.22, 125.72, 124.27, 121.74, 121.59, 120.75, 104.97, 42.66, 20.09, 13.62 ppm; **FT-IR:** ṽ = 2973, 1683, 1541, 1457, 1418, 1298, 1033 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{22}H_{24}N_2O$: 333.19614 found: 333.19681.



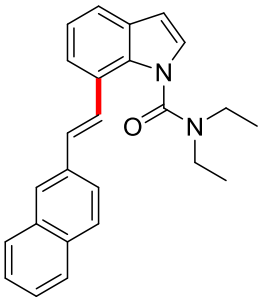
***N*,*N*-Diethyl-7-((1*E*,3*E*)-4-(4-nitrophenyl)buta-1,3-dien-1-yl)-1*H*-indole-1-carboxamide (85m):**

The product was prepared according to the general procedure D. Yield: 58%; Yellow liquid; TLC (25% EtOAc in petroleum ether): R_f = 0.15; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.19 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 7.4 Hz, 1H), 7.22 – 7.16 (m, 3H), 7.12 – 7.05 (m, 1H), 6.96 – 6.90 (m, 1H), 6.70 (d, *J* = 15.4 Hz, 1H), 6.63 (d, *J* = 3.4 Hz, 1H), 3.35 (br s, 4H), 1.21 (br s, 6H) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 154.93, 146.72, 144.03, 133.93, 132.10, 130.18, 130.07, 129.70, 129.17, 126.76, 126.72, 124.32, 123.07, 121.83, 121.60, 121.47, 105.18, 42.57, 13.27 ppm; **FT-IR:** ṽ = 2923, 1716, 1683, 1587, 1541, 1509, 1419, 1337, 1107 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{23}H_{23}N_3O_3$: 390.18122 found: 390.18294.



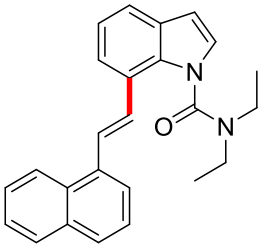
***N*,*N*-Diethyl-7-((1*E*,3*E*)-4-phenylbuta-1,3-dien-1-yl)-1*H*-indole-1-carboxamide (85n):**

The product was prepared according to the general procedure D. Yield: 59%; Yellow liquid; TLC (25% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.55 (d, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 3H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.26 – 7.23 (m, 1H), 7.20 – 7.17 (m, 2H), 7.03 (d, *J* = 14.5 Hz, 1H), 6.98 – 6.87 (m, 2H), 6.67 (d, *J* = 14.7 Hz, 1H), 6.62 (d, *J* = 3.3 Hz, 1H), 3.33 (br s, 4H), 1.19 (br s, 6H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 155.02, 137.49, 132.96, 132.93, 130.89, 129.86, 129.45, 128.83, 128.75, 127.73, 126.63, 126.49, 123.76, 121.75, 121.22, 120.82, 104.95, 42.73, 13.42 ppm; **FT-IR:** ṽ = 2973, 1717, 1698, 1684, 1558, 1541, 1522, 1508, 1473, 1457, 1033 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{23}H_{24}N_2O$: 345.19614 found: 345.19727.



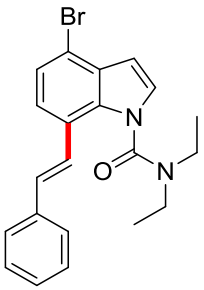
(*E*)-*N*,*N*-Diethyl-7-(2-(naphthalen-2-yl)vinyl)-1*H*-indole-1-carboxamide (85o):

The product was prepared according to the general procedure D. Yield: 68%; Yellow liquid; TLC (25% EtOAc in petroleum ether): R_f = 0.15; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.85 – 7.81 (m, 4H), 7.75 – 7.74 (m, 1H), 7.66 (d, *J* = 15.9 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.50 – 7.44 (m, 2H), 7.25 – 7.18 (m, 3H), 6.65 (d, *J* = 3.3 Hz, 1H), 3.30 (br s, 4H), 1.10 (br s, 6H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 155.11, 135.20, 133.84, 133.31, 133.17, 130.68, 129.86, 128.41, 128.13, 127.84, 126.76, 126.65, 126.45, 126.01, 125.46, 124.05, 123.83, 121.83, 121.54, 120.87, 105.02, 42.82, 13.48 ppm; **FT-IR:** ṽ = 2974, 1683, 1541, 1418, 1056, 1033 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{25}H_{24}N_2O$: 369.19614 found: 369.19795.



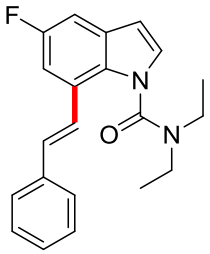
(*E*)-*N*,*N*-Diethyl-7-(2-(naphthalen-1-yl)vinyl)-1*H*-indole-1-carboxamide (85p):

The product was prepared according to the general procedure D. Yield: 96%; Yellow liquid; TLC (25% EtOAc in petroleum ether): R_f = 0.15; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.23 (d, *J* = 8.6 Hz, 1H), 7.89 – 7.78 (m, 4H), 7.62 (t, *J* = 8.6 Hz, 2H), 7.56 – 7.48 (m, 4H), 7.29 – 7.26 (m, 1H), 7.21 (d, *J* = 3.3 Hz, 1H), 6.66 (d, *J* = 3.3 Hz, 1H), 3.26 (br s, 4H), 0.99 (t, *J* = 7.2 Hz, 6H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 154.96, 135.15, 133.83, 133.31, 131.48, 129.89, 128.74, 128.14, 128.02, 127.60, 126.68, 126.19, 125.88, 125.85, 124.20, 124.01, 123.81, 121.79, 121.72, 120.97, 104.99, 42.66, 13.38 ppm; **FT-IR:** ṽ = 2973, 1683, 1418, 1306, 1033 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{25}H_{24}N_2O$: 369.19614 found: 369.19789.



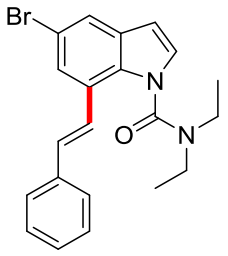
(*E*)-4-Bromo-*N*,*N*-diethyl-7-styryl-1*H*-indole-1-carboxamide (85q):

The product was prepared according to the general procedure D. Yield: 55%; Yellow liquid; TLC (25% EtOAc in petroleum ether): R_f = 0.15; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.49 (d, *J* = 7.5 Hz, 2H), 7.43 (d, *J* = 16.0 Hz, 1H), 7.38 – 7.25 (m, 5H), 7.23 (d, *J* = 3.4 Hz, 1H), 7.01 (d, *J* = 16.0 Hz, 1H), 6.70 (d, *J* = 3.4 Hz, 1H), 3.24 (br s, 4H), 1.08 (br s, 6H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 154.33, 137.39, 133.24, 131.28, 130.16, 128.82, 127.96, 127.03, 126.78, 124.70, 124.11, 123.39, 122.37, 114.39, 105.17, 42.39, 13.22 ppm; **FT-IR:** ṽ = 2974, 1685, 1558, 1541, 1473, 1421, 1385, 1274, 1033 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{21}H_{21}{}^{79}BrN_2O$: 397.09100 found: 397.09001; $C_{21}H_{21}{}^{81}BrN_2O$: 399.08896 found: 399.08713.



(*E*)-*N*,*N*-Diethyl-5-fluoro-7-styryl-1*H*-indole-1-carboxamide (85r):

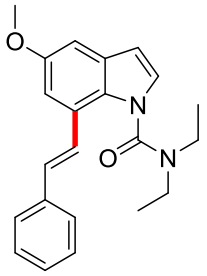
The product was prepared according to the general procedure D. Yield: 77%; Yellow liquid; TLC (25% EtOAc in petroleum ether): R_f = 0.15; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.50 (d, *J* = 7.5 Hz, 2H), 7.45 (d, *J* = 16.0 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.29 – 7.26 (m, 1H), 7.23 – 7.21 (m, 3H), 7.02 (d, *J* = 16.0 Hz, 1H), 6.59 (d, *J* = 3.3 Hz, 1H), 3.31 (br s, 4H), 1.11 (br s, 6H) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 158.90 (d, *J* = 236.8 Hz), 154.71, 137.17, 131.69, 129.92, 128.82, 128.12 (d, *J* = 5.9 Hz), 126.85, 124.99 (d, *J* = 9.3 Hz), 123.96 (d, *J* = 1.9 Hz), 109.19 (d, *J* = 26.4 Hz), 105.65 (d, *J* = 23.7 Hz), 105.77, 105.53, 105.09 (d, *J* = 4.6 Hz), 42.86, 13.59 ppm; **FT-IR:** ṽ = 2974, 1684, 1558, 1541, 1508, 1457, 1417, 1033 cm^{-1}**;** **HRMS:** calc. for $[M+H]^+$ $C_{21}H_{21}FN_2O$: 337.17107 found: 337.17168.



(*E*)-5-Bromo-*N*,*N*-diethyl-7-styryl-1*H*-indole-1-carboxamide (85s):

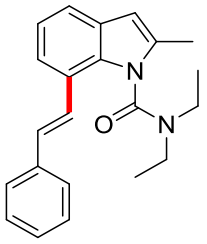
The product was prepared according to the general procedure D. Yield: 64%; Yellow liquid; TLC (25% EtOAc in petroleum ether): R_f = 0.15; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.68 (d, *J* = 1.7 Hz, 1H), 7.56 (d, *J* = 1.5 Hz, 1H), 7.49 (d, *J* = 7.4 Hz, 2H), 7.42 (d, *J* = 16.0 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.18 (d, *J* = 3.3 Hz, 1H), 7.02 (d, *J* = 16.0 Hz, 1H), 6.57 (d, *J* = 3.3 Hz, 1H), 3.28 (br s, 4H), 1.08 (br s, 6H) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 154.49, 137.12, 131.99, 131.94, 131.34, 128.83, 128.13, 127.65, 126.86, 125.56, 124.00, 123.60, 122.99, 115.01, 104.45 ,

42.75, 13.15 ppm; **FT-IR:** ṽ = 2974, 1684, 1541, 1423, 1033 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{21}H_{21}{}^{79}BrN_2O$: 397.09100 found: 397.08993; $C_{21}H_{21}{}^{81}BrN_2O$: 399.08896 found: 399.08711.



(*E*)-*N*,*N*-Diethyl-5-methoxy-7-styryl-1*H*-indole-1-carboxamide (85t):

The product was prepared according to the general procedure D. Yield: 50%; Yellow liquid; TLC (25% EtOAc in petroleum ether): R_f = 0.15; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.50 – 7.44 (m, 3H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.27 – 7.24 (m, 1H), 7.16 (d, *J* = 3.2 Hz, 1H), 7.12 (d, *J* = 2.2 Hz, 1H), 7.05 – 7.00, (m, 2H), 6.55 (d, *J* = 3.3 Hz, 1H), 3.89 (s, 3H), 3.30 (br s, 4H), 1.09 (br s, 6H) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 155.38, 155.07, 137.46, 130.95, 130.62, 128.76, 128.68, 127.82, 127.30, 126.78, 124.76, 124.70, 110.69, 104.86, 102.92, 55.97, 42.77, 13.44 ppm; **FT-IR:** ṽ = 2973, 1683, 1417, 1283, 1033 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{22}H_{24}N_2O_2$: 349.19105 found: 349.19155.



(*E*)-*N*,*N*-Diethyl-2-methyl-7-styryl-1*H*-indole-1-carboxamide (85u):

The product was prepared according to the general procedure D. Yield: 54%; Yellow liquid; TLC (25% EtOAc in petroleum ether): R_f = 0.20; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.52 – 7.45 (m, 4H), 7.38 – 7.34 (m, 3H), 7.27 – 7.21 (m, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 15.9 Hz, 1H), 6.33 (s, 1H), 3.74 – 3.61 (m, 1H), 3.37 – 3.28 (m, 1H), 2.87 – 2.67 (m, 2H), 2.40 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H), 0.86 (t, *J* = 7.2 Hz, 3H)

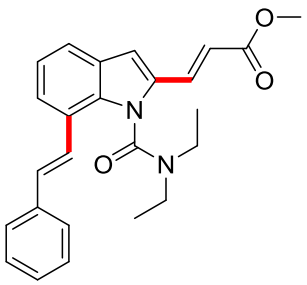
ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 154.72, 137.60, 135.33, 133.41, 130.67, 129.17, 128.78, 127.68, 126.68, 124.51, 122.74, 121.10, 120.15, 119.76, 102.64, 43.12, 42.04, 13.52, 12.81, 12.63 ppm; **FT-IR:** ṽ = 2974, 1683, 1558, 1541, 1508, 1457, 1418, 1302, 1033 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{22}H_{24}N_2O$: 333.19614 found: 333.19671.

5.2.5 Synthesis of 7-Alkenylated Indole Derivatives 85y–85aa

Procedure for the Synthesis of Compound **85y**:[85]

Compound **85d** (0.08 mmol) was dissolved in 1 mL anhydrous DCE in a 12 mL screw-capped tube. Then methyl acrylate (0.12 mmol) followed by $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), $Cu(OAc)_2{\cdot}2H_2O$ (1.0 equiv) were added to the reaction mixture at room temperature. The reaction mixture was allowed to warm up to 100 °C and stirred for 3 h. Then the reaction mixture was cooled to room temperature, loaded in silica gel column and purified with petroleum ether (40-60°C)/EtOAc mixture.

Characterization of Compound **85y:**



(*E*)-Methyl 3-(1-(diethylcarbamoyl)-7-((E)-styryl)-1*H*-indol-2-yl)acrylate (85y):

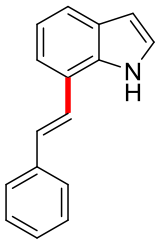
Yield: 63%; Yellow liquid; TLC (25% EtOAc in petroleum ether): R_f = 0.15; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.61 (d, *J* = 16.0 Hz, 1H), 7.58 – 7.56 (m, 1H), 7.53 – 7.46(m, 4H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.29 – 7.26 (m, 1H), 7.20 (t, *J* = 7.7 Hz, 1H), 7.04 – 7.00 (m, 2H), 6.47 (d, *J* = 16.0 Hz, 1H), 3.80 (s, 3H), 3.74 – 3.65 (m, 1H), 3.43 – 3.34 (m, 1H), 2.81 – 2.65 (m, 2 H), 1.21 (t, *J* = 7.2 Hz, 3H), 0.84 (t, *J* = 7.2 Hz, 3H) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 167.24, 153.86, 137.34, 134.92, 133.51, 132.55, 131.72, 128.84, 128.43, 127.96, 126.78, 124.02, 123.82, 123.23, 122.18, 121.27, 118.44, 107.32, 51.94, 43.36, 42.30, 13.54, 12.53 ppm; **FT-IR:** ṽ = 2975, 1684, 1635, 1558, 1541, 1507, 1434, 1350, 1277, 1172 cm^{-1}; **HRMS:** calc. for $[M+H]^+$

$C_{25}H_{26}N_2O_3$: 403.20162 found: 403.20019.

Procedure for the Synthesis of Compound **85z**:[122]

A mixture of **85d** (0.8 mmol), aqueous sodium hydroxide solution (25%, 2 mL) and ethanol (5 mL) was refluxed for 12 h in a 12 mL screw-capped tube. Then the mixture was evaporated and extracted with dichloromethane. The extract was dried over anhydrous $MgSO_4$ and concentrated under vacuum. The product was purified by normal silica gel column with petroleum ether (40-60°C)/EtOAc mixture.

Characterization of Compound **85z:**



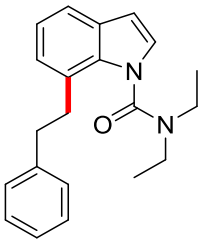
(*E*)-7-Styryl-1*H*-indole (85z):

Yield: 88%; Yellow liquid; TLC (25% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.53 (br s, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.62 (d, *J* = 7.7 Hz, 2H), 7.47 – 7.43 (m, 4H), 7.37 – 7.34 (m, 1H), 7.32 – 7.31 (m, 1H), 7.23 – 7.20 (m, 2H), 6.68 – 6.67 (m, 1H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 137.63, 133.91, 129.92, 128.91, 128.67, 127.85, 126.54, 125.27, 124.40, 121.54, 120.65, 120.62, 120.36, 103.43 ppm; **FT-IR:** $\tilde{\nu}$ = 3413, 1698, 1653, 1558, 1541, 1508, 1457 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{16}H_{13}N$: 220.11208 found: 220.11239.

Procedure for the Synthesis of Compound **85aa**:

A mixture of **4d** (0.08 mmol) and 10% Pd/C (0.01 mmol) in MeOH (2.0mL) was vigorously stirred at room temperature under 1 atm hydrogen for 12 h. Then the reaction mixture was filtered and concentrated under vacuum. The product was purified by normal silica gel column with petroleum ether (40-60°C)/EtOAc mixture.

Characterization of Compound **85aa:**



***N*,*N*-Diethyl-7-phenethyl-1*H*-indole-1-carboxamide (85aa):**

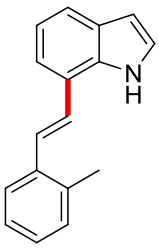
Yield: 72%; Yellow liquid; TLC (25% EtOAc in petroleum ether): R_f = 0.20; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.52 (dd, *J* = 7.3, 1.0 Hz, 1H), 7.33 – 7.26 (m, 4H), 7.23 –7.19 (m, 1H), 7.17– 7.12 (m, 3H), 6.65 (d, *J* = 3.4 Hz, 1H), 3.44 (br s, 4H), 3.15 (t, *J* = 7.9 Hz, 2H), 3.00 (t, *J* = 7.9 Hz, 2H), 1.19 (t, *J* = 7.0 Hz, 6H) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 154.88, 142.22, 134.24, 130.13, 128.57, 128.41, 126.74, 126.46, 125.99, 124.42, 121.80, 119.19, 105.42, 42.34, 36.35, 34.34, 13.32 ppm; **FT-IR:** ṽ = 2974, 1683, 1653, 1558, 1541, 1473, 1457, 1418, 1310, 1033 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{21}H_{24}N_2O$: 321.19614 found: 321.19674.

5.2.6 Synthesis of Deprotected 7-Alkenylated Indoles 85ab–85af

General Procedure E for the Synthesis of Compound **85ab–85af**:[122]

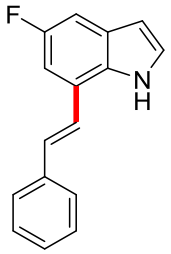
A mixture of **85** (0.2 mmol), aqueous sodium hydroxide solution (25%, 1 mL) and ethanol (1.5 mL) was refluxed for 12 h in a 12 mL screw-capped tube. Then the mixture was evaporated and extracted with dichloromethane. The extract was dried over anhydrous $MgSO_4$ and concentrated under vacuum. The product was purified by normal silica gel column with petroleum ether (40-60°C)/EtOAc mixture.

Characterization of Compound **85ab–85af**:



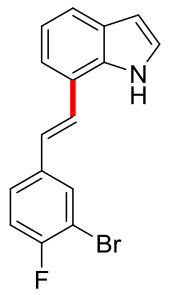
(*E*)-7-(2-Methylstyryl)-1*H*-indole (85ab):

The product was prepared according to the general procedure E. Yield: 75%; Yellow liquid; TLC (25% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.44 (brs, 1H), 7.65 (d, *J* = 7.4 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.43 – 7.38 (m, 2H), 7.28 – 7.24 (m, 3H), 7.22 – 7.21 (m, 2H), 7.16 (t, *J* = 7.6 Hz, 1H), 6.62 (dd, *J* = 3.1, 2.0 Hz, 1H), 2.45 (s, 3H).



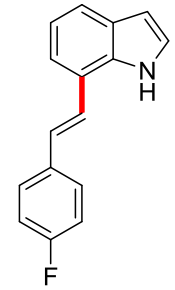
(*E*)-5-Fluoro-7-styryl-1*H*-indole (85ac):

The product was prepared according to the general procedure E. Yield: 70%; Yellow liquid; TLC (25% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.43 (brs, 1H), 7.57 – 7.55 (m, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.33 – 7.29 (m, 2H), 7.24 – 7.13 (m, 4H), 6.57 – 6.56 (m, 1H).



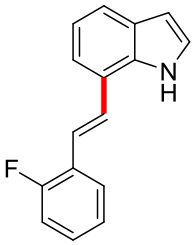
(*E*)-7-(3-Bromo-4-fluorostyryl)-1*H*-indole (85ad):

The product was prepared according to the general procedure E. Yield: 80%; Yellow liquid; TLC (25% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.45 (brs, 1H), 7.76 (dd, *J* = 6.5, 2.1 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.46 – 7.42 (m, 1H), 7.36 – 7.27 (m, 3H), 7.17 – 7.06 (m, 4H), 6.62 (dd, *J* = 3.1, 1.9 Hz, 1H).



(*E*)-7-(4-Fluorostyryl)-1*H*-indole (85ae):

The product was prepared according to the general procedure E. Yield: 80%; Yellow liquid; TLC (25% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.47 (brs, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.55 – 7.50 (m, 2H), 7.37 – 7.33 (m, 1H), 7.29 – 7.26 (m, 1H), 7.18 – 7.15 (m, 2H), 7.13 – 7.05 (m, 3H), 6.62 – 6.61 (m, 1H).



(*E*)-7-(2-fluorostyryl)-1*H*-indole (85af):

The product was prepared according to the general procedure E. Yield: 80%; Yellow liquid; TLC (25% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.52 (brs, 1H), 7.68 – 7.60 (m, 2H), 7.50 – 7.35 (m, 3H), 7.29 – 7.26 (m, 1H), 7.20 – 7.08 (m, 4H), 6.63 – 6.61 (m, 1H).

5.3 Experimental Part for 3.1.2

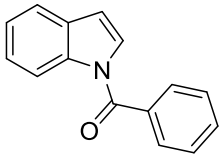
5.3.1 Synthesis of *N*-Protected Indoles 86a–86h

General Procedure F for the Synthesis of Substituted Indolines **86b, 86f–86h:**[123]

To a solution of indole (5 mmol), DMAP (0.5 mmol, 0.1 equiv) and Et_3N (7.5 mmol, 1.5 equiv) in dry dichloromethane (3.5 mL), was dropwise added acyl chloride or anhydride (6 mmol, 1.2 equiv) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred overnight. The reaction mixture was concentrated under

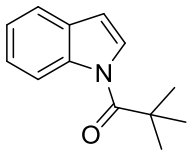
vacuum, the crude product was dissolved in Et_2O and washed with saturated NH_4Cl solution. The organic layer was separated and the aqueous phase was extracted three times with Et_2O. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The product was purified by normal silica gel column with petroleum ether (40-60°C)/EtOAc mixture.

Characterization of Compounds **86b, 86f–86h:**



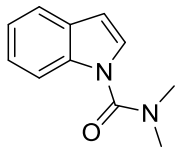
(1*H*-Indol-1-yl)(phenyl)methanone (86b):[123]

The product was prepared according to the general procedure F. Yield: 75%; White amorphous solid; TLC (1% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.41 (dd, *J* = 8.2, 0.5 Hz, 1H), 7.76 – 7.74 (m, 2H), 7.63 – 7.59 (m, 2H), 7.55 – 7.52 (m, 2H), 7.41 – 7.38 (m, 1H), 7.34 – 7.32 (m, 1H), 7.31 (d, *J* = 3.8 Hz, 1H), 6.62 (d, *J* = 3.8 Hz, 1H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 168.70, 136.03, 134.62, 131.87, 130.78, 129.15, 128.58, 127.58, 124.92, 123.94, 120.87, 116.40, 108.56 ppm.



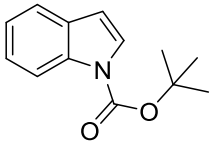
1-(1*H*-Indol-1-yl)-2,2-dimethylpropan-1-one (86f):[123]

The product was prepared according to the general procedure F. Yield: 80%; Colourless amorphous solid; TLC (2% EtOAc in petroleum ether): R_f = 0.4; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.53 – 8.51 (m, 1H), 7.74 (d, *J* = 3.8 Hz, 1H), 7.56 (ddd, *J* = 7.6, 1.1, 0.7 Hz, 1H), 7.37 – 7.33 (m, 1H), 7.29 – 7.25 (m, 1H), 6.62 (dd, *J* = 3.8, 0.7 Hz, 1H), 1.53 (s, 9H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 177.22, 136.91, 129.52, 125.78, 125.24, 123.67, 120.61, 117.47, 108.36, 41.39, 28.86 ppm.



***N*,*N*-Dimethyl-1*H*-indole-1-carboxamide (86g):[76e]**

The product was prepared according to the general procedure F. Yield: 80%; Yellow amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.3; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.65 (dd, *J* = 8.3, 0.7 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 3.5 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.21 – 7.18 (m, 1H), 6.60 (dd, *J* = 3.5, 0.6 Hz, 1H), 3.10 (s, 6H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 155.47, 135.60, 129.56, 126.36, 123.65, 121.88, 121.11, 113.58, 105.81, 38.60 ppm.



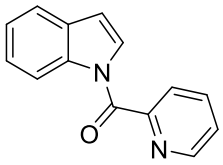
***tert*-Butyl 1*H*-indole-1-carboxylate (86h):[124]**

The product was prepared according to the general procedure F. Yield: 73%; Yellow liquid; TLC (0.5% EtOAc in petroleum ether): R_f = 0.1;**^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.17 (s, 1H), 7.63 (s, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.29 – 7.24 (m, 1H), 6.60 (d, *J* = 3.5 Hz, 1H), 1.71 (s, 9H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 149.94, 135.25, 130.66, 126.01, 124.30, 122.74, 121.06, 115.26, 107.40, 83.77, 28.33 ppm.

Procedure for the Synthesis of *N*-Protected Indole **86c:**[125]

The mixture of compound **83c** (2.27 mmol) and DDQ (2.95 mmol, 1.3 eq) in toluene (10 mL) was heated at 80 ^oC. After 12 hours, the mixture was cooled to room temperature, and ethyl acetate was added. Then the organic layer was washed with water, brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The product was purified by normal silica gel column with petroleum ether (40-60°C)/EtOAc mixture.

Characterization of Compound **86c:**



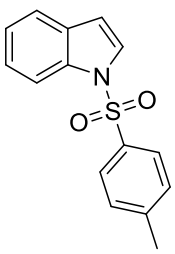
(1*H*-Indol-1-yl)(pyridin-2-yl)methanone (86c):[125]

Yield: 68%; Brown amorphous solid; TLC (10% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.75 (ddd, *J* = 4.8, 1.5, 0.8 Hz, 1H), 8.54 (d, *J* = 8.2 Hz, 1H), 8.09 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.98 (d, *J* = 3.8 Hz, 1H), 7.95 (td, *J* = 7.7, 1.7 Hz, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.52 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.41 – 7.37 (m, 1H), 7.32 (td, *J* = 7.5, 1.0 Hz, 1H), 6.66 – 6.62 (m, 1H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 142.62, 129.31, 125.49, 114.37, 113.37, 107.68, 105.37, 103.09, 102.71, 101.90, 101.14, 97.72, 93.86, 86.07 ppm.

General Procedure G for the Synthesis of *N*-Protected Indoles **86d, 86e:**[117]

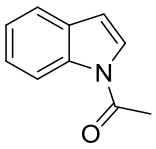
A solution of indole (20 mmol) in 10 mL THF was added to a suspension of NaH (60% in mineral oil, 1.1 equiv, 22 mmol) in 10 mL THF at 0 °C. The mixture was stirred for 20 min at room temperature. Then acyl chloride (1.1 equiv, 22 mmol) was added, and the mixture was stirred overnight at room temperature. A saturated solution of NH_4Cl was carefully added, and the resulting mixture was extracted three times with Et_2O. The combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated. The product was purified by normal silica gel column with petroleum ether (40-60°C)/EtOAc mixture.

Characterization of Compound **86d, 86e:**



1-Tosyl-1*H*-indole (86d):[123]

The product was prepared according to the general procedure G. Yield: 84%; Yellow amorphous solid; TLC (5% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.99 (dd, *J* = 8.3, 0.6 Hz, 1H), 7.77 – 7.75 (m, 2H), 7.56 (d, *J* = 3.7 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.32 – 7.29 (m, 1H), 7.24 – 7.21 (m, 3H), 6.65 (dd, *J* = 3.6, 0.5 Hz, 1H), 2.33 (s, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 145.03, 135.51, 134.85, 130.89, 130.00, 126.96, 126.48, 124.68, 123.39, 121.49, 113.69, 109.15, 21.69 ppm.



1-(1*H*-Indol-1-yl)ethan-1-one (86e):[124]

The product was prepared according to the general procedure G. Yield: 72%; White amorphous solid; TLC (2% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.45 (d, *J* = 6.4 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 2.5 Hz, 1H), 7.37 – 7.34 (m, 1H), 7.29 – 7.27 (m, 1H), 6.65 (dd, *J* = 3.8, 0.5 Hz, 1H), 2.65 (s, 3H) ppm; **^{13}C NMR (151 MHz, $CDCl_3$)** δ 168.81, 135.68, 130.54, 125.36, 125.28, 123.81, 120.98, 116.69, 109.33, 24.16 ppm.

5.3.2 Synthesis of Substituted Indoles 86i–86y

General Procedure H for the Synthesis of Substituted Indoles **86i, 86n:**

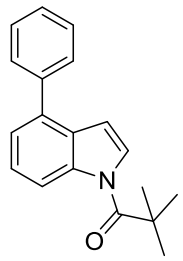
First step:[126]

To a stirred solution of phenylboronic acid (0.86 mmol) in EtOH (5mL) was added indole (0.71 mmol), K_2CO_3 (1.78 mmol), $Pd(PPh_3)_4$ (10% mmol). The reaction was refluxed for 24 h under argon atmosphere before EtOH was removed by rotary evaporation. The remained mixture was extracted with EtOAc, and the combined organic layers were washed with H_2O and brine, dried over anhydrous Na_2SO_4, evaporated under vacuum. The product was purified by normal silica gel column with petroleum ether (40-60°C)/EtOAc mixture.

Second Step:[123]

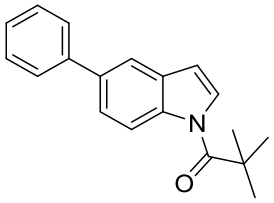
To a solution of indole (0.47 mmol), DMAP (0.05 mmol) and Et_3N (0.7 mmol) in dry dichloromethane (3.5 mL) at 0 °C was added pivaloyl chloride (0.56 mmol) dropwise. The resulting solution was allowed to warm to room temperature and stirred overnight. The reaction mixture was concentrated under vacuum, the crude product was dissolved in Et_2O and washed with a saturated solution of NH_4Cl. The organic layer was separated and the aqueous phase was extracted three times with Et_2O. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The product was purified by normal silica gel column with petroleum ether (40-60°C)/EtOAc mixture.

Characterization of Compounds **86i, 86n:**



2,2-Dimethyl-1-(4-phenyl-1*H*-indol-1-yl)propan-1-one (86i):

The product was prepared according to the general procedure H. Yield: 43%; White amorphous solid; TLC (2% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.55 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 3.9 Hz, 1H), 7.61 – 7.60 (m, 2H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.45 – 7.39 (m, 2H), 7.34 (d, *J* = 7.4 Hz, 1H), 6.78 (d, *J* = 3.9 Hz, 1H), 1.54 (s, 9H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 177.28, 140.47, 137.23, 134.58, 129.06, 128.72, 127.69, 127.34, 126.06, 125.53, 123.74, 116.43, 107.58, 41.47, 28.84 ppm; **FT-IR:** $\tilde{\nu}$ = 2360, 2341, 1686, 1538, 1472, 1305, 1203, 1169, 1094 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{19}H_{20}ON$: 278.15394, found: 278.15417.



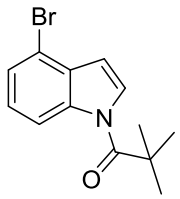
2,2-Dimethyl-1-(5-phenyl-1*H*-indol-1-yl)propan-1-one (86n):

The product was prepared according to the general procedure H. Yield: 40%; White amorphous solid; TLC (2% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.57 (d, *J* = 8.7 Hz, 1H), 7.78 (d, *J* = 3.7 Hz, 2H), 7.66 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.60 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.47 – 7.44 (m, 2H), 7.36 – 7.33 (m, 1H), 6.68 (d, *J* = 3.8 Hz, 1H), 1.54 (s, 9H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 177.20, 141.65, 137.00, 136.28, 130.04, 128.88, 127.49, 127.05, 126.40, 124.74, 119.02, 117.63, 108.62, 41.37, 28.82 ppm; **FT-IR:** ṽ = 2360, 2341, 1692, 1460, 1302, 1179, 1082 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{19}H_{20}ON$: 278.15394, found: 278.15399.

General Procedures I for the Synthesis of Substituted Indoles **86j, 86k, 86m, 86o–86t, 86x:**[123]

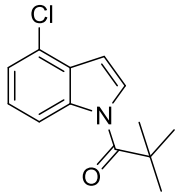
To a solution of indole (1.5 mmol), DMAP (0.15 mmol) and Et_3N (2.25 mmol) in dry dichloromethane (3.5 mL) at 0 °C, was added pivaloyl chloride (1.8 mmol) dropwise. The resulting solution was allowed to warm to room temperature and stirred overnight. The reaction mixture was concentrated under vacuum, the crude product was dissolved in Et_2O and washed with a saturated solution of NH_4Cl. The organic layer was separated, and the aqueous phase was extracted three times with Et_2O. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The product was purified by normal silica gel column with petroleum ether (40-60°C)/EtOAc mixture.

Characterization of Compounds **86j, 86k, 86m, 86o–86t, 86x:**



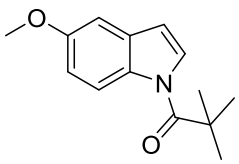
1-(4-Bromo-1*H*-indol-1-yl)-2,2-dimethylpropan-1-one (86j):[89]

The product was prepared according to the general procedure I. Yield: 75%; Colourless amorphous solid; TLC (2% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.46 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 3.9 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.21 (t, *J* = 8.4 Hz, 1H), 6.70 (d, *J* = 3.9 Hz, 1H), 1.52 (s, 9H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 177.33, 137.23, 130.15, 126.57, 126.36, 126.21, 116.48, 114.56, 108.14, 41.50, 28.76 ppm.



1-(4-Chloro-1*H*-indol-1-yl)-2,2-dimethylpropan-1-one (86k):[89]

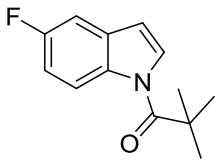
The product was prepared according to the general procedure I. Yield: 80%; Colourless liquid; TLC (2% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.42 – 8.39 (m, 1H), 7.77 (d, *J* = 3.9 Hz, 1H), 7.26 – 7.25 (m, 2H), 6.74 (dd, *J* = 3.9, 0.5 Hz, 1H), 1.51 (s, 9H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 177.28, 137.54, 128.27, 126.35, 125.95, 125.93, 123.44, 115.95, 106.41, 41.47, 28.74 ppm.



1-(5-Methoxy-1*H*-indol-1-yl)-2,2-dimethylpropan-1-one (86m):[89]

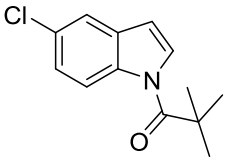
The product was prepared according to the general procedure I. Yield: 72%; Brown amorphous solid; TLC (2% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.41 (d, *J* = 9.1 Hz, 1H), 7.71 (d, *J* = 3.8 Hz, 1H), 7.02 (d, *J* = 2.5 Hz, 1H), 6.95 (dd, *J* = 9.1, 2.5 Hz, 1H), 6.55 (d, *J* = 3.8 Hz, 1H), 3.86 (s, 3H), 1.51 (s, 9H) ppm;

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.87, 156.44, 131.54, 130.42, 126.41, 118.22, 113.48, 108.24, 103.33, 55.77, 41.22, 28.88 ppm.



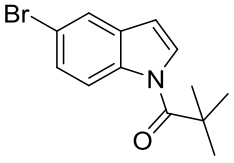
1-(5-Fluoro-1*H*-indol-1-yl)-2,2-dimethylpropan-1-one (86o):[89]

The product was prepared according to the general procedure I. Yield: 77%; Light yellow amorphous solid; TLC (2% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.47 (dd, *J* = 9.1, 4.8 Hz, 1H), 7.78 (d, *J* = 3.8 Hz, 1H), 7.20 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.08 – 7.04 (m, 1H), 6.58 (d, *J* = 3.8 Hz, 1H), 1.52 (s, 9H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 177.02, 159.69 (d, *J* = 239.9 Hz), 133.21, 130.45 (d, *J* = 10.0 Hz), 127.24, 118.47 (d, *J* = 8.9 Hz), 112.82 (d, *J* = 24.5 Hz), 108.04 (d, *J* = 3.9 Hz), 106.10 (d, *J* = 23.7 Hz), 41.33, 28.84 ppm.



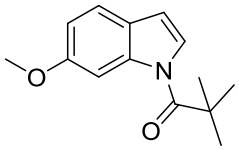
1-(5-Chloro-1*H*-indol-1-yl)-2,2-dimethylpropan-1-one (86p):[89]

The product was prepared according to the general procedure I. Yield: 85%; White amorphous solid; TLC (2% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.44 (d, *J* = 8.9 Hz, 1H), 7.76 (d, *J* = 3.8 Hz, 1H), 7.52 (d, *J* = 1.9 Hz, 1H), 7.30 (dd, *J* = 8.9, 1.9 Hz, 1H), 6.56 (dd, *J* = 3.8 Hz , *J* = 0.4 Hz, 1H), 1.51 (s, 9H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 177.12, 135.22, 130.72, 129.15, 126.99, 125.31, 120.19, 118.46, 107.65, 41.38, 28.78 ppm.



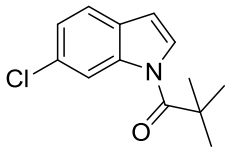
1-(5-Bromo-1*H*-indol-1-yl)-2,2-dimethylpropan-1-one (86q):[89]

The product was prepared according to the general procedure I. Yield: 69%; White amorphous solid; TLC (2% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.39 (d, *J* = 8.9 Hz, 1H), 7.74 (d, *J* = 3.8 Hz, 1H), 7.68 (d, *J* = 1.8 Hz, 1H), 7.43 (dd, *J* = 8.9, 1.8 Hz, 1H), 6.56 (d, *J* = 3.8 Hz, 1H), 1.51 (s, 9H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 177.14, 135.58, 131.24, 128.00, 126.86, 123.26, 118.85, 116.90, 107.54, 41.41, 28.77 ppm.



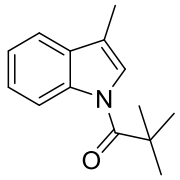
1-(6-Methoxy-1*H*-indol-1-yl)-2,2-dimethylpropan-1-one (86r):[127]

The product was prepared according to the general procedure I. Yield: 78%; White amorphous solid; TLC (2% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.15 (d, *J* = 2.3 Hz, 1H), 7.63 (d, *J* = 3.8 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 1H), 6.91 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.58 – 6.53 (m, 1H), 3.88 (s, 3H), 1.52 (s, 9H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 177.60, 158.48, 137.81, 124.57, 123.14, 120.92, 113.38, 108.32, 101.21, 55.77, 41.41, 28.79 ppm.



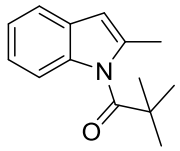
1-(6-Chloro-1*H*-indol-1-yl)-2,2-dimethylpropan-1-one (86s):[89]

The product was prepared according to the general procedure I. Yield: 66%; Brown amorphous solid; TLC (2% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.58 (dd, *J* = 1.2, 0.5 Hz, 1H), 7.73 (d, *J* = 3.8 Hz, 1H), 7.46 (d, *J* = 8.3 Hz, 1H), 7.27 – 7.22 (m, 1H), 6.61 – 6.57 (m, 1H), 1.51 (s, 9H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 177.21, 137.15, 131.17, 127.92, 126.34, 124.21, 121.19, 117.74, 108.09, 41.39, 28.71 ppm.



2,2-Dimethyl-1-(3-methyl-1*H*-indol-1-yl)propan-1-one (86t):[89]

The product was prepared according to the general procedure I. Yield: 43%; Brown amorphous solid; TLC (5% EtOAc in petroleum ether): R_f = 0.5; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.51 (d, *J* = 8.2 Hz, 1H), 7.50 – 7.49 (m, 2H), 7.37 – 7.34 (m, 1H), 7.29 (td, *J* = 7.6, 0.9 Hz, 1H), 2.30 (d, *J* = 1.2 Hz, 3H), 1.51 (s, 9H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 176.91, 137.23, 130.46, 125.33, 123.41, 122.73, 118.57, 117.54, 117.47, 41.22, 28.80, 9.94 ppm.



2,2-Dimethyl-1-(2-methyl-1*H*-indol-1-yl)propan-1-one (86x):[89]

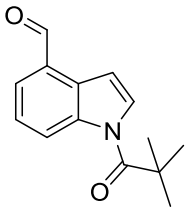
The product was prepared according to the general procedure I. Yield: 35%; Brown solid; TLC (5% EtOAc in petroleum ether): R_f = 0.5; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.49 (dd, *J* = 7.1 Hz, , *J* = 0.7 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.17 – 7.10 (m, 2H), 6.33 (s, 1H), 2.39 (d, *J* = 0.7 Hz, 3H), 1.41 (s, 9H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.57, 136.35, 136.08, 128.81, 121.88, 121.11, 120.13, 112.20, 104.61, 44.34, 28.39, 14.13 ppm.

General Procedure J for the Synthesis of Substituted Indoles **86l**, **86u**, **86y**:[117]

NaH (60% dispersion in mineral oil, 3 mmol) was added in portions at 0 °C to a stirred solution of indole (1.5 mmol) in dry THF (5 mL). After stirring for 30 min at 0 °C, pivaloyl chloride (1.8 mmol) was added, and the reaction was allowed to warm to room temperature and stirred overnight. Then the reaction mixture was poured into saturated solution of NH_4Cl and extracted with dichloromethane. The organic phase was dried over anhydrous Na_2SO_4. After evaporation of the solvents under vacuum, the product

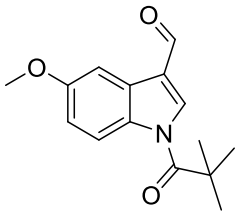
was purified by normal silica gel column with petroleum ether (40-60°C)/EtOAc mixture.

Characterization of Compounds **86l**, **86u**, **86y**:



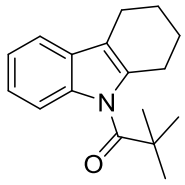
1-Pivaloyl-1*H*-indole-4-carbaldehyde (86l):

The product was prepared according to the general procedure J. Yield: 72%; White amorphous solid; TLC (5% EtOAc in petroleum ether): R_f = 0.3; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 10.24 (s, 1H), 8.79 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 3.8 Hz, 1H), 7.75 (dd, *J* = 7.4, 0.8 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.49 – 7.47 (m, 1H), 1.54 (s, 9H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 192.93, 177.54, 137.51, 129.87, 128.81, 128.09, 127.85, 124.89, 123.31, 107.69, 41.61, 28.78 ppm; **FT-IR:** ṽ = 2979, 2360, 2341, 1685, 1584, 1430, 1302, 1166, 1077 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{14}H_{16}O_2N$: 230.11756, found: 230.11761.



5-Methoxy-1-pivaloyl-1*H*-indole-3-carbaldehyde (86u):

The product was prepared according to the general procedure J. Yield: 65%; White amorphous solid; TLC (5% EtOAc in petroleum ether): R_f = 0.35; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 10.11 (s, 1H), 8.34 (d, *J* = 9.2 Hz, 1H), 8.29 (s, 1H), 7.75 (d, *J* = 2.6 Hz, 1H), 7.03 (dd, *J* = 9.2, 2.6 Hz, 1H), 3.90 (s, 3H), 1.56 (s, 9H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 185.95, 176.99, 157.79, 136.07, 132.30, 126.20, 121.93, 118.13, 116.20, 103.45, 55.86, 41.70, 28.91 ppm; **FT-IR:** ṽ = 2360, 2341, 1666, 1554, 1480, 1210, 1145, 1018 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{15}H_{18}O_3N$: 260.12812, found: 260.12826.



2,2-Dimethyl-1-(1,2,3,4-tetrahydro-9*H*-carbazol-9-yl)propan-1-one (86y):[128]

The product was prepared according to the general procedure J. Yield: 32%; White amorphous solid; TLC (5% EtOAc in petroleum ether): R_f = 0.5; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.45 – 7.40 (m, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.19 – 7.12 (m, 2H), 2.72 – 2.68 (m, 4H), 1.88 – 1.87 (m, 4H), 1.44 (s, 9H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 184.94, 135.97, 135.56, 129.05, 122.16, 121.01, 118.18, 114.64, 112.94, 43.60, 28.42, 24.29, 23.50, 22.72, 21.10 ppm.

Procedure for the Synthesis of Substituted Indole **86v**:

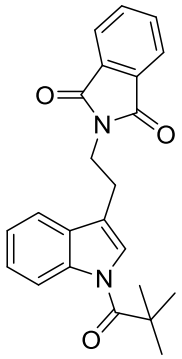
First Step:[129]

A mixture of tryptamine (3 mmol) and phthalic anhydride (3 mmol) in toluene (5 mL) was held at reflux for 2 h and then cooled to room temperature. The solvent was removed under vacuum. The crude product was purified on a silica gel column chromatography to give the corresponding product.

Second Step:[130]

To a solution of indole (2.6 mmol) in dry dichloromethane (15 mL) were successively added tetrabutylammonium hydrogen sulfate (0.26 mmol) and freshly finely powdered sodium hydroxide (13 mmol). The resulting light yellow solution was stirred for 15 minutes, and pivaloylchloride (7.8 mmol) was added in three portions over 15 minutes. The resulting slurry was vigorously stirred for 2-4 hours and quenched by addition of water. The organic layer was separated and the aqueous layer was extracted with dichloromethane. Combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The residue was then purified by flash chromatography over silica gel.

Characterization of Compound **86v**:



2-(2-(1-Pivaloyl-1*H*-indol-3-yl)ethyl)isoindoline-1,3-dione (86v):

Yield: 32%; White amorphous solid; TLC (25% EtOAc in petroleum ether): R_f = 0.2; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.49 (d, *J* = 8.2 Hz, 1H), 7.84 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.72 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.67 – 7.65 (m, 1H), 7.61 (s, 1H), 7.36 – 7.29 (m, 2H), 4.07 – 4.04 (m, 2H), 3.14 (t, *J* = 7.3 Hz, 2H), 1.47 (s, 9H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 177.06, 168.46, 137.27, 134.21, 132.14, 129.36, 125.60, 123.67, 123.44, 123.07, 118.61, 117.87, 117.62, 41.25, 37.46, 28.69, 24.27 ppm.

Procedure for the Synthesis of Substituted Indole **86w**:

First Step:

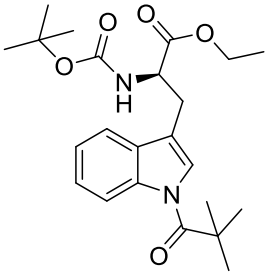
To a suspension of tryptamine (6.24 mmol) in 1, 4-dioxane (5 mL) was added Et_3N (12.9 mmol). Then a solution of $(Boc)_2O$ (6.87 mmol) in 1,4-dioxane (5 mL) was added to the reaction mixture. This mixture was stirred for 1 h, and the yellow solution was concentrated under vacuum. The crude product was purified on a silica gel column chromatography to give the corresponding product.

Second Step:[130]

To a solution of indole (1.0 mmol) in dry dichloromethane (10 mL) were successively added tetrabutylammonium hydrogen sulfate (0.1 mmol) and freshly finely powdered sodium hydroxide (5.0 mmol). The resulting light yellow solution was stirred for 15 minutes, and pivaloyl chloride (3.0 mmol) was added in three portions over 15 minutes. The resulting slurry was vigorously stirred for 2-4 hours and quenched by addition of water. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. Combined organic layers were washed with brine, dried over

anhydrous $MgSO_4$, filtered and concentrated under vacuum. The residue was then purified by flash chromatography over silica gel.

Characterization of Compound **86w**:



Ethyl N^{α}-(*tert*-butoxycarbonyl)-1-pivaloyl-*D*-tryptophanate (86w):

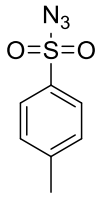
Yield: 38%; Light yellow liquid; TLC (1.5% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.49 (d, *J* = 8.3 Hz, 1H), 7.57 (s, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.35 (t, *J* = 7.7 Hz, 1H), 7.29 – 7.26 (m, 1H), 5.14 (d, *J* = 7.8 Hz, 1H), 4.69 (dd, *J* = 13.6, 5.8 Hz, 1H), 4.19 – 4.07 (m, 2H), 3.24 (ddd, J = 46.6, 15.0, 5.7 Hz, 2H), 1.50 (s, 9H), 1.43 (s, 9H), 1.21 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 176.86, 171.94, 155.12, 136.92, 129.60, 125.46, 123.79, 123.47, 118.43, 117.42, 116.09, 80.06, 61.67, 41.20, 28.66, 28.35, 27.76, 27.10, 14.10 ppm; **FT-IR:** $\tilde{\nu}$ = 2979, 2360, 2341, 1690, 1504, 1450, 1315, 1159 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{23}H_{33}O_5N_2$: 417.23840, found: 417.23858.

5.3.3 Synthesis of Azides 87

General Procedure K for the Synthesis of Azides **87a–87i, 87o**:[49c]

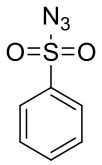
To a solution of sodium azide (3 mmol) in water (3 mL) was added a solution of sulfonyl chloride (2 mmol) in acetone (3 mL) dropwise over 1 h at 0 °C. The reaction mixture was warmed up to room temperature and then stirred for 11 h. Acetone was removed under vacuum, and the residue was extracted with ethyl acetate for three times. The combined organic layers were washed with water and saturated Na_2CO_3 solution, dried over anhydrous $MgSO_4$, and then the solvent was removed under vacuum. Crude product was used without further purification.

Characterization of Compounds **87a-87i, 87o:**



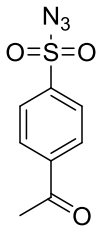
4-Methylbenzenesulfonyl azide (87a):[49c]

The product was prepared according to the general procedure K. Yield: 88%; Colourless liquid; TLC (2% EtOAc in petroleum ether): R_f = 0.15; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 2.48 (s, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 146.33, 135.68, 130.41, 127.67, 21.89 ppm.



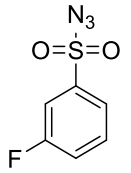
Benzenesulfonyl azide (87b):[49c]

The product was prepared according to the general procedure K. Yield: 85%; Colourless liquid; TLC (2% EtOAc in petroleum ether): R_f = 0.3; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.99 – 7.96 (m, 2H), 7.76 – 7.72 (m, 1H), 7.65 – 7.61 (m, 2H) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 138.68, 134.94, 129.84, 127.62 ppm.



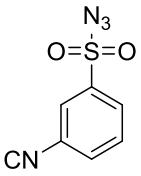
4-Acetylbenzenesulfonyl azide (87c):[131]

The product was prepared according to the general procedure K. Yield: 87%; Yellow amorphous solid; TLC (2% EtOAc in petroleum ether): R_f = 0.3; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.18 – 8.15 (m, 2H), 8.08 – 8.05 (m, 2H), 2.68 (s, 3H) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 196.34, 142.14, 141.73, 129.52, 128.00, 27.07 ppm.



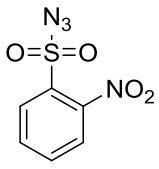
3-Fluorobenzenesulfonyl azide (87d):[132]

The product was prepared according to the general procedure K. Yield: 75%; Yellow liquid; TLC (2% EtOAc in petroleum ether): R_f = 0.3; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.78 (ddd, *J* = 7.9, 1.7, 1.0 Hz, 1H), 7.68 – 7.60 (m, 2H), 7.47 – 7.42 (m, 1H) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 162.65 (d, *J* = 253.7 Hz), 140.41, 131.74 (d, *J* = 7.8 Hz), 123.45 (d, *J* = 3.5 Hz), 122.30 (d, *J* = 21.2 Hz), 115.09 (d, *J* = 25.1 Hz) ppm.



3-Cyanobenzenesulfonyl azide (87e):

The product was prepared according to the general procedure K. Yield: 76%; White amorphous solid; TLC (2% EtOAc in petroleum ether): R_f = 0.3; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.25 – 8.25 (m, 1H), 8.20 – 8.17 (m, 1H), 8.02 – 7.99 (m, 1H), 7.79 (t, *J* = 7.9 Hz, 1H) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 140.33, 137.83, 131.39, 131.13, 130.99, 116.56, 114.73 ppm; **FT-IR:** ṽ = 2360, 2234, 2128, 1368, 1208, 1170, 1145, 1086 cm^{-1}.

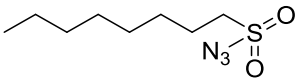


2-Nitrobenzenesulfonyl azide (87f):[133]

The product was prepared according to the general procedure K. Yield: 85%; Light yellow solid; TLC (10% EtOAc in petroleum ether): R_f = 0.3; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.21 – 8.19 (m, 1H), 7.93 – 7.80 (m, 3H) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 147.82, 135.82, 133.18, 132.86, 131.88, 125.52 ppm.

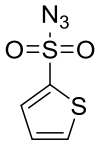
Methanesulfonyl azide (87g):[134]

The product was prepared according to the general procedure K. Yield: 83%; Light yellow liquid; TLC (2% EtOAc in petroleum ether): R_f = 0.3; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 3.26 (s, 3H) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 42.95 ppm.



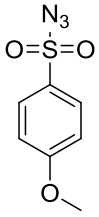
Octane-1-sulfonyl azide (87h):[135]

The product was prepared according to the general procedure K. Yield: 77%; Light yellow liquid; TLC (2% EtOAc in petroleum ether): R_f = 0.3; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 3.32 – 3.28 (m, 2H), 1.95 – 1.87 (m, 2H), 1.56 – 1.42 (m, 2H), 1.33 – 1.28 (m, 8H), 0.88 (t, *J* = 6.8 Hz, 3H) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 56.13, 31.78, 29.01, 28.98, 28.10, 23.49, 22.70, 14.16 ppm.



Thiophene-2-sulfonyl azide (87i):[132]

The product was prepared according to the general procedure K. Yield: 86%; Black liquid; TLC (15% EtOAc in petroleum ether): R_f = 0.2; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.83 – 7.80 (m, 2H), 7.22 – 7.21 (m, 1H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 138.18, 135.32, 134.91, 128.20 ppm.



4-Methoxybenzenesulfonyl azide (87o):[49c]

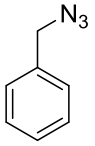
The product was prepared according to the general procedure K. Yield: 88%; Light

yellow liquid; TLC (2% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.92 – 7.89 (m, 2H), 7.07 – 7.04 (m, 2H), 3.91 (s, 3H) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.76, 130.06, 130.01, 114.97, 56.01 ppm.

Procedures for the Synthesis of Azide **87j:**[135]

To a solution of benzyl chloride (4.0 mmol) in THF (10 mL) was added NaN_3 (8.0 mmol) in water (1.0 mL). The resulting solution was stirred at 80 °C for 3 h. The reaction mixture was diluted with EtOAc (20 mL) and washed with water (20 mL) and brine (20 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated under vacuum to give the azide in quantitative yield.

Characterization of Compound **87j:**



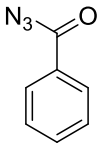
(Azidomethyl)benzene (87j):[135]

Yield: 68%; Colourless liquid; TLC (0.5% EtOAc in petroleum ether): R_f = 0.35; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.41 – 7.31 (m, 5H), 4.35 (s, 2H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 135.52, 128.98, 128.45, 128.36, 54.97 ppm.

Procedure for the Synthesis of Azide **87n:**[45]

To a solution of sodium azide (15 mmol) in H_2O (5 mL) was added dropwise a solution of benzoyl chloride (22.5 mmol) in acetone (10 mL) at 0 °C. The reaction mixture was allowed to stir overnight at room temperature. Water (40 mL) was added, and the reaction mixture was extracted three times with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under vacuum. The product was purified by normal silica gel column with petroleum ether (40-60°C)/EtOAc mixture.

Characterization of Compound **87n:**



Benzoyl azide (87n):[45]

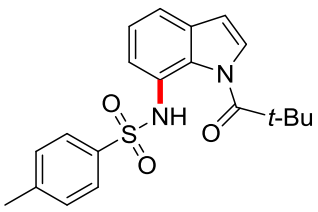
Yield: 83%; Colourless liquid; TLC (5% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.03 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.64 – 7.61 (m, 1H), 7.48 – 7.45 (m, 2H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.70, 134.50, 130.75, 129.60, 128.81 ppm.

5.3.4 Synthesis of 7-Amino Indoles 88

General Procedure L for the Synthesis of Compounds **88**:

N-Pivaloyl indole (0.1 mmol) was dissolved in a 12 mL screw-capped tube with 1 mL DCE. Then sulfonyl azide (0.22 mmol) followed by [(IrCp*Cl_2)$_2$] (4 mol %), $AgNTf_2$ (16 mol %) and LiOAc (40 mol%) were added to the reaction mixture at room temperature. The reaction mixture was allowed to warm up to 120 °C and stirred for 1-12 h. After the reaction finished, the reaction mixture was directly loaded in silica gel column and purified with petroleum ether (40-60°C)/EtOAc mixture.

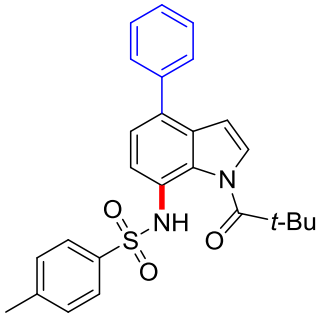
Characterization of Compounds **88**:



4-Methyl-*N*-(1-pivaloyl-1*H*-indol-7-yl)benzenesulfonamide (88f):

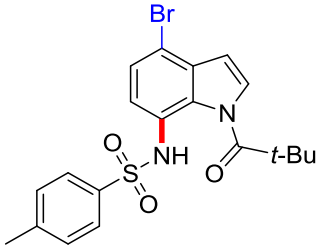
The product was prepared according to the general procedure L. Yield: 98%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, CD_2Cl_2)** δ 9.32 (brs, 1H), 7.56 (d, *J* = 3.9 Hz, 1H), 7.51 (dd, *J* = 7.8, 1.2 Hz,

1H), 7.40 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.36 – 7.35 (m, 2H), 7.31 (t, *J* = 7.7 Hz, 1H), 7.11 – 7.09 (m, 2H), 6.61 (d, *J* = 3.9 Hz, 1H), 2.29 (s, 3H), 1.38 (s, 9H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 180.22, 144.11, 137.82, 133.01, 129.96, 129.80, 127.46, 127.21, 125.78, 125.63, 122.84, 119.29, 109.76, 42.21, 29.32, 21.66 ppm; **FT-IR:** ṽ = 3854, 3734, 3629, 3286, 3136, 2985, 2360, 2342, 1541, 1117 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{20}H_{23}N_2O_3S$: 371.14239, found: 371.14304.



4-Methyl-*N*-(4-phenyl-1-pivaloyl-1*H*-indol-7-yl)benzenesulfonamide (88i):

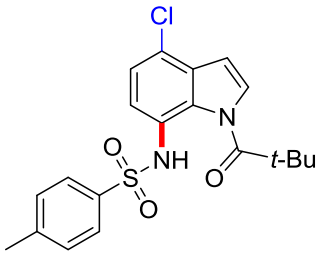
The product was prepared according to the general procedure L. Yield: 87%; Brown liquid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, CD_2Cl_2)** δ 9.20 (brs, 1H), 7.59 – 7.54 (m, 4H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.42 – 7.36 (m, 4H), 7.13 (d, *J* = 8.1 Hz, 2H), 6.74 (d, *J* = 4.0 Hz, 1H), 2.31 (s, 3H), 1.38 (s, 9H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 180.35, 144.16, 139.86, 137.83, 133.29, 130.91, 130.10, 130.01, 129.44, 129.18, 127.98, 127.63, 127.17, 125.67, 124.77, 123.16, 108.81, 42.25, 29.25, 21.65 ppm; **FT-IR:** ṽ = 2975, 2360, 2342, 1672, 1481, 1377, 1361, 1233, 1218 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{26}H_{27}N_2O_3S$: 447.17369, found: 447.17411.



***N*-(4-Bromo-1-pivaloyl-1*H*-indol-7-yl)-4-methylbenzenesulfonamide (88j):**

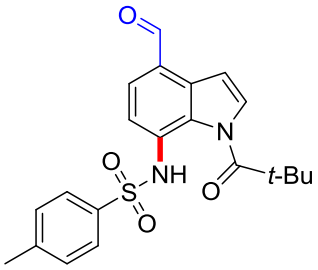
The product was prepared according to the general procedure L. Yield: 69%; Brown

amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, CD_2Cl_2)** δ 9.12 (brs, 1H), 7.62 (d, *J* = 4.0 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.12 (d, *J* = 8.2 Hz, 2H), 6.69 (d, *J* = 4.0 Hz, 1H), 2.30 (s, 3H), 1.36 (s, 9H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 180.45, 144.34, 137.46, 133.01, 130.11, 130.07, 128.38, 128.04, 127.13, 125.07, 123.92, 112.52, 109.42, 42.30, 29.16, 21.65 ppm; **FT-IR:** ṽ = 3187, 2975, 2360, 2342, 1678, 1327, 1237 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{20}H_{22}{}^{79}BrN_2O_3S$: 449.05290, found: 449.05352; **HRMS:** calc. for $[M+H]^+$ $C_{20}H_{22}{}^{81}BrN_2O_3S$: 451.05086, found: 451.05125.



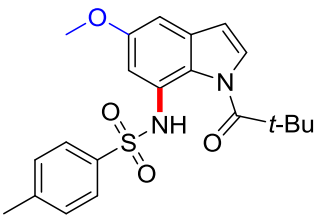
***N*-(4-Chloro-1-pivaloyl-1*H*-indol-7-yl)-4-methylbenzenesulfonamide (88k):**

The product was prepared according to the general procedure L. Yield: 76%; Brown amorphous solid; TLC (25% EtOAc in petroleum ether): R_f = 0.15; **^{1}H NMR (500 MHz, CD_2Cl_2)** δ 9.10 (brs, 1H), 7.60 (d, *J* = 4.0 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.12 (d, *J* = 8.3 Hz, 2H), 6.73 (d, *J* = 4.0 Hz, 1H), 2.30 (s, 3H), 1.36 (s, 9H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 180.37, 144.32, 137.46, 131.17, 130.43, 130.05, 128.05, 127.13, 125.19, 124.44, 124.22, 123.79, 107.58, 42.27, 29.15, 21.64 ppm; **FT-IR:** ṽ = 2360, 2342, 1673, 1480, 1322, 1181, 1162, 1085 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{20}H_{22}{}^{35}ClN_2O_3S$: 405.10342, found: 405.10461; **HRMS:** calc. for $[M+H]^+$ $C_{20}H_{22}{}^{37}ClN_2O_3S$: 407.10047, found: 407.10146.



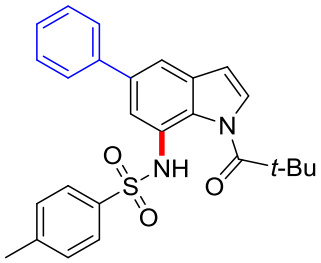
***N*-(4-Formyl-1-pivaloyl-1*H*-indol-7-yl)-4-methylbenzenesulfonamide (88l):**

The product was prepared according to the general procedure L. Yield: 92%; Yellow amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.3; **^{1}H NMR (500 MHz, CD_2Cl_2)** δ 10.33 (s, 1H), 9.81 (brs, 1H), 8.80 (dd, *J* = 8.5, 0.8 Hz, 1H), 8.08 (m, 1H), 7.72 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.49 – 7.43 (m, 1H), 7.15 (d, *J* = 8.3 Hz, 2H), 2.28 (s, 3H), 1.52 (s, 9H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 196.69, 177.56, 144.52, 136.57, 136.48, 134.68, 130.01, 128.83, 127.59, 125.67, 124.92, 122.11, 120.42, 118.00, 42.00, 28.76, 21.69 ppm; **FT-IR:** ṽ = 2360, 2342, 1706, 1668, 1561, 1217, 1154 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{21}H_{23}N_2O_4S$: 399.13730, found: 399.13721.



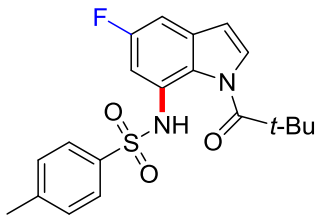
***N*-(5-Methoxy-1-pivaloyl-1*H*-indol-7-yl)-4-methylbenzenesulfonamide (88m):**

The product was prepared according to the general procedure L. Yield: 72%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.15; **^{1}H NMR (500 MHz, CD_2Cl_2)** δ 9.75 (brs, 1H), 7.54 (d, *J* = 3.9 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.13 (s, 1H), 7.11 – 7.10 (m, 2H), 6.84 (d, *J* = 2.5 Hz, 1H), 6.52 (d, *J* = 3.9 Hz, 1H), 3.84 (s, 3H), 2.30 (s, 3H), 1.37 (s, 9H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 179.68, 157.90, 144.15, 137.57, 133.82, 129.94, 128.21, 127.21, 126.57, 123.97, 109.89, 109.67, 101.86, 56.16, 42.02, 29.30, 21.65 ppm; **FT-IR:** ṽ = 2934, 2360, 2342, 1658, 1616, 1378, 1230, 1128, 1042 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{21}H_{25}N_2O_4S$: 401.15295, found: 401.15347.



4-Methyl-*N*-(5-phenyl-1-pivaloyl-1*H*-indol-7-yl)benzenesulfonamide (88n):

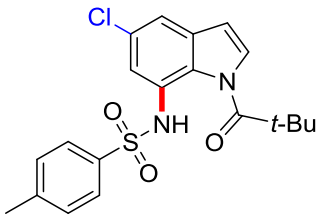
The product was prepared according to the general procedure L. Yield: 88%; Brown liquid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, CD_2Cl_2)** δ 9.49 (brs, 1H), 7.79 (d, *J* = 1.7 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.63 (d, *J* = 1.7 Hz, 1H), 7.59 (d, *J* = 3.9 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.41 – 7.37 (m, 3H), 7.12 (d, *J* = 8.3 Hz, 2H), 6.66 (d, *J* = 3.9 Hz, 1H), 2.30 (s, 3H), 1.38 (s, 9H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 180.02, 144.18, 140.47, 138.70, 137.63, 133.54, 129.97, 129.41, 128.98, 128.04, 128.00, 127.63, 127.22, 125.83, 121.85, 117.30, 110.02, 42.12, 29.22, 21.64 ppm; **FT-IR:** ṽ = 3151, 2974, 2930, 2360, 2342, 1670, 1332, 1220 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{26}H_{27}N_2O_3S$: 447.17369, found: 447.17420.



***N*-(5-Fluoro-1-pivaloyl-1*H*-indol-7-yl)-4-methylbenzenesulfonamide (88o):**

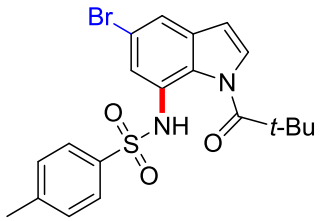
The product was prepared according to the general procedure L. Yield: 73%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.15; **^{1}H NMR (500 MHz, CD_2Cl_2)** δ 9.69 (brs, 1H), 7.62 (d, *J* = 3.9 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.29 (dd, *J* = 10.7, 2.5 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 2H), 7.04 (dd, *J* = 10.7, 2.5 Hz, 1H), 6.57 (d, *J* = 3.9 Hz, 1H), 2.30 (s, 3H), 1.38 (s, 9H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 180.18, 160.50 (d, *J* = 241.2 Hz), 144.43, 137.34, 133.73 (d, *J* = 11.2 Hz), 130.07, 129.08, 127.19, 127.00 (d, *J* = 12.0 Hz), 125.76 (d, *J* = 1.8 Hz), 109.71 (d, *J* = 4.1 Hz), 109.25 (d, *J* = 28.5 Hz), 104.25 (d, *J* = 23.6 Hz), 42.22, 29.27, 21.67 ppm; **^{19}F NMR (377 MHz, CD_2Cl_2)** δ -117.81 (dd, *J* = 10.6, 7.7 Hz) ppm; **FT-IR:** ṽ = 3198,

2975, 1661, 1600, 1473, 1334, 1184, 1160 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{20}H_{22}FN_2O_3S$: 389.13297, found: 389.13290.



N-(5-Chloro-1-pivaloyl-1*H*-indol-7-yl)-4-methylbenzenesulfonamide (88p):

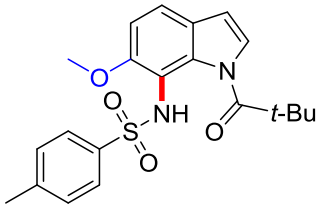
The product was prepared according to the general procedure L. Yield: 66%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.15; **^{1}H NMR (500 MHz, CD_2Cl_2)** δ 9.48 (brs, 1H), 7.59 (d, *J* = 3.9 Hz, 1H), 7.51 (d, *J* = 2.0 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 2.0 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 2H), 6.55 (d, *J* = 3.9 Hz, 1H), 2.30 (s, 3H), 1.36 (s, 9H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 180.20, 144.42, 137.36, 133.91, 130.80, 130.07, 128.78, 128.11, 127.16, 126.63, 121.95, 118.48, 109.18, 42.22, 29.20, 21.66 ppm; **FT-IR:** ṽ = 2975, 2360, 2342, 1663, 1583, 1454, 1376, 1158, 1091 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{20}H_{22}{}^{35}ClN_2O_3S$: 405.10342, found: 405.10339; **HRMS:** calc. for $[M+H]^+$ $C_{20}H_{22}{}^{37}ClN_2O_3S$: 407.10047, found: 407.10022.



***N*-(5-Bromo-1-pivaloyl-1*H*-indol-7-yl)-4-methylbenzenesulfonamide (88q):**

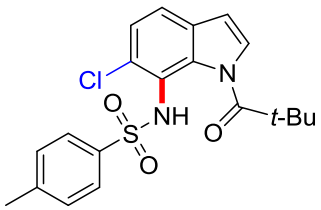
The product was prepared according to the general procedure L. Yield: 80%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.15; **^{1}H NMR (500 MHz, CD_2Cl_2)** δ 9.43 (brs, 1H), 7.64 (d, *J* = 1.9 Hz, 1H), 7.57 (d, *J* = 3.9 Hz, 1H), 7.52 (d, *J* = 1.9 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 2H), 6.55 (d, *J* = 3.9 Hz, 1H), 2.30 (s, 3H), 1.36 (s, 9H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 180.21, 144.42, 137.36, 134.31, 130.07, 128.64, 128.58, 127.15, 126.78, 124.75,

121.61, 118.27, 109.03, 42.22, 29.18, 21.66 ppm; **FT-IR:** ṽ = 2975, 2361, 2342, 1670, 1448, 1330, 1295, 1122, 1092 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{20}H_{22}{}^{79}BrN_2O_3S$: 449.05290, found: 449.05215; **HRMS:** calc. for $[M+H]^+$ $C_{20}H_{22}{}^{81}BrN_2O_3S$: 451.05086; found: 451.05115.



***N*-(6-Methoxy-1-pivaloyl-1*H*-indol-7-yl)-4-methylbenzenesulfonamide (88r):**

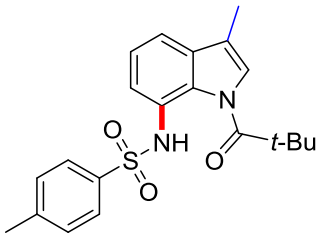
The product was prepared according to the general procedure L. Yield: 78%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.2; **^{1}H NMR (500 MHz, CD_2Cl_2)** δ 7.55 (d, *J* = 3.8 Hz, 1H), 7.49 (d, *J* = 8.2 Hz, 2H), 7.45 – 7.43 (m, 2H), 7.21 (d, *J* = 8.2 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 1H), 6.57 (d, *J* = 3.8 Hz, 1H), 3.50 (s, 3H), 2.38 (s, 3H), 1.47 (s, 9H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 179.64, 154.34, 143.73, 138.54, 133.99, 129.53, 127.57, 126.69, 126.38, 120.41, 114.00, 109.95, 108.05, 56.69, 42.13, 29.12, 21.70 ppm; **FT-IR:** ṽ = 2972, 2360, 2342, 1715, 1671, 1492, 1403, 1303, 1156 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{21}H_{25}N_2O_4S$: 401.15295, found: 401.15308.



***N*-(6-Chloro-1-pivaloyl-1*H*-indol-7-yl)-4-methylbenzenesulfonamide (88s):**

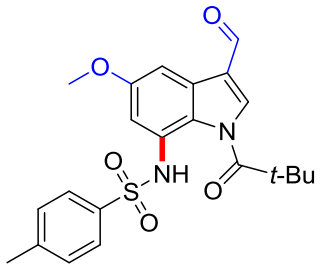
The product was prepared according to the general procedure L. Yield: 34%; Brown amorphous solid; TLC (6% EtOAc in petroleum ether): R_f = 0.2; **^{1}H NMR (500 MHz, CD_2Cl_2)** δ 7.70 (brs, 1H), 7.65 (d, *J* = 3.8 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 8.3 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 1H), 7.24 (d, *J* = 8.2 Hz, 2H), 6.65 (d, *J* = 3.8 Hz, 1H), 2.40 (s, 3H), 1.46 (s, 9H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 179.98, 144.57,

137.91, 134.53, 131.94, 131.80, 129.99, 128.23, 127.82, 126.64, 121.98, 121.38, 108.29, 42.22, 29.09, 21.80 ppm; **FT-IR:** $\tilde{\nu}$ = 3238, 2975, 2360, 2342, 1715, 1464, 1333, 1296, 1165 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{20}H_{22}{}^{35}ClN_2O_3S$: 405.10342, found: 405.10345; **HRMS:** calc. for $[M+H]^+$ $C_{20}H_{22}{}^{37}ClN_2O_3S$: 407.10047, found: 407.10040.



4-Methyl-*N*-(3-methyl-1-pivaloyl-1*H*-indol-7-yl)benzenesulfonamide (88t):

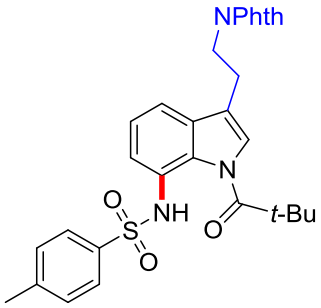
The product was prepared according to the general procedure L. Yield: 79%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (600 MHz, CD_2Cl_2)** δ 9.56 (brs, 1H), 7.52 – 7.50 (m, 1H), 7.36 – 7.31 (m, 5H), 7.10 (d, *J* = 8.0 Hz, 2H), 2.29 (s, 3H), 2.21 (d, *J* = 1.2 Hz, 3H), 1.36 (s, 9H) ppm; **^{13}C NMR (151 MHz, CD_2Cl_2)** δ 179.70, 144.03, 137.79, 133.99, 129.97, 129.93, 127.17, 125.77, 125.36, 124.23, 122.66, 118.75, 117.04, 41.99, 29.23, 21.65, 9.93 ppm; **FT-IR:** $\tilde{\nu}$ = 2976, 2919, 2360, 2342, 1662, 1321, 1258, 1119 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{21}H_{25}N_2O_3S$: 385.15804, found: 385.15888.



***N*-(3-Formyl-5-methoxy-1-pivaloyl-1*H*-indol-7-yl)-4-methylbenzenesulfonamide (88u):**

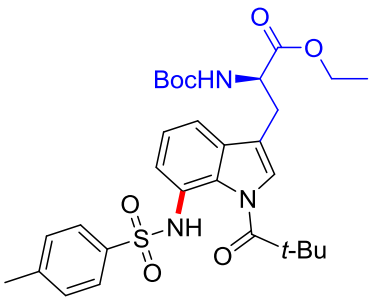
The product was prepared according to the general procedure L. Yield: 75%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.2; **^{1}H NMR (500 MHz, CD_2Cl_2)** δ 10.00 (s, 1H), 9.02 (brs, 1H), 8.38 (s, 1H), 8.25 (d, *J* = 9.2 Hz, 1H),

7.58 (d, *J* = 8.3 Hz, 2H), 7.23 (d, *J* = 8.3 Hz, 2H), 6.98 (d, *J* = 9.2 Hz, 1H), 3.45 (s, 3H), 2.39 (s, 3H), 1.53 (s, 9H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 187.17, 177.46, 151.23, 143.70, 138.54, 138.15, 133.62, 129.36, 127.58, 122.79, 122.12, 119.67, 115.88, 112.43, 56.38, 42.19, 28.90, 21.75 ppm; **FT-IR:** ṽ = 3166, 2927, 2360, 2342, 1702, 1654, 1538, 1499, 1266 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{22}H_{25}N_2O_5S$: 429.14787, found: 429.14907.



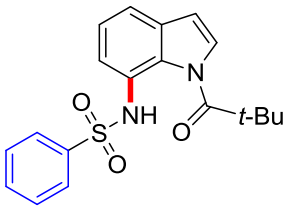
***N*-(3-(2-(1,3-Dioxoisoindolin-2-yl)ethyl)-1-pivaloyl-1*H*-indol-7-yl)-4-methylbenzenesulfonamide (88v):**

The product was prepared according to the general procedure L. Yield: 90%; Brown liquid; TLC (25% EtOAc in petroleum ether): R_f = 0.15; **^{1}H NMR (500 MHz, CD_2Cl_2)** δ 9.40 (brs, 1H), 7.81 – 7.80 (m, 2H), 7.73 – 7.72 (m, 2H), 7.49 (td, *J* = 7.9, 0.9 Hz, 2H), 7.40 (s, 1H), 7.36 – 7.32 (m, 3H), 7.09 (d, *J* = 8.0 Hz, 2H), 3.98 (t, *J* = 7.2 Hz, 2H), 3.06 (t, *J* = 7.2 Hz, 2H), 2.27 (s, 3H), 1.29 (s, 9H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 179.85, 168.62, 144.01, 137.72, 134.62, 132.87, 132.46, 130.03, 129.93, 127.09, 125.77, 125.49, 124.52, 123.60, 123.01, 119.33, 117.04, 41.96, 37.41, 29.06, 24.29, 21.63 ppm; **FT-IR:** ṽ = 3727, 2918, 2850, 2360, 2342, 1709, 1669, 1346, 1163 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{30}H_{30}N_3O_5S$: 544.19007, found: 544.19064.



Ethyl(R)-2-((*tert*-butoxycarbonyl)amino)-3-(7-((4-methylphenyl)sulfonamido)-1-pivaloyl-1*H*-indol-3-yl)propanoate (88w):

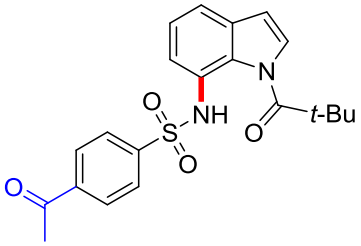
The product was prepared according to the general procedure L. Yield: 80%; Brown amorphous solid; TLC (25% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (500 MHz, CD_2Cl_2)** δ 9.39 (brs, 1H), 7.51 (dd, *J* = 6.4, 2.4 Hz, 1H), 7.38 (s, 1H), 7.36 – 7.31 (m, 4H), 7.11 (d, *J* = 8.1 Hz, 2H), 5.11 – 5.09 (brs, 1H), 4.62 – 4.58 (m, 1H), 4.16 – 4.06 (m, 2H), 3.22 (dd, *J* = 13.0, 5.9 Hz, 1H), 3.08 (dd, *J* = 13.0, 5.9 Hz, 1H), 2.30 (s, 3H), 1.40 (s, 9H), 1.35 (s, 9H), 1.23 – 1.20 (m, 3H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 179.78, 172.05, 155.42, 144.11, 137.61, 133.16, 129.96, 129.83, 127.11, 125.81, 125.46, 125.35, 122.97, 117.68, 117.03, 80.37, 62.21, 42.06, 29.57, 29.22, 28.55, 27.88, 21.65, 14.43 ppm; **FT-IR:** ṽ = 2977, 2360, 2342, 1711, 1670, 1601, 1495, 1347, 1160 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{30}H_{40}N_3O_7S$: 586.25815, found: 586.25979; $[\alpha]_D^{RT}$ = 29.8 ($CHCl_3$, *c* = 1).



***N*-(1-pivaloyl-1*H*-indol-7-yl)benzenesulfonamide (88z):**

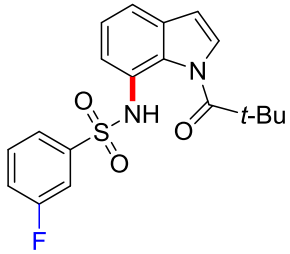
The product was prepared according to the general procedure L. Yield: 86%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (400 MHz, CD_2Cl_2)** δ 9.38 (brs, 1H), 7.55 (d, *J* = 4.0 Hz, 1H), 7.52 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.49 – 7.44 (m, 3H), 7.43 – 7.40 (m, 1H), 7.34 – 7.28 (m, 3H), 6.60 (d, *J* = 4.0 Hz, 1H), 1.38 (s, 9H) ppm; **^{13}C NMR (101 MHz, CD_2Cl_2)** δ 180.26, 140.72, 133.13,

133.04, 129.83, 129.38, 127.48, 127.17, 125.67, 125.62, 122.84, 119.41, 109.79, 42.23, 29.37 ppm; **FT-IR:** ṽ = 3118, 2360, 2342, 1663, 1580, 1363, 1326, 1174, 1163 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{19}H_{21}N_2O_3S$: 357.12674, found: 357.12782.



4-Acetyl-*N*-(1-pivaloyl-1*H*-indol-7-yl)benzenesulfonamide (88aa):

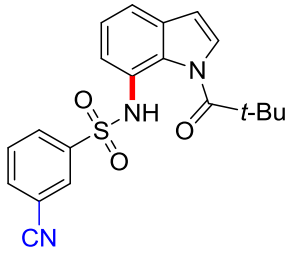
The product was prepared according to the general procedure L. Yield: 77%; Brown amorphous solid; TLC (25% EtOAc in petroleum ether): R_f = 0.15; **^{1}H NMR (500 MHz, CD_2Cl_2)** δ 9.58 (brs, 1H), 7.84 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 3.7 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 1H), 6.61 (d, *J* = 3.7 Hz, 1H), 2.52 (s, 3H), 1.36 (s, 9H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 197.03, 180.24, 144.26, 140.43, 133.06, 129.61, 129.06, 127.52, 127.50, 125.76, 125.11, 122.54, 119.59, 109.91, 42.17, 29.27, 27.20 ppm; **FT-IR:** ṽ = 2925, 2360, 2342, 1686, 1667, 1321, 1230, 1180, 1164 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{21}H_{23}N_2O_4S$: 399.13730, found: 399.13777.



3-Fluoro-*N*-(1-pivaloyl-1*H*-indol-7-yl)benzenesulfonamide (88ab):

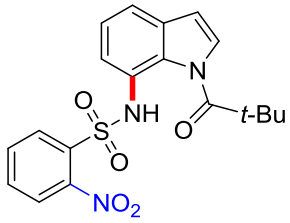
The product was prepared according to the general procedure L. Yield: 88%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (400 MHz, CD_2Cl_2)** δ 9.53 (brs, 1H), 7.58 (d, *J* = 4.0 Hz, 1H), 7.52 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.43 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.35 – 7.22 (m, 4H), 7.17 – 7.13 (m, 1H), 6.62 (d, *J* = 4.0 Hz, 1H), 1.40 (s, 9H) ppm; **^{13}C NMR (101 MHz, CD_2Cl_2)** δ 180.33, 162.69 (d,

J = 250.7 Hz), 142.66 (d, *J* = 6.8 Hz), 133.13, 131.23 (d, *J* = 7.8 Hz), 129.83, 127.57, 125.80, 125.24, 123.15 (d, *J* = 3.3 Hz), 122.83, 120.28 (d, *J* = 21.2 Hz), 119.69, 114.53 (d, *J* = 24.4 Hz), 109.94, 42.26, 29.35 ppm ; **^{19}F NMR (377 MHz, CD_2Cl_2)** δ -110.71 (td, *J* = 8.3, 5.0 Hz) ppm; **FT-IR:** ṽ = 2980, 2360, 2342, 1656, 1364, 1328, 1163, 1081 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{19}H_{20}FN_2O_3S$: 375.11732, found: 375.11799.



3-Cyano-*N*-(1-pivaloyl-1*H*-indol-7-yl)benzenesulfonamide (88ac):

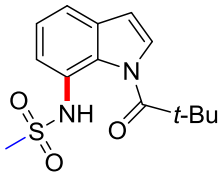
The product was prepared according to the general procedure L. Yield: 52%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (500 MHz, CD_2Cl_2)** δ 9.71 (brs, 1H), 7.78 (s, 1H), 7.73 – 7.70 (m, 2H), 7.59 (d, *J* = 3.9 Hz, 1H), 7.50 – 7.44 (m, 3H), 7.34 (t, *J* = 7.8 Hz, 1H), 6.64 (d, *J* = 3.9 Hz, 1H), 1.40 (s, 9H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 180.31, 141.95, 136.31, 133.17, 131.18, 130.83, 130.45, 129.61, 127.63, 125.94, 124.80, 122.45, 119.86, 117.44, 113.85, 110.09, 42.24, 29.34 ppm; **FT-IR:** ṽ = 2976, 2360, 2342, 2234, 1666, 1587, 1333, 1302, 1179, 1158 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{20}H_{20}N_3O_3S$: 382.12199, found: 382.12259.



2-Nitro-*N*-(1-pivaloyl-1*H*-indol-7-yl)benzenesulfonamide (88ad):

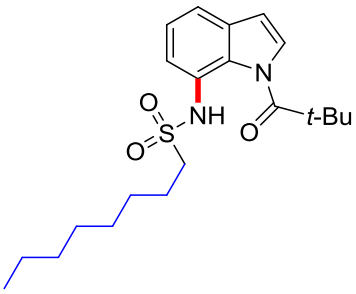
The product was prepared according to the general procedure L. Yield: 93%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (400**

MHz, CD_2Cl_2) δ 9.49 (brs, 1H), 7.77 – 7.75 (m, 1H), 7.68 (d, *J* = 3.9 Hz, 1H), 7.67 – 7.56 (m, 3H), 7.52 – 7.47 (m, 1H), 7.39 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 6.62 (d, *J* = 3.9 Hz, 1H), 1.50 (s, 9H) ppm; **^{13}C NMR (151 MHz, CD_2Cl_2)** δ 180.39, 148.39, 134.37, 133.28, 133.26, 132.52, 131.86, 129.20, 127.91, 125.62, 125.08, 125.04, 120.15, 119.15, 109.65, 42.25, 29.27 ppm; **FT-IR:** ṽ = 3101, 2987, 2360, 2342, 1685, 1672, 1588, 1365, 1127 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{19}H_{20}N_3O_5S$: 402.11182, found: 402.11254.



***N*-(1-Pivaloyl-1*H*-indol-7-yl)methanesulfonamide (88ae):**

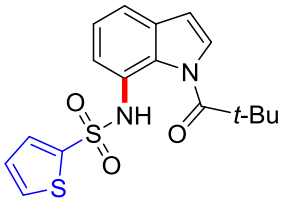
The product was prepared according to the general procedure L. Yield: 94%; Brown liquid; TLC (20% EtOAc in petroleum ether): R_f = 0.2; **^{1}H NMR (500 MHz, CD_2Cl_2)** δ 9.13 (brs, 1H), 7.79 (d, *J* = 3.9 Hz, 1H), 7.49 – 7.44 (m, 2H), 7.34 (t, *J* = 7.8 Hz, 1H), 6.73 (d, *J* = 3.9 Hz, 1H), 2.87 (s, 3H), 1.55 (s, 9H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 180.72, 133.37, 129.23, 127.77, 126.10, 125.77, 120.71, 119.00, 109.89, 42.53, 40.10, 29.46 ppm; **FT-IR:** ṽ = 3188, 2977, 2935, 2360, 2341, 1669, 1590, 1316, 1230, 1179, 1152 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{14}H_{19}N_2O_3S$: 295.11109, found: 295.11191.



***N*-(1-Pivaloyl-1*H*-indol-7-yl)octane-1-sulfonamide (88af):**

The product was prepared according to the general procedure L. Yield: 80%; Brown liquid; TLC (12% EtOAc in petroleum ether): R_f = 0.2; **^{1}H NMR (500 MHz, CD_2Cl_2)**

δ 9.05 (brs, 1H), 7.78 (d, *J* = 3.9 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 6.71 (d, *J* = 3.9 Hz, 1H), 2.97 – 2.94 (m, 2H), 1.73 – 1.67 (m, 2H), 1.56 (s, 9H), 1.33 – 1.17 (m, 10H), 0.85 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 180.79, 133.39, 129.06, 127.71, 126.43, 125.81, 119.92, 118.63, 109.95, 52.37, 42.57, 32.23, 29.54, 29.44, 29.41, 28.65, 23.95, 23.11, 14.37 ppm; **FT-IR:** ṽ = 3190, 2926, 2856, 2360, 2342, 1671, 1318, 1301, 1179, 1146 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{21}H_{33}N_2O_3S$: 393.22064, found: 393.22175.



***N*-(1-Pivaloyl-1*H*-indol-7-yl)thiophene-2-sulfonamide (88ah):**

The product was prepared according to the general procedure L. Yield: 83%; Brown amorphous solid; TLC (33% EtOAc in petroleum ether): R_f = 0.3; **^{1}H NMR (500 MHz, CD_2Cl_2)** δ 9.56 (brs, 1H), 7.60 (d, *J* = 3.9 Hz, 1H), 7.56 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.45 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.42 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.17 (dd, *J* = 5.0, 1.3 Hz, 1H), 6.89 – 6.87 (m, 1H), 6.64 (d, *J* = 3.9 Hz, 1H), 1.41 (s, 9H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 180.24, 140.92, 133.02, 132.50, 132.21, 129.92, 127.72, 127.55, 125.67, 125.16, 123.27, 119.75, 109.84, 42.20, 29.33 ppm; **FT-IR:** ṽ = 3094, 2360, 2342, 1662, 1328, 1300, 1180, 1157, 1013 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{17}H_{19}N_2O_3S_2$: 363.08316, found: 363.08379.

5.3.5 Synthesis of Bioactive Compounds 88ak, 88al

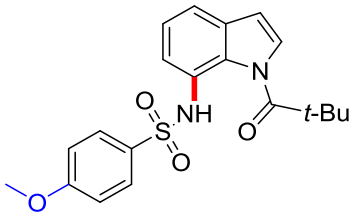
General Procedure M for the Synthesis of Compounds **88ak, 88al**:

First Step:

N-Pivaloyl indole (0.1 mmol) was dissolved in a 12 mL screw-capped tube with 1 mL of DCE. Then sulfonyl azide (0.22 mmol) followed by $[(IrCp^*Cl_2)_2]$ (4 mol %), $AgNTf_2$ (16 mol %) and LiOAc (40 mol%) were added to the reaction mixture at room temperature. The reaction mixture was allowed to warm up to 120 °C and stirred for 1-12 h. After the reaction finished, the reaction mixture was directly loaded

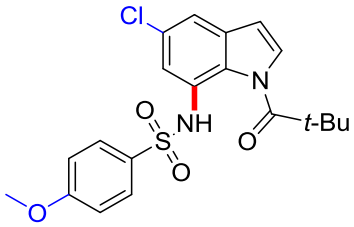
in silica gel column and purified with petroleum ether (40-60°C)/EtOAc mixture.

Characterization of Compounds **88ai, 88aj:**



4-Methoxy-*N*-(1-pivaloyl-1*H*-indol-7-yl)benzenesulfonamide (88ai):

The product was prepared according to the general procedure M. Yield: 96%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (400 MHz, CD_2Cl_2)** δ 9.31 (brs, 1H), 7.58 (d, *J* = 4.0 Hz, 1H), 7.50 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.43 – 7.39 (m, 3H), 7.31 (t, *J* = 7.7 Hz, 1H), 6.78 – 6.76 (m, 2H), 6.61 (d, *J* = 4.0 Hz, 1H), 3.75 (s, 3H), 1.41 (s, 9H) ppm; **^{13}C NMR (101 MHz, CD_2Cl_2)** δ 180.23, 163.44, 133.03, 132.36, 129.80, 129.34, 127.49, 125.91, 125.62, 122.68, 119.21, 114.49, 109.79, 56.13, 42.25, 29.40 ppm; **FT-IR:** ṽ = 3141, 2969, 2360, 2342, 1672, 1597, 1331, 1305, 1261, 1162 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{20}H_{23}N_2O_4S$: 387.13730, found: 387.13848.



***N*-(5-Chloro-1-pivaloyl-1*H*-indol-7-yl)-4-methoxybenzenesulfonamide (88aj):**

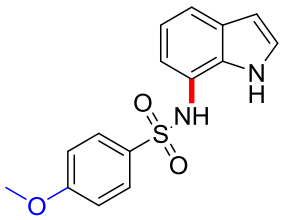
The product was prepared according to the general procedure M. Yield: 77%; Brown amorphous solid; TLC (25% EtOAc in petroleum ether): R_f = 0.15; **^{1}H NMR (500 MHz, CD_2Cl_2)** δ 9.47 (brs, 1H), 7.62 (d, *J* = 3.9 Hz, 1H), 7.50 – 7.48 (m, 3H), 7.35 (d, *J* = 2.0 Hz, 1H), 6.80 (d, *J* = 8.9 Hz, 2H), 6.56 (d, *J* = 3.9 Hz, 1H), 3.76 (s, 3H), 1.40 (s, 9H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 180.27, 163.63, 133.99, 131.97, 130.87, 129.41, 128.83, 128.13, 126.89, 121.70, 118.37, 114.62, 109.24, 56.17, 42.33, 29.35

ppm; **FT-IR:** ṽ = 2932, 2360, 2342, 1667, 1582, 1501, 1328, 1303, 1266 1095 cm^{-1}; HRMS: calc. for $[M+H]^+$ $C_{20}H_{22}{}^{35}ClN_2O_4S$: 421.09833, found: 421.09866; **HRMS:** calc. for $[M+H]^+$ $C_{20}H_{22}{}^{37}ClN_2O_4S$: 423.09538, found:423.09548.

Second Step:

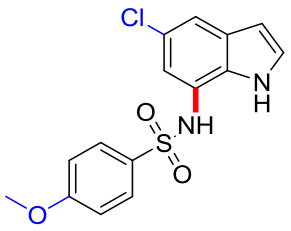
To a solution of **88ai** or **88aj** (0.1 mmol) in MeOH (1.0 mL) was added Et_3N (0.2 mL) dropwise at room temperature. Then the reaction was stirred for 24 h and quenched by addition of saturated NH_4Cl solution. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. Combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The residue was then purified by flash chromatography over silica gel with petroleum ether and ethyl acetate to give the corresponding product **88ak, 88al.**

Characterization of Compounds **88ak, 88al:**



***N*-(1*H*-indol-7-yl)-4-methoxybenzenesulfonamide (88ak):**

The product was prepared according to the general procedure M. Yield: 90%; Brown amorphous solid; TLC (25% EtOAc in petroleum ether): R_f = 0.2; **^{1}H NMR (500 MHz, CD_2Cl_2)** δ 9.32 (brs, 1H), 7.59 – 7.56 (m, 2H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.30 – 7.29 (m, 1H), 6.88 – 6.84 (m, 3H), 6.55 – 6.54 (m, 1H), 6.44 (dd, *J* = 7.5, 0.5 Hz, 1H), 3.81 (s, 3H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 163.93, 132.48, 130.68, 130.06, 130.00, 125.82, 120.80, 120.25, 120.14, 118.60, 114.66, 103.08, 56.20 ppm; **FT-IR:** ṽ = 3394, 3239, 2925, 2360, 2342, 1593, 1496, 1323, 1304, 1186 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{15}H_{15}N_2O_3S$: 303.07979, found: 303.08038.



***N*-(5-Chloro-1*H*-indol-7-yl)-4-methoxybenzenesulfonamide (88al):**

The product was prepared according to the general procedure M. Yield: 92%; Brown amorphous solid; TLC (25% EtOAc in petroleum ether): R_f = 0.2; **^{1}H NMR (500 MHz, CD_2Cl_2)** δ 9.47 (brs, 1H), 7.64 – 7.61 (m, 2H), 7.44 (d, *J* = 1.8 Hz, 1H), 7.30 (d, *J* = 2.3 Hz, 1H), 6.90 – 6.87 (m, 2H), 6.55 (d, *J* = 1.8 Hz, 1H), 6.49 (d, *J* = 2.3 Hz, 1H), 3.81 (s, 3H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 164.13, 131.24, 130.56, 130.03, 129.73, 127.23, 125.02, 121.82, 119.21, 117.91, 114.85, 102.88, 56.25 ppm; **FT-IR:** ṽ = 3400, 3244, 3196, 2928, 2838, 2360, 2342, 1302, 1262, 1120 cm^{-1}; **HRMS:** calc. for $[M+H]^+$ $C_{15}H_{14}{}^{35}ClN_2O_3S$: 337.04082, found: 337.04158; **HRMS:** calc. for $[M+H]^+$ $C_{15}H_{14}{}^{37}ClN_2O_3S$: 339.03787, found: 339.03839.

5.3.6 Deuterium Labeling Experiments

N-Pivaloyl indole **86f** (0.1 mmol) was dissolved in a 12 mL screw-capped tube with 1 mL of DCE, followed by $[(IrCp^*Cl_2)_2]$ (4 mol %), $AgNTf_2$ (16 mol %), LiOAc (40 mol%) and D_2O (2 equiv) were added to the reaction mixture at room temperature. The reaction mixture was allowed to warm up to 120 °C and stirred for 1h. After the reaction finished, the reaction mixture was directly loaded in silica gel column and purified with petroleum ether (40-60°C)/EtOAc mixture to afford the recovered starting material **86z** in 92% yield. An analysis by ^{1}H NMR showed 35% deuterium incorporation at the C-7 position of **86z**.

N-pivaloyl indole **86f** (0.1 mmol) and TsN_3 **87a** (0.22 mmol) were dissolved in a 12 mL screw-capped tube with 1 mL of DCE, followed by $[(IrCp^*Cl_2)_2]$ (4 mol %), $AgNTf_2$ (16 mol %), LiOAc (40 mol%) and D_2O (2 equiv) were added to the reaction mixture at room temperature. The reaction mixture was allowed to warm up to 120 °C and stirred for 1h. After the reaction finished, the reaction mixture was directly loaded in silica gel column and purified with petroleum ether (40-60°C)/EtOAc mixture to

afford the product **88am** in 76% yield. An analysis by ^{1}H NMR showed no deuterium incorporation on the ring of **88am**.

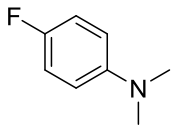
5.4 Experimental Part for 3.2.1

5.4.1 Synthesis of Substituted *N*, *N*-Dimethylanilines 89

General Procedure O for the Synthesis of Compounds **89d, 89f, 89i, 89j, 89l–89q:**[136]

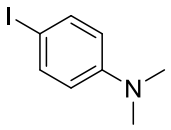
Alkyliodide (4.4 mmol) was added dropwise to a stirred suspension of aniline (2 mmol) and potassium carbonate (6 mmol) in 3 mL *N*,*N*-dimethylformamide (DMF) under argon. The reaction mixture was stirred at 23 °C for 18 h, then it was filtered and diluted with water. The resultant solution was extracted three times with diethyl ether. The combined organic phase was washed three times with water. Then it was washed with saturated aqueous sodium chloride solution, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography over silica gel.

Characterization of Compounds **89d, 89f, 89i, 89j, 89l–89q:**



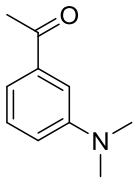
4-Fluoro-*N*,*N*-dimethylaniline (89d):[136]

The product was prepared according to the general procedure O. Yield: 45%; Colourless liquid; TLC (0.5% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 6.97 – 6.94 (m, 2H), 6.70 – 6.68 (m, 2H), 2.91 (s, 6H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 155.76 (d, *J* = 235.2 Hz), 147.67 (d, *J* = 1.8 Hz), 115.50 (d, *J* = 22.0 Hz), 114.09 (d, *J* = 7.3 Hz), 41.51 ppm.



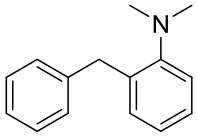
4-Iodo-*N*,*N*-dimethylaniline (88f):

The product was prepared according to the general procedure O. Yield: 41%; Colourless liquid; TLC (0.5% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.48 (d, *J* = 8.8 Hz, 2H), 6.52 (d, *J* = 7.3 Hz, 2H), 2.93 (s, 6H).



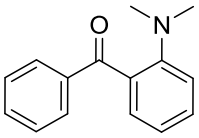
1-(3-(Dimethylamino)phenyl)ethan-1-one (89i):

The product was prepared according to the general procedure O. Yield: 55%; White amorphous solid; TLC (0.5% EtOAc in petroleum ether): R_f = 0.2; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.34 – 7.25 (m, 3H), 6.93 (d, *J* = 6.7 Hz, 1H), 2.99 (s, 6H), 2.58 (s, 3H).



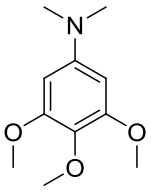
2-Benzyl-*N*,*N*-dimethylaniline (89j):[137]

The product was prepared according to the general procedure O. Yield: 38%; Colourless liquid; TLC (0.5% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.31 – 7.28 (m, 2H), 7.23 – 7.16 (m, 5H), 7.06 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.02 – 6.98 (m, 1H), 4.14 (s, 2H), 2.70 (s, 6H) ppm**; ^{13}C NMR (126 MHz, $CDCl_3$)** δ 152.96, 141.86, 136.03, 131.00, 129.27, 128.40, 127.04, 125.86, 123.47, 119.65, 45.28, 36.73 ppm.



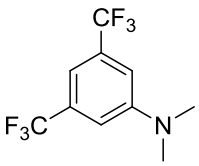
(2-(Dimethylamino)phenyl)(phenyl)methanone (89l):[138]

The product was prepared according to the general procedure O. Yield: 40%; Yellow amorphous solid; TLC (5% EtOAc in petroleum ether): R_f = 0.4; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.84 – 7.82 (m, 2H), 7.56 – 7.52 (m, 1H), 7.43 – 7.38 (m, 3H), 7.32 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 1H), 6.90 (t, *J* = 7.4 Hz, 1H), 2.70 (s, 6H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 198.30, 151.77, 137.87, 132.78, 131.57, 130.84, 130.07, 129.32, 128.24, 119.03, 116.63, 43.58 ppm.



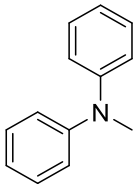
3,4,5-Trimethoxy-*N*,*N*-dimethylaniline (89m):[139]

The product was prepared according to the general procedure O. Yield: 60%; Colourless liquid; TLC (0.5% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 5.96 (s, 2H), 3.86 (s, 6H), 3.77 (s, 3H), 2.92 (s, 6H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 153.76, 147.81, 130.11, 91.09, 61.14, 56.12, 41.25 ppm.



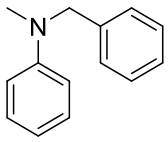
***N*,*N*-Dimethyl-3,5-bis(trifluoromethyl)aniline (89n):**

The product was prepared according to the general procedure O. Yield: 40%; Colourless liquid; TLC (0.5% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (200 MHz, $CDCl_3$)** δ 7.17 (s, 1H), 7.04 (s, 2H), 3.06 (s, 6H).



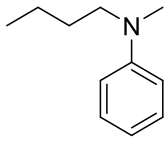
***N*-Methyl-*N*-phenylaniline (89o):[105]**

The product was prepared according to the general procedure O. Yield: 45%; Colourless liquid; TLC (0.5% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (200 MHz, $CDCl_3$)** δ 7.32 – 7.23 (m, 4H), 7.06 – 6.92 (m, 6H), 3.32 (s, 3H) ppm**; ^{13}C NMR (126 MHz, $CDCl_3$)** δ 149.17, 129.32, 121.41, 120.59, 40.38 ppm.



***N*-Benzyl-*N*-methylaniline (89p):[65]**

The product was prepared according to the general procedure O. Yield: 44%; Yellow liquid; TLC (0.5% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.34 – 7.31 (m, 2H), 7.27 – 7.22 (m, 5H), 6.78 (d, *J* = 8.2 Hz, 2H), 6.73 (t, *J* = 7.2 Hz, 1H), 4.55 (s, 2H), 3.03 (s, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 149.7, 139.0, 129.31, 128.69, 127.01, 126.91, 116.70, 112.54 , 56.82, 38.67 ppm.



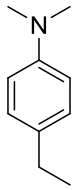
***N*-Butyl-*N*-methylaniline (89q):[140]**

The product was prepared according to the general procedure O. Yield: 42%; Colourless liquid; TLC (0.5% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.25 – 7.22 (m, 2H), 6.72 – 6.67 (m, 3H), 3.33 – 3.30 (m, 2H), 2.93 (s, 3H), 1.57 (dt, *J* = 12.4, 7.5 Hz, 2H), 1.36 (dq, *J* = 14.7, 7.5 Hz, 2H), 0.96 (t, *J* = 7.5 Hz, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 149.56, 129.26, 115.93, 112.24, 52.69, 38.42, 29.00, 20.52, 14.16 ppm.

General Procedures P for the Synthesis of Compounds **89c, 89g, 89h, 89k:**[141]

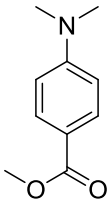
To a solution of anilines (1.5 mmol) in glacial acetic acid (5 mL) under inert atmosphere was added paraformaldehyde (15 mmol) and sodium cyanoborohydride (7.5 mmol). The addition of sodium cyanoborohydride resulted in bubbling. After stirring overnight, the reaction mixture was poured into a water/ice mixture (10 mL) containing NaOH (4 g). The addition was exothermic, and more ice was added to bring the total volume of the quench mixture to 30 mL. The mixture, which had pH 14, was extracted with dichloromethane. The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was then purified by flash chromatography over silica gel.

Characterization of Compounds **89c, 89g, 89h, 89k:**



4-Ethyl-*N*,*N*-dimethylaniline (89c):[104]

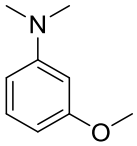
The product was prepared according to the general procedure P. Yield: 37%; Colourless liquid; TLC (0.5% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.14 – 7.12 (m, 2H), 6.77 – 6.74 (m, 2H), 2.95 (s, 6H), 2.61 (q, *J* = 7.6 Hz, 2H), 1.25 (t, *J* = 7.6 Hz, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 149.12, 132.81, 128.53, 113.29, 41.14, 27.95, 16.06 ppm.



Methyl 4-(dimethylamino)benzoate (89g):[142]

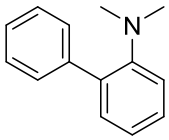
The product was prepared according to the general procedure P. Yield: 65%; White

amorphous solid; TLC (0.5% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.91 (d, *J* = 9.1 Hz, 2H), 6.67 (d, *J* = 9.1 Hz, 2H), 3.86 (s, 3H), 3.04 (s, 6H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 167.60, 153.39, 131.38, 117.21, 110.89, 51.61, 40.21 ppm.



3-Methoxy-*N*,*N*-dimethylaniline (89h):[136]

The product was prepared according to the general procedure P. Yield: 38%; Colourless liquid; TLC (0.5% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.16 (t, *J* = 8.3 Hz, 1H), 6.40 – 6.30 (m, 3H), 3.81 (s, 3H), 2.95 (s, 6H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 160.83, 152.09, 129.89, 105.98, 101.68, 99.40, 55.27, 40.82 ppm.



***N*,*N*-Dimethyl-[1,1'-biphenyl]-2-amine (89k):[143]**

The product was prepared according to the general procedure P. Yield: 43%; Colourless liquid; TLC (0.5% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.58 (d, *J* = 7.3 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.32 – 7.22 (m, 3H), 7.06 – 6.99 (m, 2H), 2.55 (s, 6H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 151.39, 142.15, 134.29, 131.84, 128.80, 128.42, 128.18, 126.59, 121.57, 117.70, 43.48 ppm.

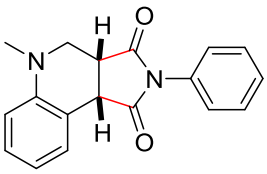
5.4.2 Synthesis of Pyrrolo[3,4-*c*]quinolone Derivatives 91a–91ab

General Procedure Q for the Synthesis of Compounds **91a–91ab**:

To a screw-capped vial maleimides (0.1 mmol, 1 equiv), tertiary anilines (0.2 mmol, 2 equiv), tetrabutyl ammonium iodides 3.69 mg (TBAI, 10 mol%), TBHP 55 µL (70% in H_2O, 0.4 mmol, 4 equiv) and DCE (1.0 mL) were added. The reaction mixture was

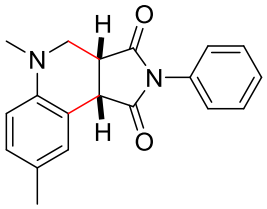
heated to 70 °C. The progress of the reaction was monitored by thin layer chromatography (ethyl acetate/petroleum ether mixture) and GC-MS. Upon completion, the crude reaction mixture was concentrated under vacuum and subsequently purified by flash column chromatography over silica gel using petroleum ether/ethyl acetate as an eluent system.

Characterization of Compounds **91a–91ab:**



(3a*R,9b*S**)-5-Methyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91a)**

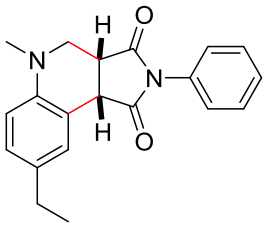
The product was prepared according to the general procedure Q. Yield: 91%; Light yellow amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.55 – 7.53 (m, 1H), 7.46 – 7.41 (m, 2H), 7.38 – 7.34 (m, 1H), 7.29 – 7.23 (m, 3H), 6.92 (ddd, *J* = 7.5, 7.5, 1.1 Hz, 1H), 6.76 – 6.75 (m, 1H), 4.17 (d, *J* = 9.6 Hz, 1H), 3.62 (dd, *J* = 11.5, 2.8 Hz, 1H), 3.54 (ddd, *J* = 9.6, 4.4, 2.8 Hz, 1H), 3.13 (dd, *J* = 11.5, 4.4 Hz, 1H), 2.85 (s, 3H) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 177.80, 175.88, 148.63, 132.15, 130.47, 129.12, 128.82, 128.63, 126.49, 119.79, 118.67, 112.66, 50.81, 43.72, 42.28, 39.56 ppm; **FT-IR**: ṽ = 1708, 1598, 1497, 1392, 1197, 1180 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{18}H_{17}O_2N_2$: 293.12845, found: 293.12911.



(3a*R,9b*S**)-5,8-Dimethyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quino**

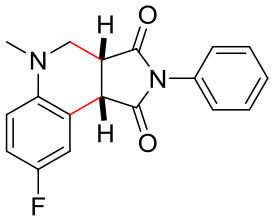
line-1,3(2*H*)-dione (91b)

The product was prepared according to the general procedure Q. Yield: 94%; Light brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.45 – 7.32 (m, 4H), 7.28 – 7.25 (m, 2H), 7.03 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.65 (d, *J* = 8.3 Hz, 1H), 4.11 (d, *J* = 9.6 Hz, 1H), 3.58 (dd, *J* = 11.3, 2.7 Hz, 1H), 3.51 (ddd, *J* = 9.6, 4.3, 2.7 Hz, 1H), 3.05 (dd, *J* = 11.3, 4.3 Hz, 1H), 2.80 (s, 3H), 2.30 (s, 3H) ppm; **^{13}C NMR (75 MHz, $CDCl_3$)** δ 177.95, 176.00, 146.46, 132.12, 130.93, 129.36, 129.11, 128.62, 126.49, 118.63, 112.68, 51.06, 43.68, 42.29, 39.71, 20.57 ppm; **FT-IR**: ṽ = 1711, 1508, 1395, 1192, 806 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{19}H_{19}O_2N_2$: 307.14410, found: 307.14528.



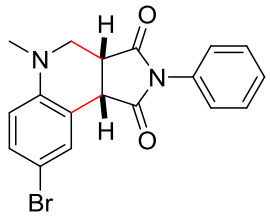
(3a*R,9b*S**)-8-Ethyl-5-methyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91c)**

The product was prepared according to the general procedure Q. Yield: 79%; Light brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.43 – 7.30 (m, 4H), 7.27 – 7.23 (m, 2H), 7.05 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.65 (d, *J* = 8.3 Hz, 1H), 4.11 (d, *J* = 9.5 Hz, 1H), 3.56 (dd, *J* = 11.3, 2.7 Hz, 1H), 3.52 – 3.46 (m, 1H), 3.05 (dd, *J* = 11.3, 4.3 Hz, 1H), 2.79 (s, 3H), 2.58 (q, *J* = 7.6 Hz, 2H), 1.20 (t, *J* = 7.6 Hz, 3H) ppm; **^{13}C NMR (75 MHz, $CDCl_3$)** δ 177.95, 175.99, 146.62, 135.59, 132.11, 129.86, 129.10, 128.60, 128.10, 126.48, 118.61, 112.65, 50.98, 43.66, 42.29, 39.69, 28.02, 15.87 ppm; **FT-IR**: ṽ = 1708, 1506, 1396, 1319, 1194, 810 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{20}H_{21}O_2N_2$: 321.15975, found: 321.16016.



(3a*R,9b*S**)-8-Fluoro-5-methyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*] quinoline-1,3(2*H*)-dione (91d)**

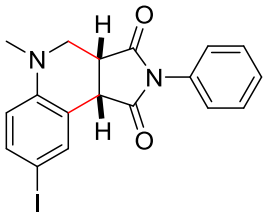
The product was prepared according to the general procedure Q. Yield: 81%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.48 – 7.45 (m, 2H), 7.41 – 7.38 (m, 1H), 7.32 – 7.29 (m, 3H), 6.99 – 6.95 (m, 1H), 6.70 (dd, *J* = 9.0, 4.6 Hz, 1H), 4.14 (d, *J* = 9.6 Hz, 1H), 3.61 (dd, *J* = 11.5, 2.8 Hz, 1H), 3.56 (ddd, *J* = 9.6, 4.3, 2.8 Hz, 1H), 3.11 (dd, *J* = 11.5, 4.3 Hz, 1H), 2.84 (s, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 177.51, 175.29, 156.81 (d, *J* = 238.8 Hz), 145.10, 132.04, 129.19, 128.75, 126.47, 120.18 (d, *J* = 7.8 Hz), 117.13 (d, *J* = 23.4 Hz), 115.23 (d, *J* = 21.9 Hz), 113.54 (d, *J* = 7.5 Hz), 51.20, 43.57, 42.37, 39.89 ppm; **FT-IR**: ṽ = 1705, 1503, 1392, 1320, 1246, 1191 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{18}H_{16}O_2N_2F$: 311.11903, found: 311.11982.



(3a*R,9b*S**)-8-Bromo-5-methyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*] quinoline-1,3(2*H*)-dione (91e)**

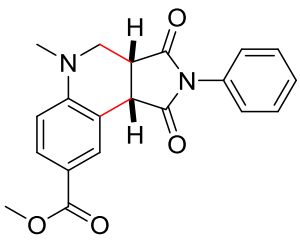
The product was prepared according to the general procedure Q. Yield: 86%; Light yellow amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.63 – 7.62 (m, 1H), 7.45 – 7.22 (m, 6H), 6.59 (d, *J* = 8.8 Hz, 1H), 4.08 (d, *J* = 9.5 Hz, 1H), 3.59 (dd, *J* = 11.5, 2.8 Hz, 1H), 3.52 (ddd, *J* = 9.5, 4.3, 2.8 Hz, 1H), 3.09 (dd, *J* = 11.5, 4.3 Hz, 1H), 2.80 (s, 3H) ppm; **^{13}C NMR (75 MHz, $CDCl_3$)** δ 177.40, 175.27, 147.61, 132.83, 131.92, 131.56, 129.18, 128.76, 126.41, 120.49, 114.36, 111.79, 50.48, 43.40, 41.89, 39.58 ppm; **FT-IR**: ṽ = 2924, 1710, 1593,

1495, 1371, 1176 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{18}H_{16}O_2N_2{}^{79}Br$: 371.03897, found: 371.04033; $C_{18}H_{16}O_2N_2{}^{81}Br$: 373.03692, found: 373.03816.



(3a*R,9b*S**)-8-Iodo-5-methyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91f)**

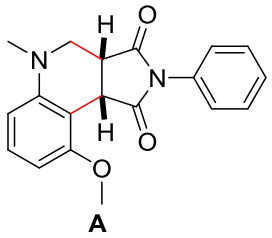
The product was prepared according to the general procedure Q. Yield: 77%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.81 – 7.80 (m, 1H), 7.49 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.46 – 7.42 (m, 2H), 7.38 – 7.35 (m, 1H), 7.28 – 7.26 (m, 2H), 6.50 (d, *J* = 8.7 Hz, 1H), 4.09 (d, *J* = 9.6 Hz, 1H), 3.60 (dd, *J* = 11.6, 2.8 Hz, 1H), 3.52 (ddd, *J* = 9.6, 4.3, 2.8 Hz, 1H), 3.12 (dd, *J* = 11.6, 4.3 Hz, 1H), 2.81 (s, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 177.29, 175.23, 148.21, 138.57, 137.51, 131.98, 129.16, 128.74, 126.41, 120.90, 114.89, 81.30, 50.37, 43.39, 41.70, 39.46 ppm; **FT-IR**: ṽ = 1709, 1493, 1369, 1319, 1177, 1101 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{18}H_{16}O_2N_2I$: 419.02510, found: 419.02558.



(3a*R,9b*S**)-Methyl 5-methyl-1,3-dioxo-2-phenyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,4-*c*]quinoline-8-carboxylate (91g)**

The product was prepared according to the general procedure Q. Yield: 45%; Yellow amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.22 (d, *J* = 1.2 Hz, 1H), 7.91 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.44 – 7.41 (m, 2H), 7.37 – 7.34 (m, 1H), 7.27 – 7.25 (m, 2H), 6.74 (d, *J* = 8.7 Hz, 1H), 4.19 (d, *J*

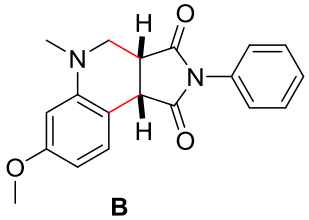
= 9.6 Hz, 1H), 3.88 (s, 3H), 3.68 (dd, *J* = 11.7, 2.9 Hz, 1H), 3.58 (ddd, *J* = 9.6, 4.3, 2.9 Hz, 1H), 3.25 (dd, *J* = 11.7, 4.3 Hz, 1H), 2.93 (s, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 177.16, 175.35, 166.98, 151.81, 132.06, 131.97, 130.84, 129.15, 128.73, 126.38, 120.98, 117.43, 112.13, 51.92, 49.83, 43.20, 41.82, 39.52 ppm; **FT-IR**: ṽ = 1706, 1607, 1498, 1374, 1275, 1177 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{20}H_{19}O_4N_2$: 351.13393, found: 351.13477.



A

(3a*R,9b*S**)-9-Methoxy-5-methyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91h)**

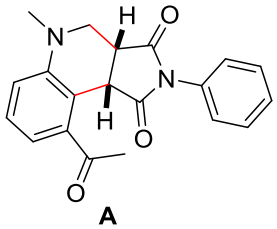
The product was prepared according to the general procedure Q. Yield: 56%; Brown amorphous solid ; TLC (20% EtOAc in petroleum ether): R_f = 0.25; [**A-major product**]-**^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.44 – 7.41 (m, 2H), 7.36 – 7.33 (m, 1H), 7.30 – 7.28 (m, 2H), 7.20 – 7.17 (m, 1H), 6.56 (d, *J* = 8.3 Hz, 1H), 6.42 (d, *J* = 8.2 Hz, 1H), 4.78 (d, *J* = 9.9 Hz, 1H), 3.91 (s, 3H), 3.56 (dd, *J* = 11.4, 1.8 Hz, 1H), 3.49 (ddd, *J* = 9.9, 4.9, 1.8 Hz, 1H), 2.98 (dd, *J* = 11.4, 4.9 Hz, 1H), 2.80 (s, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 178.64, 175.51, 158.82, 151.01, 132.38, 129.07, 129.00, 128.54, 126.61, 109.23, 105.93, 103.74, 56.36, 52.72, 44.34, 39.86, 36.82 ppm; **FT-IR**: ṽ = 1705, 1597, 1495, 1389, 1184, 1061 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{19}H_{19}O_3N_2$: 323.13902, found: 323.13990.



B

(3a*R,9b*S**)-7-Methoxy-5-methyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91h)**

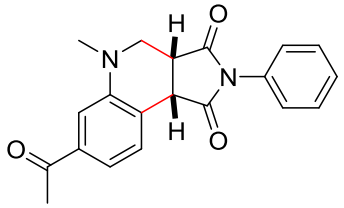
The product was prepared according to the general procedure Q. Yield: 35%; Brown amorphous solid ; TLC (25% EtOAc in petroleum ether): R_f = 0.25; [**B-minor product**]-**^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.46 – 7.41 (m, 3H), 7.37 – 7.34 (m, 1H), 7.27 – 7.26 (m, 2H), 6.48 – 6.46 (m, 1H), 6.31 (d, *J* = 2.3 Hz, 1H), 4.11 (d, *J* = 9.6 Hz, 1H), 3.80 (s, 3H), 3.61 (dd, *J* = 11.5, 2.8 Hz, 1H), 3.52 (ddd, *J* = 9.6, 4.4, 2.8 Hz, 1H), 3.14 (dd, *J* = 11.5, 4.4 Hz, 1H), 2.83 (s, 3H) ppm; **^{13}C NMR (126 MHz, CDCl3)** δ 177.75, 176.21, 160.43, 149.52, 132.17, 131.25, 129.14, 128.64, 126.51, 111.17, 104.51, 99.91, 55.43 , 50.61, 43.32, 41.60, 39.69 ppm; **HRMS**: calc. for $[M+H]^+$ $C_{19}H_{19}O_3N_2$: 323.13902, found: 323.14017.



A

(3a*R,9b*S**)-9-Acetyl-5-methyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*] quinoline-1,3(2*H*)-dione (91i)**

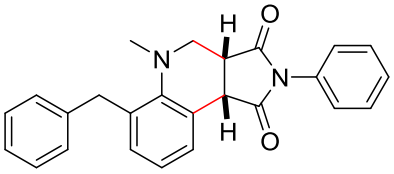
The product was prepared according to the general procedure Q. Yield: 48%; Brown amorphous solid ; TLC (20% EtOAc in petroleum ether): R_f = 0.25; [**A-major product**]-**^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.45 – 7.42 (m, 2H), 7.38 – 7.35 (m, 1H), 7.31 – 7.25 (m, 3H), 7.17 (dd, *J* = 7.6, 0.8 Hz, 1H), 6.88 (d, *J* = 8.1 Hz, 1H), 5.57 (d, *J* = 9.9 Hz, 1H), 3.62 (dd, *J* = 11.5, 2.5 Hz, 1H), 3.56 (ddd, *J* = 9.9, 4.6, 2.5 Hz, 1H), 3.18 (dd, *J* = 11.5, 4.6 Hz, 1H), 2.89 (s, 3H), 2.71 (s, 3H) ppm; **^{13}C NMR (75 MHz, $CDCl_3$)** δ 204.82, 178.20, 176.07, 149.88, 141.26, 132.02, 129.23, 128.77, 128.10, 126.51, 119.66, 116.80, 115.33, 51.04, 43.56, 40.05, 36.94, 30.46 ppm; **FT-IR**: ṽ = 1703, 1588, 1490, 1333, 1212, 1168 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{20}H_{19}O_3N_2$: 335.13902, found: 335.14033.



B

(3a*R,9b*S**)-7-Acetyl-5-methyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*] quinoline-1,3(2*H*)-dione (91i)**

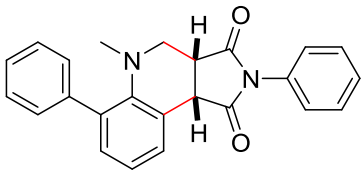
The product was prepared according to the general procedure Q. Yield: 28%; Brown amorphous solid ; TLC (25% EtOAc in petroleum ether): R_f = 0.25; [**B-minor product**]-**^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.62 (d, *J* = 7.9 Hz, 1H), 7.47 – 7.42 (m, 3H), 7.38 – 7.34 (m, 2H), 7.26 – 7.25 (m, 2H), 4.22 (d, *J* = 9.6 Hz, 1H), 3.66 (dd, *J* = 11.6, 2.7 Hz, 1H), 3.57 (ddd, *J* = 9.6, 4.4, 2.7 Hz, 1H), 3.16 (dd, *J* = 11.6, 4.4 Hz, 1H), 2.92 (s, 3H), 2.59 (s, 3H) ppm; **^{13}C NMR (75 MHz, $CDCl_3$)** δ 198.38, 177.42, 175.17, 148.84, 137.51, 131.92, 130.60, 129.23, 128.84, 126.44, 123.86, 120.27, 111.64, 50.65, 43.53, 42.41, 39.68, 26.88 ppm; **FT-IR**: ṽ = 1699, 1500, 1391, 1282, 1170, 752, 696 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{20}H_{19}O_3N_2$: 335.13902, found: 335.13952.



(3a*R,9b*S**)-6-Benzyl-5-methyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*] quinoline-1,3(2*H*)-dione (91j)**

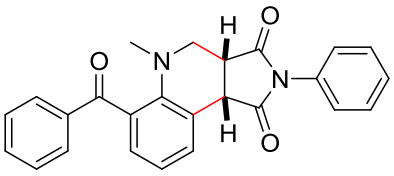
The product was prepared according to the general procedure Q. Yield: 51%; Light yellow amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.63 (d, *J* = 7.5 Hz, 1H), 7.48 – 7.46 (m, 2H), 7.41 – 7.38 (m, 1H), 7.30 – 7.26 (m, 4H), 7.22 – 7.17 (m, 3H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 4.22 (d, *J* = 9.0 Hz, 1H), 4.08 (s, 2H), 3.61 – 3.51 (m, 2H), 3.43 (dd, *J* = 13.8, 6.6 Hz, 1H), 2.74 (s, 3H) ppm; **^{13}C NMR (75 MHz, $CDCl_3$)** δ 177.94, 175.86, 146.57, 141.14, 136.16, 132.07, 130.59, 129.33, 129.15, 129.03, 128.83, 128.53, 126.39, 126.12, 124.55, 123.67, 51.49, 43.32, 41.63, 38.82, 36.32 ppm; **FT-IR**: ṽ =

1707, 1496, 1378, 1174, 909 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{25}H_{23}O_2N_2$: 383.17540, found: 383.17681.



(3a*R,9b*S**)-5-Methyl-2,6-diphenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91k)**

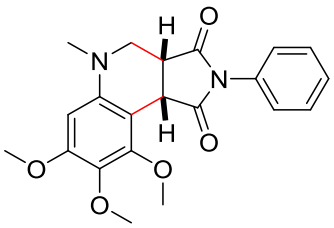
The product was prepared according to the general procedure Q. Yield: 63%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.70 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.52 – 7.50 (m, 2H), 7.48 – 7.46 (m, 2H), 7.42 – 7.37 (m, 3H), 7.35 – 7.27 (m, 3H), 7.22 – 7.15 (m, 2H), 4.22 (d, *J* = 8.5 Hz, 1H), 3.57 – 3.49 (m, 2H), 3.46 – 3.42 (m, 1H), 2.38 (s, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 177.69, 175.87, 145.90, 140.53, 135.71, 132.15, 131.06, 130.33, 129.29, 128.95, 128.78, 128.44, 127.08, 126.44, 123.42, 122.80, 50.98, 42.36, 42.14, 39.62 ppm; **FT-IR**: $\tilde{\nu}$ = 1708, 1497, 1378, 1172, 908, 821 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{24}H_{21}O_2N_2$: 369.15975, found: 369.16082.



(3a*R,9b*S**)-6-Benzoyl-5-methyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91l)**

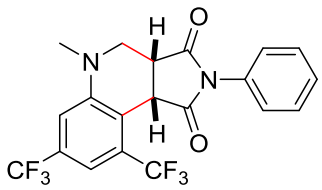
The product was prepared according to the general procedure Q. Yield: 45%; Yellow amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.82 – 7.80 (m, 2H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.58 – 7.56 (m, 1H), 7.48 – 7.42 (m, 4H), 7.41 – 7.38 (m, 1H), 7.29 – 7.24 (m, 3H), 7.05 (t, *J* = 7.6 Hz, 1H), 4.23 (d, *J* = 9.2 Hz, 1H), 3.56 – 3.51 (m, 1H), 3.41 – 3.40 (m, 2H), 2.69 (s, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 197.56, 177.28, 175.61, 146.85, 137.57, 133.32,

133.01, 132.02, 130.45, 130.09, 129.71, 129.31, 128.86, 128.51, 126.41, 121.84, 120.95, 50.20, 44.05, 42.13, 41.52 ppm; **FT-IR**: $\tilde{\nu}$ = 1709, 1497, 1375, 1174, 669 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{25}H_{21}O_3N_2$: 397.15467, found: 397.15523.



(3a*R,9b*S**)-7,8,9-Trimethoxy-5-methyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91m)**

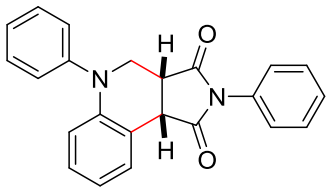
The product was prepared according to the general procedure Q. Yield: 93%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.45 – 7.42 (m, 2H), 7.37 – 7.34 (m, 1H), 7.30 – 7.28 (m, 2H), 6.11 (s, 1H), 4.66 (d, *J* = 9.9 Hz, 1H), 4.11 (s, 3H), 3.87 (s, 3H), 3.82 (s, 3H), 3.53 (dd, *J* = 11.4, 1.5 Hz, 1H), 3.47 (ddd, *J* = 9.9, 5.0, 1.5 Hz, 1H), 2.92 (dd, *J* = 11.4, 5.0 Hz, 1H), 2.78 (s, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 178.74, 175.99, 153.56, 153.00, 146.59, 135.91, 132.33, 129.15, 128.63, 126.61, 106.62, 93.45, 61.76, 60.87, 56.20, 53.33, 44.39, 39.74, 37.14 ppm; **FT-IR**: $\tilde{\nu}$ = 1708, 1599, 1495, 1372, 1180, 1113, 1029 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{21}H_{23}O_5N_2$: 383.16015, found: 383.16114.



(3a*R,9b*S**)-5-Methyl-2-phenyl-7,9-bis(trifluoromethyl)-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91n)**

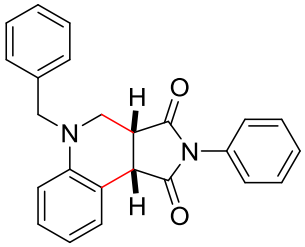
The product was prepared according to the general procedure Q. Yield: 40%; Light yellow amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.55 (s, 1H), 7.47 – 7.44 (m, 2H), 7.40 – 7.37 (m, 1H), 7.30 – 7.28 (m, 2H), 7.19 (s, 1H), 4.74 (d, *J* = 9.6 Hz, 1H), 3.66 – 3.62 (m, 2H), 3.04 (dd, *J* =

11.8, 5.9 Hz, 1H), 2.90 (s, 3H) ppm; **^{13}C NMR (151 MHz, $CDCl_3$)** δ 177.66, 173.53, 152.61, 134.35, 131.88, 131.63 (q, *J* = 31.1 Hz), 131.09 (q, *J* = 33.3 Hz), 129.28, 129.01, 128.13, 126.40, 126.22, 124.27, 123.57 (q, *J* = 274.33), 123.50 (q, *J* = 273.1), 119.97, 115.10 – 115.03 (m), 113.00 – 112.98 (m), 53.98, 46.01, 40.08 (d, *J* = 1.4 Hz), 39.86 ppm; **FT-IR**: ṽ = 1715, 1483, 1390, 1348, 1273, 1123, 1007 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{20}H_{15}O_2N_2F_6$: 429.10322, found: 429.10435.



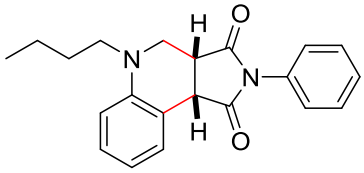
(3a*R,9b*S**)-2,5-Diphenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91o)**

The product was prepared according to the general procedure Q. Yield: 67%; Yellow amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.60 (d, *J* = 7.5 Hz, 1H), 7.43 – 7.40 (m, 2H), 7.37 – 7.32 (m, 3H), 7.19 – 7.17 (m, 2H), 7.12 – 7.08 (m, 4H), 6.97 (ddd, *J* = 7.5, 7.5, 1.1 Hz, 1H), 6.78 – 6.77 (m, 1H), 4.24 (d, *J* = 9.4 Hz, 1H), 4.20 (dd, *J* = 12.0, 3.1 Hz, 1H), 3.70 (dd, *J* = 12.0, 4.5 Hz, 1H), 3.65 (ddd, *J* = 9.4, 4.5, 3.1 Hz, 1H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 177.18, 175.73, 146.54, 146.33, 132.09, 130.87, 129.70, 129.19, 128.72, 128.47, 126.48, 124.02, 123.10, 121.60, 120.68, 117.45, 48.54, 44.70, 42.54 ppm; **FT-IR**: ṽ = 1705, 1592, 1491, 1390, 1181 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{23}H_{19}O_2N_2$: 355.14410, found: 355.14520.



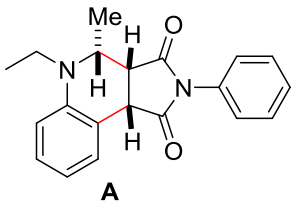
(3a*R,9b*S**)-5-Benzyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91p)**

The product was prepared according to the general procedure Q. Yield: 46%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.55 (d, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.40 – 7.37 (m, 1H), 7.31 – 7.23 (m, 7H), 7.16 – 7.13 (m, 1H), 6.89 (t, *J* = 7.5 Hz, 1H), 6.75 – 6.74 (m, 1H), 4.48 (d, *J* = 15.3 Hz, 1H), 4.29 (d, *J* = 15.3 Hz, 1H), 4.20 (d, *J* = 9.5 Hz, 1H), 3.69 (dd, *J* = 11.7, 2.9 Hz, 1H), 3.56 (ddd, *J* = 9.5, 4.2, 2.9 Hz, 1H), 3.28 (dd, *J* = 11.7, 4.2 Hz, 1H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 177.55, 175.89, 147.60, 137.80, 132.22, 130.70, 129.22, 128.74, 128.70, 127.58, 127.48, 126.48, 119.93, 119.04, 113.66, 55.59, 49.18, 44.25, 42.57 ppm; **FT-IR**: ṽ = 1708, 1598, 1496, 1386, 1200 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{24}H_{21}O_2N_2$: 369.15975, found: 369.16074.



(3a*R,9b*S**)-5-Butyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91q)**

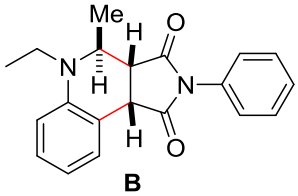
The product was prepared according to the general procedure Q. Yield: 65%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.51 (d, *J* = 7.5 Hz, 1H), 7.44 – 7.41 (m, 2H), 7.37 – 7.34 (m, 1H), 7.26 – 7.25 (m, 2H), 7.22 – 7.19 (m, 1H), 6.85 (ddd, *J* = 7.5, 7.5, 0.8 Hz, 1H), 6.76 – 6.75 (m, 1H), 4.13 (d, *J* = 9.5 Hz, 1H), 3.66 (dd, *J* = 11.7, 2.9 Hz, 1H), 3.55 – 3.52 (m, 1H), 3.31 – 3.25 (m, 1H), 3.19 (dd, *J* = 11.7, 4.3 Hz, 1H), 3.13 – 3.07 (m, 1H), 1.65 – 1.50 (m, 2H), 1.36 (q, 7.4 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 177.85, 175.95, 147.66, 132.20, 130.82, 129.15, 128.69, 128.63, 126.47, 119.15, 118.70, 112.72, 50.75, 48.46, 44.20, 42.50, 28.38, 20.50, 14.02 ppm; **FT-IR**: ṽ = 1709, 1598, 1496, 1374, 1175 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{21}H_{23}O_2N_2$: 335.17540, found: 335.17657.



A

(3a*R,9b*S**)-5-Ethyl-4-methyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91r)**

The product was prepared according to the general procedure Q. Yield: 18%; White amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **[A-minor product]-^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.49 (d, *J* = 7.4 Hz, 1H), 7.45 – 7.42 (m, 2H), 7.37 – 7.34 (m, 1H), 7.27 – 7.24 (m, 2H), 7.23 – 7.19 (m, 1H), 6.86 – 6.83 (m, 1H), 6.73 – 6.72 (m, 1H), 4.18 – 4.12 (m, 2H), 3.43 – 3.34 (m, 2H), 3.03 – 2.96 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.11 (d, *J* = 6.7 Hz, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 177.64, 176.02, 144.39, 132.19, 130.17, 129.13, 129.02, 128.58, 126.44, 118.87, 118.60, 113.54, 51.69, 50.14, 43.65, 41.28, 15.07, 13.46 ppm; **FT-IR**: ṽ = 1705, 1598, 1496, 1381, 1165 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{20}H_{21}O_2N_2$: 321.15975, found: 321.16133.

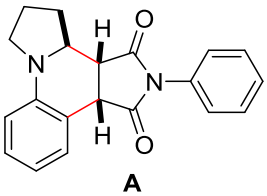


B

(3a*R,9b*S**)-5-Ethyl-4-methyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91r)**

The product was prepared according to the general procedure Q. Yield: 45%; White amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.2; **[B-major product]-^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.48 (d, *J* = 7.4 Hz, 1H), 7.43 – 7.40 (m, 2H), 7.36 – 7.33 (m, 1H), 7.26 – 7.23 (m, 2H), 7.21 – 7.18 (m, 1H), 6.84 – 6.81 (m, 1H), 6.70 – 6.69 (m, 1H), 4.16 – 4.10 (m, 2H), 3.41 – 3.32 (m, 2H), 3.01 – 2.94 (m, 1H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.09 (d, *J* = 6.7 Hz, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 177.65, 176.02, 132.19, 130.16, 129.13, 129.01, 128.58, 126.44, 118.81,

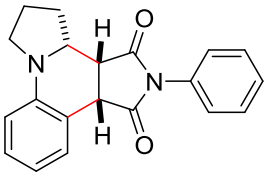
118.58, 113.54, 51.69, 50.15, 43.68, 41.29, 15.07, 13.46 ppm; **HRMS**: calc. for $[M+H]^+$ $C_{20}H_{21}O_2N_2$: 321.15975, found: 321.16136.



A

(3a*R,3b*S**,11b*S**)-2-Phenyl-3a,3b,4,5,6,11b-hexahydro-1*H*-dipyrrolo[1,2-*a*:3',4'-*c*]quinoline-1,3(2*H*)-dione (91s)**

The product was prepared according to the general procedure Q. Yield: 26%; White amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **[A-minor product]-^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.78 (d, *J* = 7.7 Hz, 1H), 7.49 – 7.46 (m, 2H), 7.41 – 7.38 (m, 1H), 7.31 – 7.29 (m, 2H), 7.26 – 7.23 (m, 1H), 6.90 (ddd, *J* = 7.6, 7.6, 0.9 Hz, 1H), 6.69 – 6.68 (m, 1H), 4.13 (d, *J* = 8.1 Hz, 1H), 3.56 – 3.51 (m, 1H), 3.20 – 3.10 (m, 2H), 2.97 – 2.92 (m, 1H), 2.47 – 2.43 (m, 1H), 2.20 – 2.16 (m, 1H), 2.13 – 1.98 (m, 2H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 175.90, 175.65, 144.81, 132.03, 130.80, 129.30, 128.76, 128.70, 126.58, 118.43, 116.02, 112.86, 58.60, 47.25, 46.09, 41.64, 31.44, 22.66 ppm; **FT-IR**: $\tilde{\nu}$ = 1699, 1600, 1501, 1458, 1375, 1158 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{20}H_{19}O_2N_2$: 319.14410; found: 319.14568.

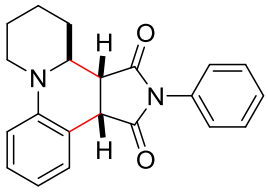


B

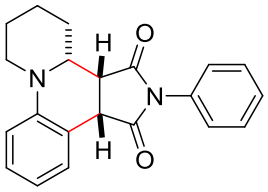
(3a*R,3b*R**,11b*S**)-2-Phenyl-3a,3b,4,5,6,11b-hexahydro-1*H*-dipyrrolo[1,2-*a*:3',4'-*c*]quinoline-1,3(2*H*)-dione (91s)**

The product was prepared according to the general procedure Q. Yield: 52%; White amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.2; **[B-major product]-^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.54 (d, *J* = 7.5 Hz, 1H), 7.42 – 7.39 (m, 2H), 7.35 – 7.32 (m, 1H), 7.22 – 7.19 (m, 3H), 6.86 (ddd, *J* = 7.5, 7.5, 0.9 Hz, 1H), 6.65 – 6.63 (m, 1H), 4.22 (d, *J* = 9.2 Hz, 1H), 3.65 (dd, *J* = 9.2, 3.9 Hz, 1H), 3.51 –

3.47 (m, 1H), 3.30 – 3.26 (m, 1H), 3.00 – 2.90 (m, 2H), 2.15 – 2.07 (m, 2H), 2.00 – 1.94 (m, 1H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 176.14, 175.69, 147.86, 132.07, 129.99, 129.05, 128.69, 128.54, 126.59, 119.20, 118.36, 112.83, 59.15, 48.04, 45.93, 44.47, 26.45, 23.45 ppm; **HRMS**: calc. for $[M+H]^+$ $C_{20}H_{19}O_2N_2$: 319.14410, found: 319.14567.



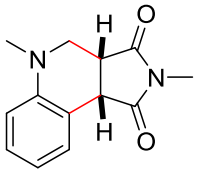
major



minor

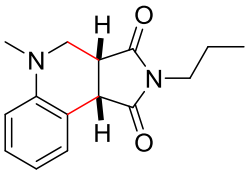
(3a*S,12a*S**,12b*R**)-2-Phenyl-9,10,11,12,12a,12b-hexahydropyrido[1,2-*a*]pyrrolo [3,4-*c*]quinoline-1,3(2*H*,3a*H*)-dione and (3a*S**,12a*R**,12b*R**)-2-phenyl-9,10,11,12,12a,12b-hexahydropyrido[1,2-*a*]pyrrolo [3,4-*c*]quinoline-1,3(2*H*,3a*H*)-dione (91t)**

The product was prepared according to the general procedure Q. Yield: 73%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$**, # denotes major signals, * denotes minor signals) δ 7.66 – 7.62#* (m), 7.46 – 7.41#* (m), 7.39 – 7.34#* (m), 7.28 – 7.21 #* (m), 6.92 – 6.84#* (m), 4.12 – 4.10#* (m), 3.96 – 3.94#* (m), 3.78 – 3.76* (m), 3.59 – 3.56# (m), 3.50 – 3.46# (m), 3.24* (d, *J* = 6.4 Hz), 3.03* (t, *J* = 12.0 Hz), 2.83# (td, *J* = 12.9, 3.0 Hz), 2.11# (qd, *J* = 12.8, 3.9 Hz), 1.88 – 1.86#* (m), 1.76 – 1.62#* (m), 1.54 – 1.47#* (m) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ **major and minor isomers**: 175.98, 175.80, 146.26, 132.07, 131.98, 130.89, 130.38, 129.19, 129.12, 128.93, 128.66,128.61, 126.54, 126.50, 119.20, 117.07, 114.11, 56.57, 56.33, 49.46, 44.89, 41.59, 40.30, 25.71, 24.69, 22.53 , 20.90 ppm; **FT-IR**: $\tilde{\nu}$ = 1705, 1598, 1494, 1376, 1137 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{21}H_{21}O_2N_2$: 333.15975, found: 333.16138.



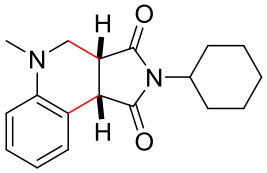
(3a*R,9b*S**)-2,5-Dimethyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91u):**

The product was prepared according to the general procedure Q. Yield: 62%; Light brown amorphous solid; TLC (25% EtOAc in petroleum ether): R_f = 0.4; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.49 – 7.47 (m, 1H), 7.23 – 7.19 (m, 1H), 6.89 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.71 – 6.69 (m, 1H), 4.00 (d, *J* = 9.4 Hz, 1H), 3.53 (dd, *J* = 11.5, 2.4 Hz, 1H), 3.36 (ddd, *J* = 9.4, 4.3, 2.4 Hz, 1H), 3.04 (dd, *J* = 11.5, 4.3 Hz, 1H), 2.99 (s, 3H), 2.80 (s, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 178.85, 176.92, 148.50, 130.33, 128.72, 119.78, 118.86, 112.63, 50.62, 43.72, 42.16, 39.54, 25.48 ppm; **FT-IR**: ṽ = 1693, 1435, 1314, 1095, 1020 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{13}H_{15}O_2N_2$: 231.11280, found: 231.11355.



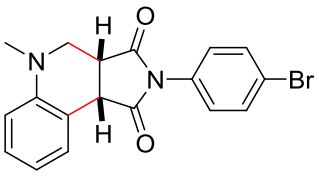
(3a*R,9b*S**)-5-Methyl-2-propyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91v)**

The product was prepared according to the general procedure Q. Yield: 66%; Brown amorphous solid; TLC (10% EtOAc in petroleum ether): R_f = 0.15; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.48 – 7.46 (m, 1H), 7.22 – 7.19 (m, 1H), 6.90 – 6.87 (m, 1H), 6.71 – 6.69 (m, 1H), 3.97 (d, *J* = 9.4 Hz, 1H), 3.51 – 3.42 (m, 3H), 3.35 (ddd, *J* = 9.3, 4.4, 2.7 Hz, 1H), 3.03 (dd, *J* = 11.5, 4.4 Hz, 1H), 2.80 (s, 3H), 1.60 – 1.52 (m, 2H), 0.82 (t, *J* = 7.5 Hz, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 178.86, 176.90, 148.56, 130.34, 128.64, 119.75, 119.13, 112.54, 50.90, 43.65, 42.14, 40.95, 39.47, 21.00, 11.13 ppm; **FT-IR**: ṽ = 1696, 1498, 1400, 1324, 1201, 1122, 1094, 1043 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{15}H_{19}O_2N_2$: 259.14410, found: 259.14461.



(3a*R,9b*S**)-2-Cyclohexyl-5-methyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91w):**

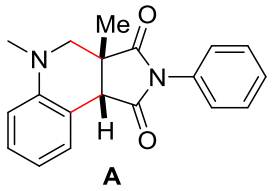
The product was prepared according to the general procedure Q. Yield: 87%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.48 – 7.46 (m, 1H), 7.22 – 7.18 (m, 1H), 6.90 – 6.87 (m, 1H), 6.71 – 6.69 (m, 1H), 3.97 – 3.89 (m, 2H), 3.45 (dd, *J* = 11.4, 2.9 Hz, 1H), 3.28 (ddd, *J* = 9.3, 4.6, 2.9 Hz, 1H), 3.03 (dd, *J* = 11.4, 4.6 Hz, 1H), 2.79 (s, 3H), 2.17 – 2.02 (m, 2H), 1.79 – 1.76 (m, 2H), 1.63 – 1.61 (m, 1H), 1.56 – 1.51 (m, 2H), 1.32 – 1.25 (m, 2H), 1.23 – 1.14 (m, 1H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 178.82, 176.96, 148.52, 130.34, 128.56, 119.61, 119.17, 112.50, 52.33, 50.97, 43.21, 41.88, 39.52, 29.00, 28.89, 25.96, 25.91, 25.19 ppm; **FT-IR**: $\tilde{\nu}$ = 2929, 1695, 1601, 1498, 1450, 1366, 1184, 1132 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{18}H_{23}O_2N_2$: 299.17540, found: 299.17594.



(3a*R,9b*S**)-2-(4-Bromophenyl)-5-methyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91x):**

The product was prepared according to the general procedure Q. Yield: 68%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.56 – 7.51 (m, 3H), 7.26 – 7.22 (m, 1H), 7.20 – 7.18 (m, 2H), 6.91 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.75 – 6.74 (m, 1H), 4.15 (d, *J* = 9.6 Hz, 1H), 3.60 (dd, *J* = 11.5, 2.6 Hz, 1H), 3.53 (ddd, *J* = 9.6, 4.4, 2.6 Hz, 1H), 3.11 (dd, *J* = 11.5, 4.4 Hz, 1H), 2.84 (s, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 177.47, 175.55, 148.61, 132.28, 131.12, 130.43, 128.92, 127.98, 122.42, 119.89, 118.47, 112.74, 50.75, 43.75,

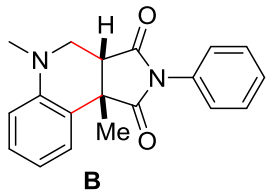
42.27, 39.57 ppm; **FT-IR**: $\tilde{\nu}$ = 1710, 1488, 1396, 1198, 812 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{18}H_{16}O_2N_2{}^{79}Br$: 371.03897, found: 371.03996; **HRMS**: calc. for $[M+H]^+$ $C_{18}H_{16}O_2N_2{}^{81}Br$: 373.03692, found: 373.03747.



A

(3a*R,9b*R**)-3a,5-Dimethyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91y):**

The product was prepared according to the general procedure Q. Yield: 11%; Yellow amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **[A-minor product]-^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.51 (d, *J* = 7.5 Hz, 1H), 7.44 – 7.41 (m, 2H), 7.37 – 7.34 (m, 1H), 7.27 – 7.22 (m, 3H), 6.91 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.76 – 6.75 (m, 1H), 3.74 (s, 1H), 3.51 (d, *J* = 11.3 Hz, 1H), 2.84 (s, 3H), 2.83 (d, *J* = 11.3 Hz, 1H), 1.51 (s, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 180.82, 175.27, 147.98, 132.21, 130.57, 129.11, 128.83, 128.60, 126.49, 119.76, 119.07, 112.54, 58.05, 50.26, 47.91, 39.46, 22.51 ppm; **FT-IR**: $\tilde{\nu}$ = 1707, 1603, 1495, 1392, 1337, 1208, 1130 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{19}H_{19}O_2N_2$: 307.14410, found: 307.14471.

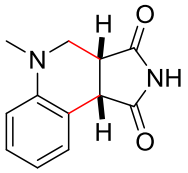


B

(3a*R,9b*S**)-5,9b-Dimethyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91y)**

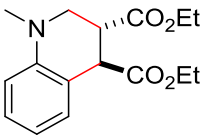
The product was prepared according to the general procedure Q. Yield: 34%; Yellow amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.2; **[B-major product]-^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.65 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.41 – 7.38 (m, 2H), 7.34 – 7.31 (m, 1H), 7.23 – 7.18 (m, 3H), 6.87 – 6.83 (m, 1H), 6.70 – 6.68 (m, 1H), 3.71 (dd, *J* = 11.7, 2.9 Hz, 1H), 3.21 (dd, *J* = 11.7, 3.6 Hz, 1H), 3.12 – 3.11

(m, 1H), 2.90 (s, 3H), 1.83 (s, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 179.20, 176.15, 146.88, 132.19, 129.05, 128.97, 128.90, 128.48, 126.38, 122.33, 119.00, 112.35, 50.83, 47.59, 44.46, 39.65, 26.56 ppm; **FT-IR**: ṽ = 1707, 1603, 1495, 1392, 1337, 1208, 1130.



(3a*R,9b*S**)-5-Methyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91z)**

The product was prepared according to the general procedure Q. Yield: 78%; Light brown amorphous solid; TLC (25% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (300 MHz, CD_3CN)** δ 8.99 (brs, 1H), 7.35 – 7.32 (m, 1H), 7.22 – 7.16 (m, 1H), 6.84 (ddd, *J* = 7.5, 7.5, 1.1 Hz, 1H), 6.77 – 6.74 (m, 1H), 4.00 (d, *J* = 9.5 Hz, 1H), 3.44 – 3.37 (m, 2H), 2.90 (dd, *J* = 11.5, 4.5 Hz, 1H), 2.76 (s, 3H) ppm; **^{13}C NMR (75 MHz, CD_3CN)** δ 180.38, 178.37, 149.92, 131.08, 129.22, 120.75, 120.09, 113.44, 51.59, 45.57, 44.14, 39.81 ppm; **FT-IR**: ṽ = 3179, 1768, 1700, 1497, 1308, 1176, 1042 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{12}H_{13}O_2N_2$: 217.09715, found: 217.09746.



(3*R,4*R**)-Diethyl 1-methyl-1,2,3,4-tetrahydroquinoline-3,4-dicarboxylate (91ab):**

The product was prepared according to the general procedure Q. Yield: 60%; Light green amorphous solid; TLC (2% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (500 MHz, CDCl3)** δ 7.22 (d, *J* = 7.6 Hz, 1H), 7.16 – 7.12 (m, 1H), 6.70 – 6.64 (m, 2H), 4.23 – 4.12 (m, 5H), 3.56 – 3.51 (m, 1H), 3.43 – 3.37 (m, 2H), 2.92 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C NMR (151 MHz, CDCl3)** δ 173.19, 172.09, 145.61, 129.16, 128.51, 118.14, 117.57, 112.22, 61.36, 61.24, 50.37, 44.82,

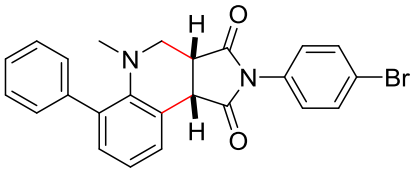
41.18, 39.60, 14.32, 14.27 ppm; **FT-IR**: $\tilde{\nu}$ = 2980, 1728, 1602, 1504, 1181, 1025 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{16}H_{22}O_4N$: 292.15433, found: 292.15505.

5.4.3 Synthesis of Analogues 91ad–91an

General Procedure R for the Synthesis of Compounds **91ad–91ah, 91an**:

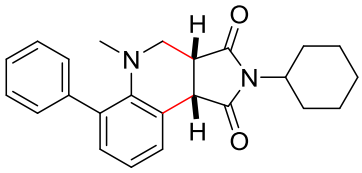
To a screw-capped vial maleimides (0.1 mmol, 1 equiv), tertiary anilines (0.2 mmol, 2 equiv), tetrabutyl ammonium iodides 3.69 mg (TBAI, 10 mol%), TBHP 55 µL (70% in H_2O, 0.4 mmol, 4 equiv) and DCE (1.0 mL) were added. The reaction mixture was heated to 70 ^oC. The progress of the reaction was monitored by thin layer chromatography (ethyl acetate/petroleum ether mixture) and GC-MS. Upon completion, the crude reaction mixture was concentrated under vacuum and subsequently purified by flash column chromatography over silica gel using petroleum ether/ethyl acetate as an eluent system.

Characterization of Compounds **91ad–91ah, 91an:**



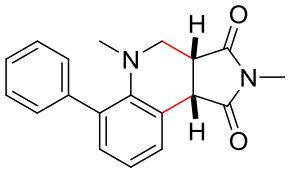
(3a*R,9b*S**)-2-(4-Bromophenyl)-5-methyl-6-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91ad):**

The product was prepared according to the general procedure R. Yield: 65%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.67 (dd, *J* = 7.5, 0.9 Hz, 1H), 7.60 – 7.58 (m, 2H), 7.51 – 7.49 (m, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.22 – 7.15 (m, 4H), 4.21 (d, *J* = 8.5 Hz, 1H), 3.56 – 3.48 (m, 2H), 3.45 – 3.40 (m, 1H), 2.37 (s, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 177.34, 175.55, 145.84, 140.45, 135.74, 132.48, 131.17, 131.12, 130.26, 128.93, 128.45, 127.90, 127.12, 123.47, 122.62, 122.52, 50.95, 42.36, 42.13, 39.63.



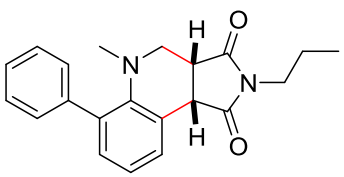
(3a*R,9b*S**)-2-Cyclohexyl-5-methyl-6-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91ae):**

The product was prepared according to the general procedure R. Yield: 75%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.62 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.49 – 7.47 (m, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.18 – 7.12 (m, 2H), 4.01 – 3.94 (m, 2H), 4.05 – 3.40 (m, 1H), 3.28 – 3.23 (m, 2H), 2.29 (s, 3H), 2.19 – 2.07 (m, 2H), 1.81 (d, *J* = 12.9 Hz, 2H), 1.65 (d, *J* = 12.4 Hz, 1H), 1.56 (d, *J* = 12.3 Hz, 2H), 1.34 – 1.16 (m, 3H).



(3a*R,9b*S**)-2,5-Dimethyl-6-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91af):**

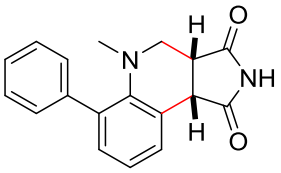
The product was prepared according to the general procedure R. Yield: 73%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.67 – 7.65 (m, 1H), 7.48 – 7.46 (m, 2H), 7.40 – 7.37 (m, 2H), 7.32 – 7.29 (m, 1H), 7.18 – 7.12 (m, 2H), 4.03 (d, *J* = 8.5 Hz, 1H), 3.45 (dd, *J* = 13.1, 4.6 Hz, 1H), 3.37 – 3.28 (m, 2H), 3.02 (s, 3H), 2.30 (s, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 178.80, 176.99, 145.83, 140.59, 135.55, 130.96, 130.10, 128.92, 128.40, 127.02, 123.24, 122.94, 50.69, 42.14, 42.00, 39.70, 25.51.



(3a*R,9b*S**)-5-Methyl-6-phenyl-2-propyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]**

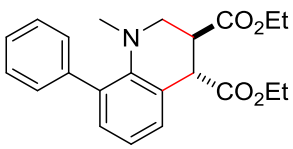
quinoline-1,3(2*H*)-dione (91ag):

The product was prepared according to the general procedure R. Yield: 77%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.67 – 7.65 (m, 1H), 7.48 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.40 – 7.37 (m, 2H), 7.32 – 7.29 (m, 1H), 7.18 – 7.12 (m, 2H), 4.01 (d, *J* = 8.6 Hz, 1H), 3.51 – 3.44 (m, 3H), 3.34 – 3.30 (m, 1H), 3.27 – 3.23 (m, 1H), 2.30 (s, 3H), 1.63 – 1.56 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 178.72, 176.92, 145.84, 140.64, 135.50, 130.91, 130.17, 128.94, 128.39, 127.00, 123.20, 122.99, 50.96, 42.18, 41.89, 40.91, 39.34, 21.04, 11.40.



(3a*R,9b*S**)-5-Methyl-6-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline -1,3(2*H*)-dione (91ah):**

The product was prepared according to the general procedure R. Yield: 65%; Light brown amorphous solid; TLC (25% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.07 (brs, 1H), 7.61 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.48 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.40 – 7.37 (m, 2H), 7.33 – 7.30 (m, 1H), 7.18 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 4.09 (d, *J* = 8.3 Hz, 1H), 3.46 (dd, *J* = 12.8, 4.2 Hz, 1H), 3.39 – 3.30 (m, 2H), 2.34 (s, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 178.32, 176.65, 145.80, 140.57, 135.59, 131.10, 130.01, 128.92, 128.43, 127.07, 123.22, 122.34, 50.77, 43.18, 42.16, 40.46.



Diethyl (3*S,4*S**)-1-methyl-8-phenyl-1,2,3,4-tetrahydroquinoline-3,4-dicarboxylate (91an)**

The product was prepared according to the general procedure R. Yield: 71%; Light green amorphous solid; TLC (2% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.51 (dd, *J* = 8.1, 1.0 Hz, 2H), 7.40 – 7.37 (m, 2H), 7.31 – 7.27 (m, 2H), 7.12 – 7.11 (m, 1H), 6.98 (t, *J* = 7.6 Hz, 1H), 4.31 – 4.17 (m, 5H), 3.42 – 3.35 (m, 2H), 3.28 – 3.23 (m, 1H), 2.39 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 173.53, 172.94, 145.60, 141.46, 134.77, 131.04, 128.80, 128.47, 127.65, 126.79, 124.29, 121.97, 61.47, 61.21, 51.96, 46.38, 43.10, 37.95, 14.37, 14.32.

General Procedure S for the Synthesis of Compounds **91ai–91am**:

First step:[126]

To a stirred solution of phenylboronic acid (0.86 mmol) in EtOH (5mL) was added anilines (0.71 mmol), K_2CO_3 (1.78 mmol), $Pd(PPh_3)_4$ (10% mmol). The reaction was refluxed for 24 h under argon atmosphere before EtOH was removed by rotary evaporation. The remained mixture was extracted with EtOAc, and the combined organic layers were washed with H_2O and brine, dried over anhydrous Na_2SO_4, evaporated under vacuum. The product was purified by normal silica gel column with petroleum ether (40-60°C)/EtOAc mixture.

Second step:

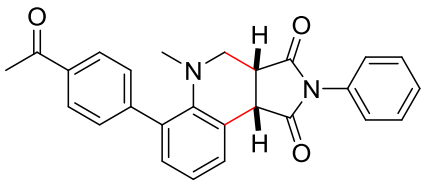
To a solution of 2-phenyl anilines (0.8 mmol) in glacial acetic acid (2.5 mL) under inert atmosphere was added paraformaldehyde (10 mmol) and sodium cyanoborohydride (3.5 mmol). The addition of sodium cyanoborohydride resulted in bubbling. After stirring overnight, the reaction mixture was poured into a water/ice mixture (10 mL) containing NaOH (4 g). The addition was exothermic, and more ice was added to bring the total volume of the quench mixture to 30 mL. The mixture, which had pH 14, was extracted with dichloromethane. The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was then purified by flash chromatography over silica gel.

Third step:

To a screw-capped vial maleimides (0.1 mmol, 1 equiv), 2-phenyl tertiary anilines

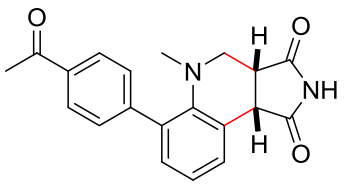
(0.2 mmol, 2 equiv), tetrabutyl ammonium iodides 3.69 mg (TBAI, 10 mol%), TBHP 55 µL (70% in H_2O, 0.4 mmol, 4 equiv) and DCE (1.0 mL) were added. The reaction mixture was heated to 70 ^oC. The progress of the reaction was monitored by thin layer chromatography (ethyl acetate/petroleum ether mixture) and GC-MS. Upon completion, the crude reaction mixture was concentrated under vacuum and subsequently purified by flash column chromatography over silica gel using petroleum ether/ethyl acetate as an eluent system.

Characterization of Compounds **91ai–91am:**



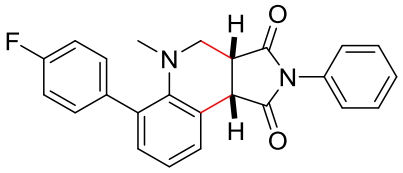
(3a*R,9b*S**)-6-(4-Acetylphenyl)-5-methyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91ai):**

The product was prepared according to the general procedure S. Yield: 21%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.20; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.01 – 7.99 (m, 2H), 7.73 (ddd, *J* = 7.1, 2.1, 0.7 Hz, 1H), 7.64 – 7.61 (m, 2H), 7.48 – 7.44 (m, 2H), 7.41 – 7.37 (m, 1H), 7.29 – 7.27 (m, 2H), 7.22 – 7.17 (m, 2H), 4.23 (d, *J* = 8.6 Hz, 1H), 3.58 – 3.50 (m, 2H), 3.47 – 3.43 (m, 1H), 2.64 (s, 3H), 2.38 (s, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 197.96, 177.52, 175.72, 145.92, 145.59, 135.83, 134.47, 132.06, 131.11, 130.86, 129.33, 129.13, 128.85, 128.62, 126.40, 123.65, 123.09, 50.79, 42.70, 42.02, 39.46, 26.77.



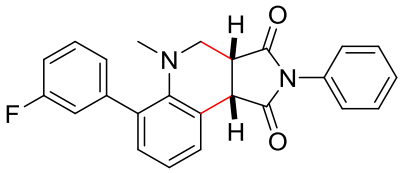
(3a*R,9b*S**)-6-(4-acetylphenyl)-5-methyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91aj):**

The product was prepared according to the general procedure S. Yield: 25%; Light brown amorphous solid; TLC (25% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.11 (brs, 1H), 8.00 – 7.99 (m, 1H), 7.98 – 7.98 (m, 1H), 7.65 (ddd, *J* = 7.3, 2.0, 0.8 Hz, 1H), 7.61 – 7.58 (m, 2H), 7.20 – 7.14 (m, 2H), 4.10 (d, *J* = 8.4 Hz, 1H), 3.46 (dd, *J* = 12.9, 4.5 Hz, 1H), 3.40 – 3.31 (m, 2H), 2.63 (s, 3H), 2.33 (s, 3H).



(3a*R,9b*S**)-6-(4-Fluorophenyl)-5-methyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91ak):**

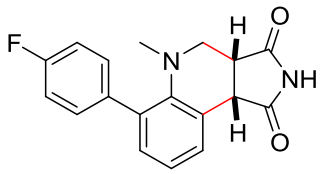
The product was prepared according to the general procedure S. Yield: 23%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.20; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.69 (ddd, *J* = 6.4, 2.9, 0.7 Hz, 1H), 7.51 – 7.44 (m, 4H), 7.40 – 7.35 (m, 1H), 7.29 – 7.27 (m, 2H), 7.19 – 7.15 (m, 2H), 7.12 – 7.07 (m, 2H), 4.22 (d, *J* = 8.8 Hz, 1H), 3.56 – 3.49 (m, 2H), 3.46 – 3.41 (m, 1H), 2.38 (s, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 177.68, 175.83, 162.10 (d, *J* = 246.1 Hz), 145.84, 136.23 (d, *J* = 3.4 Hz), 134.80, 132.00, 130.89, 130.55, 130.47 (d, *J* = 4.7 Hz), 129.33, 128.84, 126.40, 123.64, 122.97, 115.36 (d, *J* = 21.2 Hz), 50.90, 42.26, 42.00, 39.32.



(3a*R,9b*S**)-6-(3-Fluorophenyl)-5-methyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91al):**

The product was prepared according to the general procedure S. Yield: 21%; Brown amorphous solid; TLC (20% EtOAc in petroleum ether): R_f = 0.20; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.71 (ddd, *J* = 7.3, 2.0, 0.7 Hz, 1H), 7.49 – 7.44 (m, 2H), 7.40 – 7.34

(m, 3H), 7.29 – 7.25 (m, 3H), 7.21 – 7.15 (m, 2H), 7.04 – 7.00 (m, 1H), 4.22 (d, *J* = 8.6 Hz, 1H), 3.57 – 3.49 (m, 2H), 3.47 – 3.42 (m, 1H), 2.41 (s, 3H).



(3a*R,9b*S**)-6-(4-Fluorophenyl)-5-methyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (91am):**

The product was prepared according to the general procedure S. Yield: 26%; Light brown amorphous solid; TLC (25% EtOAc in petroleum ether): R_f = 0.1; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.05 (brs, 1H), 7.61 (ddd, *J* = 6.7, 2.6, 0.8 Hz, 1H), 7.47 – 7.44 (m, 2H), 7.16 – 7.12 (m, 2H), 7.09 – 7.06 (m, 2H), 4.09 (d, *J* = 8.6 Hz, 1H), 3.45 (dd, *J* = 13.1, 4.7 Hz, 1H), 3.39 – 3.35 (m, 1H), 3.33 – 3.29 (m, 1H), 2.33 (s, 3H).

5.5 Experimental Part for 3.2.2

5.5.1 Synthesis of Compounds 92

Procedure for the Synthesis of Compound **92a**:

3-Amino-2-chloro-pyridines (2.33 mmol) was dissolved in a 10 mL microwave tube with 2.5 mL pyridines. The reaction proceeded in microwave with 150 W at 200 ^oC. The starting materials completed, after 35 min. The reaction mixture was quenched at room temperature with saturated NH_4Cl solution. Then it was extracted with EtOAc, washed with water, brine and dried over anhydrous $MgSO_4$. The organic extracts were concentrated under vacuum and purified by normal silica gel column chromatography.

Characterization of Compound **92a**:

2-(Piperidin-1-yl)pyridin-3-amine (92a):[112]

The product was prepared according to the general procedure. Yield: 75%; White amorphous solid; TLC (2% methanol in dichloromethane): R_f = 0.2; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.78 (dd, *J* = 4.8, 1.6 Hz, 1H), 6.91 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.79 (dd, *J* = 7.7, 4.8 Hz, 1H), 3.80 (brs, 2H), 3.04 – 3.02 (m, 4H), 1.72 – 1.67 (m, 4H), 1.62 – 1.57 (m, 2H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 152.32, 137.56, 135.73, 121.36, 119.30, 50.25, 26.58, 24.60 ppm.

General Procedure T for the Synthesis of Compounds **92b, 92c, 92e, 92f**:[115]

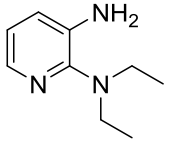
First Step:

2-Chloro-3-nitropyridine (6.31 mmol), Et_3N (12.61 mmol) and amine (7.57 mmol) were dissolved in *n*-BuOH (25 mL). After refluxing for 3 h, the starting materials completed. The solvent was removed under vacuum, and the residue was partitioned between water and EtOAc. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The product was used for the second step without purification.

Second Step:

To a solution of nitropyridines (6.3 mmol) in ethanol (10 mL) was added 10% palladium on charcoal catalyst (10% w/w). The suspension was hydrogenated at room temperature overnight. The Pd/C was removed by filtration through a pad of celite, and the extracts were concentrated under vacuum. The product was purified by column chromatography on silica gel.

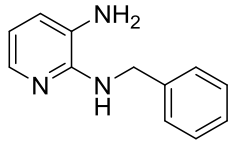
Characterization of Compound **92b, 92c, 92e, 92f**:



***N^2,N^2*-Diethylpyridine-2,3-diamine (92b):**

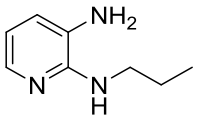
The product was prepared according to the general procedure T. Yield: 46%; Dark red liquid; TLC (2% methanol in dichloromethane): R_f = 0.2; **^{1}H NMR (500 MHz,**

$CDCl_3$) δ 7.82 – 7.80 (m, 1H), 6.94 – 6.92 (m, 1H), 6.81 (dd, *J* = 7.6, 4.8 Hz, 1H), 3.88 (brs, 2H), 3.11 (q, *J* = 7.1 Hz, 4H), 1.02 (t, *J* = 7.1 Hz, 6H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 150.74, 137.73, 137.53, 121.50, 119.60, 45.18, 13.14; **FT-IR**: ṽ = 2970, 2360, 1603, 1444, 1382, 1305, 1243, 1131 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_9H_{16}N_3$:166.13387, found: 166.13415.



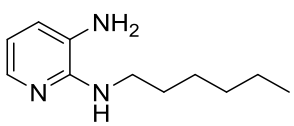
***N^2*-Benzylpyridine-2,3-diamine (92c):[144]**

The product was prepared according to the general procedure T. Yield: 58%; Pink amorphous solid; TLC (2% methanol in dichloromethane): R_f = 0.25; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.77 (d, *J* = 4.0 Hz, 1H), 7.41 (d, *J* = 7.4 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.29 (d, *J* = 7.3 Hz, 1H), 6.88 (dd, *J* = 7.4, 1.5 Hz, 1H), 6.57 (dd, *J* = 7.4, 5.2 Hz, 1H), 4.65 (d, *J* = 3.6 Hz, 2H), 4.59 (brs, 1H), 3.27 (brs, 2H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 150.14, 139.93, 139.02, 128.61, 128.51, 128.11, 127.24, 122.04, 113.78, 46.12 ppm.



***N^2*-Propylpyridine-2,3-diamine (92e):[145]**

The product was prepared according to the general procedure T. Yield: 60%; Black amorphous solid; TLC (2% methanol in dichloromethane): R_f = 0.2; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.75 (dd, *J* = 5.2, 1.4 Hz, 1H), 6.84 (dd, *J* = 7.4, 1.4 Hz, 1H), 6.50 (dd, *J* = 7.4, 5.2 Hz, 1H), 4.21 (brs, 1H), 3.40 (t, *J* = 7.1 Hz, 2H), 3.19 (brs, 2H), 1.72 – 1.64 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 150.76, 139.19, 128.35, 122.09, 113.17, 43.85, 23.18, 11.83 ppm.



***N*^{2}-Hexylpyridine-2,3-diamine (92f):**

The product was prepared according to the general procedure T. Yield: 56%; Black liquid; TLC (2% methanol in dichloromethane): R_f = 0.25; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.75 (dd, *J* = 5.1, 1.5 Hz, 1H), 6.84 (dd, *J* = 7.4, 1.5 Hz, 1H), 6.50 (dd, *J* = 7.4, 5.1 Hz, 1H), 4.18 (brs, 1H), 3.42 (t, *J* = 7.3 Hz, 2H), 3.20 (brs, 2H), 1.68 – 1.61 (m, 2H), 1.45 – 1.38 (m, 2H), 1.36 – 1.29 (m, 4H), 0.90 – 0.87 (m, 3H) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 150.75, 139.14, 128.37, 122.03, 113.16, 42.11, 31.82, 29.95, 27.05, 22.77, 14.20 ppm; **FT-IR**: $\tilde{\nu}$ = 2923, 2855, 2360, 2341, 1601, 1504, 1463, 1255 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{11}H_{20}N_3$: 194.16517, found: 194.16531.

Procedure for the Synthesis of Compound **92d**:

First Step:[115]

2-Chloro-3-nitropyridines (6.31 mmol), Et_3N (12.61 mmol) and benzylamines (7.57 mmol) were dissolved in *n*-BuOH (25 mL). After refluxing for 3 h, the starting materials completed. The solvent was removed under vacuum, and the residue was partitioned between water and EtOAc. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The product was used for the next step without purification.

Second Step:[117]

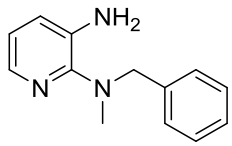
To a solution of 2-benzylamino-3-nitropyridines (6.31 mmol) in 10 mL DMF was added NaH (60% in mineral oil, 7.57 mmol) and MeI (6.94 mmol) at 0 ^{o}C. Then it was heated up to 60 ^{o}C for 12 h. After the reaction cooled to room temperature, a saturated solution of NH_4Cl was carefully added, and the resulting mixture was extracted three times with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, and the solvent evaporated under vacuum. The product was purified by column chromatography on silica gel.

Third Step:[115]

To a solution of nitropyridines (6.3 mmol) in ethanol (10 mL) was added 10% palladium on charcoal catalyst (10% w/w). The suspension was hydrogenated at room temperature overnight. The Pd/C was removed by filtration through a pad of celite

and concentrated under vacuum. The product was purified by column chromatography on silica gel.

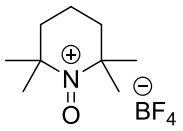
Characterization of Compound **92d**:



***N*^{2}-Benzyl-*N*^{2}-methylpyridine-2,3-diamine (92d):**

Yield: 32%; Brown liquid; TLC (2% methanol in dichloromethane): R_f = 0.25; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.82 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.38 – 7.31 (m, 4H), 7.28 – 7.24 (m, 1H), 6.96 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.85 (dd, *J* = 7.7, 4.8 Hz, 1H), 4.24 (s, 2H), 3.87 (brs, 2H), 2.70 (s, 3H) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 151.90, 139.06, 137.42, 135.79, 128.54, 128.34, 127.16, 121.86, 119.56, 57.31, 38.51 ppm; **FT-IR**: ṽ = 2360, 1604, 1584, 1494, 1449, 1361, 1234, 1107 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{13}H_{16}N_3$: 214.13387, found: 214.13437.

5.5.2 Synthesis of Compound 127



Procedure for the Synthesis of Compound **127**:[146]

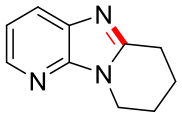
To a suspension of TEMPO (11.39 mmol) in H_2O (32 mL, 2 M) was dropwise added 42% HBF_4 (1.75 mL) over 1 h at room temperature. After the solution turned to amber color, NaOCl (11-14%, 3.9 mL) was added over 1 h at 0 °C and stirred for an additional 1 h at 0°C. The reaction mixture was filtered, and the yellow crystalline precipitate was washed with ice-cold 5% $NaHCO_3$ (4 mL), water (8 mL) and ice-cold Et_2O (80 mL). The solid was dried over 24 h at 50 °C under vacuum to yield T^+BF4^- **127** as the bright yellow solid in 75% yield .

5.5.3 Synthesis of Imidazo[4,5-*b*]pyridines 93

General Procedure U for the Synthesis of Compounds **93**:

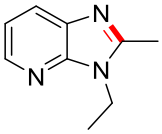
To a solution of **92** (0.2 mmol) in DCE (1 mL) was added **127** ($T^+BF_4^-$) at room temperature. After 30 min, starting materials completed. The reaction mixture was directly loaded in silica gel column and purified with DCM/MeOH mixture.

Characterization of Compound **93a,93b**:



6,7,8,9-Tetrahydroimidazo[1,2-*a*:5,4-*b*']dipyridine (93a):

The product was prepared according to the general procedure U. Yield: 70%; Pink amorphous solid; TLC (2% MeOH in DCM): R_f = 0.25; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.35 (dd, *J* = 4.8, 1.4 Hz, 1H), 7.99 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.27 – 7.23 (m, 1H), 4.27 (t, *J* = 6.0 Hz, 2H), 3.19 (t, *J* = 6.4 Hz, 2H), 2.20 – 2.03 (m, 4H) ppm; **^{13}C NMR (75 MHz, $CDCl_3$)** δ 153.22, 143.72, 132.90, 125.85, 119.11, 77.36, 41.78, 25.28, 22.25, 20.21 ppm; **FT-IR**: ṽ = 2361, 1598, 1506, 1441, 1395, 1279, 1213, 1151, 1111 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_{10}H_{12}N_3$: 174.10257, found: 174.10283.



3-Ethyl-2-methyl-3*H*-imidazo[4,5-*b*]pyridine (93b):

The product was prepared according to the general procedure U. Yield: 57%; Brown liquid; TLC (2% MeOH in DCM): R_f = 0.2;**^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.31 (dd, *J* = 4.8, 1.4 Hz, 1H), 7.93 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.17 (dd, *J* = 8.0, 4.8 Hz, 1H), 4.31 (q, *J* = 7.3 Hz, 2H), 2.65 (s, 3H), 1.43 (t, *J* = 7.3 Hz, 3H) ppm; **^{13}C NMR (75 MHz, $CDCl_3$)** δ 152.75, 147.91, 143.15, 134.68, 126.27, 118.15, 37.46, 15.23, 14.40 ppm; **FT-IR**: ṽ = 2360, 2341, 1509, 1427, 1391, 1269, 1133, 1035 cm^{-1}; **HRMS**: calc. for $[M+H]^+$ $C_9H_{16}N_3$: 166.13387, found: 166.13415.

VI References

[1] a) E. Negishi, A. de Meijere, *Handbook of Organopalladium Chemistry for Organic Synthesis*, Wiley-Interscience, New York, **2002**; b) A. R. Muci, S. L. Buchwald, *Top. Curr. Chem.* **2002**, *219*, 131; c) A. de Meijere, F. Diederich, *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, **2004**; d) L. Ackermann, *Modern Arylation Methods*, Wiley-VCH, Weinheim, **2009**.

[2] a) M. C. Bagley, J. W. Dale, E. A. Merritt, X. Xiong, *Chem. Rev.* **2005**, *105*, 685; b) M. E. Webb, A. Marquet, R. R. Mendel, F. Ré beillé, A. G. Smith, *Nat. Prod. Rep.* **2007**, *24*, 988; c) J. Kim, M. Movassaghi, *Chem. Soc. Rev.* **2009**, 38, 3035.

[3] R. G. Bergman, *Nature* **2007**, *446*, 391.

[4] a) W. Hübel, E. H. Braye, *J. Inorg. Nucl. Chem.* **1959**, *10*, 250; b) J. P. Kleiman, M. Dubeck, *J. Am. Chem. Soc.* **1963**, *85*, 1544; c) G. W. Parshall, W. H. Knoth, R. A. Schunn, *J. Am. Chem. Soc.* **1969**, *91*, 4990.

[5] a) F. Kakiuchi, N . Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077; b) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654.

[6] a) P. Thansandote, M. Lautens, *Chem. Eur. J.* **2009**, *15*, 5874; b) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem., Int. Ed.* **2012**, *51*, 8960.

[7] a) S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, *Nature*, **199**3, *366*, 529; b) R. A. Periana, D. J. Taube, E. R. Evitt, D. G. Loffler, P. R. Wentrcek, G. Voss,T. Masuda, *Science* **1993**, *259*, 340; c) H. M. L. Davies, T. Hansen, M. R. Churchill, *J. Am. Chem. Soc.* **2000,** *122*, 3063; d) J. A. Labinger, J. E. Bercaw, *nature* **2002**, *417*, 507; e) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315; f) R. Waterman, *Organometallics* **2013**, *32*, 7249.

[8] O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074.

[9] a) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem., Int. Ed.* **2009**, *48*, 5094; b) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Commun.* **2010**, *46*, 677; c) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147.

[10] P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879.

[11] D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624

[12] I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890.

[13] a) A. D. Sadow, T. D, Tilley, *Angew. Chem. Int. Ed.* **2003**, *42*, 803; b) N. Maudoux, J. Fang, T. Roisnel, V. Dorcet, L. Maron, J. Carpentier, Y. Sarazin, *Chem. Eur. J.* **2014**, *20*, 7706.

[14] a) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Rev.* **2011**, *111*, 1293; b) K. Gao, N. Yoshikai, *Acc. Chem. Res.*, **2014**, *47*, 1208; c) B. Su, Z.-C. Cao, Z.-J. Shi, *Acc. Chem. Res.* **2015**, *48*, 886.

[15] a) A. D. Ryabov, *Chem. Rev.* **1990**, *90*, 403; b) A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, *97*, 2879.

[16] a) M. Zhang, Y. Zhang, X. Jie, H. Zhao, G. Li, W. Su, *Org. Chem. Front.*, **2014**, *1*, 843; b) G. Shia, Y. Zhang, *Adv. Synth. Catal.* **2014**, *356*, 1419; c)Z. Huang, H. N. Lim, F. Mo, M. C. Young, G. Dong, *Chem. Soc. Rev.* **2015**, *44*, 7764.

[17] a) R. Giri, B.-F. Shi, K. M. Engle, N. Maugelc, J.-Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242; b) B. Ye, N. Cramer, *Acc. Chem. Res.* **2015**, *48*, 1308.

[18] a) G. Song, F. Wang, X. Li, *Chem. Soc. Rev.* **2012**, *41*, 3651; b) D. A. Colby, A. S. Tsai, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2012**, *45*, 814.

[19] K. Ueura, T. Satoh, M. Miura, *J. Org. Chem.* **2007**, *72*, 5362.

[20] F. W. Patureau, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9982.

[21] F. W. Patureau, T. Besset, F. Glorius, *Angew. Chem., Int. Ed.* **2011**, *50*, 1064.

[22] a) S. Mochida, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2010**, *12*, 5776; b) S. Mochida, K. Hirano, T. Satoh, M. Miura, *J. Org.Chem.* **2011**, *76*, 3024.

[23] S. H. Park, J. Y. Kim, S. Chang, *Org. Lett.* **2011**, *13*, 2372.

[24] a) T.-J. Gong, B. Xiao, Z.-J. Liu, J. Wan, J. Xu, D.-F. Luo, Y. Fu, L. Liu, *Org. Lett.* **2011**, *13*, 3235; b) C. Feng, T.-P. Loh, *Chem. Commun.* **2011**, *47*, 10458; c) Q. Zhang, H.-Z. Yu, Y.-T. Li, L. Liu, Y. Huang, Y. Fu, *Dalton Trans.* **2013**, *42*, 4175.

[25] a) N. Umeda, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2009**, *74*, 7094; b) B. Gong, J. Shi, X. Wang, Y. Yan, Q. Li, Y. Meng, H. E. Xu, W. Yi, *Adv. Synth.*

Catal. **2014**, *356*, 137.

[26] A. S. Tsai, M. Brasse, R. G. Bergman, J. A. Ellman, *Org. Lett.* **2011**, *13*, 540.

[27] C. Wang, H. Chen, Z. Wang, J. Chen, Y. Huang, *Angew. Chem., Int. Ed.* **2012**, *51*, 7242.

[28] B. Liu, Y. Fan, Y. Gao, C. Sun, C. Xu, J. Zhu, *J. Am. Chem. Soc.* **2013**, *135*, 468.

[29] H. Li, Y. Li, X.-S. Zhang, K. Chen, X. Wang, Z.-J. Shi, *J. Am. Chem. Soc.* **2011**, *133*, 15244.

[30] X. Li, X. Gong, M. Zhao, G. Song, J. Deng, X. Li, *Org. Lett.* **2011**, *13*, 5808.

[31] T. Iitsuka, K. Hirano, T. Satoh, M. Miura, *Chem. Eur. J.* **2014**, *20*, 385.

[32] F. W. Patureau, C. Nimphius, F. Glorius, *Org. Lett.* **2011**, *13*, 6346.

[33] S. Rakshit, C. Grohmann, T. Besset, F. Glorius, *J. Am. Chem. Soc.* **2011**, *133*, 2350.

[34] X. Huang, J. Huang, C. Du, X. Zhang, F. Song, J. You, *Angew. Chem., Int. Ed.* **2013**, *52*, 12970.

[35] J. Bariwal, E. Van der Eycken, *Chem. Soc. Rev.* **2013**, *42*, 9283.

[36] a) Lawrence, S. A. *Amines:Synthesis Properties and Applications*; Cambridge University Press, Cambridge, **2004**;.b) Hili, R.; Yudin, A. K. *Nat. Chem. Biol.* **2006**, *2*, 284; c) *Amino Group Chemistry, From Synthesis to the Life Sciences*; Ricci, A., Ed.; Wiley-VCH: Weinheim, **2007**.

[37] a) F. Ullmann, *Ber. Dtsch. Chem. Ges.*, **1903**, *36*, 2382; b) I. Goldberg, *Ber. Dtsch. Chem. Ges.*, **1906**, *39*, 1691.

[38] a)J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534; b) D. S. Surry and S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27.

[39] J. X. Qiao, P. Y. S. Lam, *Synthesis* **2011**, 829.

[40] K. Shin, H. Kim, S. Chang, *Acc. Chem. Res.* **2015**, *48*, 1040.

[41] For selected publications on Rh-catalyzed C-N bond formation, see: a) J. Ryu, K. Shin, S. H. Park, J. Y. Kim, S. Chang, *Angew. Chem., Int. Ed.* **2012**, *51*, 9904; b) K. Shin, Y. Baek, S. Chang, *Angew. Chem., Int. Ed.* **2013**, *52*, 8031; c) T. Ryu, J. Min, W. Choi, W. H. Jeon, P. H. Lee, *Org. Lett.* **2014**, *16*, 2810; d) H.

Wang, Y. Yu, X. Hong, Q. Tan, B. Xu, *J. Org. Chem.* **2014**, *79*, 3279; e) X. Jia, J. Han, *J. Org. Chem.* **2014**, *79*, 4180.

[42] For selected publications on Ru-catalyzed C-N bond formation, see: a) M. Bhanuchandra, M. R. Yadav, R. K. Rit, M. R. Kuram, A. K. Sahoo, *Chem. Commun.* **2013**, *49*, 5225; b) V. S. Thirunavukkarasu, K. Raghuvanshi, L. Ackermann, *Org. Lett.* **2013**, *15*, 3286; c) Q.-Z. Zheng, Y.-F. Liang, C. Qin, N. Jiao, *Chem. Commun.* **2013**, *49*, 5654; d) V. S. Thirunavukkarasu, S. I. Kozhushkov, L. Ackermann, *Chem. Commun.* **2014**, *50*, 29.

[43] For selected publications on Ir-catalyzed C-N bond formation, see: [40] and H. Chen, M. P. Huestis, *ChemCatChem* **2015**, *7*, 743.

[44] a) Y.-K. Sau, X.-Y. Yi, K.-W. Chan, C.-S. Lai, I. D. Williams, W.-H Leung, *J. Organomet. Chem.* **2010**, *695*, 1399; b) Z. Liu, P. Sadler, *Acc. Chem. Res.* **2014**, *47*, 1174.

[45] J. Ryu, J. Kwak, K. Shin, D. Lee, S. Chang, *J. Am. Chem. Soc.* **2013**, *135*, 12861.

[46] a) J. Kim, S. Chang, *Angew. Chem., Int. Ed.* **2014**, *53*, 2203; b) H. Hwang, J. Kim, J. Jeong, S. Chang, *J. Am. Chem. Soc.* **2014**, *136*, 10770.

[47] a) D. Lee, S. Chang, *Chem. Eur. J.* **2015**, *21*, 5364; b) P. Becker, R. Pirwerdjan, C. Bolm, *Angew. Chem., Int. Ed.* **2015**, *54*, 15493.

[48] G. N. Hermann, P. Becker, C. Bolm, *Angew. Chem., Int. Ed.* **2016**, *55*, 3781.

[49] a) D. Lee, Y. Kim, S. Chang, *J. Org. Chem.* **2013**, *78*, 11102; b) H. Kim, J. Park, J. G. Kim, S. Chang, *Org. Lett.* **2014**, *16*, 5466; c) K. Shin, S. Chang, *J. Org. Chem.* **2014**, *79*, 12197; d) W. Hou, Y. Yang, W. Ai, Y. Wu, X. Wang, B. Zhou, Y. Li, *Eur. J. Org. Chem.* **2015**, 395.

[50] D. Gwon, D. Lee, J. Kim, S. Park, S. Chang, *Chem. Eur. J.* **2014**, *20*, 12421.

[51] a) T. Kang, H. Kim, J. G. Kim, S. Chang, *Chem. Commun.* **2014**, *50*, 12073; b) T. Kang, Y. Kim, D. Lee, Z. Wang, S. Chang, *J. Am. Chem. Soc.* **2014**, 136, 4141.

[52] D. L. Davies, O. Al-Duaij, M. Giardiello, S. T. Hilton, D. R. Russel, *Dalton. Trans.* **2003**, 4132.

[53] H. Kim, K. Shin, S. Chang, *J. Am. Chem. Soc.* **2014**, *136*, 5904.

[54] H. Kim, S. Chang, *ACS Catal.* **2015**, *5*, 6665.

[55] P. Patel, S. Chang, *Org. Lett.* **2014**, *16*, 3328.

[56] a) J. P.Michael, *Nat. Prod. Rep.*, **2008**, *25*, 166; b) S.-I. Murahashi, D. Zhang, *Chem. Soc. Rev.* **2008**, *37*, 1490; c) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335; d) L. Shi, W. Xia, *Chem. Soc. Rev.* **2012**, *41*, 7687.

[57] S. S. Kim, Y. J. Mah, A. R. Kim, *Tetrahedron Letters **2001**, 42*, 8315.

[58] Y. Pan, C. W. Kee, L. Chen, C.-H. Tan, *Green Chem.* **2011**, *13*, 2682.

[59] Z. Liang, S. Xu, W. Tian, R. Zhang, *Beilstein J. Org. Chem.* **2015,** *11*, 425.

[60] K. Itoh, R. Kato, D. Kinugawa, H. Kamiya, R. Kudo, M. Hasegawa, H. Fujii, H. Suga, *Org. Biomol. Chem.* **2015**, *13*, 8919.

[61] a) Y. Miyake, K. Nakajima, Y. Nishibayashi, *Chem. Eur. J.* **2012**, *18*, 16473; b) Y. Miyake, K. Nakajima, Y. Nishibayashi, *J. Am. Chem. Soc.* **2012**, *134*, 3338; c) Y.-Q. Zou, J.-R. Chen, W.-J. Xiao, *Angew. Chem., Int. Ed.* **2013**, *52*, 11701; d) L. R. Espelt, E. M. Wiensch, T. P. Yoon, *J. Org. Chem.* **2013**, *78*, 4107; e) X. Dai, D. Cheng, B. Guan, W. Mao, X. Xu, X. Li, *J. Org. Chem.* **2014**, *79*, 7212; f) X. Dai, R. Mao, B. Guan, X. Xu, X. Li, *RSC Adv.* **2015**, *5*, 55290.

[62] A. McNally, C. K. Prier, D. W. C. MacMillan, *Science* **2011**, *334*, 1114.

[63] A. Noble, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 11602.

[64] J. Xuan, T.-T. Zeng, Z.-J. Feng, Q.-H. Deng, J.-R. Chen, L.-Q. Lu, W.-J. Xiao, H. Alper, *Angew. Chem., Int. Ed.* **2015**, *54*, 1625.

[65] S. Zhu, A. Das, L. Bui, H. Zhou, D. P. Curran, M. Rueping, *J. Am. Chem. Soc.* **2013**, *135*, 1823.

[66] J. Xie, S. Shi, T. Zhang, N. Mehrkens, M. Rudolph, A. S. K. Hashmi, *Angew. Chem., Int. Ed.* **2015**, *54*, 6046.

[67] a) T. Yoshimitsu, Y. Arano, H. Nagaoka, *J. Am. Chem. Soc.* **2005**, *127*, 11610; b) T. Yoshimitsu, K. Matsuda, H. Nagaoka, K. Tsukamoto, T. Tanaka, *Org. Lett.* **2007**, *9*, 5115; c) L. Liu, Z. Wang, X. Fu, C.-H. Yan, *Org. Lett.* 2012, *14*, 5693; d) Y.-Y. Chen, X.-J Zhang, H.-M. Yuan, W.-T. Wie, M. Yan, *Chem. Commun.* **2013**, *49*, 10974.

[68] A. G. Condie, J. C. González-Gómez, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2010**, *132*, 1464.

[69] a) J. Xuan, Y. Cheng, J. An, L.-Q. Lu, X.-X. Zhang, W.-J. Xiao, *Chem. Commun.* **2011**, *47*, 8337; b) M. Rueping, D. Leonori, T. Poisson, *Chem. Commun.* **2011**, *47*, 9615; c) Y.-Q. Zou, L.-Q. Lu, L. Fu, N.-J. Chang, J. Rong, J.-R. Chen, W.-J. Xiao, *Angew. Chem., Int. Ed*. **2011**, *50*, 7171; d) G. Zhao, C. Yang, L. Guo, H. Sun, C. Chen, W. Xia, *Chem. Commun.* **2012**, *48*, 2337; e) Q. Xue, J. Xie, H. Jin, Y. Cheng, C. Zhu, *Org. Biomol. Chem.* **2013**, *11*, 1606; f) W. Li, X. Zhu, H. Mao, Z. Tang, Y. Cheng, C. Zhu, *Chem. Commun.* **2014**, *50*, 7521; g) G.-Q. Xu, C.-G. Li, M.-Q. Liu, J. Cao, Y.-C. Luo, P.-F. Xu, *Chem. Commun.* **2016**, *52*, 1190.

[70] J. F. Franz, W. B. Kraus, K. Zeitler, *Chem. Commun.* **2015**, *51*, 8280.

[71] a) Z.-Q. Lao, W.-H. Zhong, Q.-H. Lou, Z.-J. Li, X.-B. Meng, *Org. Biomol. Chem.* **2012**, *10*, 7869; b) J. Xie, H. Li, J. Zhou, Y. Cheng, C. Zhu, *Angew. Chem., Int. Ed.* **2012**, *51*, 1252; c) E. Boess, C. Schmitz, M. Klussmann, *J. Am. Chem. Soc.* **2012**, *134*, 5317; d) J. Dhineshkumar, M. Lamani, K. Alagiri, K. R. Prabhu, *Org. Lett.* **2013**, *15*, 1092; e) M. L. Deb, S. S. Dey, I. Bento, M. T. Barros, C. D. Maycock, *Angew. Chem., Int. Ed.* **2013**, *52*, 9791; f) M. O. Ratnikov, X. Xu, M. P. Doyle, *J. Am. Chem. Soc.* **2013**, *135*, 9475; g) A. Modak, U. Dutta, R. Kancherla, S. Maity, M. Bhadra, S. M. Mobin, D. Maiti, *Org. Lett.* **2014**, *16*, 2602; h) S. A. Girard, T. Knauber, C.-J. Li, *Angew. Chem., Int. Ed.* **2014**, *53*, 74.

[72] H. Richter, R. Fröhlich, C.-G. Daniliuc, O. G. Mancheño, *Angew. Chem., Int. Ed.* **2012**, *51*, 8656.

[73] a) Z. Li, C.-J. Li, *Org. Lett.* **2004**, *6*, 4997; b) Z. Li, P. D. MacLeod, C.-J. Li, *Tetrahedron: Asymmetry* **2006**, *17*, 590; c) C. Dubs, Y. Hamashima, N. Sasamoto, T. M. Seidel, S. Suzuki, D. Hashizume, M. Sodeoka, *J. Org. Chem.* **2008**, *73*, 5859; d) A. Sud, D. Sureshkumar, M. Klussmann, *Chem. Commun.* **2009**, 3169; e) J. Zhang, B. Tiwari, C. Xing, X. Chen, Y. R. Chi, *Angew. Chem., Int. Ed.* **2012**, *51*, 3649; f) S. Stockerla, O. G. Mancheño, *Org. Chem.*

Front. **2016**, *3*, 277.

[74] A. J. Neel, J. P. Hehn, P. F. Tripet, F. D. Toste, *J. Am. Chem. Soc.* **2013**, *135*, 14044.

[75] a) Y. Ban, Y. Murakami, Y. Iwasawa, M. Tsuchiya, N. Takano, *Med. Res. Rev.* **1988**, *8*, 231; b) M. Somei, F. Yamada, *Nat. Prod. Rep*. **2005**, *22*, 73; c) T. Kawasaki, K. Higuchi, *Nat. Prod. Rep.* **2005**, *22*, 761; d) K. Higuchi, T. Kawasaki, *Nat. Prod. Rep.* **2007**, *24*, 843; e) M. Bandini, A. Eichholzer, *Angew. Chem., Int. Ed.* **2009**, *48*, 9608; f) A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev.* **2010**, *110*, 4489; g) M. Z. Zhang, Q. Chen, G. F. Yang, *Eur. J. Med. Chem.* **2015**, *89*, 421; h) A. H. Sandtorv, *Adv. Synth. Catal.* **2015**, *357*, 2403.

[76] For selected publications on C2-position functionalization of indoles, see: a) X. Wang, B. S. Lane, D. Sames, *J. Am. Chem. Soc*. **2005**, *127*, 4996; b) N. R. Deprez, D. Kalyani, A. Krause, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 4972; c) S.-D. Yang, C.-L. Sun, Z. Fang, B.-J. Li, Y.-Z. Li, Z.-J. Shi, *Angew. Chem., Int. Ed.* **2008**, *47*, 1473; d) A. Garcia-Rubia, R. G. Arrayás, J. C. Carretero, *Angew. Chem., Int. Ed.* **2009**, *48*, 6511; e) D. J. Schipper, M. Hutchinson, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 6910; f) Z. Ding, N. Yoshikai, *Angew. Chem., Int. Ed.* **2012**, *51*, 4698; g) S. Pan, N. Ryu, T. Shibata, *J. Am. Chem. Soc.* **2012**, *134*, 17474; h) L. Jiao, E. Herdtweck, T. Bach, *J. Am. Chem. Soc.* **2012**, *134*, 14563; i) B. Li, J. Ma, W. Xie, H. Song, S. Xu, B. Wang, *Chem. Eur. J.* **2013**, *19*, 11863.

[77] For selected publications on C3-position functionalization of indoles, see: a) N. P. Grimster, C. Gauntlett, C. R. A. Godfrey, M. J. Gaunt, *Angew. Chem., Int. Ed.* **2005**, *44*, 3125; b) R. J. Phipps, N. P. Grimster, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 8172; c) W. Wu, W. Su, *J. Am. Chem. Soc.* **2011**, *133*, 11924; d) Y. Li, T. Yan, K. Junge, M. Beller, *Angew. Chem., Int. Ed.* **2014**, *53*, 10476; e) J. S. Alford, H. M. L. Davies, *J. Am. Chem. Soc.* **2014**, *136*, 10266; f) S. G. Modha, M. F. Greaney, *J. Am. Chem. Soc.* **2015**, *137*, 1416.

[78] For Pd-catalyzed indole C-2 alkenylation, see: a) E. Capito, J. M. Brown, A.

Ricci, *Chem. Commun.* **2005**, 1854; b) N. P. Grimster, C. Gauntlett, C. R. A. Godfrey, M. J. Gaunt, *Angew. Chem., Int. Ed.* **2005**, *44*, 3125; c) A. Maehara, H. Tsurugi, T. Satoh, M. Miura, *Org. Lett.* **2008**, *10*, 1159. For rhodium(III)-catalyzed indole C-2 alkenylation, see: d) F. W. Patureau, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9982; e) B. Li, J. Ma, W. Xie, H. Song, S. Xu, B. Wang, *Chem. Eur. J.* **2013**, *19*, 11863.

[79] For C-3 alkenylation, see: a) T. Itahara, K. Kawasaki, F. Ouseto, *Synthesis* **1984**, 236; b) W.-L. Chen, Y.-R. Gao, S. Mao, Y.-L. Zhang, Y.-F. Wang, Y.-Q. Wang, *Org. Lett.* **2012**, *14*, 5920; c) Q. Huang, Q. Song, J. Cai, X. Zhang, S. Lin, *Adv. Synth. Catal.* **2013**, *355*, 1512.

[80] Q. Liu, Q. Li, Y. Ma, Y. Jia, *Org. Lett.* **2013**, *15*, 4528.

[81] a) T. Asai, T. Yamamoto, Y. Oshima, *Tetrahedron Lett.* **2011**, *52*, 7042; b) M. Ishikura, T. Abe, T. Choshi, S. Hibino, *Nat. Prod. Rep.* **2013**, *30*, 694.

[82] For indoline C-7 position arylations: a) D. Kalyani, N. R. Deprez, L. V. Desai, M. S. Sanford, *J. Am. Chem. Soc.* **2005**, *127*, 7330; b) Z. Shi, B. Li, X. Wan, J. Cheng, Z. Fang, B. Cao, C. Qin, Y. Wang, *Angew. Chem., Int. Ed.* **2007**, *46*, 5554; c) T. Nishikata, A. R. Abela, S. Huang, B. H. Lipshutz, *J. Am. Chem. Soc.* **2010**, *132*, 4978; d) L.-Y. Jiao, M. Oestreich, *Chem. Eur. J.* **2013**, *19*, 10845; e) L.-Y. Jiao, M. Oestreich, *Org. Lett.* **2013**, *15*, 5374.

[83] For oxidation of indoline to indole using MnO_2, see: a) Y. S. Lo, D. A. Walsh, W. J., Jr. Welstead, R. P. Mays, E. K. Rose, D. H. Causey, R. L. J. Duncan, *Heterocycl. Chem.* **1980**, *17*, 1663; b) T. Kametani, T. Ohsawa, M. J. Ihara, *Chem. Soc., Perkin Trans. 1* **1981**, 290.

[84] a) N. Guimond, C. Gouliaras, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 6908; b) T. K. Hyster, T. Rovis, *J. Am. Chem. Soc*. **2010**, *132*, 10565.

[85] V. Lanke, K. R. Prabhu, *Org. Lett.* **2013**, *15*, 2818.

[86] a) C. G. Hartung, A. Fecher, B. Chapell, V. Snieckus, *Org. Lett.* **2003**, *5*, 1899; b) S. Paul, G. A. Chotana, D. Holmes, R. C. Reichle, R. E. Maleczka, M. R. Smith, *J. Am. Chem. Soc.* **2006**, *128*, 15552.

[87] a) M. Kim, N. K. Mishra, J. Park, S. Han, Y. Shin, S. Sharma, Y. Lee, E. Lee, J.

H. Kwak, I. S. Kim, *Chem. Commun.* **2014**, *50*, 14249; b) S. Pan, T. Wakaki, N. Ryu, T. Shibata, *Chem. Asian J.* **2014**, *9*, 1257; c) W. Ai, X. Yang, Y. Wu, X. Wang, Y. Li, Y. Yang, B. Zhou, *Chem. Eur. J.* **2014**, *20*, 17653; d) S. Pan, N. Ryu, T. Shibata, *Adv. Synth. Catal.* **2014**, *356*, 929; e) X. Yang, X. Hu, T. Loh, *Org. Lett.* **2015**, *17*, 1481; f) N. K. Mishra, T. Jeong, S. Sharma, Y. Shin, S. Han, J. Park, J. S. Oh, J. H. Kwak, Y. H. Jung, I. S. Kim, *Adv. Synth. Catal.* **2015**, *357*, 1149; g) Y. X. Wu, Y. X. Yang, B. Zhou, Y. C. Li, *J. Org. Chem.* **2015**, *80*, 1946; h) X. Wang, H. Y. Tang, H. J. Feng, Y. C. Li, Y. X. Yang, B. Zhou, *J. Org. Chem.* **2015**, *80*, 6238; i) J. Park, N. K. Mishra, S. Sharma, S. Han, Y. Shin, T. Jeong, J. S. Oh, J. H. Kwak, Y. H. Jung, I. S. Kim, *J. Org. Chem.* **2015**, *80*, 1818; j) W. Xie, B. Li, B. Wang, *J. Org. Chem.* **2016**, *81*, 396.

[88] D. W. Robbins, T. A. Boebel, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 4068.

[89] L. Xu, C. Zhang, Y. He, L. Tan, D. Ma, *Angew. Chem., Int. Ed.* **2016**, *55*, 321.

[90] Y. Yang, X. Qiu, Y. Zhao, Y. Mu, Z. Shi, *J. Am. Chem. Soc.* **2016**, *138*, 495.

[91] A search in Reaxys database (February 2016) for 7-(sulfonamido)-indole scaffold resulted in over 900 compounds with diverse bioactivity.

[92] During we preparing the manuscript, Chang and co-workers reported a method on a direct access to 7-aminoindoles *via* Iridium-catalyzed mild C−H amidation of *N*-pivaloylindoles with organic azides: Y. Kim, J. Park, S. Chang, *Org. Lett.* **2016**, *18*, 1892.

[93] C. Pan, A. Abdukader, J. Han, Y. Cheng, C. Zhu, *Chem. Eur. J.* **2014**, *20*, 3606.

[94] a) F. Xie, Z. Qi, S. Yu, X. Li, *J. Am. Chem. Soc.* **2014**, *136*, 4780; b) H. Wang, F. Xie, Z. Qi, X. Li, *Org. Lett.* **2015**, *17*, 920; c) P. Gao, W. Guo, J. Xue, Y. Zhao, Y. Yuan, Y. Xia, Z. Shi, *J. Am. Chem. Soc.* **2015**, *137*, 12231.

[95] a) T. Owa, H. Yoshino, T. Okauchi, K. Yoshimatsu, Y. Ozawa, N. H. Sugi, T. Nagasu, N. Koyanagi, K. Kitoh, *J. Med. Chem.* **1999,** *42*, 3789; b) R. Mohan, M. Banerjee, A. Ray, T. Manna, L. Wilson, T. Owa, B. Bhattacharyya, D. Panda, *Biochemistry* **2006**, *45*, 5440.

[96] M Banerjee, A. Poddar, G. Mitra, A. Surolia, T. Owa, B. Bhattacharyya, *J.*

Med. Chem. **2005,** *48*, 547.

[97] T. M. Figg, S. Park, J. Park, S. Chang, D. G. Musaev, *Organometallics* **2014**, *33*, 4076.

[98] C. R. Turlington, P. S. White, M. Brookhart, J. L. Templeton, *J. Am. Chem. Soc.* **2014**, *136*, 3981.

[99] a) A. G. Griesbeck, N. Hoffmann, K.-D. Warzecha, *Acc. Chem. Res.* **2007,** *40*, 128; b) Y. Miyake, K. Nakajima, Y. Nishibayashi, *J. Am. Chem. Soc.* **2012**, *134*, 3338; c) Y.-Q. Zou, J.- R. Chen, W.-J. Xiao, *Angew. Chem., Int. Ed.* **2013**, *52*, 11701; d) H. Zhou, P. Lu, X. Gu, P. Li, *Org. Lett.* **2013**, *15*, 5646; e) D. M. Schultz, T. P. Yoon, *Science* **2014**, *343*, 1239176; f) J. Xuan, T.-T. Zeng, Z.-J. Feng, Q.-H. Deng, J.-R. Chen, L.-Q. Lu, W.-J. Xiao, H. Alper, *Angew. Chem., Int. Ed.* **2015**, *54*, 1625.

[100] T. P. Nicholls, G. E. Constable, J. C. Robertson, M. G. Gardiner, A. C. Bissember, *ACS Catal.* **2016**, *6*, 451.

[101] R. B. Roy, G. A. Swan, *J. Chem. Soc. C,* **1969**, 1886.

[102] S. Murata, K. Teramoto, M. Miura, M. Nomura, *Heterocycles* **1993**, *36*, 2147.

[103] M. Nishino, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2011**, *76*, 6447.

[104] X. Ju, D. Li, W. Li, W. Yu, F. Bian, *Adv. Synth. Catal.* **2012**, *354*, 3561.

[105] J. Tang, G. Grampp, Y. Liu, B.-X. Wang, F.-F. Tao, L.-J. Wang, X.-Z. Liang, H.-Q. Xiao, Y.-M. Shen, *J. Org. Chem.* **2015**, *80*, 2724.

[106] a) A. Rudi, Y. Kashman, *J. Org. Chem.* **1989**, *54*, 5331; b) J. M. Fevig, I. S. Mitchell, T. Lee, W. Chen, J. Cacciola, "Substituted pyrroloquinolines and pyridoquinolines as serotonin agonists and antagonists," PCT/US01/49380, Dec. 19, 2001; c) J. M. Fevig, J. Feng, S Ahmad, "Pyrrolo(oxo)quinolones as 5HT ligands," US 2006/0014778 Al, Jan. 19, 2006; d) S. Si, N. Li, D. Li, Y. Xue, Y. Li, C. Liu, T. Feng, W. Jiang, W. Liu, Z. Wang, X. He, Y. Wu, X. Wang, "Substituted benzamides as liver X receptors agonist and application," CN 104151287 A, Nov. 19, 2014.

[107] a) W.-P. Mai, G. Song, J.-W. Yuan, L.-R. Yang, G.-C. Sun, Y.-M. Xiao, P. Mao, L.-B. Qu, *RSC Adv.* **2013**, *3*, 3869; b) S. Wang, J. Wang, R. Guo, G. Wang,

S.-Y. Chen, X.-Q. Yu, *Tetrahedron Lett.* **2013**, *54*, 6233; c) A. Gogoi, A. Modi, S. Guin, S. K. Rout, D. Das, B. K. Patel, *Chem. Commun.* **2014**, *50*, 10445; d) X.-F. Wu, J.-L. Gong, X. Qi, *Org. Biomol. Chem.* **2014**, *12*, 5807.

[108] C. Zhang, C. Liu, Y. Shao, X. Bao, X. Wan, *Chem. Eur. J.* **2013**, *19*, 17917.

[109] a) A. Strub, W.-R. Ulrich, C. Hesslinger, M. Eltze, T. Fuchß, J. Strassner, S. Strand, M. D. Lehner, R. Boer, *Mol Pharmacol* **2006**, *69*, 328; b) V. Bavetsias, C. Sun, N. Bouloc, J. Reynisson, P. Workman, S. Linardopoulos, E. McDonald, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6567; c) A. J. Rosenberg, J. Zhao, D. A. Clark, *Org. Lett.*, **2012**, *14*, 1764.

[110] K. V. Bukhryakov, A. V. Kurkin, M. A. Yurovskaya, *Chemistry of Heterocyclic Compounds* **2011**, *47*, 533.

[111] a) B. L. Zou, Q. L. Yuan, D. W. Ma, *Angew. Chem., Int. Ed.* **2007**, *46*, 2598; b) N. Zheng, K. W. Anderson, X. H. Huang, H. N. Nguyen, S. L. Buchwald, *Angew. Chem., Int. Ed.* **2007**, *46*, 7509; c) C. Salomé, M. Schmitt, J.-J. Bourguignon, *Tetrahedron Letters*. **2009**, *50*, 3798.

[112] A. D. Dunn, *OPPI BRIEFS*, **1998**, *30*, 709.

[113] S. Wertz, S. Kodama, A. Studer, *Angew. Chem., Int. Ed.* **2011**, *50*, 11511.

[114] B. L. Ryland, S. D. McCann, T. C. Brunold, S. S. Stahl, *J. Am. Chem. Soc.* **2014**, *136*, 12166.

[115] a) Y. Ma, C. Loyns, P. Price, V. Chechik, *Org. Biomol. Chem.* **2011**, 9, 5573; b) M. Hayashi, M. Shibuya, Y. Iwabuchi, *J. Org. Chem.* **2012**, *77*, 3005.

[116] F. Shi, X. Xu, L. Zheng, Q. Dang, X. Bai, *J. Comb. Chem.* **2008,** *10*, 158.

[117] D. Yang, S. Mao, Y.-R. Gao, D.-D. Guo, S.-H. Guo, B. Li, Y.-Q. Wang, *RSC Adv.* **2015**, *5*, 23727.

[118] C.-W. Chan, Z. Zhou, W.-Y. Yua, *Adv. Synth. Catal.* **2011**, *353*, 2999.

[119] S. J. Cho, N. H. Jensen, T. Kurome, S. Kadari, M. L. Manzano, J. E. Malberg, B. Caldarone, B. L. Roth, A. P. Kozikowski, *J. Med. Chem.* **2009,** *52*, 1885.

[120] B. L. Kohn, T. Rovis, *Chem. Sci.* **2014**, *5*, 2889.

[121] R.-R. Liu, J.-J. Hong, C.-J. Lu, M. Xu, J.-R. Gao, Y.-X. Jia, *Org. Lett.* **2015**, *17*, 3050.

[122] J.-S. Yang, C.-P. Liu, G.-H. Lee, *Tetrahedron Letters* **2000**, *41*, 7911.

[123] T. Hostier, V. Ferey, G. Ricci, D. G. Pardo, J. Cossy, *Chem. Commun.* **2015**, *51*, 13898.

[124] Z.-L. Yan, W.-L. Chen, Y.-R. Gao, S. Mao, Y.-L. Zhang, Y.-Q. Wang, *Adv. Synth. Catal.* **2014**, *356*, 1085.

[125] G. He, C. Lu, Y. Zhao, W. A. Nack, G. Chen, *Org. Lett.* **2012**, *14*, 2944.

[126] Z. Liu, D. Zhu, B. Luo, N. Zhang, Q. Liu, Y. Hu, R. Pi, P. Huang, S. Wen, *Org. Lett.* **2014**, *16*, 5600.

[127] D. R. Stuart, E. Villemure, K. Fagnou, *J. Am. Chem. Soc.* **2007**, *129*, 12072.

[128] Y. Nakano, D. W. Lupton, *Chem. Commun.* **2014**, *50*, 1757.

[129] P. Feng, Y. Fan, F. Xue, W. Liu, S. Li, Y. Shi, *Org. Lett.* **2011**, *13*, 5827.

[130] T. Benkovics, I. A. Guzei, T. P. Yoon, *Angew. Chem., Int. Ed.* **2010**, *49*, 9153.

[131] C. Pi, X. Cui, Y. Wu, *J. Org. Chem.* **2015**, *80*, 7333.

[132] L. Wang, A. J. Borah, G. Yan, *Tetrahedron Letters* **2015**, *56*, 1353.

[133] Y. K. Kumar, G. R. Kumar, T. J. Reddy, B. Sridhar, M. S. Reddy, *Org. Lett.* **2015**, *17*, 2226.

[134] Y. Matano, H. Ohkubo, Y. Honsho, A. Saito, S. Seki, H. Imahori, *Org. Lett.* **2013**, *15*, 932.

[135] Z. Fu, J. Lee, B. Kang, S. H. Hong, *Org. Lett.* **2012**, *14*, 6028.

[136] R. S. Lewis, M. F. Wisthoff, J. Grissmerson, W. J. Chain, *Org. Lett.* **2014**, *16*, 3832.

[137] E. C. Creencia, K. Taguchi, T. Horaguchi, *J. Heterocyclic Chem.* **2008**, *45*, 837.

[138] V. A. Ozeryanskii, A. F. Pozharskii, A. S. Antonova, A. Filarowski, *Org. Biomol. Chem.* **2014**, *12*, 2360.

[139] O. Santoro, F. Lazreg, Y. Minenkov, L. Cavallob, C. S. J. Cazin, *Dalton Trans.* **2015**, *44*, 18138.

[140] S. Sueki, Y. Kuninobu, *Org. Lett.* **2013**, *15*, 1544.

[141] G. W. Gribble, C. F. Nutaitis, *Synthesis*, **1987**, 709.

[142] Y. Hua, S. Jung, J. Roh, J. Jeon, *J. Org. Chem.* **2015**, *80*, 4661.

[143] X. Ye, C. Xie, Y. Pan, L. Han, T. Xie, *Org. Lett.* **2010**, *12*, 4240.

[144] P. M. Lukasik, S. Elabar, F. Lam, H. Shao, X. Liu, A. Y. Abbas, S. Wang, *Eur. J. Med. Chem.* **2012**, *57*, 311.

[145] R. Hermann, M. Otto, Berichte der Deutschen Chemischen Gesellschaft [Abteilung] B: Abhandlungen, **1938**, *71B*, 1243.

[146] M. Shibuya, M. Tomizawa, Y. Iwabuchi, *J. Org. Chem.* **2008**, *73*, 4750.

VII Appendix

7.1 X-Ray Crystal Structure Data

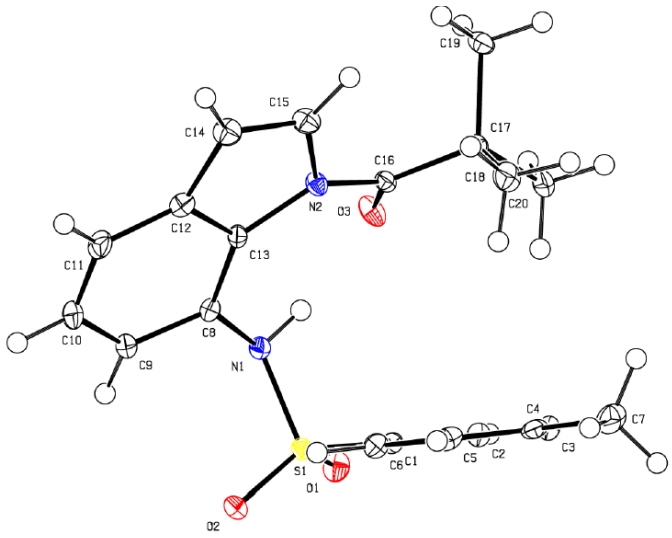


Figure 7.1 Crystal structure of product **88f**. X-Ray structure analysis was performed by Christopher Golz (TU Dortmund).

Table 7.1 Crystal data and structure refinement for **81a**.

Empirical formula	$C_{20}H_{22}N_2O_3S$
Formula weight	370.45
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	P 1 21/c 1
Unit cell dimensions	a = 13.479(3) Å α = 90° b = 9.092(2) Å β = 100.304(5)° c = 15.294(3) Å γ = 90°
Volume	1844.1(7) $Å^3$
Z	4
Density (calculated)	1. 334 g/cm^3
Absorption coefficient	0.198 mm^{-1}
F(000)	784
Crystal size	0.092 x 0.134 x 0.208 mm

Theta range for data collection	2.62 to 29.00°
Index ranges	-18<=h<=18, -12<=k<=12, -17<=1<=20
Reflections collected	25217
Independent reflections	4904 [R(int) = 0.0510]
Completeness to theta = 28.998°	99.9%
Max. and min. transmission	0.746 and 0.621
Data / restraints / parameters	4904 / 0 / 239
Refinement method	Full-matrix least-squares on F2
Goodness-of-fit on F^2	1.040
Final R indices [I>2sigma(I)]	R1 = 0.0386, wR2 = 0.0969
R indices (all data)	R1 = 0.0492, wR2 = 0.1029
Largest diff. peak and hole	0.372 and -0.593 $eÅ^{-3}$

Table 7.2 Atomic coordinates ($\times 10^4$) and equivalent isotropic atomic displacement parameters ($Å^2 \times 10^3$) for **81a**.

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
S(1)	0.21185(2)	4748(3)	6119(2)	113(9)
O(1)	0.11208(7)	4143(11)	5920(7)	170(2)
O(2)	0.29598(7)	3943(11)	5902(6)	161(2)
O(3)	0.13419(7)	7224(10)	7820(7)	164(2)
N(1)	0.23274(8)	5032(12)	7196(7)	119(2)
N(2)	0.29221(8)	8162(12)	8130(7)	119(2)
C(1)	0.20967(10)	6489(14)	5613(8)	119(2)
C(2)	0.11742(10)	7170(15)	5301(9)	144(3)
C(3)	0.11729(11)	8560(15)	4923(9)	169(3)
C(4)	0.20693(11)	9279(15)	4854(8)	165(3)
C(5)	2981(11)	8564(15)	5158(9)	166(3)
C(6)	3005(10)	7171(15)	5538(9)	146(3)

C(7)	2056(13)	806(16)	4470(10)	240(3)
C(8)	3291(10)	5488(14)	7666(8)	114(2)
C(9)	4078(10)	4468(15)	7748(9)	153(3)
C(10)	5054(11)	4803(16)	81789(9)	182(3)
C(11)	5274(10)	6158(16)	8567(9)	172(3)
C(12)	4494(10)	7185(15)	8525(9)	138(3)
C(13)	3504(9)	6864(14)	8081(8)	110(2)
C(14)	4503(10)	8665(15)	8857(9)	167(3)
C(15)	3568(10)	9216(15)	8614(9)	156(3)
C(16)	1872(10)	8316(14)	7899(8)	110(2)
C(17)	1403(10)	9851(14)	7709(9)	124(2)
C(18)	2010(12)	812(15)	7165(10)	195(3)
C(19)	1257(11)	616(15)	8576(9)	170(3)
C(20)	349(10)	9600(16)	7156(9)	181(3)

Table 7.3 Bond lengths (Å) and angles [°] for **81a**.

S(1)-O(1)	1.4345(10)	S(1)-O(2)	1.4375(10)
S(1)-N(1)	1.6412(12)	S(1)-C(1)	1.7598(14)
O(3)-C(16)	1.2165(16)	N(1)-C(8)	1.4288(17)
N(1)-H(1)	0.8801	N(2)-C(16)	1.4039(17)
N(2)-C(15)	1.4118(17)	N(2)-C(13)	1.4265(16)
C(1)-C(2)	1.3946(18)	C(1)-C(6)	1.3952(19)
C(2)-C(3)	1.3895(19)	C(2)-H(2)	0.95
C(3)-C(4)	1.394(2)	C(3)-H(3)	0.95
C(4)-C(5)	1.394(2)	C(4)-C(7)	1.5064(19)
C(5)-C(6)	1.3919(19)	C(5)-H(5)	0.95
C(6)-H(6)	0.95	C(7)-H(7)A	0.98
C(7)-H(7)B	0.98	C(7)-H(7)C	0.98
C(8)-C(9)	1.3977(18)	C(8)-C(13)	1.4094(18)

C(9)-C(10)	1.3944(19)	C(9)-H(9)	0.95
C(10)-C(11)	1.377(2)	C(10)-H(10)	0.95
C(11)-C(12)	1.3992(19)	C(11)-H(11)	0.95
C(12)-C(13)	1.4150(18)	C(12)-C(14)	1.4366(19)
C(14)-C(15)	1.346(2)	C(14)-H(14)	0.95
C(15)-H(15)	0.95	C(16)-C(17)	1.5374(18)
C(17)-C(20)	1.5352(19)	C(17)-C(18)	1.5387(19)
C(17)-C(19)	1.5414(18)	C(18)-H(18)A	0.98
C(18)-H(18)B	0.98	C(18)-H(18)C	0.98
C(19)-H(19)A	0.98	C(19)-H(19)B	0.98
C(19)-H(19)C	0.98	C(20)-H(20)A	0.98
C(20)-H(20)B	0.98	C(20)-H(20)C	0.98
O(1)-S(1)-O(2)	120.24(6)	O(1)-S(1)-N(1)	105.06(6)
O(2)-S(1)-N(1)	108.11(6)	O(1)-S(1)-C(1)	108.08(6)
O(2)-S(1)-C(1)	107.97(6)	N(1)-S(1)-C(1)	106.64(6)
C(8)-N(1)-S(1)	121.85(9)	C(8)-N(1)-H(1)	109.8
S(1)-N(1)-H(1)	109.9	C(16)-N(2)-C(15)	124.34(11)
C(16)-N(2)-C(13)	127.48(11)	C(15)-N(2)-C(13)	107.20(11)
C(2)-C(1)-C(6)	121.11(12)	C(2)-C(1)-S(1)	119.56(10)
C(6)-C(1)-S(1)	119.33(10)	C(3)-C(2)-C(1)	118.73(13)
C(3)-C(2)-H(2)	120.6	C(1)-C(2)-H(2)	120.6
C(2)-C(3)-C(4)	121.42(13)	C(2)-C(3)-H(3)	119.3
C(4)-C(3)-H(3)	119.3	C(5)-C(4)-C(3)	118.68(12)
C(5)-C(4)-C(7)	120.55(13)	C(3)-C(4)-C(7)	120.77(13)
C(6)-C(5)-C(4)	121.15(13)	C(6)-C(5)-H(5)	119.4
C(4)-C(5)-H(5)	119.4	C(5)-C(6)-C(1)	118.88(12)
C(5)-C(6)-H(6)	120.6	C(1)-C(6)-H(6)	120.6
C(4)-C(7)-H(7)A	109.5	C(4)-C(7)-H(7)B	109.5
H(7)A-C(7)-H(7)B	109.5	C(4)-C(7)-H(7)C	109.5

H(7)A-C(7)-H(7)C	109.5	H(7)B-C(7)-H(7)C	109.5
C(9)-C(8)-C(13)	117.30(12)	C(9)-C(8)-N(1)	117.41(11)
C(13)-C(8)-N(1)	125.25(11)	C(10)-C(9)-C(8)	122.26(13)
C(10)-C(9)-H(9)	118.9	C(8)-C(9)-H(9)	118.9
C(11)-C(10)-C(9)	120.77(12)	C(11)-C(10)-H(10)	119.6
C(9)-C(10)-H(10)	119.6	C(10)-C(11)-C(12)	118.34(12)
C(10)-C(11)-H(11)	120.8	C(12)-C(11)-H(11)	120.8
C(11)-C(12)-C(13)	121.39(12)	C(11)-C(12)-C(14)	130.48(12)
C(13)-C(12)-C(14)	108.10(12)	C(8)-C(13)-C(12)	119.85(11)
C(8)-C(13)-N(2)	133.55(12)	C(12)-C(13)-N(2)	106.51(11)
C(15)-C(14)-C(12)	107.62(12)	C(15)-C(14)-H(14)	126.2
C(12)-C(14)-H(14)	126.2	C(14)-C(15)-N(2)	110.56(12)
C(14)-C(15)-H(15)	124.7	N(2)-C(15)-H(15)	124.7
O(3)-C(16)-N(2)	119.42(11)	O(3)-C(16)-C(17)	120.57(12)
N(2)-C(16)-C(17)	119.96(11)	C(20)-C(17)-C(16)	106.11(10)
C(20)-C(17)-C(18)	108.37(11)	C(16)-C(17)-C(18)	112.19(11)
C(20)-C(17)-C(19)	107.02(11)	C(16)-C(17)-C(19)	111.02(11)
C(18)-C(17)-C(19)	111.79(11)	C(17)-C(18)-H(18)A	109.5
C(17)-C(18)-H(18)B	109.5	H(18)A-C(18)-H(18)B	109.5
C(17)-C(18)-H(18)C	109.5	H(18)A-C(18)-H(18)C	109.5
H(18)B-C(18)-H(18)C	109.5	C(17)-C(19)-H(19)A	109.5
C(17)-C(19)-H(19)B	109.5	H(19)A-C(19)-H(19)B	109.5
C(17)-C(19)-H(19)C	109.5	H(19)A-C(19)-H(19)C	109.5
H(19)B-C(19)-H(19)C	109.5	C(17)-C(20)-H(20)A	109.5
C(17)-C(20)-H(20)B	109.5	H(20)A-C(20)-H(20)B	109.5
C(17)-C(20)-H(20)C	109.5	H(20)A-C(20)-H(20)C	109.5
H(20)B-C(20)-H(20)C	109.5		

Table 7.4. Anisotropic atomic displacement parameters ($Å^2 \times 10^3$) for **81a**.

The anisotropic atomic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S(1)	12(16)	9(15)	12(15)	-1(10)	0(11)	0(11)
O(1)	14(5)	5(5)	20(5)	0(4)	-2(4)	0(4)
O(2)	18(5)	4(4)	16(5)	-2.7(3)	1(4)	5(4)
O(3)	12(5)	0(4)	28(5)	-1(4)	6(4)	-1(3)
N(1)	11(5)	2(5)	12(5)	0(4)	1(4)	1(4)
N(2)	11(5)	9(5)	15(5)	-1(4)	2(4)	0(4)
C(1)	15(6)	10(5)	10(6)	0(4)	1(5)	1(5)
C(2)	14(6)	16(6)	13(6)	0(5)	1(5)	2(5)
C(3)	21(7)	16(6)	13(6)	1(5)	1(5)	6(5)
C(4)	29(8)	12(6)	8(6)	-1(4)	1(5)	0(5)
C(5)	21(7)	16(6)	12(6)	-1(5)	2(5)	-5(5)
C(6)	14(6)	16(6)	14(6)	-0(5)	1(5)	0(5)
C(7)	39(9)	14(7)	17(7)	4(5)	0(6)	-1(6)
C(8)	12(6)	12(6)	10(6)	2(4)	0(5)	0(5)
C(9)	17(7)	14(6)	14(6)	(5)	0(5)	4(5)
C(10)	14(7)	22(7)	18(6)	1(5)	0(5)	8(5)
C(11)	11(6)	23(7)	16(6)	1(5)	-1(5)	2(5)
C(12)	13(6)	16(6)	12(6)	0(5)	2(5)	-2(5)
C(13)	10(6)	12(6)	11(6)	2(4)	2(4)	2(4)
C(14)	14(6)	17(6)	18(7)	-3(5)	1(5)	-3(5)
C(15)	16(6)	13(6)	18(6)	-3(5)	2(5)	-3(5)
C(16)	12(6)	10(5)	11(6)	0(4)	4(5)	1(4)
C(17)	15(6)	9(5)	13(6)	0(4)	3(5)	2(5)
C(18)	26(8)	14(6)	20(7)	5(5)	8(6)	1(5)
C(19)	22(7)	14(6)	15(6)	-2(5)	6(5)	4(5)

C(20)	16(7)	18(7)	19(7)	-2(5)	-1(5)	7(5)

7.2 Abbreviations

Ac	acetyl
acac	acetylacetonate
Ad	adamantly
Ag	silver
AIBN	azobisisobutyronitrile
aq.	aqueous
atm	standard atmosphere
Boc	*tert*-butyloxycarbonyl
bpy	bipyridine
BQ	1,4-benzoquinone
Bz	benzoyl
Cbz	carboxybenzyl
CDC	cross-dehydrogenative coupling
Co	cobalt
COMAS	Compound Management and Screening Center
conc.	concentrated
Cp*	pentamethylcyclopentadieny
Cu	copper
DCBP	4,4′-dichlorobenzophenone
DCE	1,2-dichloroethane
DCM	dichloromethane

DCP	dicumyl peroxide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DG	directing group
DIAD	diisopropyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppm	bis(diphenylphosphanyl)methane
dtb	di-*tert*-butyl
DTBP	di-*tert*-butyl peroxide
EWG	electron-withdrawing group
Fe	iron
Fw	molecular weight
HFIP	hexafluoro-2-propanol
IC_{50}	half maximal inhibitory concentration
Ir	iridium
NFSI	*N*-fluorobenzenesulfonimide
4-NHAcT^{+}BF$_4^{-}$	4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxo-ammonium tetrafluoroborate
Ni	nickel
NIS	*N*-iodosuccinimide
nm	nanometer

o	ortho
oxone	potassium peroxomonosulfate
p	para
PAs	phosphoric acid
Pd	palladium
PhINTs	*N*-tosyliminobenzyliodinane
Phth	phthaloyl
PIDA	(diacetoxyiodo)benzene
piv	pivaloyl
ppy	2-phenylpyridine
RB	Rose Bengal
Rh	rhodium
Ru	ruthenium
rt	room temperature
SET	single electron transfer
TBAI	tetrabutylammonium iodide
$T^+BF_4^-$	2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate
TBHP	*tert*-butyl hydroperoxide
TBPB	*tert*-butyl peroxybenzoate
TBTU	2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate

TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TFA	trifluoroacetic acid
TMS	trimethylsilyl
Troc	trichloroethyl carbamate
Ts	*para*-toluenesulfonyl
UV	ultraviolet

7.3 Ackonwledgements

First of all, I would like to express my gratitude to Prof. Dr. H. Waldmann for giving me the opportunity to perform my PhD studies in his department. His broad knowledge in chemical biology and his enthusiasm in academic have deeply impressed me and influenced me in my studies; his brilliant ideas and great patience always inspire me and guide me in doing my research.

I also would like to express my gratefulness to Dr. Andrey P. Antonchick for his supervision during my PhD studies. I thank him to give me the chance to work with these fascinating projects, his valuable suggestions and discussions, especially, his patience with day-to-day scientific problems. His help in the research and beyond gave me the strong courage and motivation to overcome all the problems, which I met in my studies in here. Without his supervision, I am not able to carry the work reported in this thesis.

Special thanks go to Prof. Dr. Rajashi Samanta for his collaboration and contribution on my first paper. His expertise in organic chemistry and good experimental skill helped me a lot during our cooperation.

I gratefully acknowledge the Chinese Scholarship Council (CSC) for the financial support during my studies in Germany.

I wish to thank Luis Bering, Dr. Jomy Kuruthukulangara-Joseph, Dr. Michael Sheremet, Dr. Marco Potowski and Zhi-Jun Jia for careful proof and correction of my thesis.

I would like to thank Dr. Sonja Sievers, Dr. Shobhna Kapoor, Sumersing Patil and Marjorie Carnero-Corrales for help in biological part of my thesis.

Great thanks go to all my colleagues who have accompanied me in these four years. I thank Dr. Michael Sheremet, Yen-Chun Lee, Walter Hofer, Dr. Srinivas Kalidindi, Zhi-Jun Jia, Dr. Rishikesh Narayan, Dr. Sandip Murarka, Srimanta Manna, Dr. Kiran Matcha, Dr. Sara López-Tosco, Dr. Srinivasa Rao-Vidadala, Luis Bering, Dr. Marco Potowski, Dr. Hao Xu, Dr. Erchang Shang, Dr. Gontla Rajesh, Dr. Andrei Ursu, Malte Metz, Dr. Jomy Kuruthukulangara-Joseph, Sumersing Patil, Svetlana Gerdt, Katharina

Kuhr, Chantale Martin and Roberta Caporaso for creating a great working atmosphere and enjoyable times, which will be a good memory in my whole life. I also acknowledge other members in our department and university for their help and impressive time together.

In addition, I would like to thanks all employees of the analytic team and COMAS team. Especially, I want to thanks Chantale Martin, Katharina Kuhr, Malte Metz, Christiana Heitbrink for HRMS measurements, Svetlana Gerdt for LC-MS, GC-MS measurements and Christopher Golz for X-ray measurements.

Finally, I want to express my profound gratitude to my family, relatives and friends, especially, my parents, my brother and my sister, for their constant support and encouragement during these four years.

Thanks!

7.4 Eidesstattliche Versicherung (Affidavit)

Name, Vorname
(Surname, first name)

Matrikel-Nr.
(Enrolment number)

Belehrung: Wer vorsätzlich gegen eine die Täuschung über Prüfungsleistungen betreffende Regelung einer Hochschulprüfungsordnung verstößt, handelt ordnungswidrig. Die Ordnungswidrigkeit kann mit einer Geldbuße von bis zu 50.000,00 € geahndet werden. Zuständige Verwaltungsbehörde für die Verfolgung und Ahndung von Ordnungswidrigkeiten ist der Kanzler/die Kanzlerin der Technischen Universität Dortmund. Im Falle eines mehrfachen oder sonstigen schwerwiegenden Täuschungsversuches kann der Prüfling zudem exmatrikuliert werden, § 63 Abs. 5 Hochschulgesetz NRW. Die Abgabe einer falschen Versicherung an Eides statt ist strafbar. Wer vorsätzlich eine falsche Versicherung an Eides statt abgibt, kann mit einer Freiheitsstrafe bis zu drei Jahren oder mit Geldstrafe bestraft werden, § 156 StGB. Die fahrlässige Abgabe einer falschen Versicherung an Eides statt kann mit einer Freiheitsstrafe bis zu einem Jahr oder Geldstrafe bestraft werden, § 161 StGB. Die oben stehende Belehrung habe ich zur Kenntnis	Official notification: Any person who intentionally breaches any regulation of university examination regulations relating to deception in examination performance is acting improperly. This offence can be punished with a fine of up to EUR 50,000.00. The competent administrative authority for the pursuit and prosecution of offences of this type is the chancellor of the TU Dortmund University. In the case of multiple or other serious attempts at deception, the candidate can also be unenrolled, Section 63, paragraph 5 of the Universities Act of North Rhine-Westphalia. The submission of a false affidavit is punishable. Any person who intentionally submits a false affidavit can be punished with a prison sentence of up to three years or a fine, Section 156 of the Criminal Code. The negligent submission of a false affidavit can be punished with a prison sentence of up to one year or a fine,Section 161 of the Criminal Code.

Ort, Datum
(Place, date)

Unterschrift
(Signature)

Titel der Dissertation:
(Title of the thesis):

Ich versichere hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Titel selbstständig und ohne unzulässige fremde Hilfe angefertigt habe. Ich habe keine anderen als die angegebenen Quellen und Hilfsmittel benutzt sowie wörtliche und sinngemäße Zitate kenntlich gemacht. Die Arbeit hat in gegenwärtiger oder in einer anderen Fassung weder der TU Dortmund noch einer anderen Hochschule im Zusammenhang mit einer staatlichen oder akademischen Prüfung vorgelegen.	I hereby swear that I have completed the present dissertation independently and without inadmissible external support. I have not used any sources or tools other than those indicated and have identified literal and analogous quotations. The thesis in its current version or another version has not been presented to the TU Dortmund University or another university in connection with a state or academic examination.

Ort, Datum
(Place, date)

Unterschrift
(Signature)

7.5 Curriculum Vitae

Personal:

Name:	Zengqiang Song
Date of birth:	24/08/1987
Place of birth:	Tianshui, China

Education:

09/2012-08/2016	**PhD Studies** Department of Chemistry and Chemical Biology of the Technical University of Dortmund and the Max Planck Institute of Molecular Physiology, Dortmund (Germany) Supervisor: Prof. Dr. H. Waldmann and Dr. A. P. Antonchick Topic: Development of Efficient Methods for the Synthesis of Heterocycles *via* Direct C–H Bond Fucntionalization Scholarship: China Scholarship Council (CSC)
09/2009-08/0212	**Master Studies** State Key Laboratory of Applied Organic Chemistry, Lanzhou University (China) Supervisor: Prof. Dr. H. Zhai Topic: Studies on Construction of Heterocycles from Benzyl Azides
09/2005-08/2009	**Bachelor Studies** Chemistry and chemical engineering college, Lanzhou University (China)

7.6 Spectra of Part 3.2.1.4

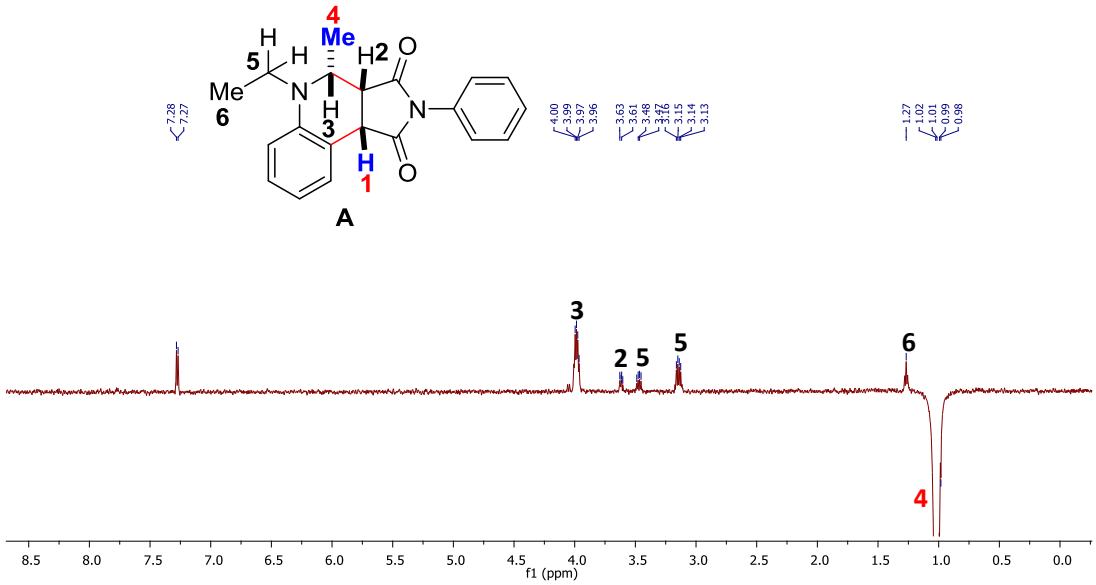


Figure 7.2 NOE spectra of **91r** (**A**).

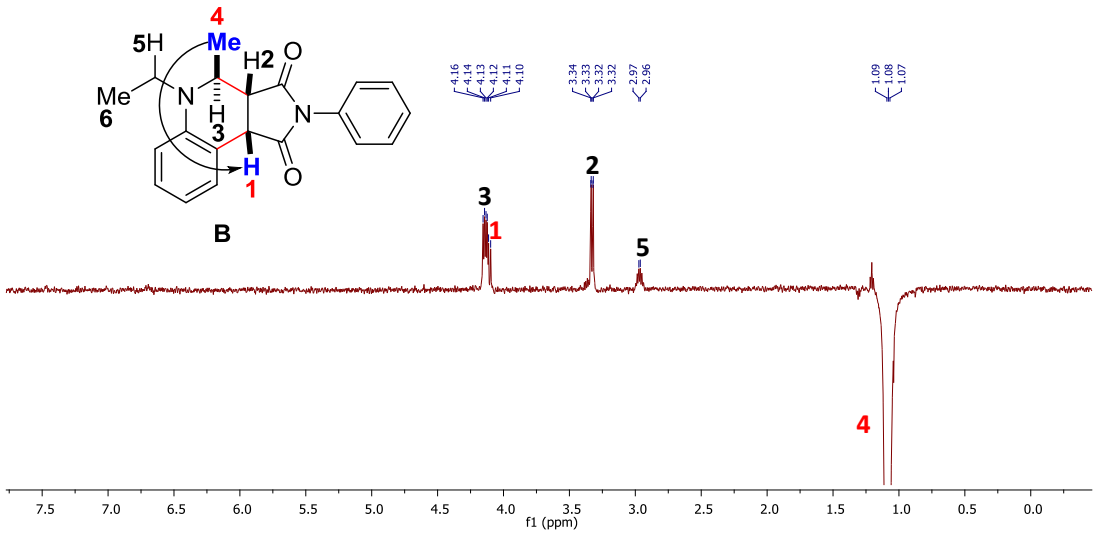


Figure 7.3 NOE spectra of **91r** (**B**).

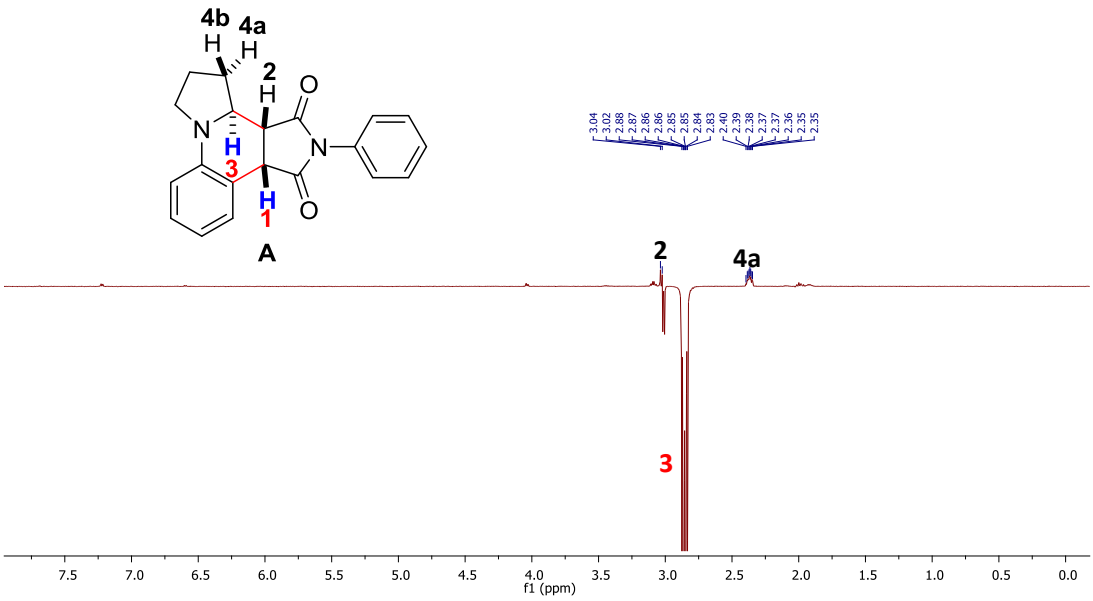


Figure 7.4 NOE spectra of **91s** (**A**).

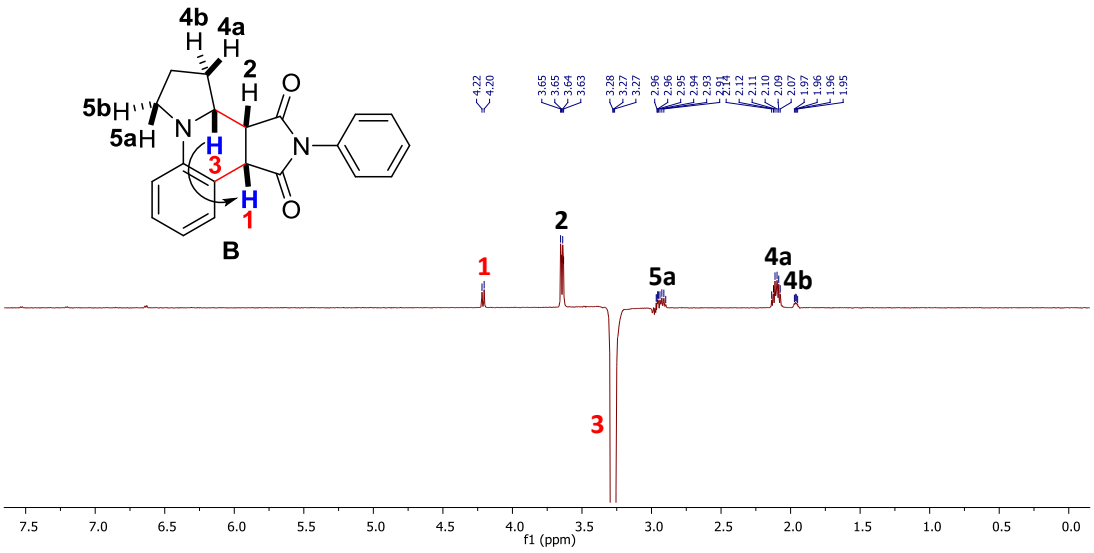


Figure 7.5 NOE spectra of **91s** (**B**).

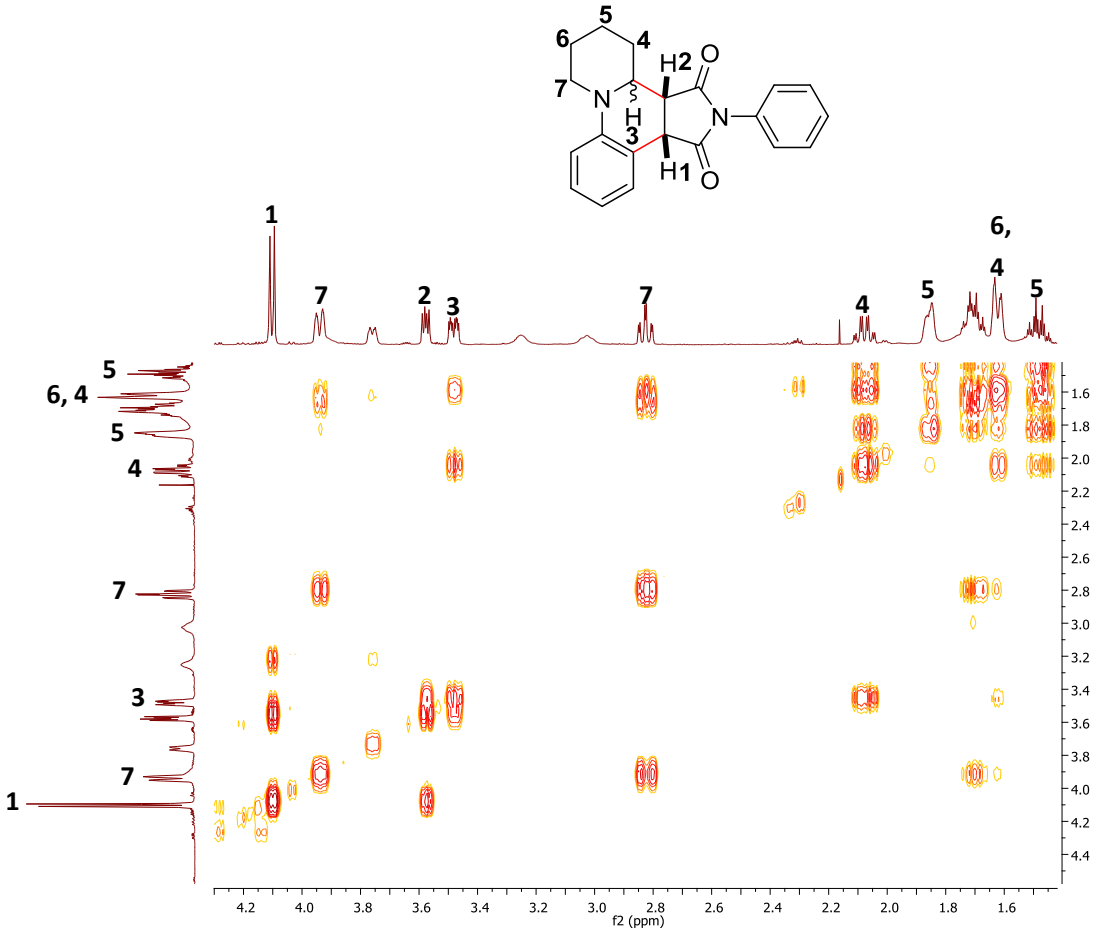


Figure 7.6 H–H COSY spectra of **91t**.

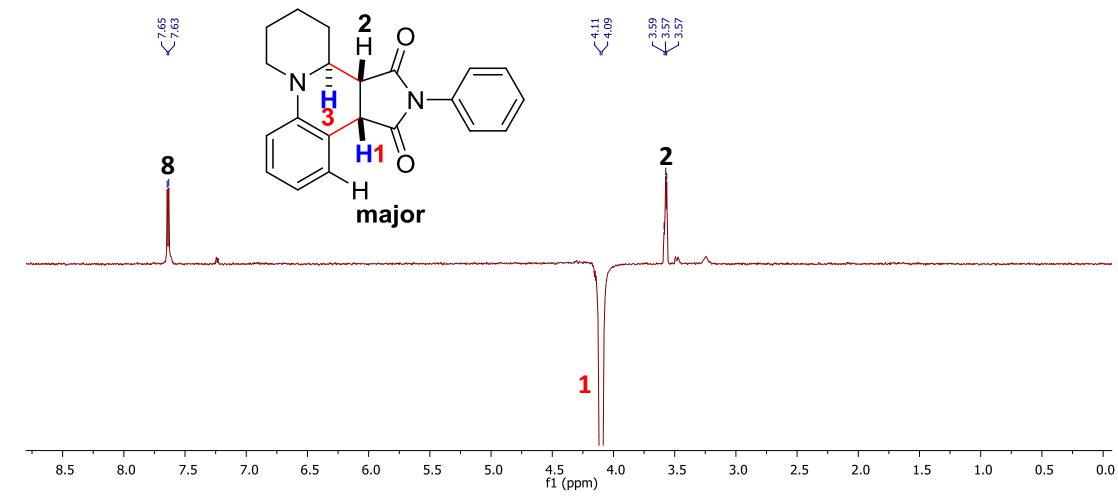


Figure 7.7 NOE spectra of **91t** (**major**).