이학석사 학위논문

Indolyl 1,3-Heteroatom Transposition: Mechanistic Investigation and Application

인돌릴 1,3-헤테로원자 전위:
반응 기작 조사와 적용

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Department of Chemistry
The Graduate School
Seoul National University

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위 원 장 _____(인)

부위원장 _____(인)

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Abstract

Indolyl 1,3-Heteroatom Transposition: Mechanistic Investigation and Application

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As an effective and versatile approach to indole C3-Heterofunctionalization, the 1,3-Heteroatom Transposition reaction of *N*-hydroxyindole was developed. To elucidate the unique nature of this reaction, experiments were conducted from various perspectives: ^{18}O labeling experiments, crossover experiments, and radical experiments. The results revealed the simultaneous involvement of two independent mechanisms, highlighting the unique duality nature of the reaction. In addition, the electronics of the internal substitution regulate the main pathways of the reaction and control the activation energy of each pathway. Furthermore, the possibility of enantioselective version was explored using an external chiral guanidinium organic catalyst, which promotes the IHT reaction through hydrogen bonding.

Keywords: *N*-hydroxyindole, hetero atom, mechanism, duality, guanidinium catalyst, hydrogen bonding

Student Number: 2021-25569

Respective Contributions

This work is the result of extensive collaboration between the author and other researchers. The specific contributions of the author are outlined below.

Chapter 1

Yujin Lee conceived the research and identified the reactivity for the first time. The author and Yujin Lee developed the synthetic protocol and conducted experiments to demonstrate the substrate scope. Yujin Lee carried out the investigation of reaction mechanism. The author carried out the synthesis of starting materials, including tryptamine derivatives, indole derivatives, and indoline derivatives. Soo Young Kim and Jeongeun Ki participated in the synthesis of indoline derivatives.

Contents

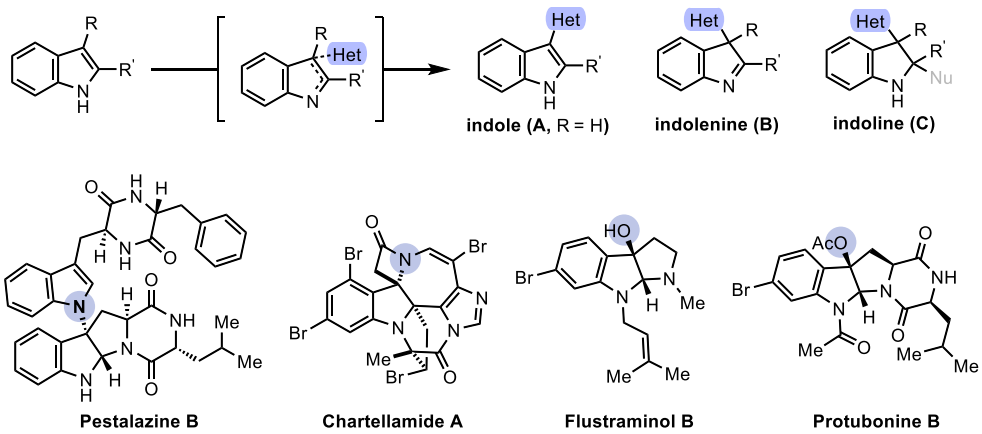
Chapter 1. Indolyl 1,3-Heteroatom Transposition Reaction: Mechanistic Investigation and C3-Heteroatom Functionalization of Indole Derivatives

Part 1. Mechanistic Investigation of IHT Reaction

1.1. Introduction

Indole is one of the most important and abundant heteroaromatic scaffold in both alkaloid natural products and various biologically active molecules.[1] However, tautomeric form of indole known as indolenine and its reduced analogs, referred to as indoline also possess substantial importance. Particuarly, by introducing a heteroatom at the 3-position of indole derivatives, the resulting molecules can exhibit diverse chemical and biological characteristics, providing opportunities for the discovery of new drugs, agrochemicals, materials, and other applications (Figure 1.1).

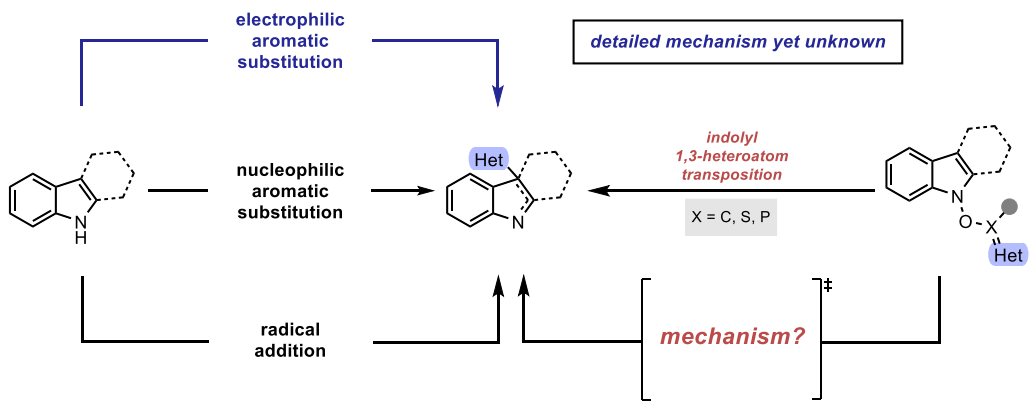
Figure 1.1. C3-Hetreo-Functionalized Indole Derivatives



Therefore, a considerable amount of research has been dedicated to the development of C3-heterofunctionalized structures, either in the form of an indole (**A**), indolenine (**B**), or indoline

(**C**) (Figure 1.2). One of the most classic approaches involves electrophilic aromatic substitution, taking advantage of the inherent nucleophilic nature of the indole C3 position, which readily reacts with external electrophilic heteroatoms.[2] An alternative strategy involves employing the nucleophilic heteroatoms through nucleophilic aromatic substitution.[3] Oxidation of indole brings about a reversal of its primary reactivity, resulting in the induction of electrophilic properties at the 3-position. The use of radical addition strategy also has emerged as a growing field to functionalize the indolyl framework.[4] However, still general access to all three types of indole derivatives remains a challenging task. This is mainly due to the inherent reactivity of the products and the compatibility of the reagents employed for their synthesis. Indolyl-1,3-heteroatom transposition (**IHT**) is a viable approach for addressing such synthetic problems (Figure 1.2 (d)).

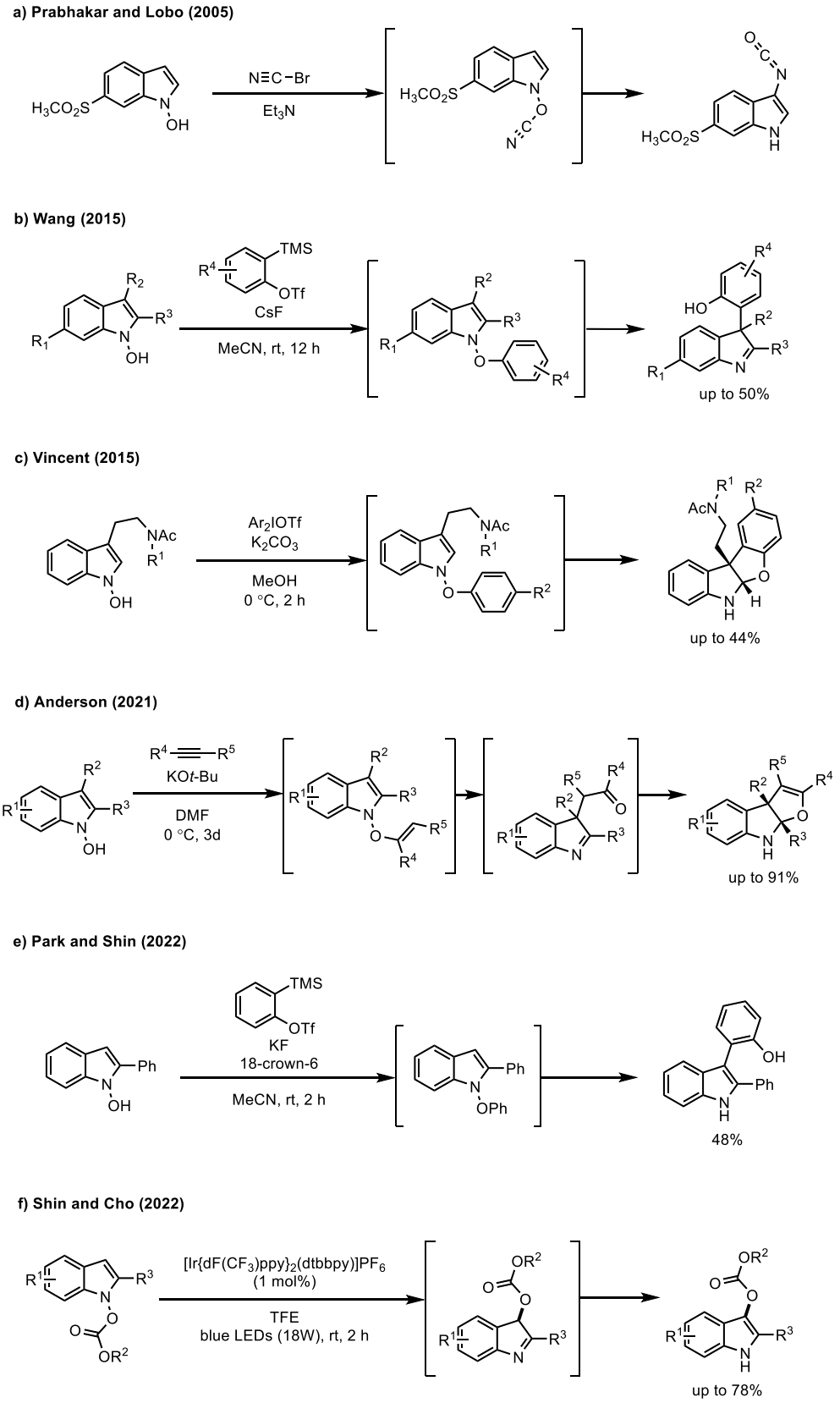
Figure 1.2. Synthetic Strategies for the C3-Hetero-Functionalization



Sundberg first described the rearrangement reaction of readily accessible *N*-hydroxyindole derivatives, which was later expanded by Hamana and Somei. This reaction involves the C3-oxygenation with the intermediacy of the corresponding ester, phosphonate, or sulfonate.[5] Over time, the **IHT** strategy and its variants were used to functionalize the 3-position of indole derivatives (Scheme 1.1)[6-11] along with other related heterocycles.[12-13] In 2005, Prabhakar and Lobo reported C3-amidation of 6-(methylsulfonyl)-1H-indol-1-ol in the presence of Et_3N and

cyanogen bromide.[6] The C3-aryl indolenine product with 2,3-substituted hydroxyindole was obtained by the Wang group in 2015, and they presumed that the mechanism is [3,3]-rearrangement.[7] In the same year, the Vincent group reported a reaction between tryptamine and highly electron-deficient 2,4-dinitrofluorobenzene, which could directly yield benzofuroindoline at 0 °C.[8] Anderson group utilized 2,3-substituted *N*-hydroxyindole to generate the *N*-alkenyloxyindole intermediates. The intermediates were allowed to undergo N–O bond cleavage to drive aromatization and quaternary center formation, forming furo[2,3-b]indolines.[9] In 2022, Park and Shin group also observed smooth [3,3]-sigmatropic rearrangement of *N*-phenoxy-2-Ph-indole.[10] Shin and Cho reported visible light promoted intramolecular radical rearrangement of *N*-indolyl carbonate, affording valuable 3-oxyindole derivatives.[11]

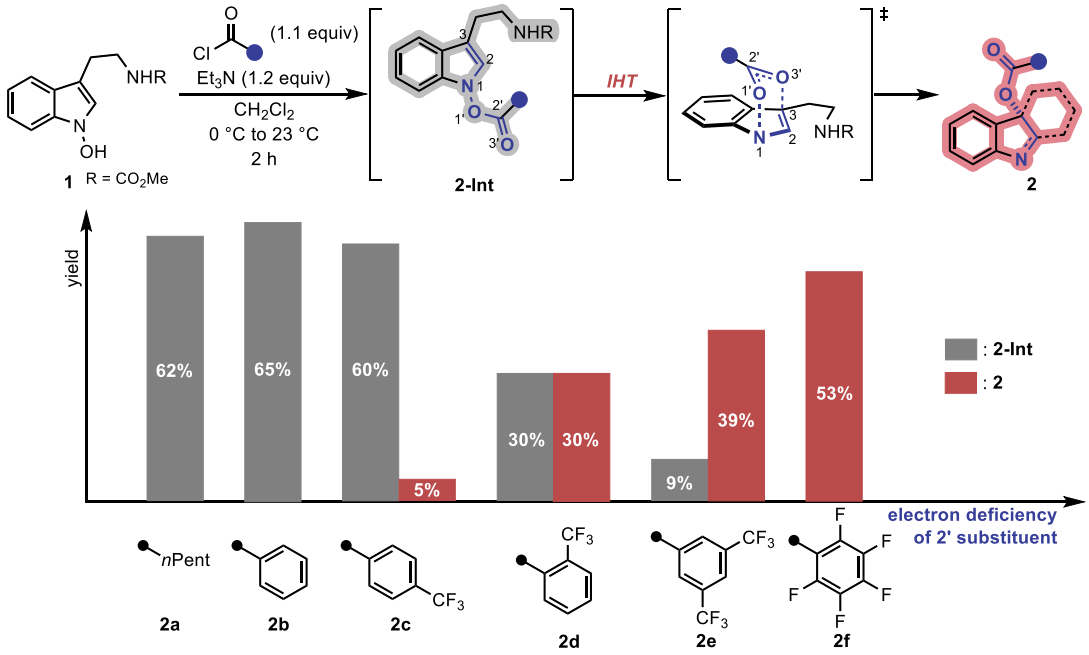
Scheme 1.1. C3-Functionalization of Indole Derivatives with **IHT** Strategy



Related rearrangements of N-oxyenamines[14] and the mechanisms of 1-aza-1'-oxa-cope have undergone thorough investigations.[15] It is confirmed to be a [3,3]-sigmatropic rearrangement, driven by a symmetry-allowed concerted pericyclic process. However, the understanding of the mechanistic aspects underlying the **IHT** system remains limited. Therefore, our aim was to uncover the distinct mechanistic strategy demonstrated by **IHT** reaction using *N*-hydroxyindole and apply it as a basis for developing the general synthetic strategy for functionalization of indole derivatives.

We initially observed the **IHT** reaction tuned by electronic properties of the 2'-postion (Figure 1.3). *N*-hydroxytryptamine derivative (**1a**) underwent **IHT** reaction at room temperature with carboxylic acids having different electronic properties. When coupling with *n*-hexanoic acid (entry 1) or unsubstituted benzoic acid (entry 2), the reaction resulted in solely direct *O*-acylation products (**2-int**). However, with increased electron-deficiency in the arene portion of the acyl donor, the rearrangement products were produced as a mixture with the acylation intermediate (entry 3–5). Finally, the use of pentafluorobenzoic acid exclusively furnished the rearrangement product with a 53% yield (entry 6). This outcome clearly indicates a strong correlation between reaction efficiency and the electron deficiency of the substituent at the 2'-position.

Figure 1.3. Identification of 2'-Substituent Effect in the **IHT** Reaction[a]



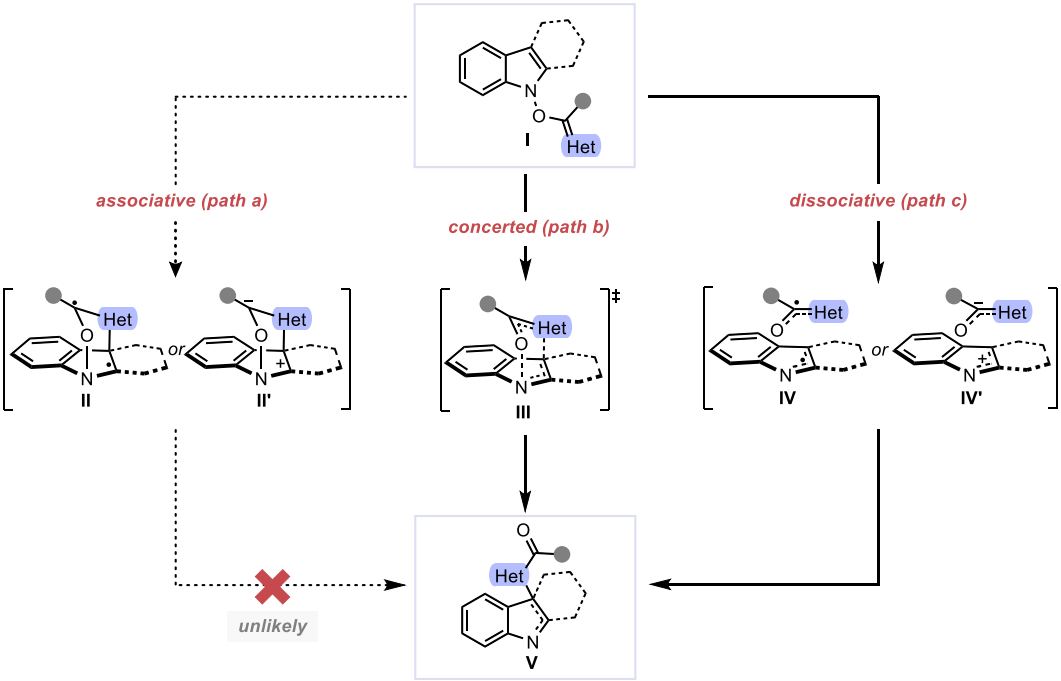
[a]Reaction conditions: **1a** (0.201 mmol, 1.0 equiv) in CH_2Cl_2 (0.05 M), benzoyl chloride (1.1 equiv), Et_3N (1.2 equiv), 23 °C for 2 h. [b]Product was mixture of **2-Int** and **2.** The yields were determined by ^{1}H NMR analysis of the mixture.

1.2. Results and Discussion

There are three different mechanistic possibilites for the **IHT** reaction, starting from the functionalized *N*-hydroxyindole (**I**) and leading to the rearrangement product (**V**) (Figure 1.4).[16] The first pathway is an associative mechanism, in which the C–X (X = heteroatom) bond is initially formed, resulting in the generation of a diradical (**II**) or a zwitterionic (**II'**) intermediate (**path a**). The second pathway involves a classical concerted pathway, where the formation of the C–X bond and the cleavage of the N–O bond occur simultaneously (**path b**). In the third pathway, the labile N–O bond of *N*-hydroxyindole (**I**) is initially dissociated in the first step, leading to the formation of either a radical pair (**IV**) or an ion pair (**IV'**). Subsequently, recombination takes place (**path c**). The lability of the N–O bond is ~57 kcal/mol, while the newly formed C–X (X = O, N) bond's lability is 69–91 kcal/mol.[17] Consequently, the associative pathway (**path a**) is considered highly unlikely among the three main possibilities. Indeed, it is known that the one of

key driving forces of related systems. Therefore, we made efforts to evaluate the mechanisms, emphasizing the concerted (**path b**) and dissociative (**path c**) mechanisms specifically.

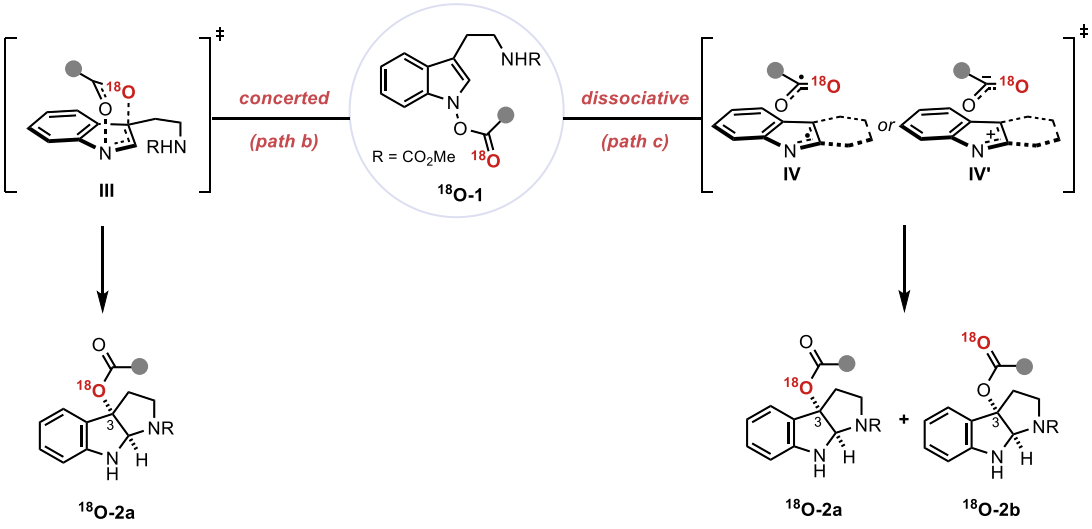
Figure 1.4. Mechanistic Possibilities for the **IHT** Reaction



1.2.1. Mechanistic Investigation I: ^{18}O-Labeling Studies

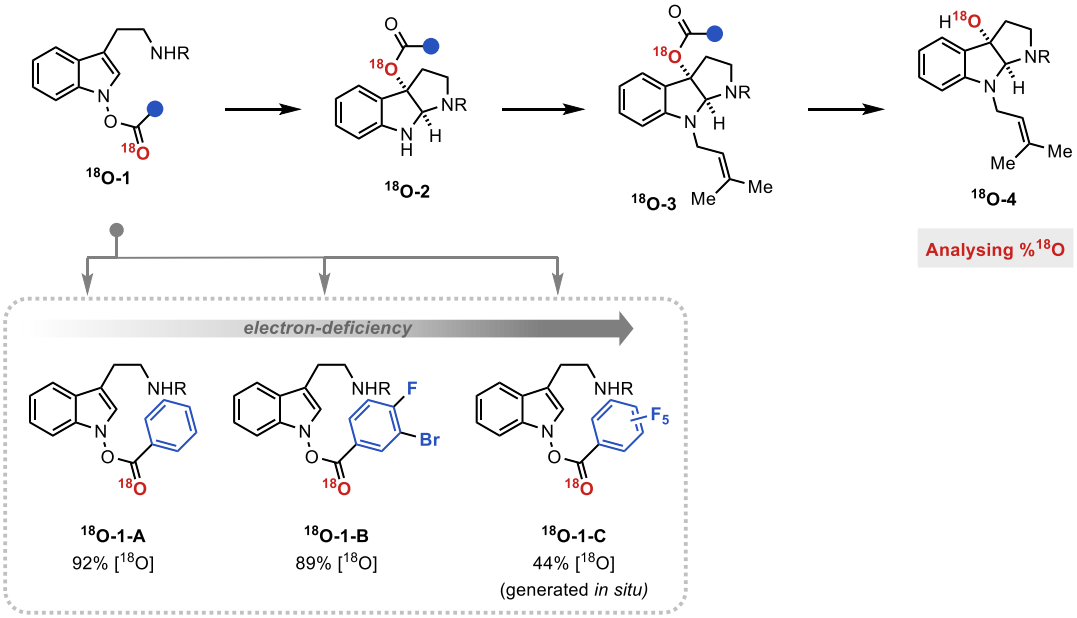
We initially performed the ^{18}O atom isotope labeling studies (Figure 1). We could trace the involvement of the specific pathway by determining the precise the localization of the ^{18}O atom (Figure 1.5).[18] In the case of the concerted pathway, exclusive migration of ^{18}O migration to the C3-position of pyrroloindoline (**^{18}O-2a**) is expected. On the other hand, in the case of the dissociative pathway, complete scrambling of ^{18}O migration is expected. As a result, a mixture of products, **^{18}O-2a** and **^{18}O-2b,** would be observed.

Figure 1.5. Projected Migration of ^{18}O Isotope during the **IHT**.



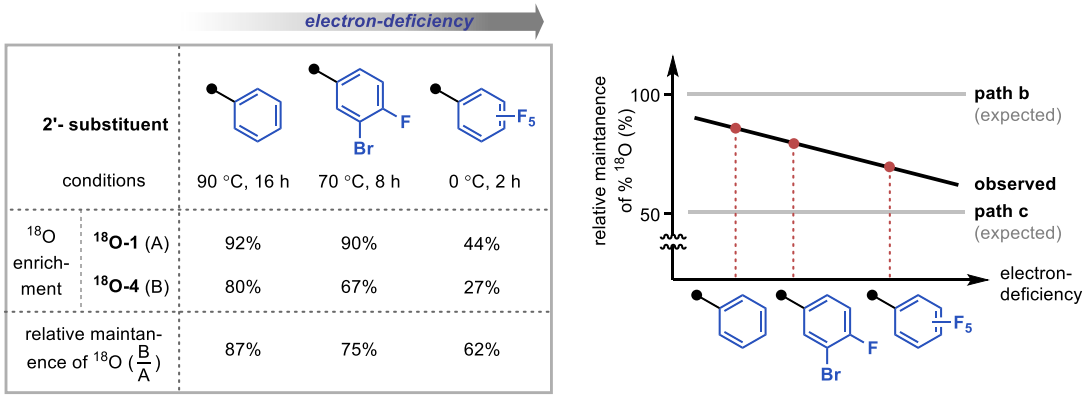
To investigate the assumptions, three different benzoates (**^{18}O-1-A, ^{18}O-1-B, ^{18}O-1-C**) were prepared (Figure 1.6). The ^{18}O-enriched indolyl benzoates were independently subjected to following rearrangement, N-alkylation and ester cleavage reactions. The final products, 3-hydroxypyrroloindolines **^{18}O-4**, were subsequently analyzed using HRMS to determine the degree of ^{18}O enrichment.

Figure 1.6. Experimental Design for ^{18}O Labeling Experiment.



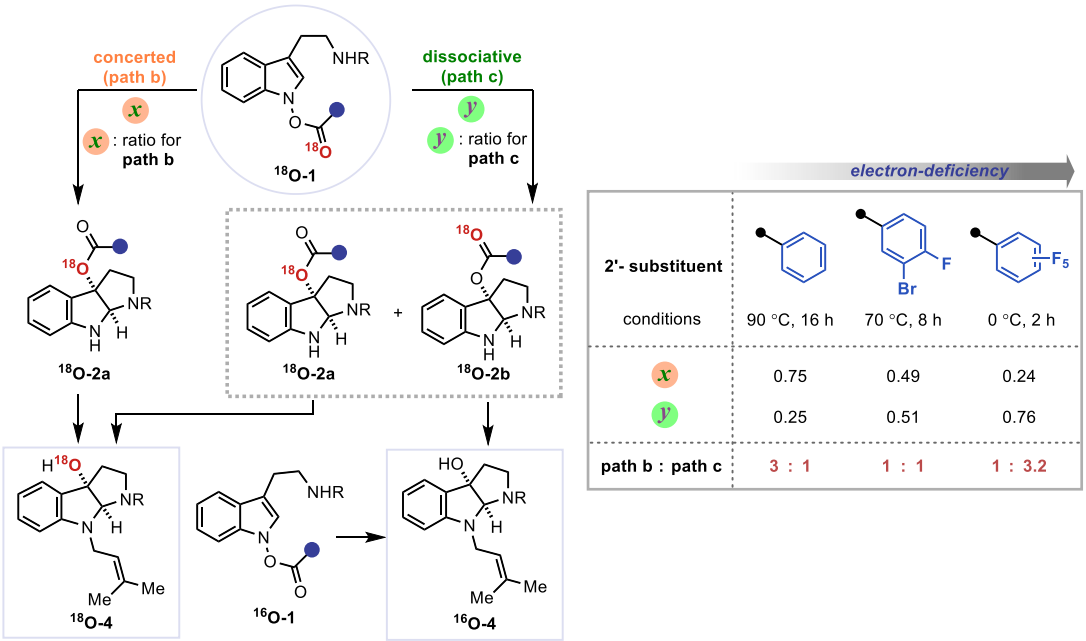
None of the tested cases showed the initially expected concerted pathway (**path b**) with complete maintenance of ^{18}O or dissociative pathway (**path c**) of full scrambling of ^{18}O (Figure 1.7). According to the report, the analogous rearrangement process completely preserves the isotopically labeled atom even in the most asynchronous concerted pathway.[19] Therefore, these experimental results revealed that at least two seperate reaction mechanisms are operating simultaneously.

Figure 1.7. Result of the ^{18}O Labeling Experiment and the Influence of Electronic Property



We assumed that the **path b** and **path c** are predominantly activating the **IHT** process and performed the quantitative analysis of the degree of ^{18}O labeling (Figure 1.8).

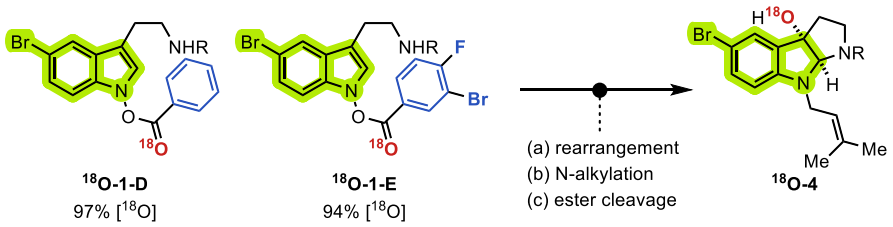
Figure 1.8. Definition of x, y and Schematic Explanation for the Calculation of the Mechanistic Ratio

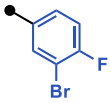


The combination of **path b** of **^{18}O-1** and half of **^{18}O-1**'s **path c** would produce **^{18}O-4**. Similarly, rearrangement of **^{16}O-1** and the remaining half of **^{18}O-1**'s **path c** would generate **^{16}O-4.** The relative participation of **path b** and **path c** is denoted as x and y, respectively. The ratio of x to y could be ascertained by examining the ratio of **^{18}O-4** and **^{16}O-4** present in the final product. Consequently, quantifying the contribution of **path b** and **path c** to the overall reaction was possible. The electronic characteristics of the substituent at the 2'-position have a direct impact on the ratio of each pathway. As the benzoate becomes more electron-deficient, a shift in the dominant pathway contributing to the **IHT** reaction was observed, transitioning from **path b** to **path c**. The exact structure of the fragment pair remains uncertain, but the inductive stabilization of the fragment pair is the reason for changing the reactivity preference. This unique mechanistic duality is inherently present in the general indolyl framework.

Next, further investigations were carried out to explore the mechanistic duality of the **IHT** reaction in relation to other parameters (Figure 1.9). We conducted the **IHT** reaction on **^{18}O-1-D** and **^{18}O-1-E**, which carry a 5-bromo substituent in indole backbone and both benzoates favored the concerted pathway (**path b**).

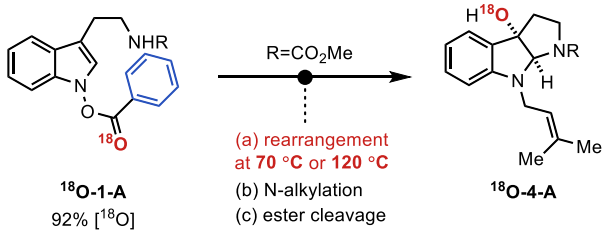
Figure 1.9. The Influence of Electronic Distribution in Indole Scaffold



2'- substituent			
conditions		90 °C, 16 h	70 °C, 8 h
^{18}O enrich-ment	**^{18}O-1** (A)	97%	94%
	^{18}O-4 (B)	94%	90%
relative maintan-ence of ^{18}O ($\frac{B}{A}$)		97%	96%
x		0.93	0.92
y		0.07	0.08
path b : path c		13 : 1	12 : 1

Furthermore, we investigated the temperature independence of the mechanistic duality in the **IHT** reaction (Figure 1.10). There was no significant change observed in the degree of ^{18}O scrambling when benzoate **^{18}O-1-A** underwent the **IHT** reaction at the temperature of 70, 90, or 120 °C. The results reveal that as the reaction temperature varies within the examined range, both mechanistic pathways undergo comparable modifications in their activation barriers.

Figure 1.10. The Influence of Reaction Temperature

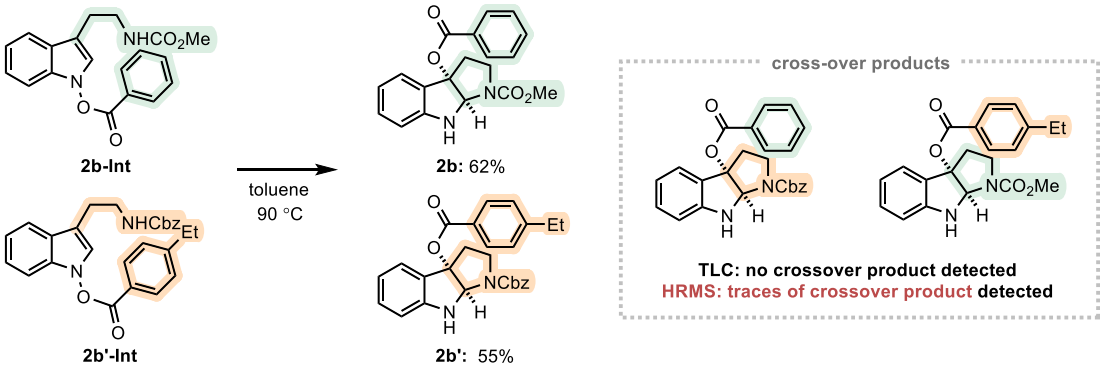


conditions		70 °C, 60 h	90 °C, 16 h	120 °C, 1 h
^{18}O enrich-ment	**^{18}O-1** (A)	92%	92%	92%
	^{18}O-4 (B)	82%	80%	79%
relative maintan-ence of ^{18}O ($\frac{B}{A}$)		89%	87%	86%
x		0.80	0.75	0.73
y		0.20	0.25	0.27
path b : path c		4 : 1	3 : 1	2.7 : 1

1.2.2. Mechanistic Insights II: Additional Mechanistic Studies

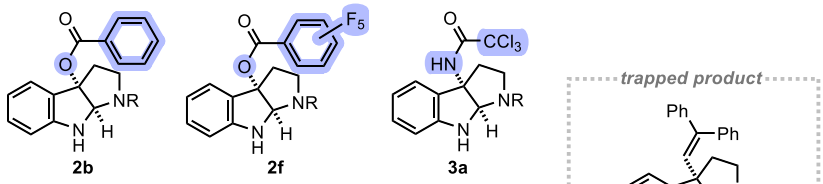
Additional experiments were carried out to gain a more profound understanding of the **IHT** reaction. First, crossover experiment between **2b-Int** and **2b'-Int** was performed (Figure 1.11). Under standard conditions, reaction of the mixture produced only **2b** and **2b'**, with no appreciable amount of crossover products observed by TLC or ^{1}H NMR. However, upon conducting HRMS analysis, traces of both crossover products were observed. This finding indicates that rapid recombination of fragmented components occurred (**path c**).

Figure 1.11. Crossover Experiment



Next, to find determine the characteristics of the fragments involved, a series of radical trapping experiments were conducted (Figure 2.17).[21] Reaction of *N*-hydroxytryptamine **1a** under standard C–O or C–N bond-forming conditions, the presence of a radical scavenger did not make significant yield decrease. However, 1,1-diphenly ethylene-adduct trapping product was detected on HRMS analysis. The radical pair formation is still contributing factor in dissociative pathway.

Figure 1.12. Radical Trap Experiment

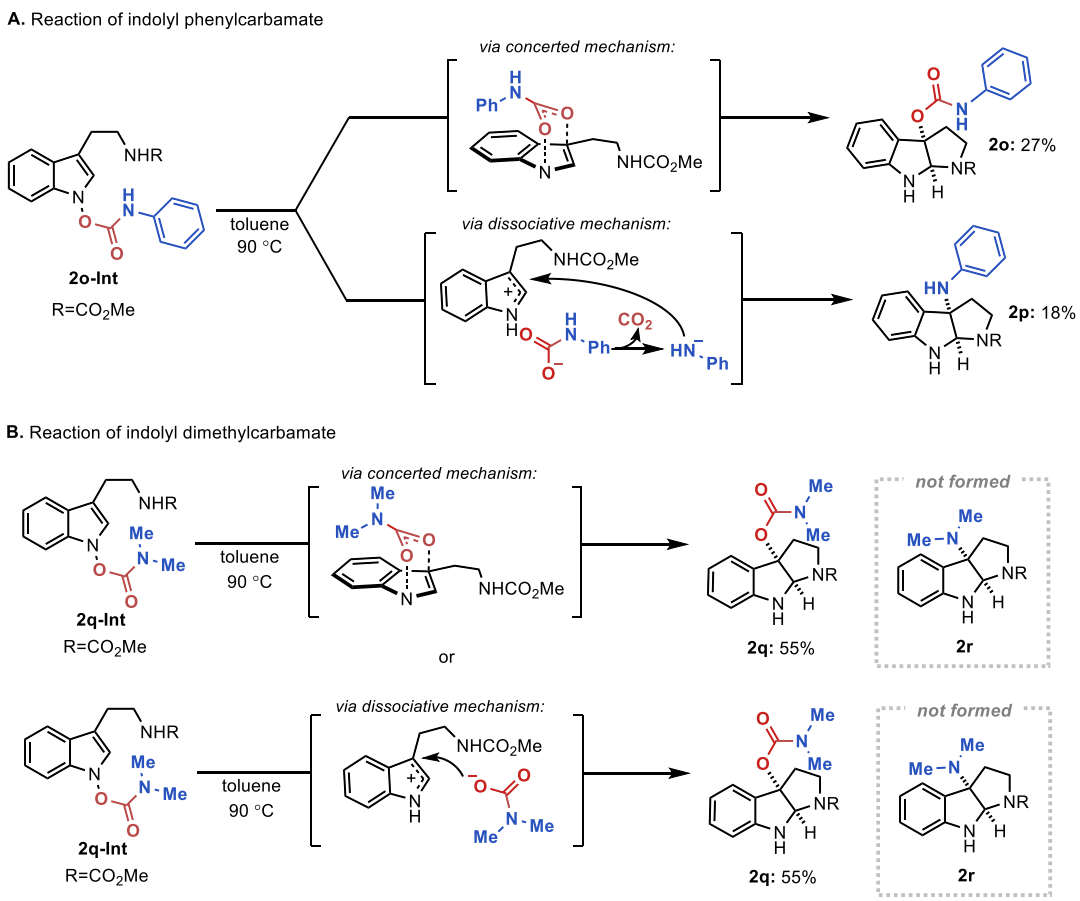


radical scavenger	yield	yield	yield
none	68%	53%	78%
BHT	65%	49%	53%
1,1-diphenyl ethylene	57%	45%	60%

Finally, the indolyl carbamates **2o-Int** was used to investigated the mechanistic duality of the **IHT** reaction (Figure 1.13A). In theory, the concerted pathway would lead to the formation of **2o**. On the other hand, dissociative pathway would involve a rapid decarboxylation step of the initially generated carbamate anion to yield the product **2p**.[22] A 2:1 mixture of **2o** and **2p** products were gained, solidifying the existence of two independently operating mechanisms.

However, when indolyl *N,N*-dimethyl carbamate (**2q-Int**) was subjected to the same reaction conditions, the oxygenation product (**2q**) was obtained exclusively (Figure 1.13B). It is because the dimethylamino group highly enriches electrons in the 2'-position, inducing the concerted pathway. However, different explanation can be considered: when the parent amine's basicity increases the stability of the carbamate is significantly enhanced.[22] Due to the notably higher basicity of dimethylamine (pK_a of conjugate acid = 10.7)[23] compared to aniline (pK_a of conjugate acid = 4.6)[24], the carbamate anion is prevented from undergoing carboxyl group elimination, thus exclusively forming the carbamate **2q**.

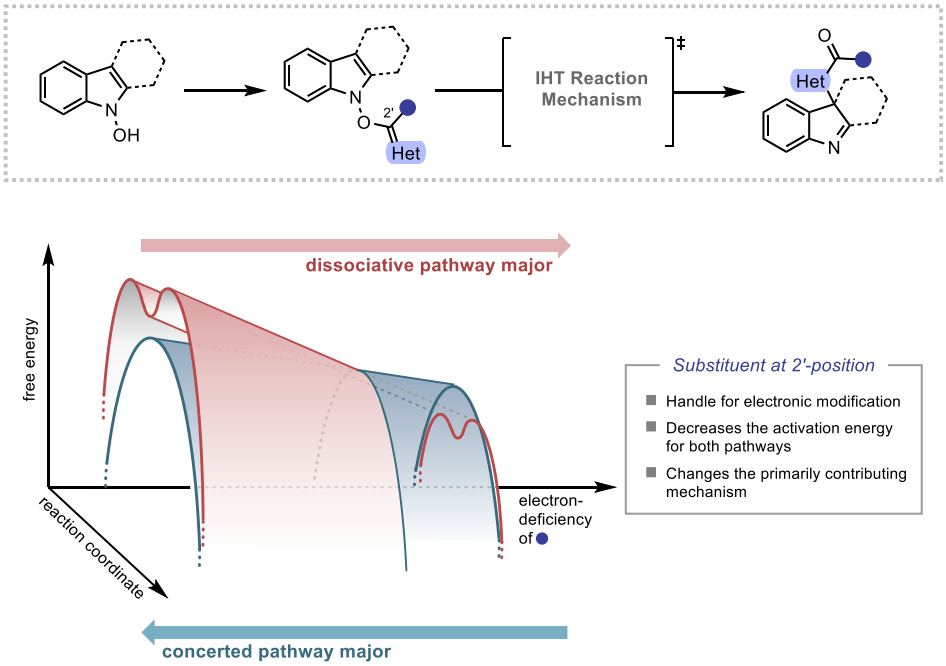
Figure 1.13. IHT Reaction of Indolyl *N*-carbamate



The conclusions derived from the aforementioned experiments are as described (Figure 1.14). (A) In the **IHT** reaction system, both a concerted and a dissociative mechanism operate

simultaneously. (B) Modifying the electronic properties at the 2'-position changes the dominant mechanism. (C)The activation energy decreases as the 2'-position becomes more electron deficient. (D) The exact nature of the fragment pair in the dissociative mechanism remains elusive, with evidence supporting the participation of both radical pairs and ion pairs.

Figure 1.14. Mechanistic Highlights of **IHT** Reaction



1.3. Conclusion

With in-depth studies of the mechanism, the **IHT** reaction found to be proceeds through two simultaneous reaction pathway: the concerted and dissociative mechanisms. When the benzoate or imidate group becomes electron deficient, it lowers the activation energy of the **IHT** reaction promotes the dissociative mechanism as the dominant pathway, replacing the concerted mechanism. This elucidated reaction strategy enables reliable access to a wide range of indole derived scaffolds, which is significant advantage form a synthetic perspective.

1.4. References

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1.5. Experiemental Section

1.5.1. General Experimental Information of HRMS

Reagents and Chemicals

MeCN (LC-MS grade), H_2O with 0.1% formic acid (LC-MS grade) were obtained from Samchun Chemical.

Instrumentation and Experimental

HRMS experiments were performed using a Thermo Scientific™ Orbitrap Exploris 120 equipped with a Hypersil GOLD™ C18 Selectivity HPLC column and Thermo Scientific™ mass spectrometer with Thermo Scientific™ Xcalibur™ software for instrument control and data processing. The aqueous mobile phase A is H_2O with 0.1% formic acid (v/v), and organic mobile phase B is MeCN with 0.1% formic acid (v/v). 20 μL of samples were injected onto the column with a flow rate of 0.4 mL/min at 40 °C. The chromatographic conditions is as followed: 30 min method consisting with 5% B over 0.0–2.0 min, then a gradient of 5% B to 95% B over 2.0–20.0 min, then maintain 95% B over 20.0–24.9 min followed by a gradient of 95% B to 5% B over 24.9–25.0 min, then hold 5% B for 5 min. The eluents were monitored by a UV detector with a range of 210 nm to 400 nm, followed by HRMS detection in electrospray ionization with both

positive and negative mode. The MS conditions were as followed: voltage for positive ion mode 3500 V, voltage for negative ion mode 3000 V, sheath gas flow rate 55 Arb; aux gas flow rate 15 Arb; sweep gas flow rate 1 Arb, ion transfer tube temperature 320 °C, vaporizer temperature 350 °C, orbitrap resolution 120000, m/z range 100–1000 Da.

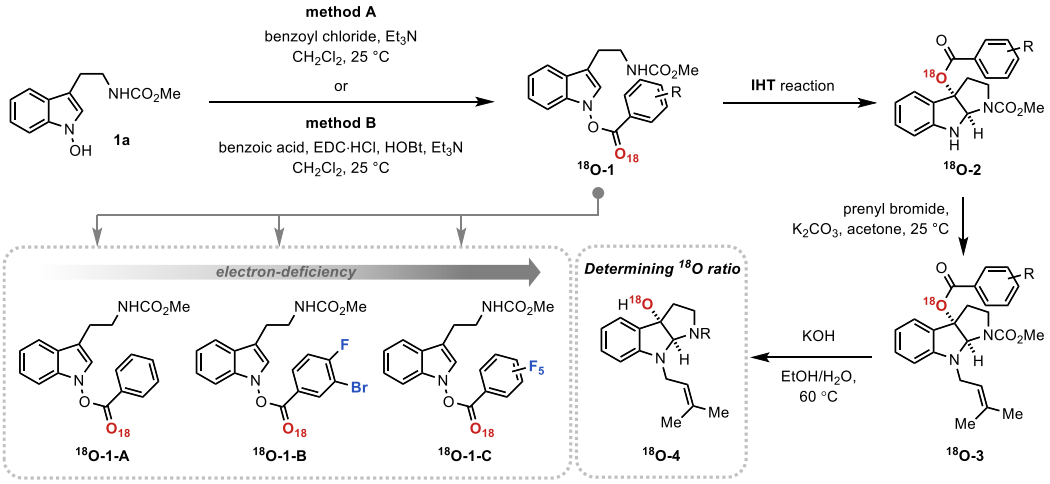
The conditions above were used for all the HRMS analysis in mechanistic section.

The M + 2 isotopic enrichment values (M = mass of unlabeled compound), and full isotopic incorporation data were calculated using the relative abundance in mass spectra for each M + n (n = 0, 2) peak in HRMS.

1.5.2. Mechanistic Investigation

1.5.2.1. Genernal Method of ^{18}O Isotope Experiment

Scheme 1.2. General Scheme and Method for ^{18}O Labeling Experiment



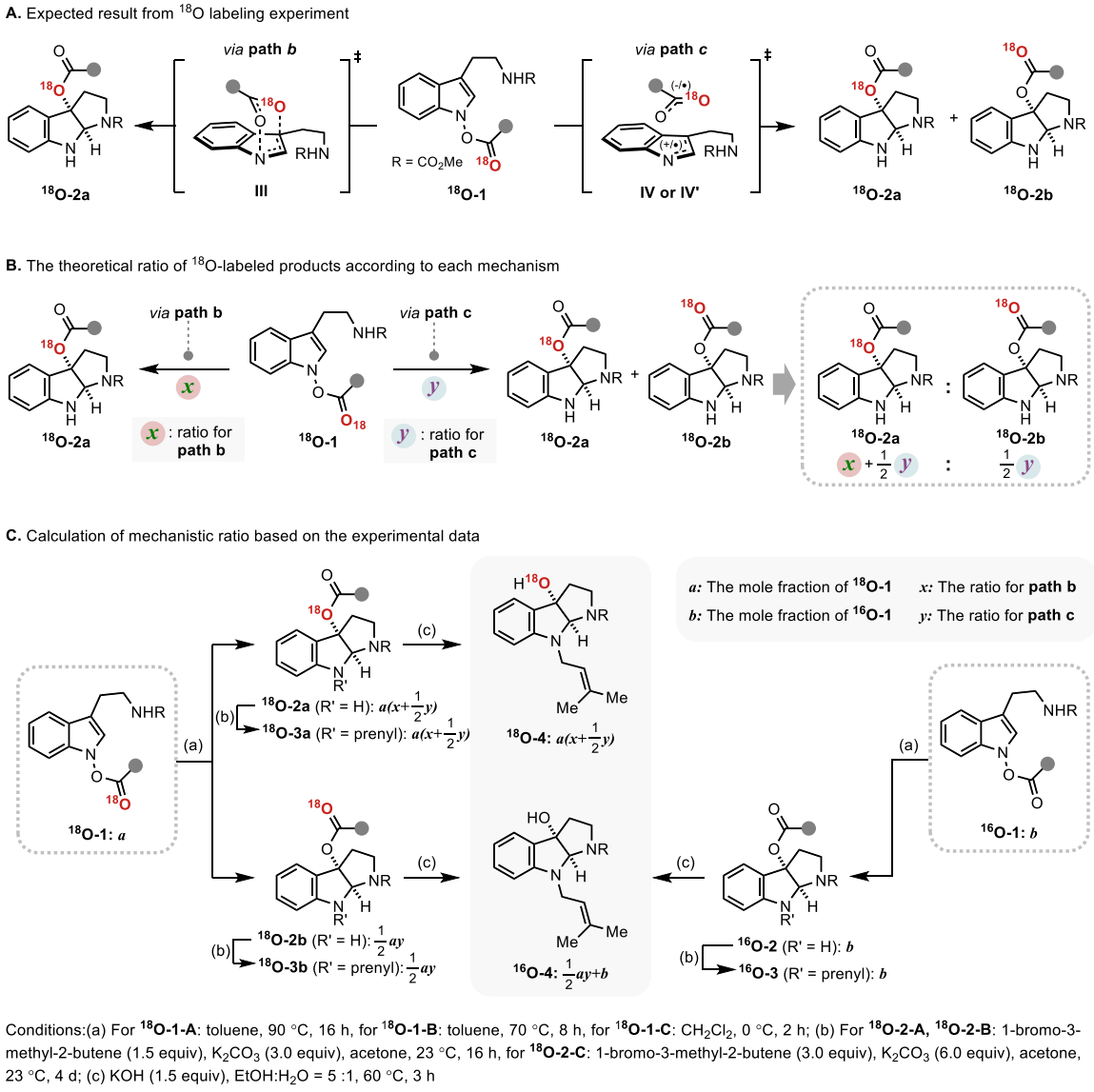
The general method for measuring ^{18}O saturation is as follows: First, the ^{18}O enrichment levels for each independently prepared ^{18}O benzoic acid were measured. Indolyl N-carboxylates, precursors of the [3,3]-sigmatropic rearrangement, were synthesized using the prepared ^{18}O benzoic acids, isolated by flash column chromatography, and then the ^{18}O enrichment levels for **^{18}O-1-A**, **^{18}O-1-B** and **^{18}O-1-C** were measured. (In the case of **^{18}O-1-C**, the ^{18}O enrichment of

^{18}O-1-C was estimated from the ^{18}O enrichment level of **^{18}O-2-C** due to the rapid rearrangement occurred spontaneously with the ester coupling. Theoretically ^{18}O enrichment level should be the same before and after the [3,3]-sigmatropic rearrangement regardless of type of mechanisms and the assumption has been empirically proven from the **^{18}O-A** and **^{18}O-B** cases, thus the estimate made above could be rationalized.) Then, at each step of [3,3]-sigmatropic rearrangement, alkylation and ester cleavage, the ^{18}O enrichment levels of **^{18}O-2**, **^{18}O-3** and **^{18}O-4** of indolyl N-carboxylate, indolyl 4-fluoro-3-bromobenzoate and indolyl pentafluorobenzoate were measured.

1.5.2.2. Quantitative Analysis of ^{18}O-Labeling Experiment Results

1.5.2.2.1. Dependence of the Electronic Properties

Figure 1.15. Schematic Explanation for the Calculation of the Ratio of Each Pathway.



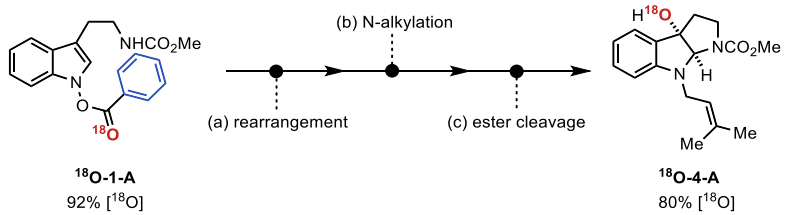
Conditions:(a) For **^{18}O-1-A**: toluene, 90 °C, 16 h, for **^{18}O-1-B**: toluene, 70 °C, 8 h, for **^{18}O-1-C**: CH_2Cl_2, 0 °C, 2 h; (b) For **^{18}O-2-A, ^{18}O-2-B**: 1-bromo-3-methyl-2-butene (1.5 equiv), K_2CO_3 (3.0 equiv), acetone, 23 °C, 16 h, for **^{18}O-2-C**: 1-bromo-3-methyl-2-butene (3.0 equiv), K_2CO_3 (6.0 equiv), acetone, 23 °C, 4 d; (c) KOH (1.5 equiv), EtOH:H_2O = 5 :1, 60 °C, 3 h

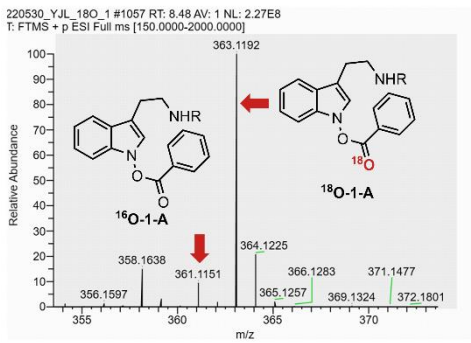
The relative contribution of each pathway for the formation of the **IHT** product was determined based on the following premises. **path b** will exclusively produce **^{18}O-2a** as a sole product while **path c** will form **^{18}O-2a** and **^{18}O-2b** in a 1:1 ratio, respectively.

The mole fraction of **^{18}O-1** is denoted as a, and since the ^{18}O enrichment is not 100%, the mole fraction of naturally existing **^{16}O-1** is defined as b. Also, the relative contribution of **path b** for the formation of the product is denoted as x, and the relative contribution of **path c** for the formation of the product is defined as y. The ratio between **^{18}O-4** and **^{16}O-4** is expressed as $a(x+\frac{1}{2}y)$: $\frac{1}{2}ay+b$.

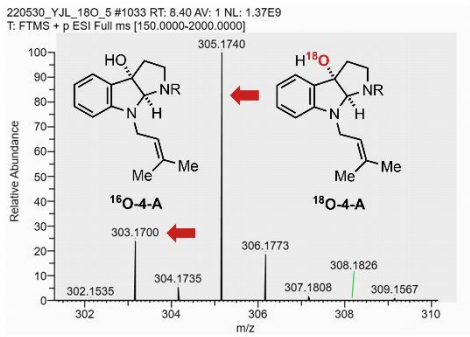
Detailed calculation process is attached below.

(1) **IHT** reaction with benzoyl substituent





^{18}O-1-A:^{16}O-1-A = $a : b = 100 : 9.3$



^{18}O-4-A:^{16}O-4-A = $a(x+\frac{1}{2}y) : \frac{1}{2}ay+b = 100 : 25.1$

The system of equations is established by the two proportional expressions:

$$\begin{cases} a:b = 100:9.3 & (1) \\ a(x+\frac{1}{2}y):\frac{1}{2}ay+b = 100:25.1 & (2) \end{cases}$$

From equation 1, ***b*** can be expressed as:

$$b = \frac{93}{1000}a \qquad (3)$$

Insertion of the equation 3 into equation 2 gives equation 4:

$$\mathrm{a}(x+\frac{1}{2}y):\frac{1}{2}ay+\frac{93}{1000}a = 100:25.1 \qquad (4)$$

$$\therefore x + \frac{1}{2}y : \frac{1}{2}y + \frac{93}{1000} = 100 : 25.1$$

$$\therefore 50y + 9.3 = 25.1x + \frac{251}{20}y$$

$$\therefore 25.1x - \frac{749}{20}y = 9.3 \qquad (5)$$

Since ***y*** is defined in terms of 1–***x***, the equation 5 can be re-written as:

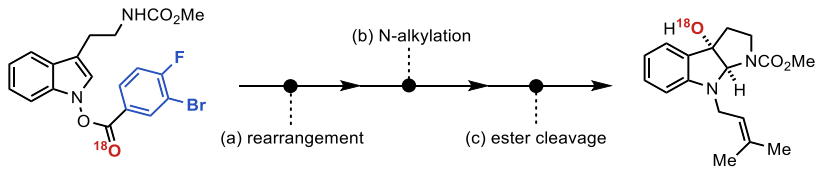
$$25.1x - \frac{749}{20}(1 - x) = 9.3$$

$$\therefore 62.6x = 46.8$$

$$\therefore x = 0.75 \qquad (6)$$

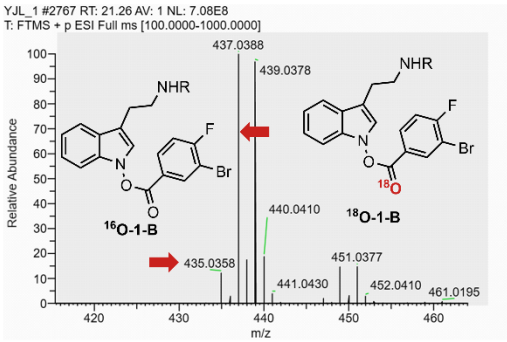
$$\therefore y = 1 - x = 0.25 \qquad (7)$$

(2) **IHT** reaction with 3-bromo-4-fluorobenzoyl substituent

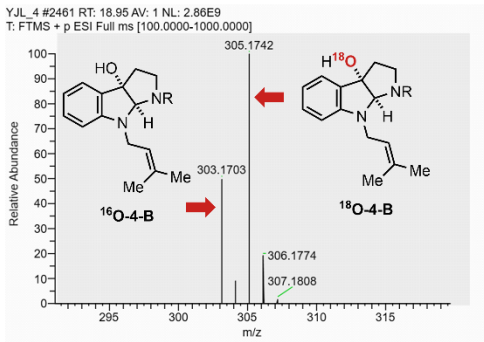


^{18}O-1-B
89% [^{18}O]

^{18}O-4-B
67% [^{18}O]



^{18}O-1-B:^{16}O-1-B = *a : b = 100 : 11.7*



^{18}O-4-B:^{16}O-4-B = $a(x+\frac{1}{2}y) : \frac{1}{2}ay+b = 100 : 49.4$

The system of equations is established by the two proportional expressions:

$$\begin{cases} a: b = 100: 11.7 & (1) \\ a(x+\frac{1}{2}y): \frac{1}{2}ay + b = 100: 49.4 & (2) \end{cases}$$

From equation 1, ***b*** can be expressed as:

$$b = \frac{117}{1000}a \qquad (3)$$

Insertion of the equation 3 into equation 2 gives equation 4:

$$\mathrm{a}(x+\frac{1}{2}y): \frac{1}{2}ay + \frac{117}{1000}a = 100: 49.4 \qquad (4)$$

$$\therefore x + \frac{1}{2}y: \frac{1}{2}y + \frac{117}{1000} = 100: 49.4$$

$$\therefore 50y + 11.7 = 49.4x + \frac{494}{20}y$$

$$\therefore 49.4x - \frac{506}{20}y = 11.7 \qquad (5)$$

Since $\boldsymbol{y}$ is defined in terms of 1−$\boldsymbol{x}$, the equation 5 can be re-written as:

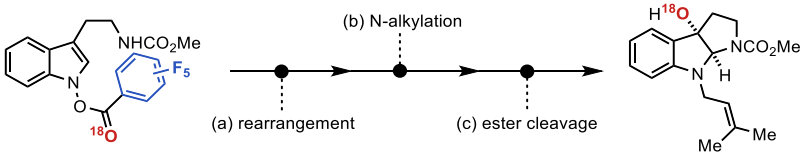
$$49.4x - \frac{506}{20}(1 - x) = 11.7$$

$$\therefore 74.7x = 37$$

$$\therefore x = 0.49 \qquad (6)$$

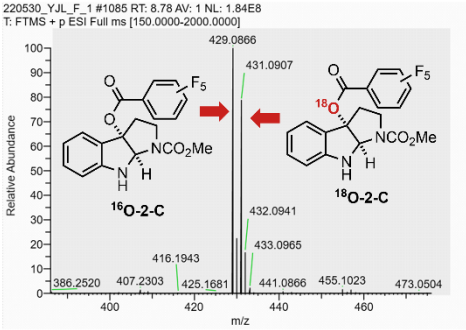
$$\therefore y = 1 - x = 0.51 \qquad (7)$$

(3) **IHT** reaction with pentafluorobenzoyl substituent

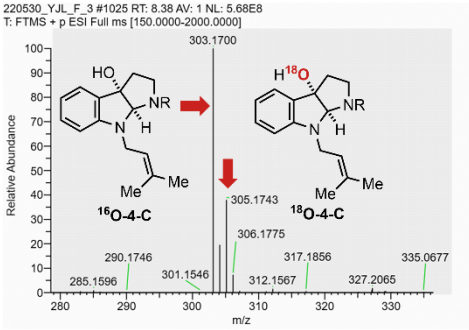


^{18}O-1-C
44% [^{18}O]

^{18}O-4-C
27% [^{18}O]



^{18}O-2-C:^{16}O-2-C = $a : b = 79.8 : 100$



^{18}O-4-C:^{16}O-4-C = $a(x+\frac{1}{2}y) : \frac{1}{2}ay+b = 37.8 : 100$

The system of equations is established by the two proportional expressions:

$$\begin{cases} a : b = 79.8 : 100 & (1) \\ a(x+\frac{1}{2}y) : \frac{1}{2}ay + b = 37.8 : 100 & (2) \end{cases}$$

From equation 1, ***b*** can be expressed as:

$$b = \frac{1000}{798}a \qquad (3)$$

Insertion of the equation 3 into equation 2 gives equation 4:

$$a(x+\frac{1}{2}y) : \frac{1}{2}ay + \frac{1000}{798}a = 37.8 : 100 \qquad (4)$$

$$\therefore x + \frac{1}{2}y : \frac{1}{2}y + \frac{1000}{798} = 37.8 : 100$$

$$\therefore 37.8(\frac{1}{2}y + \frac{1000}{798}) = 100x + 50y$$

$$\therefore 100x + 31.1y = \frac{37800}{798} = 47.4 \qquad (5)$$

Since ***y*** is defined in terms of 1–***x***, the equation 5 can be re-written as:

$$100x + 31.1(1 - x) = 47.4$$

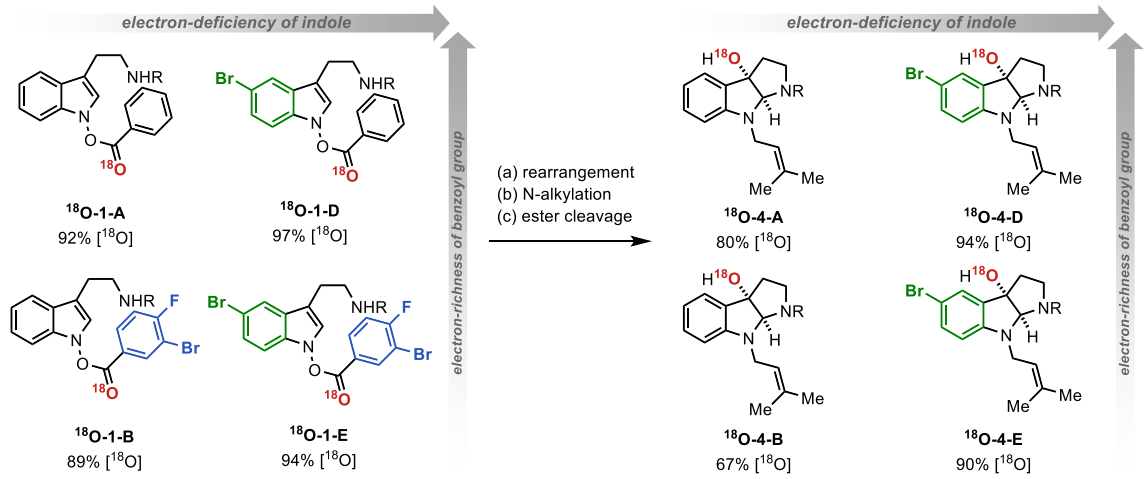
$$\therefore 68.9x = 16.3$$

$$\therefore x = 0.24 \qquad (6)$$

$$\therefore y = 1 - x = 0.76 \qquad (7)$$

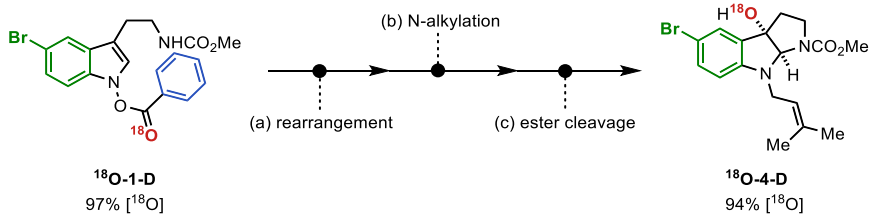
1.5.2.2.2. The Influence of Electronic Properties of the Indole Backbone

Figure 1.16. The influence of electronic properties of the indole backbone



The determination of the relative contribution of **path b** and **path c** in each case was carried out via analogous calculations used for section 1.5.2.2.1.

(1) **IHT** reaction with benzoyl substituent



The system of equations is established by the two proportional expressions:

$$\begin{cases} a:b = 100:3.1 & (1) \\ a(x+\frac{1}{2}y):\frac{1}{2}ay+b = 100:7.0 & (2) \end{cases}$$

From equation 1, ***b*** can be expressed as:

$$b = \frac{31}{1000}a \qquad (3)$$

Insertion of the equation 3 into equation 2 gives equation 4:

$$\mathrm{a}(x + \frac{1}{2}y) : \frac{1}{2}ay + \frac{31}{1000}a = 100 : 7.0 \qquad (4)$$

$$\therefore x + \frac{1}{2}y : \frac{1}{2}y + \frac{31}{1000} = 100 : 7.0$$

$$\therefore 50y + 3.1 = 7x + 3.5y$$

$$\therefore 7x - 46.5y = 3.1 \qquad (5)$$

Since ***y*** is defined in terms of 1–***x***, the equation 5 can be re-written as:

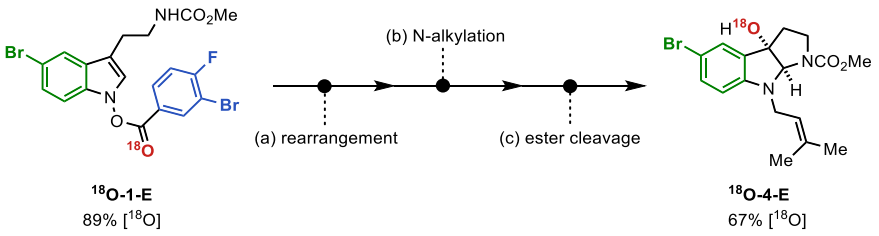
$$7x - 46.5(1 - x) = 3.1$$

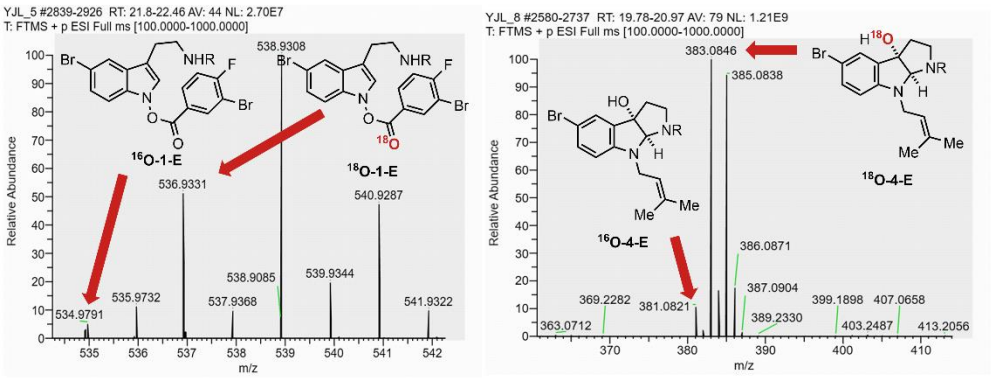
$$\therefore 53.5x = 49.6$$

$$\therefore x = 0.93 \qquad (6)$$

$$\therefore y = 1 - x = 0.7 \qquad (7)$$

(2) **IHT** reaction with 3-bromo-4-fluorobenzoyl substituent





^{18}O-1-E:^{16}O-1-E = $a : b = 50.9 : 3.1$ ^{18}O-4-E:^{16}O-4-E = $a(x+\frac{1}{2}y) : \frac{1}{2}ay+b = 100 : 10.6$

The system of equations is established by the two proportional expressions:

$$\begin{cases} a:b = 50.9:3.1 & (1) \\ a(x+\frac{1}{2}y):\frac{1}{2}ay+b = 100:10.6 & (2) \end{cases}$$

From equation 1, ***b*** can be expressed as:

$$b = \frac{31}{509}a \qquad (3)$$

Insertion of the equation 3 into equation 2 gives equation 4:

$$\mathrm{a}(x+\frac{1}{2}y):\frac{1}{2}ay+\frac{31}{509}a = 100:10.6 \qquad (4)$$

$$\therefore x+\frac{1}{2}y:\frac{1}{2}y+\frac{31}{509} = 100:10.6$$

$$\therefore 50\mathrm{y}+\frac{3100}{509} = 10.6x+5.3y$$

$$\therefore 10.6x-44.7y = \frac{3100}{509} \qquad (5)$$

Since $\boldsymbol{y}$ is defined in terms of 1–$\boldsymbol{x}$, the equation 5 can be re-written as:

$$10.6x - 44.7(1 - \mathrm{x}) = \frac{3100}{509}$$

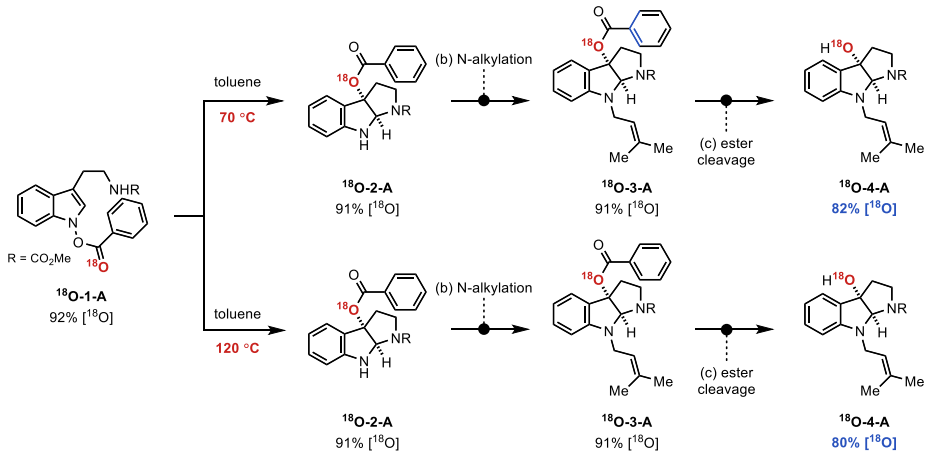
$$\therefore 55.3x = 50.8$$

$$\therefore x = 0.92 \qquad (6)$$

$$\therefore y = 1 - x = 0.08 \qquad (7)$$

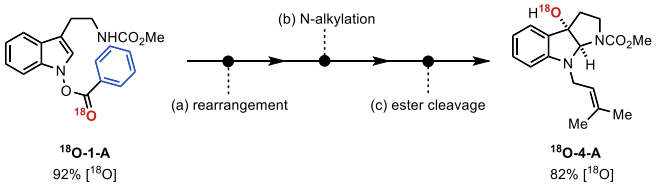
1.5.2.2.3. The Influence of Reaction Temperature

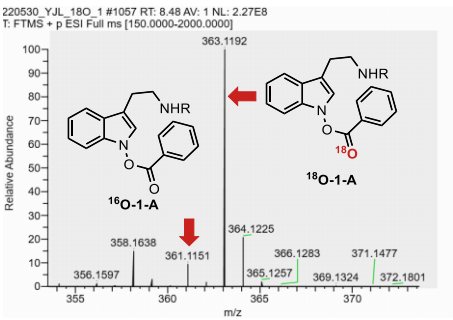
Figure 1.16. Evaluation of Temperatures as Factor Affecting the Level of ^{18}O-Enrichment.



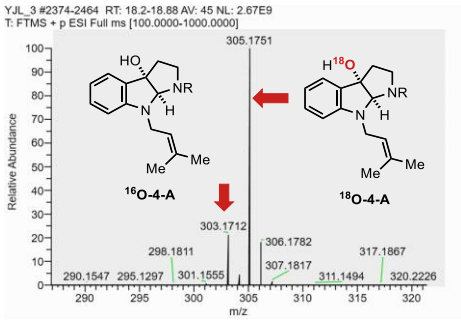
To the two oven-dried heavy-wall pressure tubes equipped with a stir bar and septum were added indolyl N-carboxylate **^{18}O-1-A** (0. 200 mmol, 1.0 equiv) and toluene (0.05 M in **^{18}O-1-A**) at 23 °C, respectively. One of the prepared tubes was heated to 70 °C in a pre-heated oil bath and stirred for 60 h until full conversion was observed, while the other tube was heated to 120 °C in a pre-heated oil bath and stirred for 1 h before they were cooled to rt and directly concentrated under reduced pressure to obtain the crude product, respectively. The crude mixtures were then analyzed by HRMS. HRMS result of the resulting crude mixtures indicated no significant loss of ^{18}O enrichment.

(1) **IHT** reaction at 70 °C





^{18}O-1-A:^{16}O-1-A = $a : b = 100 : 9.3$



^{18}O-4-A:^{16}O-4-A = $a(x+\frac{1}{2}y) : \frac{1}{2}ay+b = 100 : 21.7$

The system of equations is established by the two proportional expressions:

$$\begin{cases} a : b = 100 : 9.3 & (1) \\ a(x + \frac{1}{2}y) : \frac{1}{2}ay + b = 100 : 21.7 & (2) \end{cases}$$

From equation 1, ***b*** can be expressed as:

$$b = \frac{93}{1000}a \qquad (3)$$

Insertion of the equation 3 into equation 2 gives equation 4:

$$\mathrm{a}\left(x + \frac{1}{2}y\right) : \frac{1}{2}ay + \frac{93}{1000}a = 100 : 21.7 \qquad (4)$$

$$\therefore x + \frac{1}{2}y : \frac{1}{2}y + \frac{93}{1000} = 100 : 21.7$$

$$\therefore 50y + \frac{93}{10} = 21.7x + \frac{21.7}{2}y$$

$$\therefore 21.7x - \frac{78.3}{2}y = \frac{93}{10} \qquad (5)$$

Since ***y*** is defined in terms of 1–***x***, the equation 5 can be re-written as:

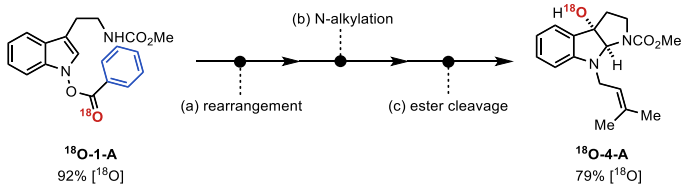
$$21.7x - \frac{78.3}{2}(1-x) -= 9.3$$

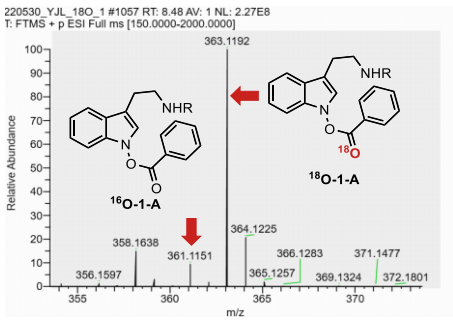
$$\therefore 60.85x = 9.3 + 39.15 = 48.45$$

$$\therefore x = 0.8 \qquad (6)$$

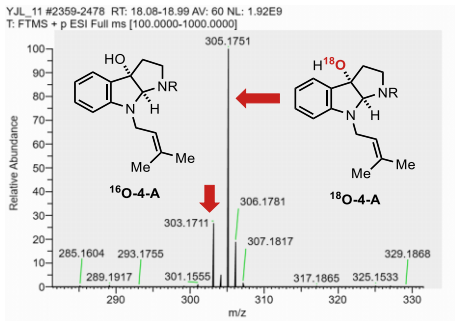
$$\therefore y = 1 - x = 0.2 \qquad (7)$$

(2) **IHT** reaction at 120 °C





^{18}O-1-A:^{16}O-1-A = *a : b = 100 : 9.3*



^{18}O-4-A:^{16}O-4-A = $a(x+\frac{1}{2}y) : \frac{1}{2}ay+b = 100 : 26.3$

The system of equations is established by the two proportional expressions:

$$\begin{cases} a : b = 100 : 9.3 & (1) \\ a(x + \frac{1}{2}y) : \frac{1}{2}ay + b = 100 : 26.3 & (2) \end{cases}$$

From equation 1, ***b*** can be expressed as:

$$b = \frac{93}{1000}a \qquad (3)$$

Insertion of the equation 3 into equation 2 gives equation 4:

$$\mathrm{a}\left(x + \frac{1}{2}y\right) : \frac{1}{2}ay + \frac{93}{1000}a = 100 : 26.3 \qquad (4)$$

$$\therefore x + \frac{1}{2}y : \frac{1}{2}y + \frac{93}{1000} = 100 : 26.3$$

$$\therefore 50y + \frac{93}{10} = 26.3x + \frac{26.3}{2}y$$

$$\therefore 26.3x - \frac{73.7}{2}y = \frac{93}{10} \qquad (5)$$

Since ***y*** is defined in terms of 1–***x***, the equation 5 can be re-written as:

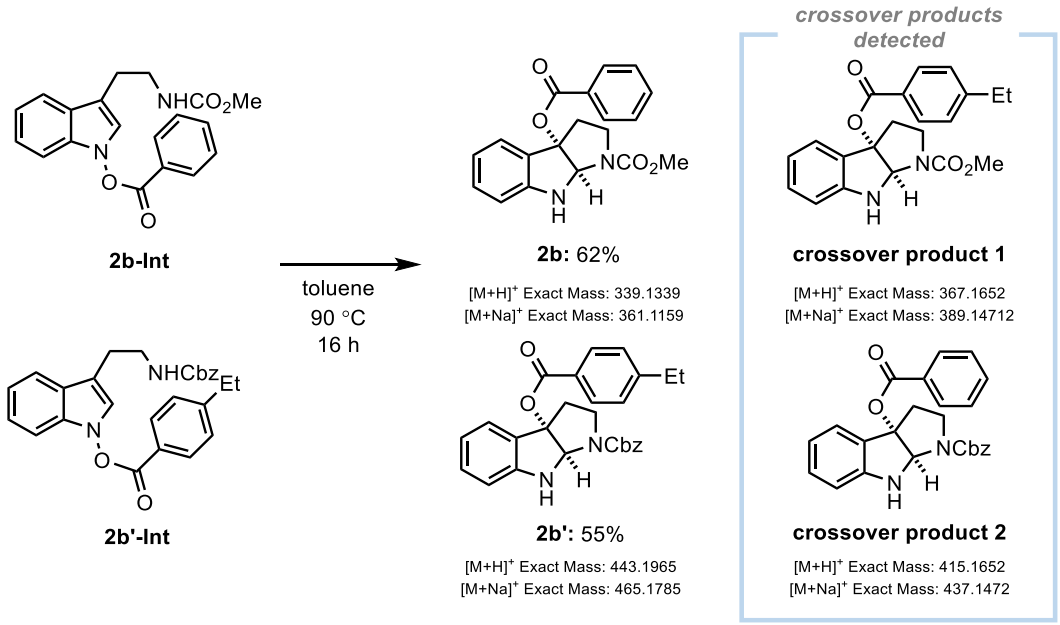
$$26.3x - \frac{73.7}{2}(1 - x) -= 9.3$$

$$\therefore 63.15x = 9.3 + 36.85 = 46.15$$

$$\therefore x = 0.73 \qquad (6)$$

$$\therefore y = 1 - x = 0.27 \qquad (7)$$

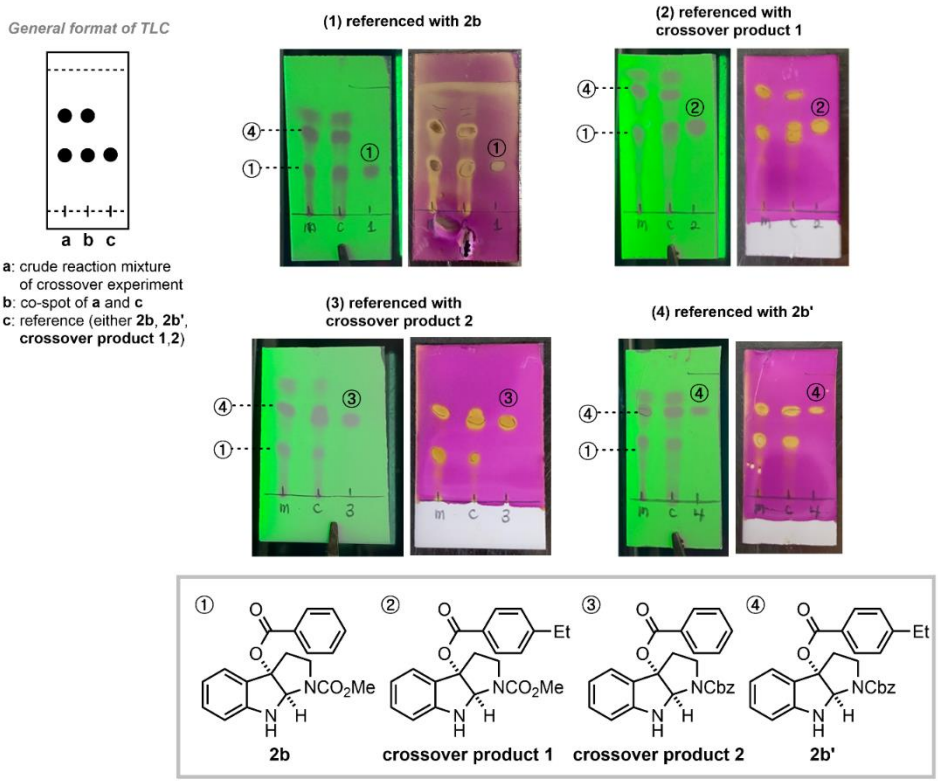
1.5.2.3. Crossover Experiment



To a 10 mL flame-dried reaction tube equipped with a stir bar were added **2b-Int** (67.6 mg, 0.200 mmol, 1.0 equiv), **2b'-Int** (88.5 mg, 0.200 mmol, 1.0 equiv) and toluene (2 mL). The reaction tube was sealed under N_2 and the resulting mixture was heated to 90 °C in a pre-heated oil bath and stirred for 16 h, before it was cooled to 23 °C and directly concentrated under reduced pressure to provide the crude product. A small portion of the crude mixture was then analyzed by TLC and HRMS. The crude mixture of crossover experiment was purified by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3) to afford the product **2b** (41.7 mg, 62%) and **2b'** (48.9 mg, 55%).

1.5.2.3.1. TLC analysis of the Crossover Experiment

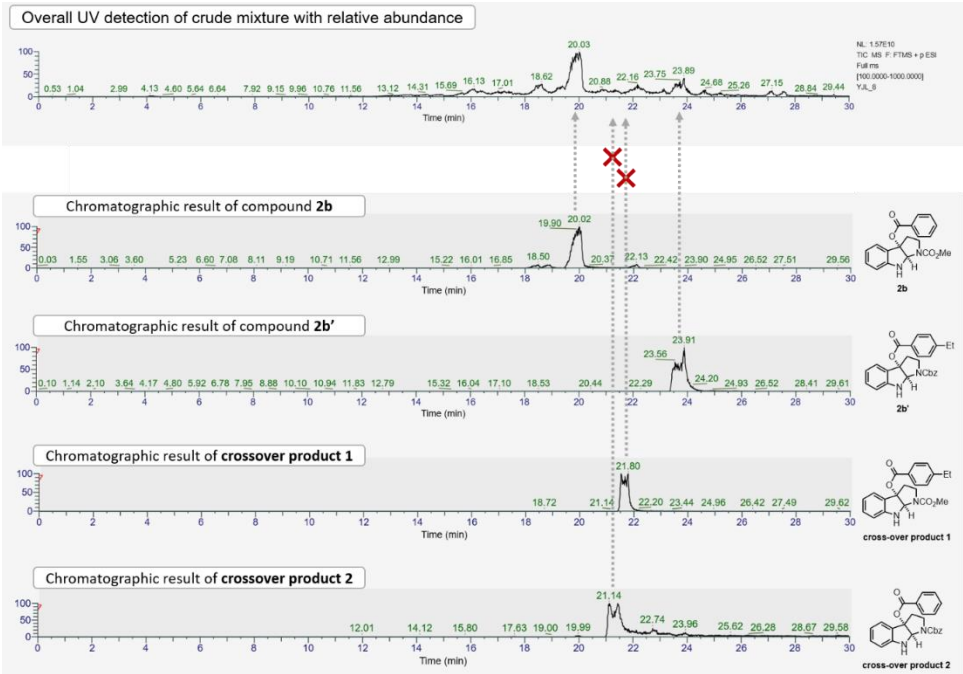
Figure 1.17. TLC Analysis of Crossover Experiment



TLC was checked with the reference compounds, which are the pyrroloindoline **2b**, **2b'**, **crossover product 1,** and **crossover product 2,** respectively. Each TLC sample was visualized by 254 nm UV lamp and stained with $KMnO_4$ stain with heating. Among the photos of the TLC plates with two differently visualized forms, the one visualized by 254 nm UV lamp is on the left and the one stained with $KMnO_4$ is on the right. TLC analysis indicates that no detectable spots corresponding to the **crossover product 1**, **2** were observed in each TLC while formation of **2b** and **2b'** was clearly detected.

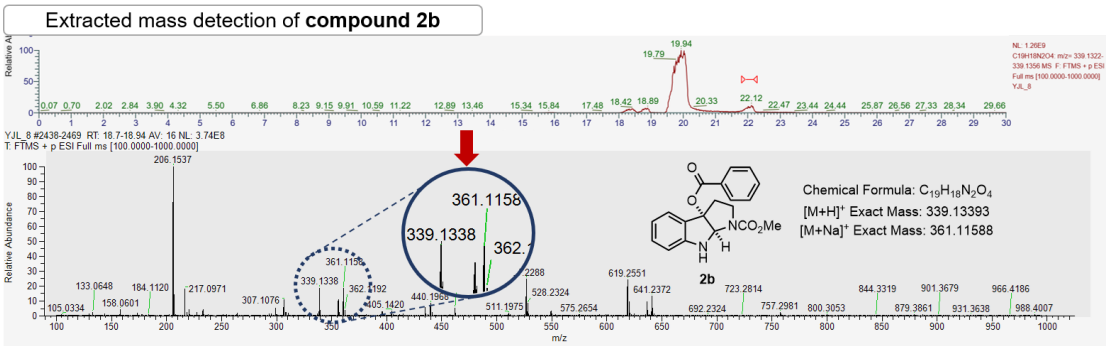
1.5.2.3.2. HRMS Analysis of the Crossover Experiment

(1) Result of UV detection for the crude mixture of the crossover experiment and the relative location of each product

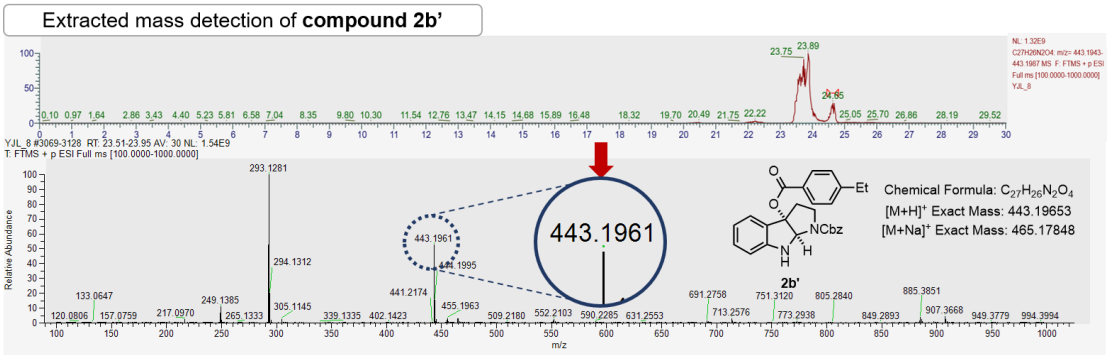


For all HRMS peaks shown below, the red arrow was used to indicate the detected mass of the desired products.

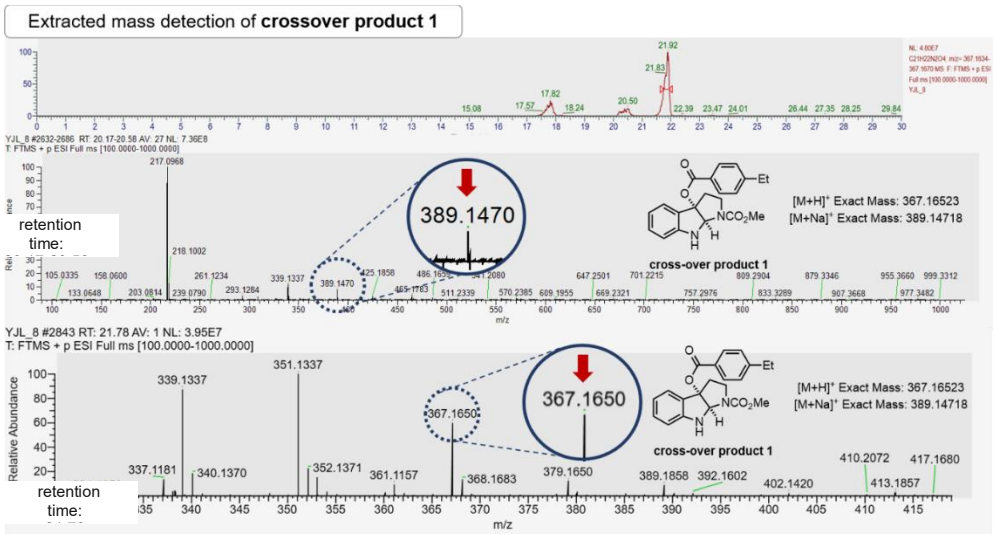
(2) Result of mass detection at peak corresponding to compound **2b**



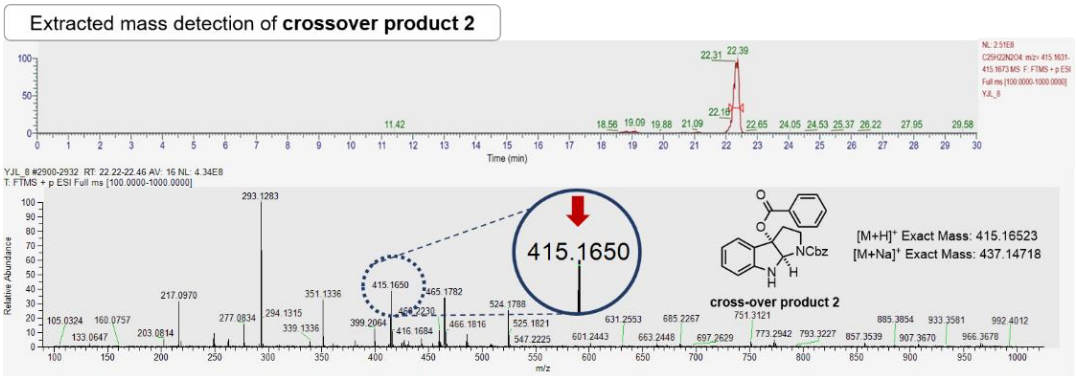
(3) Result of mass detection at peak corresponding to compound **2b'**



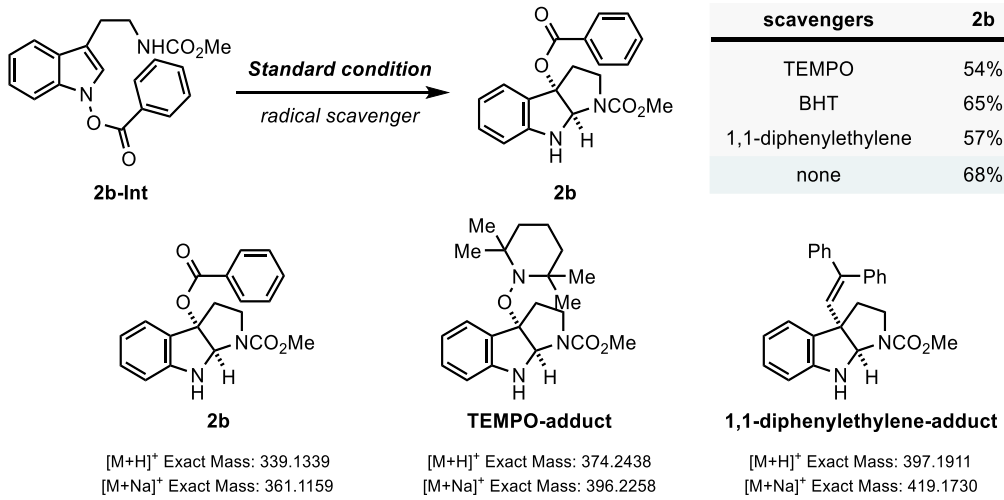
(4) Result of mass detection at peaks corresponding to **crossover product 1**



(5) Result of mass detection at peaks corresponding to **crossover product 2**



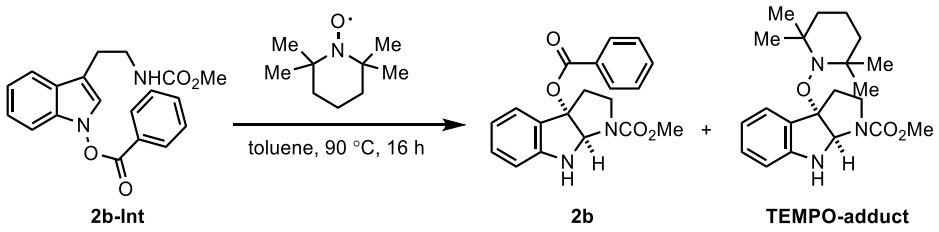
1.5.2.4. Radical-trapping Experiment with Indolyl *N*-Carboxylate 2b-Int



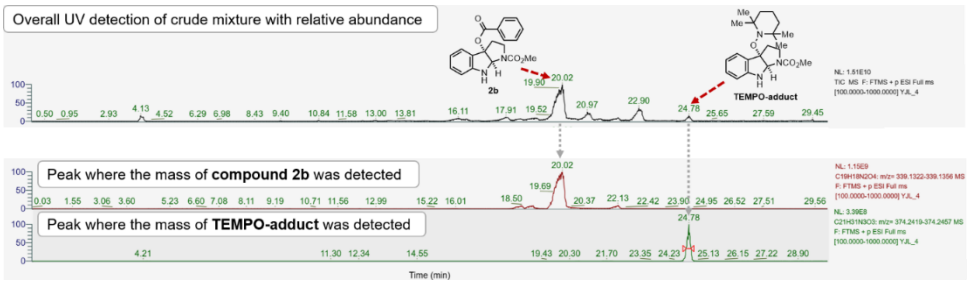
scavengers	2b
TEMPO	54%
BHT	65%
1,1-diphenylethylene	57%
none	68%

To a 10 mL flame-dried reaction tube equipped with a stir bar were added indolyl *N*-carboxylate **2b-Int** (67.6 mg, 0.200 mmol, 1.0 equiv) and toluene (4 mL, 0.05 M in **2b-Int**) at 23 °C, followed by radical-trapping reagent (2.0 equiv). The reaction tube was sealed under N_2 and the resulting mixture was heated to 90 °C in a pre-heated oil bath and stirred for 16 h, before it was cooled to 23 °C and directly concentrated under reduced pressure to provide the crude product. The crude mixture was then analyzed by HRMS. HRMS result of the resulting crude mixture indicated the formation of **TEMPO-adduct** or **1,1-diphenylethylene-adduct** when TEMPO or 1,1-diphenylethylene were used as a radical scavenger, even though no significant yield loss was observed for **2b.** Each crude mixture of radical-trapping experiment was purified by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 1:1) to afford the product **2b** (when using TEMPO: 40.3 mg, 54%, when using BHT: 44.1 mg, 65%, when using 1,1-diphenylethylene: 38.6 mg, 57%)

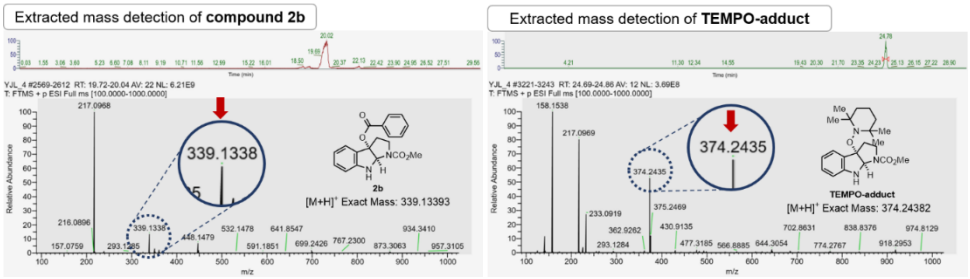
1.5.2.4.1. HRMS Results using TEMPO as a Radical Scavenger



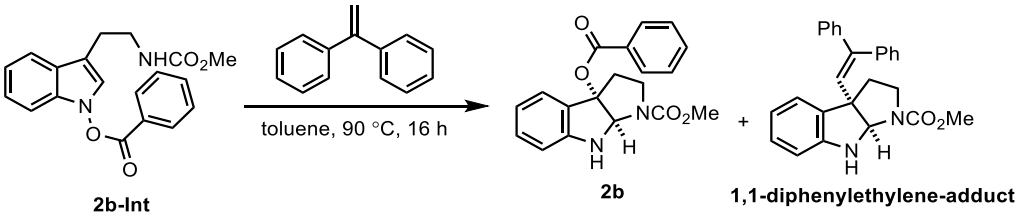
(1) Result of UV detection for the radical-trapping experiment and the relative location of each product detected



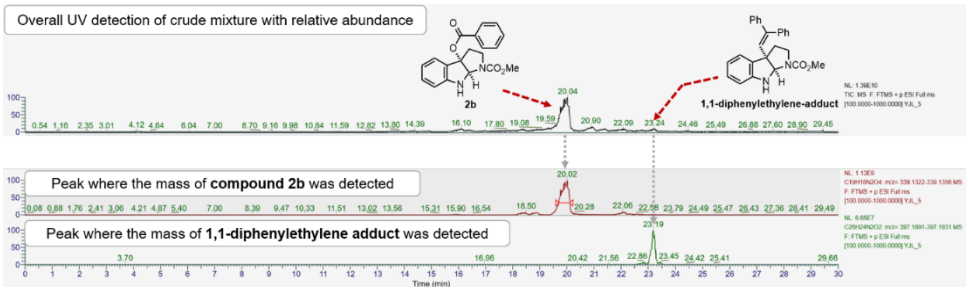
(2) Result of mass detection at peaks corresponding to compound **2b** and **TEMPO-adduct**



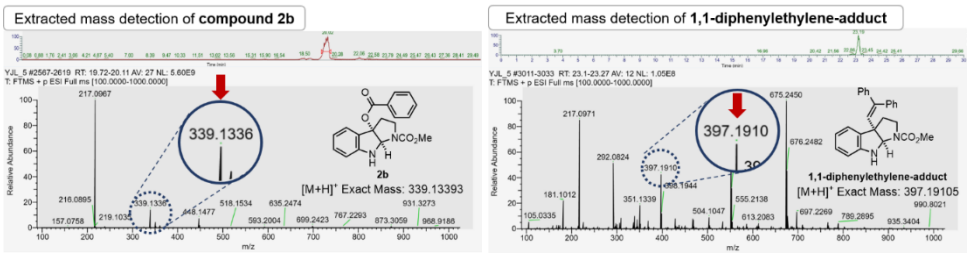
1.5.2.4.2. HRMS Results using 1,1-Diphenylethylene as a Radical Scavenger



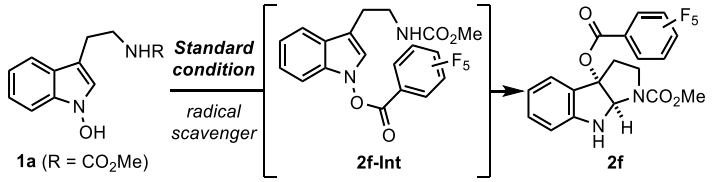
(1) Result of UV detection for the radical-trapping experiment and the relative location of each product detected



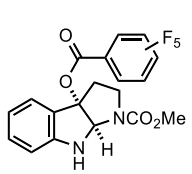
(2) Result of mass detection at peaks corresponding to compound **2b** and **1,1-diphenylethylene-adduct**



1.5.2.4.3. Radical-trapping Experiment with Electron-deficient Indolyl *N*-Carboxylate

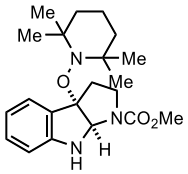


scavengers	2f
TEMPO	0%
BHT	49%
1,1-diphenylethylene	45%
none	53%



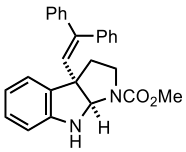
2f

$[M+H]^+$ Exact Mass: 429.0868
$[M+Na]^+$ Exact Mass: 451.0688



TEMPO-adduct

$[M+H]^+$ Exact Mass: 374.2438
$[M+Na]^+$ Exact Mass: 396.2258

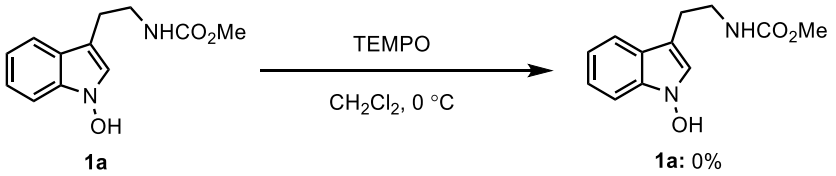


1,1-diphenylethylene-adduct

$[M+H]^+$ Exact Mass: 397.1911
$[M+Na]^+$ Exact Mass: 419.1730

To a flame-dried round-bottom flask equipped with a stir bar and septum were added *N*-hydroxyindole **1a** (50.0 mg, 0.213 mmol, 1.0 equiv) and CH_2Cl_2 (4.2 mL, 0.05 M in **1a**) at 23 °C. The resulting solution was cooled to 0 °C and 2,3,4,5,6-pentafluorobenzoyl chloride (1.1 equiv), Et_3N (1.1 equiv) and radical-trapping reagent (2.0 equiv) were successively added to the solution. The reaction mixture was warmed up to 23 °C and stirred for 2 h, before it was quenched with H_2O (2 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude product. The crude mixture was then analyzed by HRMS. When 1,1-diphenylethylene was used as the radical scavenger, **1,1-diphenylethylene-adduct** was detected by HRMS analysis, while no significant decrease in the reaction yield was observed. On the other hand, the formation of **2f** was noticeably suppressed when TEMPO was used as the radical scavenger due to the rapid decomposition of **1a** induced by TEMPO. Each crude mixture of radical-trapping experiment was purified by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 1:1) to afford the product **2f** (when using TEMPO: 0 mg, 0%, when using BHT: 44.7 mg, 49%, when using 1,1-diphenylethylene: 41.1 mg, 45%)

1.5.2.4.4. Control Experiment using TEMPO as a Radical Scavenger

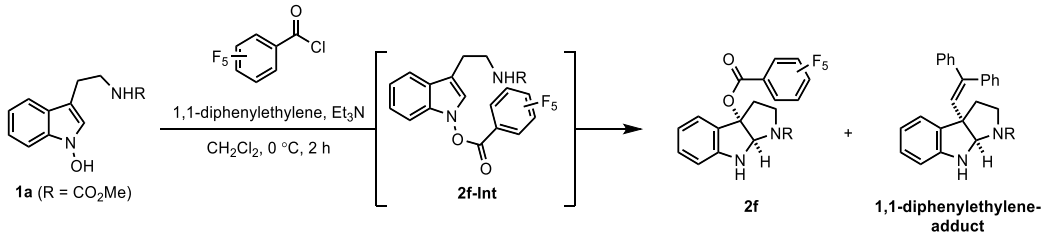


1a **1a:** 0%

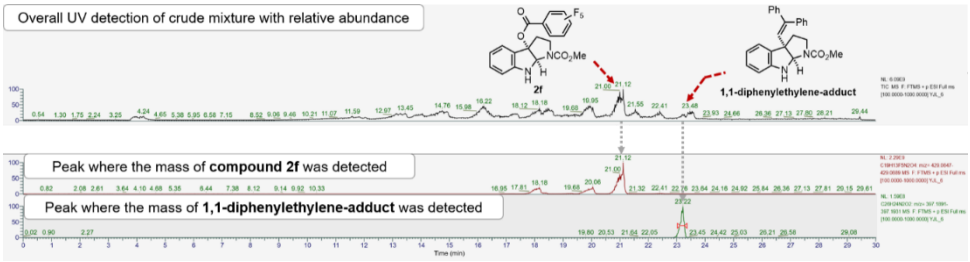
*Fast decomposition of **1a** was observed*

To confirm that the TEMPO is interacting with the *N*-hydroxyindole, *N*-hydroxyindole **1a** (50.0 mg, 0.213 mmol, 1.0 equiv) and CH_2Cl_2 (4.2 mL, 0.05 M in **1a**) were added to an flame-dried round-bottom flask equipped with a stir bar and septum at 23 °C. The resulting solution was cooled to 0 °C, and TEMPO (2.0 equiv) was added to the solution. The reaction mixture was stirred while the reaction was monitored by TLC. TLC indicated that fast decomposition of **1a** occurred immediately after TEMPO was added. This clearly indicates that the result of radical-trapping experiment with TEMPO is derived from the decomposition of **1a**, not from the inhibition of the radical-involved reaction pathway.

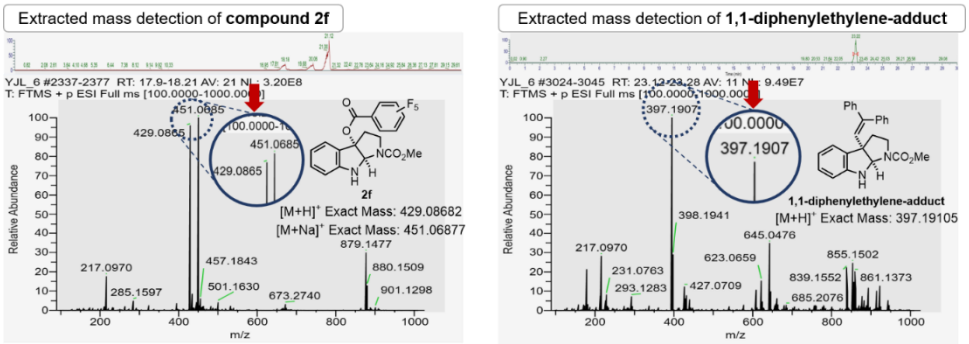
1.5.2.4.5. HRMS Results using 1,1-Diphenylethylene as a Radical Scavenger



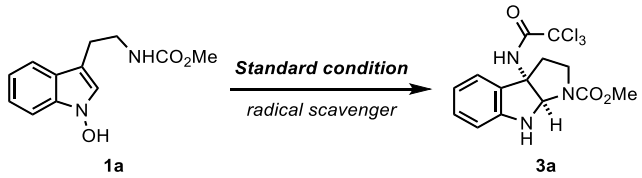
(1) Result of UV detection for the radical-trapping experiment and the relative location of each product detected



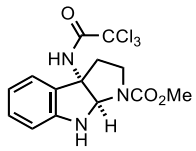
(2) Result of mass detection at peaks corresponding to compound **2f** and **1,1-diphenylethylene-adduct**



1.5.2.4.6. Radical-trapping Experiment with Indolyl Acetimidate

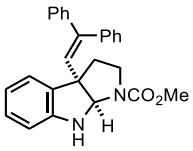


scavengers	3a
BHT	53%
1,1-diphenylethylene	60%
none	78%



3a

$[M+H]^+$ Exact Mass: 378.01735
$[M+Na]^+$ Exact Mass: 399.99930

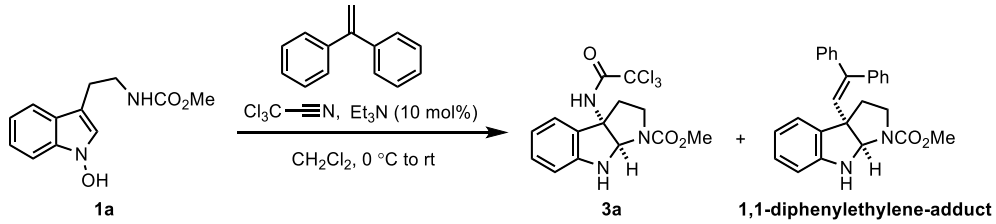


1,1-diphenylethylene-adduct

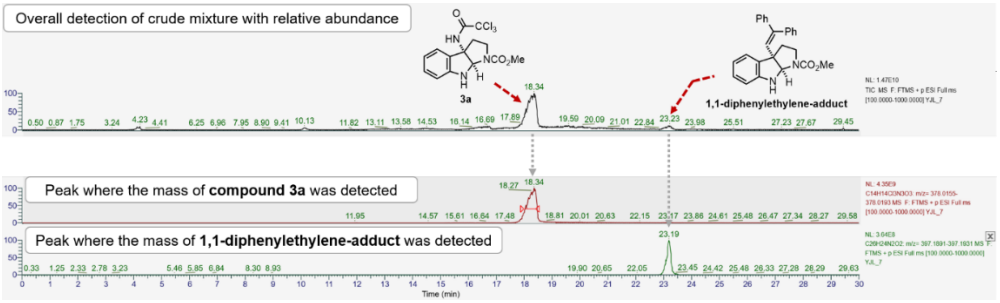
$[M+H]^+$ Exact Mass: 397.19105
$[M+Na]^+$ Exact Mass: 419.17300

To an oven-dried round-bottom flask equipped with a stir bar and septum were added *N*-hydroxyindole **1a** (50.0 mg, 0.213 mmol, 1.0 equiv) and CH_2Cl_2 (4.2 mL, 0.05 M in **1a**) at 23 °C. The resulting solution was cooled to 0 °C, and trichloroacetonitrile (3.0 equiv), Et_3N (0.1 equiv), and radical-trapping reagent (2.0 equiv) were added to the solution. The reaction mixture was warmed up to rt and stirred for 3 h, before it was quenched with H_2O (2 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to obtain the crude product, which was then analyzed by HRMS. When 1,1-diphenylethylene was used as the radical scavenger, **1,1-diphenylethylene-adduct** was detected by HRMS analysis while slight yield loss of **3a** was observed. Each crude mixture of radical-trapping experiment was purified by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 1:1) to afford product **3a** (when using BHT: 42.8 mg, 53%, when using 1,1-diphenylethylene: 48.5 mg, 60%)

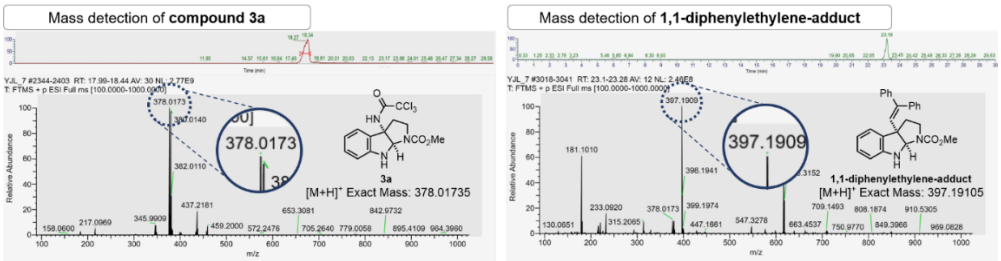
1.5.2.4.7. HRMS results using 1,1-diphenylethylene as a radical scavenger



(1) Result of UV detection for the radical-trapping experiment and the relative location of each product detected



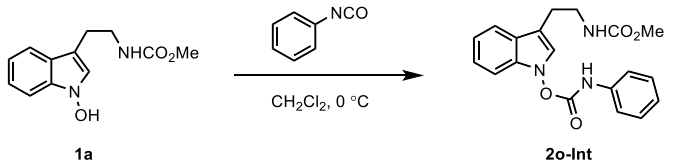
(2) Result of mass detection at peaks corresponding to compound **3a** and **1,1-diphenylethylene-adduct**



1.5.2.5. [3,3]-Sigmatropic Rearrangement of Indolyl Carbamate

1.5.2.5.1. Preparation of Indolyl Carbamate

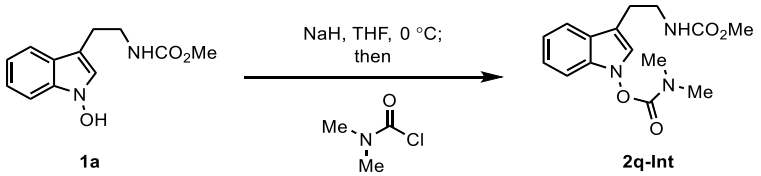
Methyl (2-(1-((phenylcarbamoyl)oxy)-1H-indol-3-yl)ethyl)carbamate (2o-Int)



To an oven-dried round-bottom flask equipped with a stir bar and septum were added *N*-hydroxyindole **1a** (318 mg, 1.36 mmol, 1.0 equiv) and CH_2Cl_2 (14 mL, 0.1 M in **1a**) at 23 °C. The resulting solution was cooled to 0 °C, and phenyl isocyanate (155 µL, 1.42 mmol, 1.04 equiv) was added to the solution. The reaction mixture was stirred for 2 h, before it was diluted with H_2O (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with brine (1 × 20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3) to afford indolyl N-carboxylate **2o-Int** (336 mg, 70%) as a pale yellow oil.

R_f=0.47 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.59 (d, *J* = 8.1 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.37 (t, *J* = 7.8 Hz, 2H), 7.33 – 7.26 (m, 2H), 7.17 (q, *J* = 7.1 Hz, 2H), 7.06 (s, 1H), 4.84 (s, 1H), 3.66 (s, 3H), 3.52 (q, *J* = 6.7 Hz, 2H), 2.95 (t, *J* = 6.9 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 157.4, 151.8, 136.7, 135.7, 129.3, 124.7, 124.6, 124.0, 123.6, 122.2, 121.0, 119.3, 119.1, 111.5, 111.4, 109.0, 52.2, 41.1, 25.7; **HRMS** calcd. for $C_{19}H_{20}N_3O_4^+$ $[M + H]^+$ 354.1448, found 354.1445.

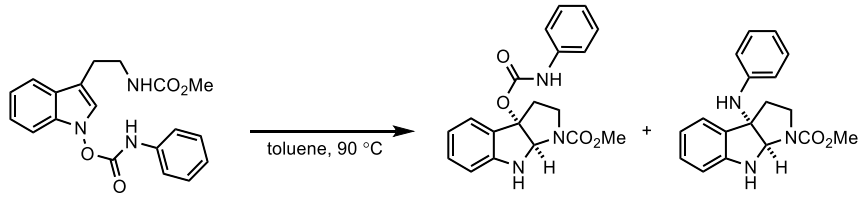
3-(2-((Methoxycarbonyl)amino)ethyl)-1H-indol-1-yl dimethylcarbamate (2q-Int)



To an oven-dried round-bottom flask equipped with a stir bar and septum were added *N*-hydroxyindole **1** (362 mg, 1.55 mmol, 1.0 equiv) and THF (20 mL, 0.08 M in **1a**) at 23 °C. The resulting solution was cooled to 0 °C, and NaH (60% in mineral oil, 93.0 mg, 2.32 mmol, 1.5 equiv) was added to the solution. The reaction mixture was stirred for 10 min, then dimethylcarbamyl chloride (0.21 mL, 2.32 mmol, 1.5 equiv) was added. The resulting mixture was stirred for additional 1 h at 0 °C before it was quenched with brine (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine(1 × 20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 1:1) to afford indolyl N-carboxylate **2q-Int** (288 mg, 61%) as a pale yellow oil.

$\boldsymbol{R_f}$=0.11 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.0 Hz, 1H), 7.31 – 7.27 (m, 2H), 7.17 (ddd, *J* = 8.1, 5.7, 2.4 Hz, 1H), 7.06 (s, 1H), 4.98 (s, 1H), 3.69 (s, 3H), 3.52 (q, *J* = 6.6 Hz, 2H), 3.19 (s, 3H), 3.08 (s, 3H), 2.96 (t, *J* = 6.9 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 157.1, 154.6, 135.3, 124.4, 123.9, 123.2, 120.5, 119.1, 110.6, 108.6, 52.0, 41.1, 37.6, 36.2, 25.7; **HRMS** calcd. for $C_{15}H_{20}N_3O_4^+$ $[M + H]^+$ 306.1448, found 306.1456.

1.5.2.5.2. [3,3]-Sigmatropic Rearrangement of Indolyl *N*-carboxylate 2o-Int

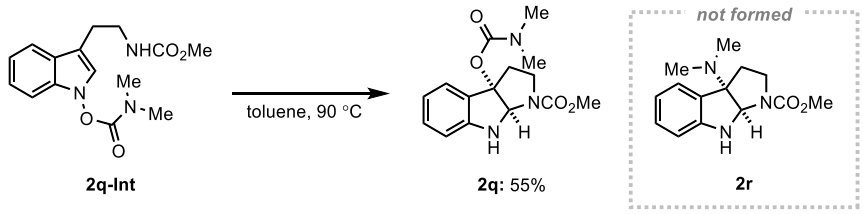


To a 10 mL oven-dried Schlenk tube equipped with a stir bar were added indolyl N-carboxylate **2o-Int** (0.120 g, 0.340 mmol, 1.0 equiv) and toluene (7 mL, 0.05 M in **2o-Int**) at 23 °C. The resulting mixture was heated to 90 °C in a pre-heated oil bath and stirred for 16 h, before it was cooled to rt and directly concentrated under reduced pressure to obtain the crude product. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3) to afford product **2o** and **2p** (**2o**: 32.4 mg, 27%, **2p**: 18.9 mg, 18%) as a pale yellow oil.

2o: R_f=0.47 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.61 and 7.53 (d, *J* = 7.6 Hz, 1H), 7.36 – 7.26 (m, 5H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.05 (t, *J* = 7.1 Hz, 1H), 6.81 (q, *J* = 7.4 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.65 – 6.61 (m, 1H), 5.68 and 5.63 (s, 1H), 5.21 and 4.85 (s, 1H), 3.89 and 3.79 (t, *J* = 9.8 Hz, 1H), 3.79 and 3.72 (s, 3H), 3.18 (td, *J* = 10.9, 6.3 Hz, 1H), 3.00 and 2.85 (dd, *J* = 12.9, 6.4 Hz, 1H), 2.70 (p, *J* = 11.6 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 155.7, 154.9, 152.0, 151.9, 150.9, 150.6, 137.7, 137.6, 131.2, 129.2, 126.6, 126.0, 125.9, 123.8, 119.8, 119.6, 119.0, 110.5, 110.4, 94.1, 92.8, 80.4, 79.6, 52.9, 52.7, 45.8, 45.6, 35.7, 35.5; **HRMS** calcd. for $C_{19}H_{20}N_3O_4^+$ $[M + H]^+$ 354.14483, found 354.1445.

2p: R_f=0.45 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$s): δ 7.18 (d, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 7.7 Hz, 1H), 7.10 (t, *J* = 7.0 Hz, 2H), 6.77 (q, *J* = 7.1 Hz, 1H), 6.72 (t, *J* = 7.3 Hz, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 6.51 (dd, *J* = 11.4, 8.0 Hz, 2H), 5.73 and 5.69 (s, 1H), 5.14 and 4.80 (s, 1H), 4.05 and 4.00 (s, 1H), 3.85 and 3.74 (ddd, *J* = 11.5, 7.7, 3.7 Hz, 1H), 3.76 and 3.73 (s, 3H), 3.27 (ddd, *J* = 19.8, 16.6, 9.3 Hz, 1H), 2.63 (ddt, *J* = 30.8, 12.8, 8.5 Hz, 1H), 2.37 – 2.29 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 156.0, 155.3, 149.1, 148.9, 145.10, 145.09, 129.9, 129.4, 129.3, 123.6, 123.5, 119.6, 119.4, 118.7, 118.5, 115.5, 115.2, 109.9, 109.7, 73.6, 72.4, 52.9, 52.7, 44.8, 44.6, 37.8, 37.6; **HRMS** calcd. for $C_{18}H_{20}N_3O_2^+$ $[M + H]^+$ 310.1550, found 310.1546.

1.5.2.5.3. [3,3]-Sigmatropic Rearrangement of Indolyl *N*-carboxylate 2q-Int



To a 10 mL oven-dried Schlenk tube equipped with a stir bar were added indolyl N-carboxylate **2q-Int** (61.0 mg, 0.200 mmol, 1.0 equiv) and toluene (4 mL, 0.05 M in **2q-Int**) at 23 °C. The resulting mixture was heated to 90 °C in a pre-heated oil bath and stirred for 16 h, before it was cooled to rt and directly concentrated under reduced pressure to obtain the crude product. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3) to afford product **2q** (33.7 mg, 55%) as a pale yellow oil.

R_f=0.25 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.58 and 7.48 (d, *J* = 7.6 Hz, 1H), 7.17 (td, *J* = 7.6, 1.3 Hz, 1H), 6.79 (q, *J* = 7.1 Hz, 1H), 6.64 (d, J = 7.9 Hz, 1H), 5.67 and 5.62 (s, 1H), 5.13 and 4.79 (s, 1H), 3.85 and 3.78 (t, *J* = 9.1 Hz, 1H), 3.77 and 3.71 (s, 3H), 3.15 (td, *J* = 10.8, 6.4 Hz, 1H), 2.85 (s, 6H), 2.91 and 2.75 (dd, *J* = 13.2, 6.1 Hz, 1H), 2.67 – 2.56 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 155.8, 155.1, 155.0, 150.9, 150.6, 130.9, 126.9, 126.7, 126.6, 125.8, 119.6, 119.3, 110.4, 110.3, 93.7, 92.4, 80.6, 79.8, 52.8, 52.6, 45.6, 45.4, 36.4, 36.2, 36.0; **HRMS** calcd. for $C_{15}H_{20}N_3O_4^+$ $[M + H]^+$ 306.1448, found 306.1449.

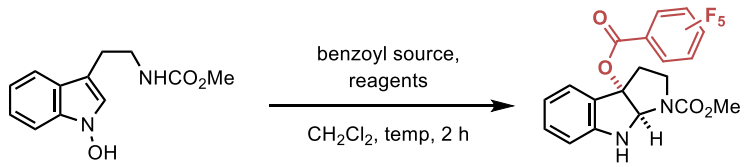
Part 2. Application of IHT Reaction

2.1. Results and Discussion

2.1.1. Evaluation of the C3-Acyloxylation Reaction Conditions

First, optimization of esterification conditions for pentafluorobenzoyl sources was carried out (Table 1.1). When coupling with pentafluorobenzoic acid using EDC·HCl (entry 1), 2f afforded in 31% yield. And the yield was slightly decreased when using pentafluorobenzoic acid and DCC (entry 2). Then, coupling partner was replaced with pentafluorobenzoyl chloride, the yield increased to 38% (entry 3). The highest yield was obtained when pentafluorobenzoyl chloride and triethylamine were added at 0 °C, and the reaction mixture was then warmed up to 23 °C and stirred for 2 h (entry 5).

Table 1.1. Evaluation of Esterification Conditions for Pentafluorobenzoyl Sources[a]



1a **2f**

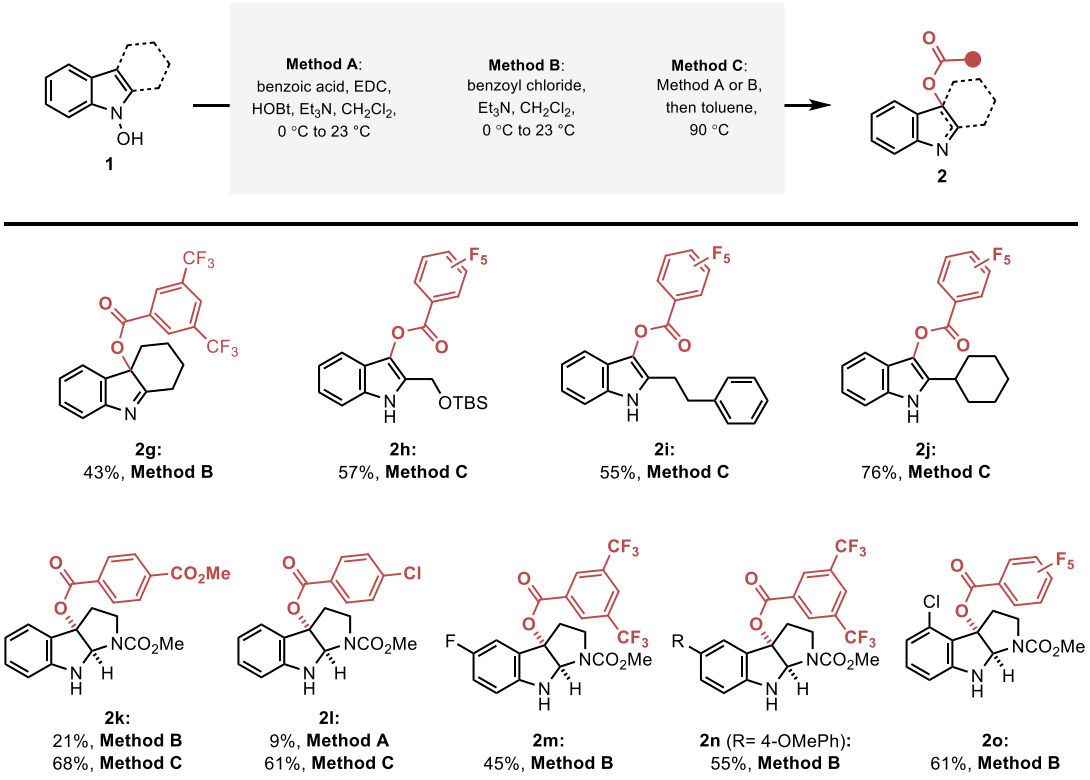
entry	benzoyl source	conditions	temperature (°C)	yield (%)[b]
1	C_6F_5COOH	EDC·HCl (1.1 equiv), HOBt (1.1 equiv), Et_3N (2.2 equiv)	23	31
2	C_6F_5COOH	DCC (1.1 equiv), DMAP (1.1 equiv)	23	27
3	C_6F_5COCl	Et_3N (1.2 equiv)	23	38
4	**C_6F_5COCl**	**Et_3N (1.2 equiv)**	**0 to 23**	**55**

[a]Reaction conditions: **1a** (0.5–1.0 mmol, 1.0 equiv) in CH_2Cl_2 (0.05 M), benzoyl source (1.1 equiv), for 2 h. [b]Determined by ^{1}H NMR analysis using TCE as an internal standard.

2.1.2. Substrate Scope of the C3-Acyloxylation Reaction

With the optimized reaction conditions in hand, the generality of the reaction was examined (Scheme 1.4). By utilizing the electronics-based rate enhancement protocol, a delicate indolenine product could be smoothly synthesized at ambient temperature (**2g**). And the method allowed for the highly straightforward synthesis of 3-acyl indole products (**2h-2j**). The developed method also enabled the production of various pyrroloindolines (**2k-2o**). The rearrangement reaction could also be mediated by benzoyl coupling partners containing electron-withdrawing groups such as ester or halide, although higher reaction temperatures were required for higher yield (**2k, 2l**). Substituted pyrroloindoline products bearing fluoro (**2m**), aryl (**2n**), or chloro (**2o**) groups could be successfully synthesized using the strongly electron-withdrawing 3,5-bistrifluoromethyl benzoyl group or pentafluorobenzoyl group.

Scheme 1.4. Substrate Scope of C3-Acyloxylation[a]

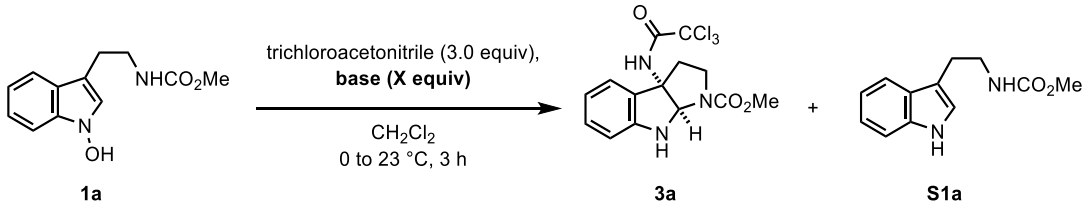


[a]**Method A**: Reaction conditions: **1** (0.1−0.3 mmol, 1.0 equiv) in CH_2Cl_2 (0.05 M), benzoyl chloride (1.1 equiv), Et_3N (1.2 equiv) in CH_2Cl_2 (0.05 M), 0 °C to 23 °C for 2 h. **Method B**: Reaction conditions: **1** (0.2−0.6 mmol, 1.0 equiv) in CH_2Cl_2 (0.05 M), benzoic acid (1.0 equiv), EDC·HCl (1.1 equiv), HOBt (1.1 equiv), Et_3N (2.2 equiv), 0 °C to 23 °C for 2 h. **Method C**: Reaction conditions: **1** (0.1−0.7 mmol, 1.0 equiv) in CH_2Cl_2 (0.05 M), **Method A** or **B**, 23 °C for 16 h. Then, the reaction mixture filtrated through silica gel, the solvent was exchanged to toluene (0.05 M), 90 °C for 16 h. Yields of the isolated products.

2.1.3. Evaluation of the C3-Amidation Reaction Conditions

Initial optimization was carried out with Methyl (2-(1-hydroxy-1H-indol-3-yl)ethyl)carbamate **1a** and trichlorocetonitrile (Table 1.2). The desired **3a** was gained in 51% yield when DIPEA was employed as base (entry 1). When DBU, DABCO and NaH were used as bases, the yields increased to 70%, 59%, and 68%, respectively (entries 2, 3, and 5). However, pyridine base was not suitable for synthesizing **3a,** as it instead produced **S1a** in 54% yield (entry 4). The reaction was further improved with Et_3N, which gave the best yield of 75% (entry 6). With this promising result, 1.0 equivalent of Et_3N was tested, yield of **3a** was decreased to 37% and yield of **S1a** was increased to 21% (entry 7).

Table 1.2. Evaluation of Bases[a]

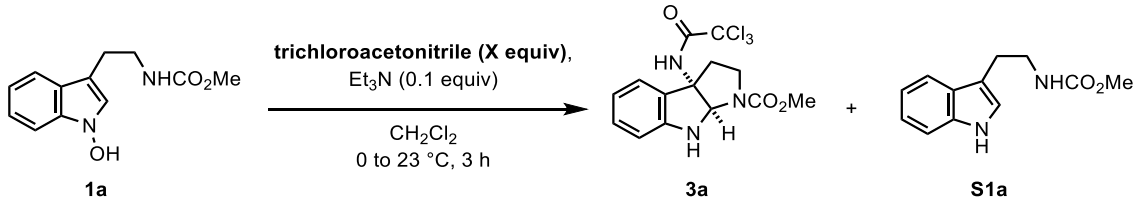


entry	base	equiv	yield of 3a (%)[b]	yield of S1a (%)[b]
1	DIPEA	0.1	51	7
2	DBU	0.1	70	5
3	DABCO	0.1	59	6
4	pyridine	0.1	<5	54
5	NaH	1.1	68	5
6	**Et_3N**	**0.1**	**75 (71)**	**<1**
7	Et_3N	1.0	37	21

[a]Reaction conditions: **1a** (0.3–1.2 mmol, 1.0 equiv) in CH_2Cl_2 (0.05 M), trichloroacetonitrile (3.0 equiv), 0 to 23 °C for 3 h. [b]Determined by ^{1}H NMR analysis using TCE as an internal standard and the isolated yield was included in the parentheses.

Next, stoichiometry of coupling partner trichloroacetonitrile was examined (Table 1.3). When equivalent of trichloroacetonitrile increased from 1.0 equivalent to 2.0 equivalent and 3.0 equivalent, the yield of desired **3a** considerably increased from 36% to 55% and 79%, respectively (entries 1–3). However, yield was decreased to 48% when using 4.0 equivalent of trichloroacetonitrile (entry 4).

Table 1.3. Optimization of the Stoichiometry of Trichloroacetonitrile[a]

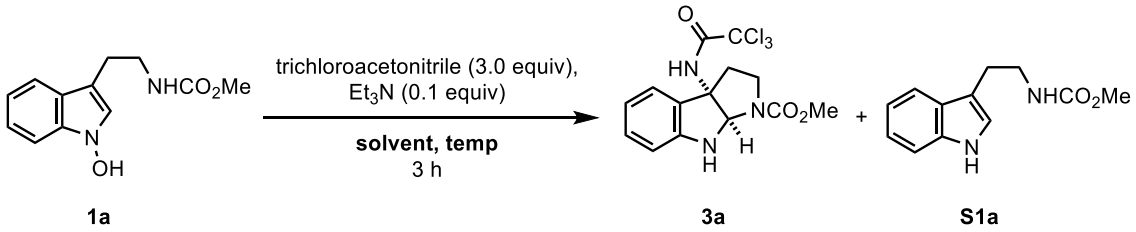


entry	equiv	yield of 3a (%)[b]	yield of S1a (%)[b]
1	1.0	36	22
2	2.0	55	9
3	**3.0**	**79% (78)**	**<1**
4	4.0	48	11

[a]Reaction conditions: **1a** (0.3–1.2 mmol, 1.0 equiv) in CH_2Cl_2 (0.05 M), Et_3N (0.1 equiv), 0 to 23 °C for 3 h. [b]Determined by ^1H NMR analysis using TCE as an internal standard and the isolated yield was included in the parentheses.

Finally, solvent and temperature dependence experiments were done to find optimal reaction conditions. (Table 1.4). The yield of **3a** was sensitive to the solvents (entries 1–5). Reactions performed with THF, toluene, MeCN, and DMF mainly synthesized **S1a** rather than the desired **3a** (entries 1–4). Optimal solvent was CH_2Cl_2 with 75% yield, and further screening on temperature was conducted using CH_2Cl_2 (entry 5). When reactants were added at 23 °C and stirred for 3 h, yield of **3a** was slightly decreased to 67% (entry 6). And when reaction was performed at 0 °C for 24 h, yield of **3a** was decreased to 38% and **S1a** was produced with a yield of 33% (entry 7).

Table 1.4. Evaluation of Solvents and Temperatures[a]



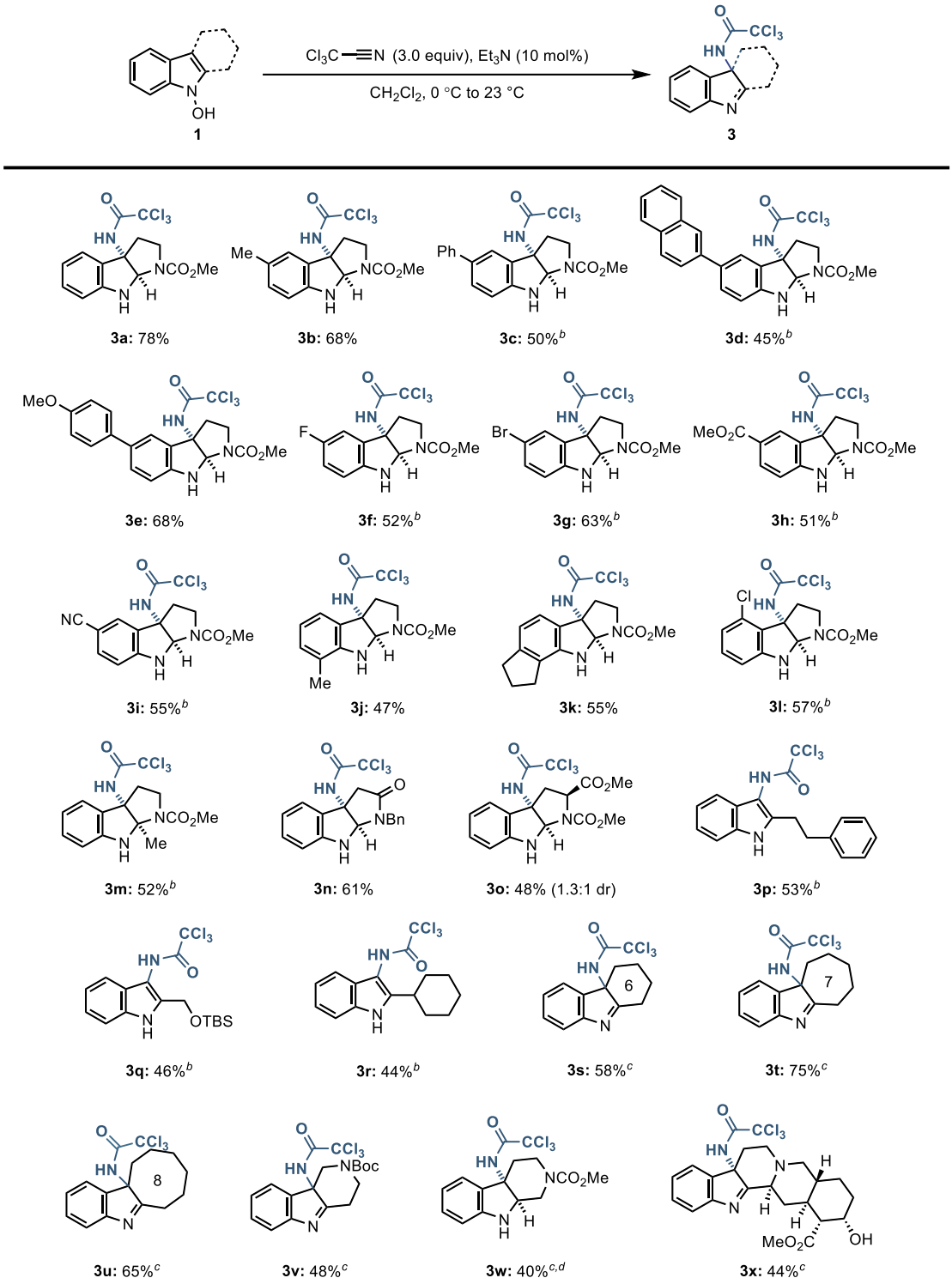
entry	solvent	temperature (°C)	time (h)	yield of 3a (%)[b]	yield of S1a (%)[b]
1	THF	0 to 23	3	4	48
2	toluene	0 to 23	3	11	63
3	MeCN	0 to 23	3	16	72
4	DMF	0 to 23	3	<5	56
5	**CH_2Cl_2**	**0 to 23**	**3**	**75 (73)**	**<1**
6	CH_2Cl_2	23	3	67	<1
7	CH_2Cl_2	0	24	38	33

[a]Reaction conditions: **1a** (0.3–1.2 mmol, 1.0 equiv) in solvent (0.05 M), trichloroacetonitrile (3.0 equiv), Et_3N (0.1 equiv) for 3 h. [b]Determined by ^1H NMR analysis using TCE as an internal standard and the isolated yield was included in the parentheses.

2.1.4. Substrate Scope of the C3-Amidation Reaction

With the optimized reaction conditions in hand, the generality of the reaction was examined (Scheme 1.5). First, A range of functionalized pyrroloindolines bearing a nitrogen substituent at the 5-position was synthesized from *N*-hydroxytryptamines (**3a-3m**). Substrates bearing various electronic properties at the 5-position of indole were proceeded smoothly to afforded the desired products in good yield (**3a-3i**). Also, various substituents at indole 4-, 6-, or 7-position were well compatible in this reaction (**3j-3l**). Interestingly, mild thermal activation of reaction was needed for completion of starting material conversion in the case of indole skeleton featured substituents with electron-withdrawing properties (**3f-3i**) or steric hindrance adjacent to the reaction center (**3m**). Finally, the interception of the initially formed imine intermediate could be realized by a pendant amide (**3n**) or a substituted carbamate (**3o**). Pleasingly, the developed strategy provided a convenient method to synthesize 3-aminated indoles (**3p-3r**). The developed method is noteworthy for its applicability in manufactring indolenine products with sensitive C=N bond. Tricyclic indolenines, featuring diverse carbocycles or a piperidine ring, were also readily formed in a low temperature (**3s-3v**). In addition, the formation of a hexahydropyrridoindole structure was achieved by *in situ* addition of a hydride nucleophile (**3w**). Finally, this method demontrates reactivity even in a complex natural product such as yohimbine, without the need for introducing protecting groups (**3x**).[67]

Scheme 1.5. Substrate Scope of C3-Amidation of Indole Derivatives[a]

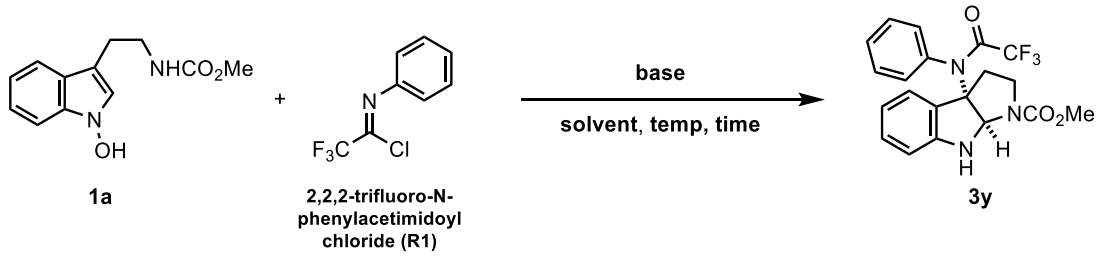


[a]Reaction conditions: **1** (0.1−0.7 mmol, 1.0 equiv) in CH_2Cl_2 (0.05 M), trichloroacetonitrile (3.0 equiv), Et_3N (0.1 equiv), 0 °C to 23 °C for 3 h. [b]Reaction conditions: **1** (0.1−0.3 mmol, 1.0 equiv) in DCE (0.05

M), trichloroacetonitrile (3.0 equiv), Et_3N (0.1 equiv), 23 °C to 90 °C for 2 h. [c]Reaction conditions: **1** (0.1−0.7 mmol, 1.0 equiv) in CH_2Cl_2 (0.05 M), trichloroacetonitrile (3.0 equiv), Et_3N (0.1 equiv), 0 °C for 3 h [d]Product was isolated after reduction with $NaBH_4$ in MeOH. Yields of the isolated products.

To obtain more structurally diverse pyrroloindoline, we planned to use trifluoroimidoyl chloride as a coupling partner. Initial optimization was carried out with Methyl (2-(1-hydroxy-1H-indol-3-yl)ethyl)carbamate **1a** and 2,2,2-trifluoro-N-phenylacetimidoyl chloride **R1** (Table 1.5). To find the most effective base, reaction was carried out with **1a** and 1.5 equivalent of **R1a** in THF for 1 h at 0 °C (entries 1−5). When 1.1 equivalent of Et_3N, LDA, LiHMDS, and NaHMDS were used as bases, yields were 8%, 13%, 17% and 16%, respectively (entries 1−4). When switching the base to 1.1 equivalent of NaH, desired **3y** was obtained in 34% NMR yield and 28% isolated yield (entry 5). Then, several conditions were tested with NaH (entries 6−10). When CH_2Cl_2 was used instead of THF, yield was decreased to 26% NMR yield and 20% isolated yield ((entry 6). Using 2.0 equivalent of NaH instead of 1.1 equivalent NaH, result showed decreased yield of **3y** (entry 7). Increased euivalent of **R1** condition also showed decreased yield of **3y** to 21% (entry 8). Furthermore, temperature and time were examined (entries 9 and 10). When the temperature was −20 °C, reaction was stirred for 12 h and yield of **3y** was 11% (entry 9). When it comes to −78 °C for 24 h condition, yield of **3y** was 19% (entry 10).

Table 1.5. Evaluation of Reaction Conditions using Trifluoroacetimidoyl Chloride[a]

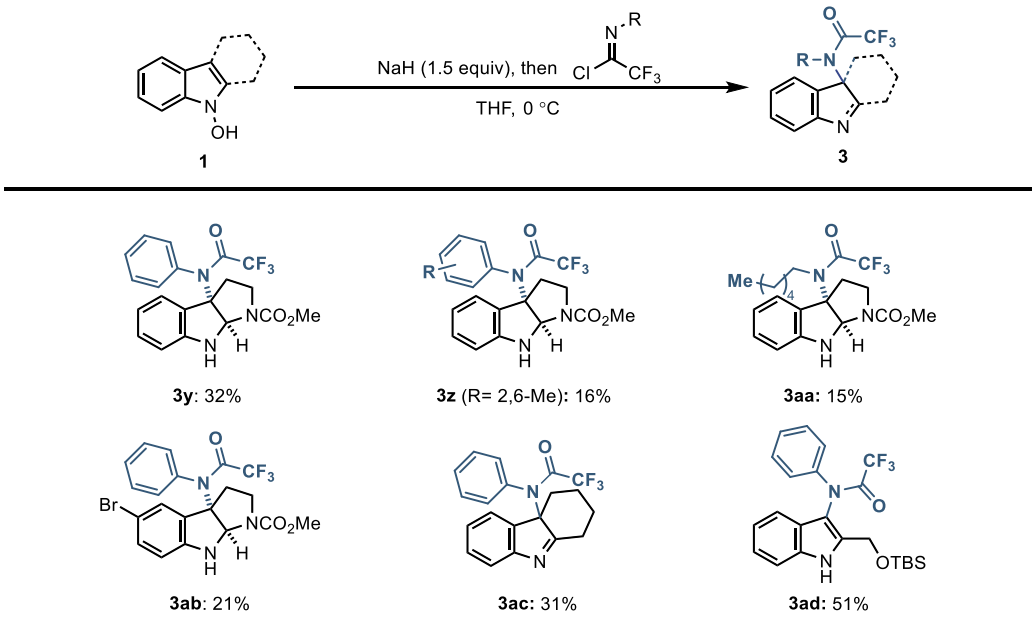


entry	base (equiv)	equiv of R1	solvent	temperature (°C)	time (h)	yield of 3y (%)[b]
1	Et_3N (1.1 equiv)	1.5	THF	0	1	8
2	LDA (1.1 equiv)	1.5	THF	0	1	13
3	LiHMDS (1.1 equiv)	1.5	THF	0	1	17
4	NaHMDS (1.1 equiv)	1.5	THF	0	1	16
5	**NaH (1.1 equiv)**	**1.5**	**THF**	**0**	**1**	**34 (28)**
6	NaH (1.1 equiv)	1.5	CH_2Cl_2	0	1	26 (20)
7	NaH (2.0 equiv)	1.5	THF	0	1	24
8	NaH (1.1 equiv)	3.0	THF	0	1	21
9	NaH (1.1 equiv)	1.5	THF	–20	12	11
10	NaH (1.1 equiv)	1.5	THF	–78	24	19

[a]Reaction conditions: **1a** (0.3–1.2 mmol, 1.0 equiv) in solvent (0.05 M), imidoyl chloride (1.0 equiv). [b]Determined by ^{1}H NMR analysis using TCE as an internal standard and the isolated yield was included in the parentheses.

The use of trifluoroimidoyl chloride as a coupling partner allowed for even greater structural diversity to be achieved (Scheme 1.6). The trifluoromethyl group, which is even more electron-withdrawing, made it possible to install an additional carbon-based substituent at the C3-nitrogen atom. Pyrroloindoline products with phenyl and sterically bulky 2,6-dimethylphenyl groups at the nitrogen substituent were obtained (**3y, 3z**), as well as those with an aliphatic n-hexyl chain (**3aa**). The reaction was accomplished in the presence of an electron-withdrawing substituent at the 5-position of indole (**3ab**). Finally, this strategy for expanding the diversity of products was also applied to the synthesis of both indolenine (**3ac**) and indole structures (**3ad**).

Scheme 1.6. Substrate Scope of C3-Amidation of Indole Derivatives[a]



[a]Reaction conditions: **1** (0.3−1.2 mmol, 1.0 equiv) in THF (0.05 M), imidoyl chloride (1.5 equiv), NaH (1.5 equiv), 0 °C for 1 h. Yields of the isolated products.

2.2. Conclusion

In conclusion, a novel method for the efficient C3-hetero-functionalization of indoles has been developed through facilitated Indolyl 1,3-Heteroatom Transposition. The effectiveness of the developed approach is attributed to the utilization of a crucial electronic effect of the system, especially at the 2'-position. The reaction exhibited high efficiency under mild conditions and enabled the preparation of a wide range of C3-acyloxylated or C3-amidated indole products with ease. From a synthetic perspective, this unified strategy allowed access to sensitive and/or complex products of indole, indolenine, or indoline.

2.3. Experimental Section

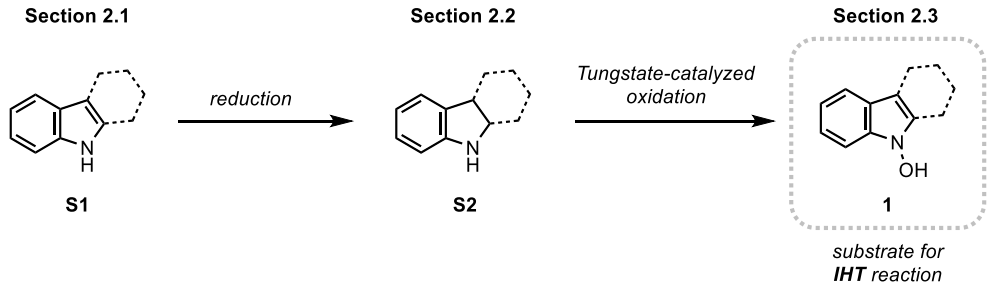
2.3.1. General Experimental Information

Unless stated, reactions were carried out in flame-dried glassware under an argon atmosphere with dry solvents under anhydrous conditions. Tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were were obtained from a PureSolv solvent purification system and toluene was dried over CaH_2 and distilled under N_2 atmosphere. *N,N*-Dimethylformamide (DMF), dimethyl sulfoxide (DMSO), 1,2-dichloroethane (DCE), acetonitrile (MeCN), and 1,4-dioxane were purchased in anhydrous form from Sigma-Aldrich. Acetone, ethyl acetate (EtOAc), diethyl ether (Et_2O), CH_2Cl_2, hexanes, and water (H_2O) were purchased from Samchun Chemical and used without further purification. $H_2{}^{18}O$ (97 atom% ^{18}O) was purchased from Sigma-Aldrich and used as received. Other reagents were purchased from Sigma Aldrich, Alfa Aesar, Acros Organics, and TCI with the and used as received. Thin-layers chromatography (TLC) analysis of reactions was performed on 0.25 mm E. Merck silica gel plates (60 F_{254}). TLC plates were visualized by UV light and treated with staining solution such as an acidic ethanolic anisaldehyde or potassium permanganate ($KMnO_4$). Flash column chromatography was performed on Intertec Silica gel (60–200 μm). ^1H, ^{13}C and ^{19}F NMR spectra were recorded with Agilent 400-MR DD2 Magnetic Resonance System, Bruker 500 MHz instrument of Varian/Oxford As-500 instrument in solvents as indicated. Chemical shifts are quoted in parts per million (ppm) and referenced to residual un-deuterated solvent signal ($CHCl_3$ in $CDCl_3$: δ 7.26 ppm for ^1H, δ 77.16 ppm for ^{13}C; CH_3OH in MeOD: δ 3.31 ppm for ^1H, δ 49.00 ppm for ^{13}C). ^{19}F NMR spectra were calibrated to an external standard of neat $PhCF_3$ (δ –63.72 ppm). Coupling constants are reported in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, qui= quintet, h = heptet, dd = doublet of doublets, dq = doublet of quartets, dm= doublet of multiplets, td = triplet of doublets, tt = triplet of triplets, qd =quartet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, ddt = doublet of doublet of triplets, dtd = doublet of triplet of doublets, dtt=doublet of triplet of triplets, tdd = triplet of doublet of doublets, m = multiplet, br = broad. High-resolution mass spectrometry (HRMS) was performed using a HRMS-ESI Q-TOF 5600 spectrometer at National Instrumentation Center for Environmental Management (NICEM) in Seoul National University,

Ultra High Resolution ESI Q-TOF mass spectrometer (Bruker compact) at the Organic Chemistry Research Center in Sogang University, or ThermoFisher Scientific mass spectrometer (Orbitrap Exploris 120) at Department of Chemistry at Seoul National University.

2.3.2. Preparation of Starting Materials

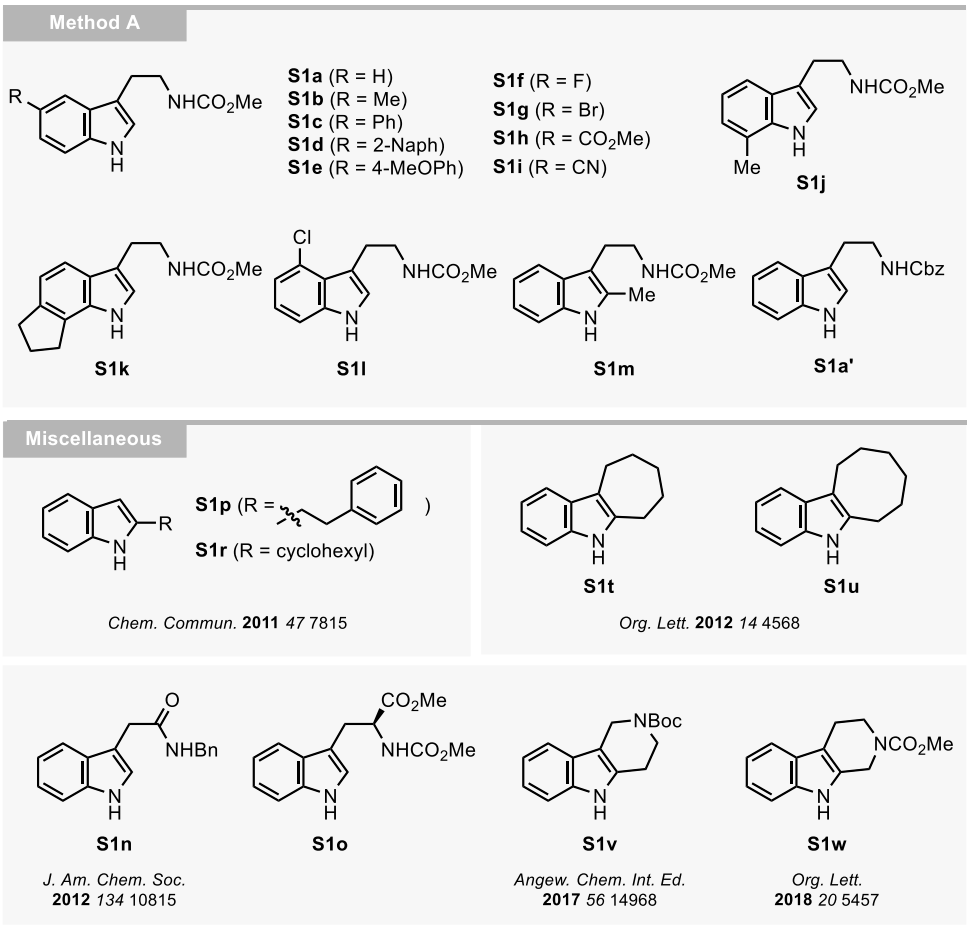
Scheme 1.7. Synthetic Scheme for *N*-hydroxyindole **1**.



The synthetic scheme of the preparation of *N*-hydroxyindole **1**, the substrate of indolyl 1,3-heteroatom transposition (**IHT**) reaction, is depicted in Scheme **1**. The two-step sequence, reduction of indole **S1** followed by tungstate-catalyzed oxidation, was utilized to provide a series of *N*-hydroxyindole **1.** Detailed information on the preparation and characterization of **S1**, **S2** and **1** is described in Section **2.1**, **2.2** and **2.3**, respectively.

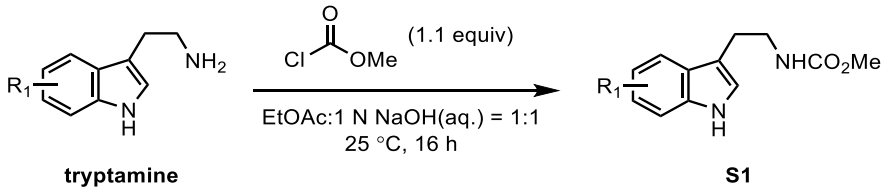
2.3.2.1. Preparation of Indole Derivatives

Figure 1.8. List of Tryptamine Derivatives Categorized by Methods of Preparation



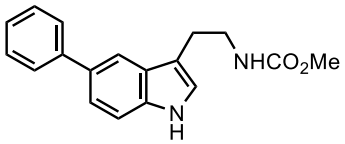
S1a[1], S1b[1], S1f[1], S1g[2], S1j[2], S1l[1], S1m[3], S1n[4], S1o, S1p[5], S1r[5], S1t[6], S1u[6], S1v[7], S1w[8], S1a[9]: Spectral data is in agreement with the reported literature values

General procedure A



Reactions were performed in flame-dried round-bottom flask equipped with a magnetic stir bar and septum. Tryptamine (1.0 equiv) and EtOAc:1 N NaOH (1:1, 0.2 M in tryptamine) were added to the flask at 23 °C, followed by methyl chloroformate (1.1 equiv). The reaction mixture was stirred for 16 h, then the reaction was quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo.* The crude product was purified by flash column chromatography to afford the desired indole.

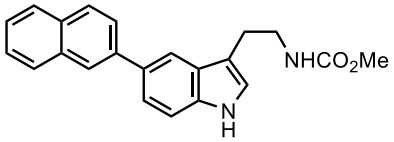
Methyl (2-(5-phenyl-1H-indol-3-yl)ethyl)carbamate (S1c)



Following the **general procedure A**, 5-phenyl tryptamine (0.580 g, 1.97 mmol) afforded tryptamine **S1c** (465 mg, 80%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3).

R$_f$=0.40 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.42 (br s, 1H), 7.84 (s, 1H), 7.71 (d, *J* = 7.6 Hz, 2H), 7.51 – 7.47 (m, 3H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.06 – 6.96 (m, 1H), 4.94 (br s, 1H), 3.70 (s, 3H), 3.60 – 3.55 (m, 2H), 3.03 (t, *J* = 6.8 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.3, 142.5, 135.9, 132.8, 128.7, 127.8, 127.3, 126.3, 123.0, 121.7, 117.0, 112.9, 111.6, 52.0, 41.5, 25.6; **HRMS** calcd. for $C_{18}H_{19}N_2O_2^+$ $[M + H]^+$ 295.1441, found 295.1438.

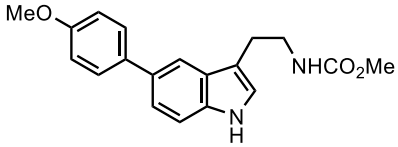
Methyl (2-(5-(naphthalen-2-yl)-1H-indol-3-yl)ethyl)carbamate (S1d)



Following the **general procedure A**, 5-(naphthalen-2-yl)-tryptamine (0.490 g, 1.71 mmol) afforded tryptamine **S1d** (0.340 g, 58%) as a pale yellow amorphous amorphous solid after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3).

R_f=0.4 (silica gel, hexanes:EtOAc = 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.11 (br s, 1H), 8.09 (s, 1H), 7.94 – 7.90 (m, 3H), 7.88 – 7.83 (m, 2H), 7.60 (d, *J* = 8.3 Hz, 1H), 7.53 – 7.45 (m, 3H), 7.09 (s, 1H), 4.80 (s, 1H), 3.67 (s, 3H), 3.61 – 3.58 (br q, *J* = 6.5 Hz, 2H), 3.05 (t, *J* = 6.8 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.2, 139.9, 136.1, 134.0, 133.1, 132.3, 128.4, 128.2, 128.1, 127.8, 126.4, 126.3, 125.7, 125.6, 123.0, 122.4, 117.7, 113.5, 111.7, 52.2, 41.5, 25.9; **HRMS** calcd. for $C_{22}H_{21}N_2O_2^+$ $[M + H]^+$ 345.1598, found 345.1591.

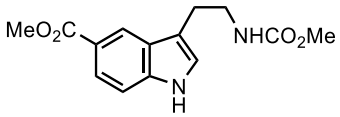
Methyl (2-(5-(4-methoxyphenyl)-1H-indol-3-yl)ethyl)carbamate (S1e)



Following the **general procedure A**, 5-(4-methoxyphenyl)-tryptamine (0.750 g, 2.82 mmol) afforded tryptamine **S1e** (0.630 g, 69%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3).

R_f=0.27 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.15 (br s, 1H), 7.74 (s, 1H), 7.58 (d, *J* = 8.6 Hz, 1H), 7.44 – 7.38 (m, 2H), 7.04 (s, 1H), 7.00 (d, *J* = 8.6 Hz, 2H), 4.81 (br s, 1H), 3.87 (s, 3H), 3.67 (s, 3H), 3.57 – 3.53 (m, 2H), 3.01 (t, *J* = 6.8 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 158.65, 157.21, 135.73, 135.26, 132.96, 128.47, 127.95, 122.87, 121.99, 116.87, 114.25, 113.35, 111.54, 55.50, 52.15, 41.48, 25.88; **HRMS** calcd. for $C_{19}H_{21}N_2O_3^+$ $[M + H]^+$ 325.1547, found 325.1556.

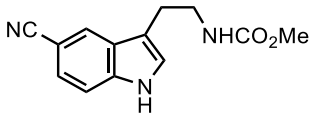
Methyl 3-(2-((methoxycarbonyl)amino)ethyl)-1H-indole-5-carboxylate (S1h)



Following the **general procedure A**, Methyl tryptamine-5-carboxylate (0.300 g, 1.36 mmol) afforded tryptamine **S1h** (0.210 g, 56%) as a pale yellow amorphous amorphous solid after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 6:4).

R_f =0.4 (silica gel, hexanes:EtOAc = 4:6); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.78 (br s, 1H), 8.35 (s, 1H), 7.89 (d, *J* = 8.6 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 1H), 7.06 (s, 1H), 4.88 (br s, 1H), 3.93 (s, 3H), 3.65 (s, 3H), 3.53 – 3.48 (m, 2H), 2.97 (t, *J* = 6.5 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 168.4, 157.3, 139.1, 127.0, 123.6, 123.5, 121.7, 121.4, 114.3, 111.1, 52.2, 52.0, 41.4, 25.7; **HRMS** calcd. for $C_{14}H_{17}N_2O_4^+$ $[M + H]^+$ 277.1187, found 277.1182.

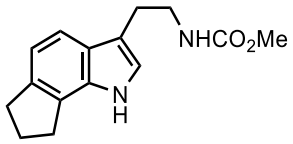
Methyl (2-(5-cyano-1H-indol-3-yl)ethyl)carbamate (S1i)



Following the **general procedure A**, 5-cyanotryptamine (352 mg, 1.88 mmol) afforded tryptamine **S1i** (0.250 g, 55%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 6:4).

R_f =0.2 (silica gel, hexanes:EtOAc = 4:6); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.58 (br s, 1H), 7.94 (s, 1H), 7.42 (s, 2H), 7.16 (s, 1H), 4.81 (br s, 1H), 3.67 (s, 3H), 3.53 – 3.48 (m, 2H), 2.97 (t, *J* = 6.5 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.2, 138.1, 127.4, 125.2, 124.6, 124.3, 120.9, 114.2, 112.3, 102.7, 52.3, 41.4, 25.7; **HRMS** calcd. for $C_{13}H_{14}N_3O_2^+$ $[M + H]^+$ 244.1076, found 244.1081.

Methyl (2-(1,6,7,8-tetrahydrocyclopenta[g]indol-3-yl)ethyl)carbamate (S1k)

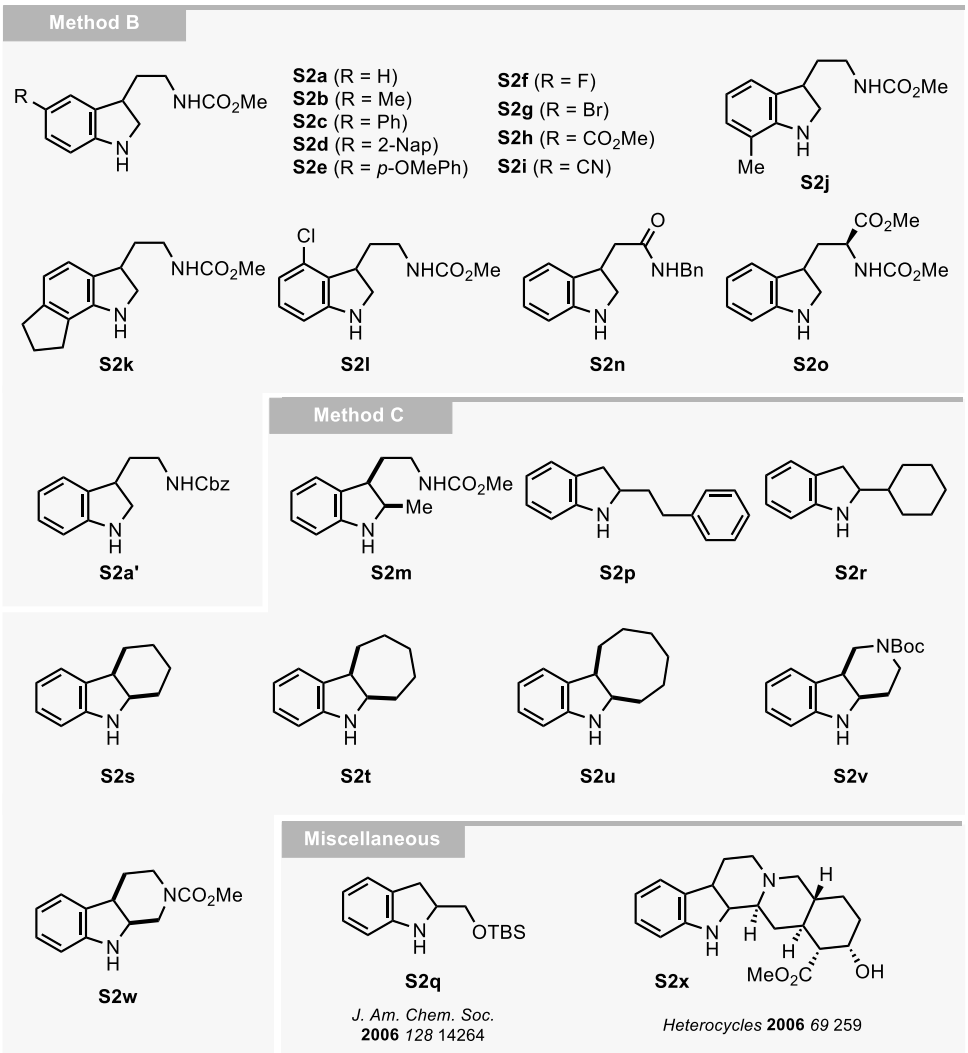


Following the **general procedure A**, 2-(1,6,7,8-tetrahydrocyclopenta[g]indol-3-yl)ethan-1-amine (0.230 g, 1.14 mmol) afforded tryptamine **S1k** (191 mg, 65%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3).

***R*$_f$**=0.6 (silica gel, hexanes:EtOAc = 6:4); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.93 (br s, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.97 (s, 1H), 4.77 (br s, 1H), 3.66 (s, 3H), 3.52 (d, *J* = 6.6 Hz, 2H), 3.05 (q, *J* = 8.0 Hz, 4H), 2.97 (t, *J* = 6.9 Hz, 2H), 2.22 (p, *J* = 7.3 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.2, 138.9, 133.7, 126.0, 125.7, 121.4, 116.9, 116.6, 113.6, 52.1, 41.4, 33.2, 29.9, 26.1, 25.5; **HRMS** calcd. for $C_{15}H_{20}N_2O_2^+$ $[M + H]^+$ 259.1441, found 259.1439.

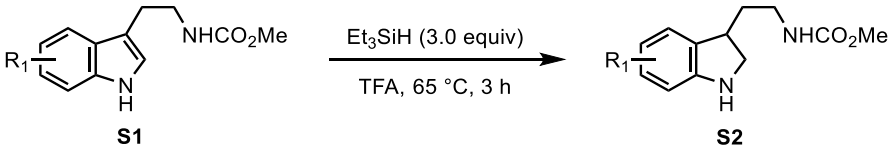
2.3.2.2. Preparation of Indoline Derivatives

Figure 1.9. List of Indoline Derivatives Categorized by Methods of Preparation



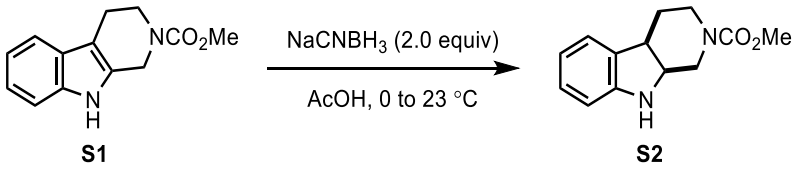
S2p[10], S2q[10], S2r[11], S2s[10], S2t[10], S2u[12], S2x[13]: Spectral data is in agreement with the reported literature values

General procedure B



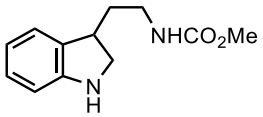
Reactions were performed in flame-dried round-bottom flask equipped with a magnetic stir bar and septum. Indole **S1** (1.0 equiv) and TFA (0.3 M in **S1**) were added to the flask at 23 °C, followed by Et_3SiH (3.0 equiv). The reaction mixture was stirred for 3 h at 65 °C in an oil bath. Then the reaction mixture was cooled to 23 °C, then it was directly concentrated *in vacuo* to remove most of TFA. The crude reaction mixure was re-dissolved in CH_2Cl_2 and basified to pH 9−10 with ammonia solution (25.0−30.0 wt% in H_2O). The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo.* The crude product was purified by flash column chromatography to afford indoline **S2.**

General procedure C



Reactions were performed in flame-dried round-bottom flask equipped with a magnetic stir bar and septum. Indole **S1**(1.0 equiv) and AcOH (0.1 M in **S1**) were added to the flask at 23 °C, and $NaBH_3CN$ (2.0 equiv) was added to the solution at 0 °C. The reaction mixture was warmed up to 23 °C and stirred until TLC indicated complete conversion, then it was directly concentrated *in vacuo*. The crude reaction mixure was re-dissolved in CH_2Cl_2 and basified to pH 9−10 with ammonia solution (25.0−30.0 wt% in H_2O). The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo.* The crude product was purified by flash column chromatography to afford indoline **S2.**

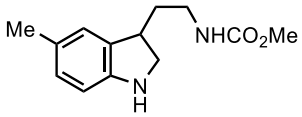
Methyl (2-(indolin-3-yl)ethyl)carbamate (S2a)



Following the **general procedure B**, tryptamine **S1a** (3.50 g, 16.0 mmol) afforded indoline **S2a** (3.30 g, 94%) as a pale yellow amorphous solid after purification by flash column chromatography (silica gel, hexanes:EtOAc = 8:2 → 6:4).

R_f=0.20 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.08 (d, *J* = 7.3 Hz, 1H), 7.03 (t, *J* = 7.6 Hz, 1H), 6.72 (t, *J* = 7.4 Hz, 1H), 6.64 (d, *J* = 7.7 Hz, 1H), 5.03 (s, 1H), 3.78 – 3.62 (m, 5H), 3.35 – 3.26 (m, 2H), 3.22 (m, 2H), 2.04 – 1.93 (m, 1H), 1.73 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 157.2, 151.3, 132.1, 127.7, 123.9, 118.8, 109.7, 53.3, 52.1, 39.6, 39.1, 34.5; **HRMS** calcd. for $C_{12}H_{17}N_2O_2^+$ $[M + H]^+$ 221.1285, found 221.1278.

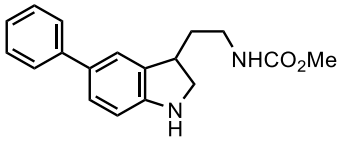
Methyl (2-(5-methylindolin-3-yl)ethyl)carbamate (S2b)



Following the **general procedure B**, tryptamine **S1b** (0.100 g, 0.431 mmol) afforded indoline **S2b** (75.0 mg, 74%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 8:2 → 6:4).

R_f=0.34 (silica gel, hexanes:EtOAc = 4:6); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.91 (s, 1H), 6.85 (d, *J* = 7.9 Hz, 1H), 6.57 (d, *J* = 7.8 Hz, 1H), 4.86 (br s, 1H), 3.68 (t, *J* = 7.3 Hz, 2H), 3.66 (s, 3H), 3.35 – 3.18 (m, 4H), 2.26 (s, 3H), 2.04 – 1.95 (m, 1H), 1.78 – 1.69 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.2, 148.8, 132.5, 128.1, 127.9, 124.5, 109.7, 53.4, 51.9, 39.5, 39.0, 34.3, 20.8; **HRMS** calcd. for $C_{13}H_{19}N_2O_2^+$ $[M + H]^+$ 235.1442, found 235.1441.

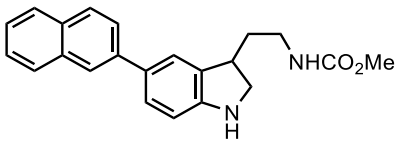
Methyl (2-(5-phenylindolin-3-yl)ethyl)carbamate (S2c)



Following the **general procedure B**, tryptamine **S1c** (0.300 g, 1.02 mmol) afforded indoline **S2c** (0.265 g, 88%) as a pale yellow amorphous solid after purification by flash column chromatography (silica gel, hexanes:EtOAc = 8:2 → 6:4).

***R*$_f$** =0.30 (silica gel, hexanes:EtOAc = 4:6); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.54 (d, *J* = 7.7 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.34 (s, 1H), 7.33 – 7.27 (m, 2H), 6.71 (d, *J* = 8.0 Hz, 1H), 5.01 (br s, 1H), 3.75 (t, *J* = 8.7 Hz, 1H), 3.68 (s, 3H), 3.41 – 3.35 (m, 1H), 3.33 – 3.24 (m, 3H), 2.09 – 2.03 (m, 1H), 1.79 (dt, *J* = 14.2, 7.1 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 157.2, 150.7, 141.6, 132.9, 132.2, 128.7, 126.8, 126.6, 126.2, 122.8, 109.8, 53.5, 52.1, 39.5, 39.1, 34.6; **HRMS** calcd. for $C_{18}H_{21}N_2O_2^+$ $[M + H]^+$ 297.1592, found 297.1598.

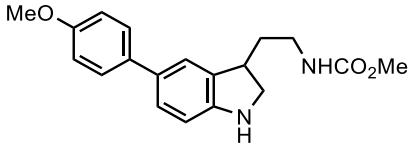
Methyl (2-(5-(naphthalen-2-yl)indolin-3-yl)ethyl)carbamate (S2d)



Following the **general procedure B**, tryptamine **S1d** (0.450 g, 1.31 mmol) afforded indoline **S2d** (0.330 g, 73%) as a pale yellow amorphous solid after purification by flash column chromatography (silica gel, hexanes:EtOAc = 8:2 → 6:4).

***R*$_f$**=0.33 (silica gel, hexanes:EtOAc = 4:6); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.87 (d, *J* = 8.2 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.71 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.52 – 7.40 (m, 4H), 6.74 (d, *J* = 8.0 Hz, 1H), 4.92 (s, 1H), 3.77 (t, *J* = 8.7 Hz, 1H), 3.68 (s, 3H), 3.45 – 3.37 (m, 1H), 3.37 – 3.24 (m, 3H), 2.15 – 2.03 (m, 1H), 1.88 – 1.76 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 157.3, 150.9, 139.1, 134.0, 133.0, 132.2, 132.0, 128.3, 128.0, 127.7, 127.2, 126.2, 125.6, 125.5, 124.6, 123.1, 109.9, 53.5, 52.2, 39.7, 39.2, 34.7; **HRMS** calcd. for $C_{22}H_{23}N_2O_2^+$ $[M + H]^+$ 347.1754, found 347.1748.

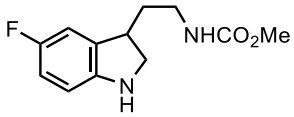
Methyl (2-(5-(4-methoxyphenyl)indolin-3-yl)ethyl)carbamate (S2e)



Following the **general procedure B**, tryptamine **S1e** (0.370 g, 1.14 mmol) afforded indoline **S2e** (0.280 g, 75%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 8:2 → 6:4).

R$_f$=0.10 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.3 Hz, 2H), 7.21 (d, *J* = 6.5 Hz, 1H), 6.92 (d, *J* = 8.2 Hz, 2H), 6.61 (d, *J* = 8.0 Hz, 1H), 5.33 (br s, 1H), 3.85 (s, 1H), 3.77 (s, 3H), 3.64 (s, 3H), 3.32 – 3.12 (m, 4H), 2.02 – 1.96 (m, 1H), 1.73 – 166 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 158.1, 157.1, 150.2, 134.1, 132.7, 131.3, 127.2, 126.0, 122.1, 113.9, 109.5, 55.1, 53.2, 51.8, 39.3, 38.9, 34.2; **HRMS** calcd. for $C_{19}H_{23}N_2O_3^+$ $[M + H]^+$ 327.1701, found 327.1703.

Methyl (2-(5-fluoroindolin-3-yl)ethyl)carbamate (S2f)

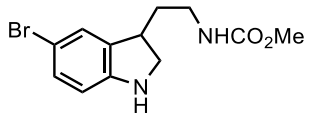


Following the **general procedure B**, tryptamine **S1f** (1.80 g, 7.62 mmol) afforded indoline **S2f** (1.30 g, 72%) as a brown oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 8:2 → 1:1).

R$_f$=0.28 (silica gel, hexanes:EtOAc = 2:8); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.81 (d, *J* = 8.3 Hz, 1H), 6.73 (t, *J* = 8.8 Hz, 1H), 6.54 (dd, *J* = 8.5, 4.3 Hz, 1H), 4.88 (br s, 1H), 3.71 (t, *J* = 8.0 Hz, 2H), 3.66 (s, 3H), 3.35 – 3.17 (m, 4H), 2.03 – 1.90 (m, 1H), 1.79 – 1.68 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.2 (d, *J* = 235.6 Hz), 157.2, 147.3 (d, *J* = 1.4 Hz), 134.0 (d, *J* = 6.1 Hz), 113.8 (d, *J* = 23.4 Hz), 111.4 (d, *J* = 23.9 Hz), 110.0 (d, *J* = 8.2 Hz), 53.9, 52.2, 40.0, 39.0, 34.4; **^{19}F**

NMR (376 MHz, $CDCl_3$): δ −126.1; **HRMS** calcd. for $C_{12}H_{16}FN_2O_2^+$ $[M + H]^+$ 239.1188, found 239.1190.

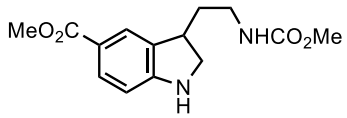
Methyl (2-(5-bromoindolin-3-yl)ethyl)carbamate (S2g)



Following the **general procedure B**, tryptamine **S1g** (0.500 g, 1.68 mmol) afforded indoline **S2g** (0.400 g, 80%) as a yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 8:2 → 1:1).

R_f=0.23 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.16 (s, 1H), 7.12 (d, *J* = 7.9 Hz, 1H), 6.50 (d, *J* = 8.2 Hz, 1H), 4.80 (br s, 1H), 3.75 – 3.65 (m, 4H), 3.36 – 3.20 (m, 4H), 2.01 – 1.93 (s, 1H), 1.80 – 1.69 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.2, 150.4, 134.6, 130.4, 127.0, 110.9, 110.3, 53.5, 52.2, 39.6, 39.0, 34.5; **HRMS** calcd. for $C_{12}H_{16}BrN_2O_2^+$ $[M + H]^+$ 299.0390, found 299.0390.

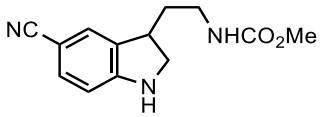
Methyl 3-(2-((methoxycarbonyl)amino)ethyl)indoline-5-carboxylate (S2h)



Following the **general procedure B**, tryptamine **S1h** (0.340 g, 1.23 mmol) afforded indoline **S2h** (0.212 g, 76%) as a colorless oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 8:2 → 1:1).

R_f=0.45 (silica gel, hexanes:EtOAc = 2:8); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.78 (s, 1H), 8.35 (s, 1H), 7.89 (d, *J* = 8.6 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 1H), 7.06 (s, 1H), 4.88 (s, 1H), 3.93 (s, 3H), 3.65 (s, 3H), 3.57 – 3.42 (m, 2H), 2.97 (t, *J* = 6.5 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 168.4, 157.3, 139.1, 127.0, 123.6, 123.5, 121.8, 121.4, 114.3, 111.1, 52.2, 52.0, 41.4, 25.7; **HRMS** calcd. for $C_{14}H_{19}N_2O_4^+$ $[M + H]^+$ 279.1341, found 279.1339.

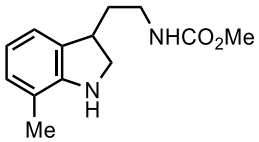
Methyl (2-(5-cyanoindolin-3-yl)ethyl)carbamate (S2i)



Following the **general procedure B**, tryptamine **S1i** (0.900 g, 3.70 mmol) afforded indoline **S2i** (0.700 g, 77%) as a pale yellow amorphous solid after purification by flash column chromatography (silica gel, hexanes:EtOAc = 8:2 → 1:1).

R_f=0.34 (silica gel, hexanes:EtOAc = 2:8); **^{1}H NMR** (400 MHz, MeOD): δ 7.33 – 7.26 (m, 2H), 6.54 (d, *J* = 8.2 Hz, 1H), 3.79 – 3.72 (m, 1H), 3.63 (s, 3H), 3.35 – 3.27 (m, 2H), 3.19 (t, *J* = 7.6 Hz, 2H), 1.97 – 1.90 (m, 1H), 1.75 – 1.65 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.3, 155.1, 133.5, 132.6, 127.6, 120.8, 108.4, 99.7, 53.0, 52.3, 38.8, 38.7, 34.8; **HRMS** calcd. for $C_{13}H_{16}N_3O_2^+$ $[M + H]^+$ 246.1234, found 246.1237.

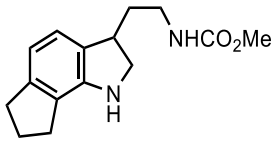
Methyl (2-(7-methylindolin-3-yl)ethyl)carbamate (S2j)



Following the **general procedure B**, tryptamine **S1j** (0.450 g, 1.94 mmol) afforded indoline **S2j** (0.345 g, 76%) as a pale yellow amorphous solid after purification by flash column chromatography (silica gel, hexanes:EtOAc = 8:2 → 6:4).

R_f=0.34 (silica gel, hexanes:EtOAc = 2:8); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.96 (d, *J* = 7.4 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 6.69 (t, *J* = 7.4 Hz, 1H), 4.91 (br s, 1H), 3.76 – 3.69 (m, 2H), 3.67 (s, 2H), 3.39 – 3.30 (m, 1H), 3.30 – 3.17 (m, 3H), 2.13 (s, 3H), 2.06 – 1.93 (m, 1H), 1.81 – 1.68 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.2, 149.8, 131.5, 128.7, 121.5, 119.3, 119.1, 53.2, 52.2, 40.0, 39.2, 34.7, 16.9; **HRMS** calcd. for $C_{13}H_{19}N_2O_2^+$ $[M + H]^+$ 235.1441, found 235.1441.

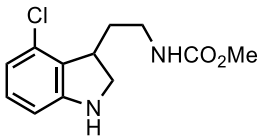
Methyl (2-(1,2,3,6,7,8-hexahydrocyclopenta[g]indol-3-yl)ethyl)carbamate (S2k)



Following the **general procedure B**, tryptamine **S1k** (0.230 g, 0.891 mmol) afforded indoline **S2k** (0.210 g, 91%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 8:2 → 6:4).

R_f=0.24 (silica gel, hexanes:EtOAc = 7:3); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.91 (d, *J* = 7.4 Hz, 1H), 6.66 (d, *J* = 7.4 Hz, 1H), 4.83 (br s, 1H), 3.73 (t, *J* = 8.2 Hz, 1H), 3.67 (s, 3H), 3.57 (s, 1H), 3.37 – 3.15 (m, 4H), 2.86 (t, *J* = 7.5 Hz, 2H), 2.70 (t, *J* = 7.3 Hz, 2H), 2.17 (s, 1H), 2.08 (p, *J* = 7.5 Hz, 2H), 1.99 (dq, *J* = 13.9, 7.0 Hz, 1H), 1.74 (dq, *J* = 14.4, 7.6 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 157.2, 147.3, 144.8, 129.7, 125.2, 121.9, 114.8, 77.4, 77.2, 76.9, 53.9, 52.2, 39.7, 39.3, 34.9, 32.9, 31.1, 29.5, 25.6; **HRMS** calcd. for $C_{15}H_{21}N_2O_2^+$ $[M + H]^+$ 261.1598, found 261.1590.

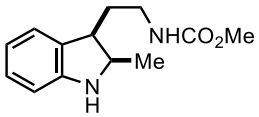
Methyl (2-(4-chloroindolin-3-yl)ethyl)carbamate (S2l)



Following the **general procedure B**, tryptamine **S1l** (0.100 g, 0.396 mmol) afforded indoline **S2l** (80.0 mg, 89%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 8:2 → 1:1).

R_f=0.34 (silica gel, hexanes:EtOAc = 2:8); **^{1}H NMR** (400 MHz, $CDCl_3$):) δ 6.95 (t, *J* = 7.9 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 6.50 (d, *J* = 7.8 Hz, 1H), 4.97 (s, 1H), 3.87 (s, 1H), 3.68 (d, *J* = 8.8 Hz, 1H), 3.65 (s, 3H), 3.51 – 3.34 (m, 2H), 3.31 – 3.07 (m, 2H), 2.00 – 1.81 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.2, 152.8, 130.8, 129.6, 129.4, 119.1, 107.9, 77.5, 77.2, 76.8, 52.2, 52.1, 39.3, 38.7, 32.6; **HRMS** calcd. for $C_{12}H_{16}ClN_2O_2^+$ $[M + H]^+$ 255.0895, found 255.0892.

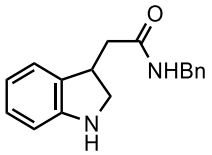
Methyl (2-(2-methylindolin-3-yl)ethyl)carbamate (S2m)



Following the **general procedure C** for 1 h, tryptamine **S1m** (0.500 g, 2.15 mmol) afforded indoline **S2m** (0.430 g, 85%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 8:2 → 1:1).

***R*$_f$**=0.48 (silica gel, hexanes:EtOAc = 2:8); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.09 – 7.04 (m, 1H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.70 (q, *J* = 6.9 Hz, 1H), 6.59 (t, *J* = 8.7 Hz, 1H), 5.09 (br s, 1H), 3.95 and 3.59 (t, *J* = 6.1 Hz, 1H), 3.80 – 3.70 (m, 1H), 3.65 (s, 3H), 3.23 – 3.18 (m, 2H), 3.10 and 2.84 (q, *J* = 6.2 Hz, 1H), 1.91 – 1.73 (m, 2H), 1.22 and 1.16 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.2, 150.4, 150.0, 131.8, 131.3, 127.7, 127.5, 124.3, 124.3, 118.6, 118.5, 109.6, 109.4, 60.4, 58.3, 52.0, 47.1, 42.2, 39.3, 38.7, 34.3, 28.4, 22.2, 16.0; **HRMS** calcd. for $C_{13}H_{19}N_2O_2^+$ $[M + H]^+$ 235.1442, found 235.1441.

***N*-benzyl-2-(indolin-3-yl)acetamide (S2n)**

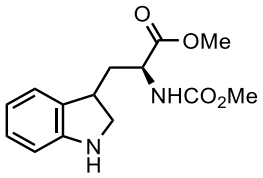


Following the **general procedure B**, indole **S1n** (2.30 g, 8.70 mmol) afforded indoline **S2n** (1.37 g, 59%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 1:1).

***R*$_f$**=0.26 (silica gel, hexanes:EtOAc = 6:4); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.36 – 7.27 (m, 3H), 7.26 – 7.21 (m, 2H), 7.07 (d, *J* = 7.6 Hz, 2H), 6.75 (t, *J* = 7.3 Hz, 1H), 6.67 (d, *J* = 7.5 Hz, 1H), 6.34 (s, 1H), 5.12 (s, 1H), 4.40 (d, *J* = 5.8 Hz, 2H), 3.80 – 3.74 (m, 1H), 3.70 (t, *J* = 9.0 Hz, 1H), 3.30 – 3.22 (m, 1H), 2.50 (ddd, *J* = 61.3, 14.5, 7.3 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$ δ 171.4,

150.0, 138.2, 138.2, 132.1, 132.1, 128.7, 128.1, 127.8, 127.5, 124.3, 119.7, 110.6, 110.6, 52.8, 43.6, 41.2, 38.9; **HRMS** calcd. for $C_{17}H_{19}N_2O^+$ $[M + H]^+$ 267.1492, found 267.1491.

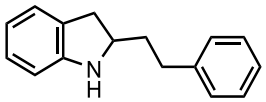
Methyl (2S)-3-(indolin-3-yl)-2-((methoxycarbonyl)amino)propanoate (S2o)



Following the **general procedure B**, tryptophan **S1o** (1.50 g, 5.43 mmol) afforded indoline **S2o** (1.07 g, 71%) as an inconsequential 1:1 mixture of diastereomers in the form of a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 1:1). The resulting diastereomeric mixture was used directly in the subsequent reaction without separation. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture.

R_f=0.25 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$, 50:50 mixture of diastereomers): δ 7.15 (d, *J* = 7.3 Hz, 0.5H), 7.05 (d, *J* = 7.3 Hz, 0.5H), 7.03 (t, *J* = 7.6 Hz, 1H), 6.74 – 6.69 (m, 1H), 6.63 (t, *J* = 7.2 Hz, 1H), 5.61 (br s, 1H), 4.52 – 4.43 (m, 1H), 3.80-3.70 (m, 1H), 3.72 and 3.69 (s, 6H), 3.39 – 3.33 (m, 1H), 3.28 and 3.21 (t, *J* = 7.4 Hz, 1H), 2.29 and 1.87 (dt, *J* = 13.3, 6.1 Hz, 1H), 2.10 – 2.01 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 173.2, 156.9, 156.7, 151.2, 151.1, 131.7, 131.4, 127.9, 127.8, 124.3, 123.6, 118.9, 118.7, 109.8, 109.7, 53.7, 52.9, 52.6, 52.5, 52.4, 38.8, 38.6, 37.2; **HRMS** calcd. for $C_{14}H_{19}N_2O_4^+$ $[M + H]^+$ 279.1339, found 279.11340.

2-Phenethylindoline (S2p)

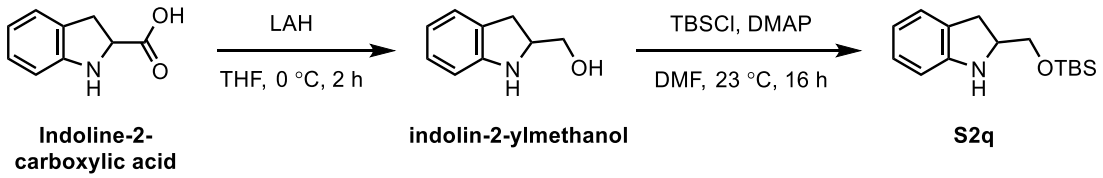


Following the **general procedure C** for 2 h, indole **S1p** (0.280 g, 1.27 mmol) afforded indoline **S2p** (0.230 g, 81%) as a pale yellow oil after purification by flash column chromatography (silica

gel, hexanes:EtOAc = 1:0 → 95:5).The identity of synthesized product was confirmed based on reported NMR spectra.[11]

***R*$_f$**=0.24 (silica gel, hexanes:EtOAc = 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.39 – 7.32 (m, 2H), 7.28 – 7.24 (m, 3H), 7.05 (d, *J* = 7.4 Hz, 1H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.67 (t, *J* = 7.4 Hz, 1H), 6.61 (d, *J* = 7.7 Hz, 1H), 3.96 – 3.87 (m, 1H), 3.20 (dd, *J* = 15.4, 8.7 Hz, 1H), 2.80 – 2.73 (m, 3H), 2.03 – 1.97 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 151.0, 141.9, 128.8, 128.6, 128.4, 127.4, 126.1, 124.8, 118.7, 109.3, 59.6, 38.6, 36.2, 33.0.

2-(((*tert*-Butyldimethylsilyl)oxy)methyl)indoline (S2q)



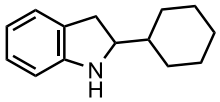
Reactions were performed in flame-dried round-bottom flask equipped with a magnetic stir bar and septum. I indoline-2-carboxylic acid (2.00 g, 12.3 mmol, 1.0 equiv) and THF (30 mL) were added to the flask at 23 °C, and LAH (0.412 g, 13.7 mmol, 1.11 equiv) was added to the solution at 0 °C. The reaction mixture was stirred 2 h, then the reaction was quenched with brine (20 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with brine (3 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo.* The resulting crude **indolin-2-ylmethanol** was used directly in the subsequent reaction without further purification.

Reactions were performed in flame-dried round-bottom flask equipped with a magnetic stir bar and septum. Crude indolin-2-ylmethanol and DMF (20 mL) were added to the flask at 23 °C, followed by TBSCl (1.88 g, 12.5 mmol, 1.01 equiv) and DMAP (1.50 g, 12.3 mmol, 1.0 equiv). The reaction mixture was stirred 16 h, then the reaction was quenched with brine (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with brine (3 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo.* The resulting crude product was purified by flash column chromatography (silica gel, hexanes:EtOAc

= 1:0 → 95:5) to afford the product **S2q** (2.09 g, 73%) as a pale yellow oil. The identity of synthesized product was confirmed based on reported NMR spectra.[11]

***R**$_f$*=0.24 (silica gel, hexanes:EtOAc = 95:5); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.10 (d, *J* = 7.3 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.72 (t, *J* = 7.4 Hz, 1H), 6.65 (d, *J* = 7.7 Hz, 1H), 4.01 – 3.93 (m, 1H), 3.67 – 3.54 (m, 2H), 3.14 (dd, *J* = 15.8, 9.1 Hz, 1H), 2.68 (dd, *J* = 15.8, 5.8 Hz, 1H), 0.96 (s, 9H), 0.11 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 150.6, 128.2, 127.5, 124.9, 118.5, 109.4 5, 66.7, 60.5, 32.2, 26.0, 18.4, –5.2.

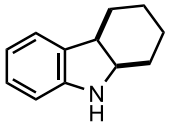
2-Cyclohexylindoline (S2r)



Following the **general procedure C** for 2 h, indole **S1r** (0.100 g, 0.502 mmol) afforded indoline **S2r** (82.0 mg, 81%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 95:5).The identity of synthesized product was confirmed based on reported NMR spectra.[12]

***R**$_f$*=0.24 (silica gel, hexanes:EtOAc = 7:3); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.08 (d, *J* = 7.3 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.68 (t, *J* = 7.4 Hz, 1H), 6.61 (d, *J* = 7.7 Hz, 1H), 3.94 (br s, 1H), 3.56 (q, *J* = 8.8 Hz, 1H), 3.07 (dd, *J* = 15.5, 8.7 Hz, 1H), 2.75 (dd, *J* = 15.5, 9.8 Hz, 1H), 1.89 (d, *J* = 12.3 Hz, 1H), 1.51 – 1.41 (m, 1H), 1.34 – 1.13 (m, 3H), 1.06 – 0.94 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 151.3, 129.2, 127.3, 124.6, 118.5, 109.0, 65.7, 44.0, 34.3, 30.3, 29.7, 26.6, 26.2, 26.1.

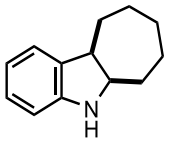
2,3,4,4a,9,9a-Hexahydro-1H-carbazole (S2s)



Following the **general procedure C** for 1 h, 1,2,3,4-tetrahydrocarbazole (3.00 g, 17.5 mmol) afforded indoline **S2s** (2.37 g, 78%) as a white amorphous solid after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 95:5).The identity of synthesized product was confirmed based on reported NMR spectra.[11]

R_f =0.68 (silica gel, hexanes:EtOAc = 9:1); ^{1}**H NMR** (300 MHz, $CDCl_3$): δ 7.10 (d, *J* = 7.3 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.76 (t, *J* = 7.4 Hz, 1H), 6.69 (d, *J* = 7.7 Hz, 1H), 3.74 (q, *J* = 6.1 Hz, 1H), 3.11 (q, *J* = 6.7 Hz, 1H), 1.72 – 1.65 (m, 1H), 1.62 – 1.53 (m, 2H), 1.58 (dq, *J* = 12.5, 7.0, 5.5 Hz, 2H), 1.48 – 1.32 (m, 3H); ^{13}**C NMR** (75 MHz, $CDCl_3$): δ 150.9, 133.9, 127.1, 123.3, 118.9, 110.3, 59.8, 41.1, 29.3, 27.1, 22.7, 21.8.

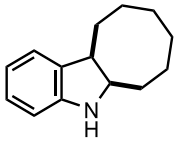
5,5a,6,7,8,9,10,10a-Octahydrocyclohepta[b]indole (S2t)



Following the **general procedure C** for 1 h, indole **S1t** (0.300 g, 1.62 mmol) afforded indoline **S2t** (0.280 g, 92%) as a white amorphous solid after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 95:5).The identity of synthesized product was confirmed based on reported NMR spectra.[11]

R_f =0.68 (silica gel, hexanes:EtOAc = 9:1); ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.01 – 6.93 (m, 2H), 6.68(t, *J* = 7.3 Hz, 1H), 6.55 (d, *J* = 7.6 Hz, 1H), 4.07 – 4.01 (m, 1H), 3.47 (td, *J* = 10.4, 3.9 Hz, 1H), 2.00 – 1.93 (m, 1H), 1.89 – 1.69 (m, 6H), 1.44 – 1.32 (m, 3H); ^{13}**C NMR** (101 MHz, $CDCl_3$): δ 150.3, 133.7, 127.5, 124.3, 118.3, 108.6, 63.6, 47.5, 33.7, 31.5, 30.0, 26.2.

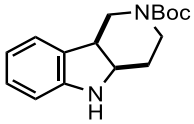
5a,6,7,8,9,10,11,11a-Octahydro-5H-cycloocta[b]indole (S2u)



Following the **general procedure C** for 1 h, indole **S1u** (0.250 g, 1.25 mmol) afforded indoline **S2u** (0.221 g, 88%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 95:5).The identity of synthesized product was confirmed based on reported NMR spectra.[13]

R_f =0.68 (silica gel, hexanes:EtOAc = 9:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.07 (d, *J* = 7.4 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.71 (t, *J* = 7.4 Hz, 1H), 6.57 (d, *J* = 7.7 Hz, 1H), 3.88 (t, *J* = 9.9 Hz, 1H), 3.21 (t, *J* = 9.7 Hz, 1H), 2.01 (dq, *J* = 45.0, 12.4, 11.5 Hz, 2H), 1.78 – 1.50 (m, 10H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 149.5, 135.4, 127.3, 124.3, 118.6, 108.6, 63.9, 46.2, 30.3, 30.1, 28.8, 27.7, 25.9, 25.5.

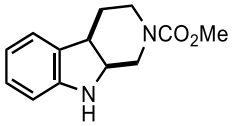
***tert*-Butyl 1,3,4,4a,5,9b-hexahydro-2H-pyrido[4,3-b]indole-2-carboxylate (S2v)**



Following the **general procedure C** for 2 h, indole **S1v** (0.200 g, 0.734 mmol) afforded indoline **S2v** (0.127 g, 63%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3).

R_f =0.24 (silica gel, hexanes:EtOAc = 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.12 (d, *J* = 7.1 Hz, 1H), 7.05 (td, *J* = 7.7, 1.3 Hz, 1H), 6.73 (td, *J* = 7.4, 1.0 Hz, 1H), 6.66 (d, *J* = 7.8 Hz, 1H), 3.97 (dt, *J* = 7.4, 5.0 Hz, 1H), 3.45 – 3.27 (m, 5H), 1.93 – 1.84 (m, 1H), 1.77 – 1.71 (m, 1H), 1.45 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 155.1, 151.0, 128.1, 124.4, 119.1, 110.1, 79.6, 57.6, 43.9, 41.2, 40.1, 39.5, 28.6, 28.2; **HRMS** calcd. for $C_{16}H_{23}N_2O_2^+$ $[M + H]^+$ 275.1754, found 275.1759.

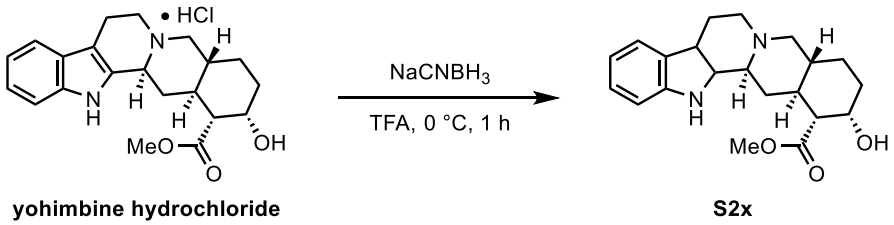
Methyl 1,3,4,4a,9,9a-hexahydro-2H-pyrido[3,4-b]indole-2-carboxylate (S2w)



Following the **general procedure C** for 1 h, indole **S1w** (0.500 g, 1.84 mmol) afforded indoline **S2w** (0.262 g, 52%) as a white amorphous solid after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3).

R$_f$=0.24 (silica gel, hexanes:EtOAc = 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.07 – 7.01 (m, 2H), 6.73 (t, *J* = 7.4 Hz, 1H), 6.62 (d, *J* = 7.7 Hz, 1H), 3.97 – 3.86 (m, 2H), 3.68 (s, 3H), 3.58 – 3.53 (m, 1H), 3.39 – 3.34 (m, 3H), 2.04 – 1.96 (m, 1H), 1.87 – 1.79 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 150.6, 131.2, 127.9, 123.7, 119.0, 109.8, 57.4, 52.6, 44.4, 41.1, 39.3, 26.4 ; **HRMS** calcd. for $C_{13}H_{17}N_2O_2^+$ $[M + H]^+$ 233.1285, found 233.1288.

Methyl (1R,2S,4aR,13bS,14aS)-2-hydroxy-1,2,3,4,4a,5,7,8,8a,13,13a,13b,14,14a-tetradecahydroindolo [2',3':3,4]pyrido [1,2-b]isoquinoline-1-carboxylate (S2x)

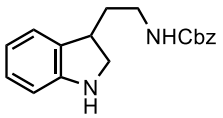


Reactions were performed in flame-dried round-bottom flask equipped with a magnetic stir bar and septum. Yohimbine hydrochloride (0.100 g, 0.256 mmol, 1.0 equiv) and TFA (5 mL) were added to the flask at 23 °C, and $NaBH_3CN$ (48.2 mg, 0.767 mmol, 3.0 equiv) was added to the solution at 0 °C. The reaction mixture was stirred for 1 h, then it was directly concentrated *in vacuo.* The crude reaction mixure was re-dissolved in CH_2Cl_2 (20 mL) and basified to pH 9−10 with ammonia solution (25.0−30.0 wt% in H_2O). The combined organic layer was washed with brine (1 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo.* The crude product was purified by flash column chromatography (silica gel, CH_2Cl_2:MeOH = 1:0 → 9:1) to

afford indoline **S2x** (83.0 mg, 91%) as a pale yellow viscous oil. It was a single diastereomer, in accordance with the literature observations.[1]

***R*$_f$**=0.31 (silica gel, CH_2Cl_2:MeOH = 9:1); **^{1}H NMR** (500 MHz, MeOD): δ 7.05 (d, *J* = 7.2 Hz, 1H), 6.97 (t, *J* = 7.7 Hz, 1H), 6.67 – 6.64 (m, 2H), 4.25 (s, 1H), 3.69 (s, 3H), 3.55 (d, *J* = 4.8 Hz, 1H), 2.99 (dt, *J* = 12.5, 6.6 Hz, 1H), 2.88 (d, *J* = 11.4 Hz, 1H), 2.83 (d, *J* = 11.8 Hz, 1H), 2.51 (d, *J* = 11.6 Hz, 1H), 2.35 – 2.27 (m, 2H), 2.13 (t, *J* = 10.3 Hz, 1H), 1.91 – 1.89 (m. 3H), 1.79 (dd, *J* = 14.1, 6.3 Hz, 1H), 1.65 (t, *J* = 12.6 Hz, 1H), 1.55 – 1.43 (m, 3H), 1.38 – 1.28 (m, 2H); **^{13}C NMR** (126 MHz, MeOD): δ 175.0, 151.5, 135.6, 128.5, 124.1, 119.8, 111.5, 68.4, 64.2, 64.0, 62.4, 54.7, 53.7, 52.0, 49.8, 41.0, 40.6, 37.1, 35.0, 33.3, 30.1, 24.0; **HRMS** calcd. for $C_{21}H_{29}N_2O_3^+$ $[M + H]^+$ 357.2173, found 357.2180.

Benzyl (2-(indolin-3-yl)ethyl)carbamate (S2a')

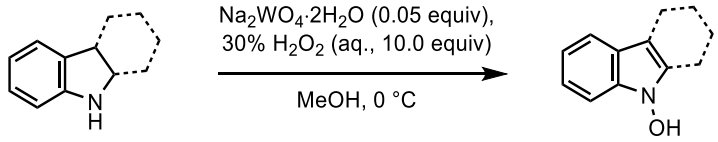


Following the **general procedure B**, tryptamine **S1a'** (3.50 g, 16.0 mmol) afforded indoline **S2a'** (3.30 g, 94%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 6:4).

***R*$_f$**=0.18 (silica gel, hexanes:EtOAc = 6:4); **^{1}H NMR** (500 MHz, $CDCl_3$): 7.36 (d, *J* = 4.3 Hz, 4H), 7.34 – 7.28 (m, 1H), 7.10 (d, *J* = 7.3 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.74 (t, *J* = 7.5 Hz, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 5.10 (s, 2H), 4.89 (s, 1H), 3.71 (t, *J* = 8.7 Hz, 1H), 3.33 (q, *J* = 7.2 Hz, 1H), 3.27 (t, *J* = 7.4 Hz, 1H), 2.01 (dq, *J* = 13.2, 6.3 Hz, 1H), 1.77 (dt, *J* = 13.8, 7.0 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 156.5, 151.2, 136.6, 132.0, 128.4, 128.0, 127.6, 123.8, 118.6, 109.6, 66.5, 53.1, 39.4, 39.0, 34.3; **HRMS** calcd. for $C_{12}H_{17}N_2O_2^+$ $[M + H]^+$ 221.1285, found 221.1278.

2.3.2.3. Preparation of *N*-Hydroxyindole Derivatives

General procedure D



S2 **1**

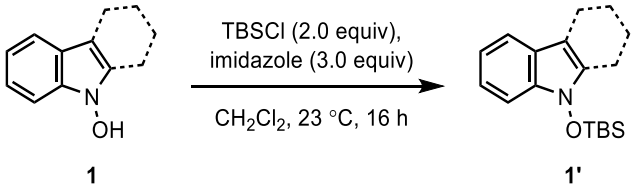
The compounds were synthesized according to a known literature procedure.[14] Reactions were performed in flame-dried round-bottom flask equipped with a magnetic stir bar and septum. Indoline **S2** (1.0 equiv) and MeOH (0.1 M in **S2**) were added to the flask at 23 °C, and sodium tungstate dihydrate (0.05 equiv) and H_2O_2 (30 wt% in H_2O, 10.0 equiv) were successively added to the solution at 0 °C. The reaction mixture was warmed up to 23 °C and stirred until TLC indicated complete conversion, then the reaction was quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo.* The resulting crude *N*-hydroxyindole **1** was used directly without further purification.

note: In most cases, *N*-hydroxyindoles are unstable and slowly undergo decomposition, thus was unable to be stored for an extended period of time. However, most of *N*-hydroxyindoles could be obtained in excellent state which are clean enough to be characterized without purification. *N*-hydroxyindoles enlisted in this section were characterized without further purification (**1a–1o**, **1s**, **1x**) or otherwise protected with TBS group (**1p'**, **1q'**, **1r'**, **1v'**, **1w', 1a''**) for characterization. In case of the *N*-hydroxyindoles **1t** and **1u**, the products could be obtained in affordable quality. However, they could not be fully characterized due to their fast decomposition.

Determination of the reaction yield for the preparation of *N*-hydroxyindoles: The crude product was dissolved in CH_2Cl_2 to provide a solution with a total volume of 10.0 mL. 1.0 mL of the resulting solution was syringed out and dried separately in a 4 mL vial. To the 4 mL vial containing the separated sample was added 10.0 μL of 1,1,2,2-tetrachloroethane (TCE) as an internal standard and the resulting mixture was dissolved entirely in d4-methanol. The yield of product was determined by the integration of peaks from the ^{1}H NMR spectra relative to the

internal standard, TCE. The calculated amount of the product in the sample (A) was then multiplied by 10 to provide the total mass of the *N*-hydroxyindole product. The remaining 9.0 mL of the stock solution was dried under reduced pressure and used directly for the next step. The calculated amount of the product in the sample (A) was multiplied by 9 to provide the quantity of the starting material for the next reaction.

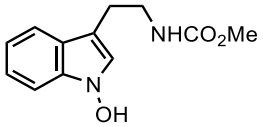
General Procedure E



For compounds **1p'**, **1q'**, **1r'**, **1v'**, **1w'**, **1a''**:

Reactions were performed in flame-dried round-bottom flask equipped with a magnetic stir bar and septum. Crude *N*-hydroxyindole **1** (1.0 equiv) and CH_2Cl_2 (0.2 M in **1**) were added to the flask at 23 °C, followed by TBSCl (2.0 equiv) and imidazole (3.0 equiv). The reaction mixture was stirred 16 h, then the reaction was quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo.* The crude product was purified by flash column chromatography to afford TBS protected *N*-hydroxyindole.

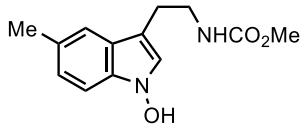
Methyl (2-(1-hydroxy-1H-indol-3-yl)ethyl)carbamate (1a)



Following the **general procedure D** for 2 h, indoline **S2a** (0.120 g, 0.545 mmol) afforded *N*-hydroxyindole **1a** (93.0 mg, 73%) as a yellow oil and was used directly in the subsequent reaction without further purification.

R_f=0.45 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, MeOD): δ 7.53 (d, *J* = 8.1 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.13 (t, *J* = 7.7 Hz, 1H), 7.10 (s, 1H), 6.99 (t, *J* = 7.5 Hz, 1H), 3.62 (s, 3H), 3.36 (t, *J* = 7.5 Hz, 2H), 2.89 (t, *J* = 7.7 Hz, 2H); **^{13}C NMR** (126 MHz, MeOD): δ 159.6, 135.7, 125.0, 124.4, 122.7, 119.7, 119.5, 109.2, 108.8, 75.8, 52.4, 42.8, 26.6; **HRMS** calcd. for $C_{12}H_{15}N_2O_3^+$ $[M + H]^+$ 235.1077, found 235.1077.

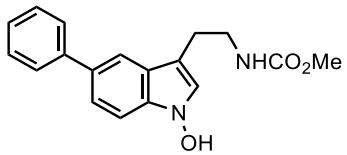
Methyl (2-(1-hydroxy-5-methyl-1H-indol-3-yl)ethyl)carbamate (1b)



Following the **general procedure D** for 2 h, indoline **S2b** (75.0 mg, 0.320 mmol) afforded *N*-hydroxyindole **1b** (48.0 mg, 60%) as a pale yellow oil and was used directly in the subsequent reaction without further purification.

R_f=0.24 (silica gel, hexanes:EtOAc = 7:3); **^{1}H NMR** (500 MHz, MeOD): δ 7.32 (s, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 7.04 (s, 1H), 6.97 (dd, *J* = 8.4, 1.6 Hz, 1H), 3.62 (s, 3H), 3.34 (t, *J* = 7.4 Hz, 2H), 2.85 (t, *J* = 7.4 Hz, 2H), 2.41 (s, 3H); **^{13}C NMR** (126 MHz, MeOD): δ 159.6, 134.3, 128.8, 125.3, 124.5, 124.3, 119.1, 109.0, 108.2. 52.4, 42.8, 26.6, 21.6; **HRMS** calcd. for $C_{13}H_{17}N_2O_3^+$ $[M + H]^+$ 249.1234, found 249.1233.

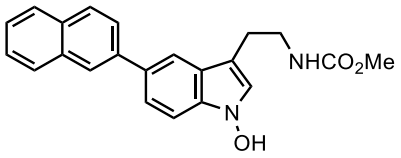
Methyl (2-(1-hydroxy-5-phenyl-1H-indol-3-yl)ethyl)carbamate (1c)



Following the **general procedure D** for 2 h, indoline **S2c** (60.0 mg, 0.202 mmol) afforded *N*-hydroxyindole **1c** (29.0 mg, 47%) as a pale yellow oil and was used directly in the subsequent reaction without further purification.

R_f=0.40 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, MeOD): δ 7.76 (s, 1H), 7.64 (d, *J* = 7.7 Hz, 2H), 7.44 – 7.37 (m, 4H), 7.26 (t, *J* = 7.4 Hz, 1H), 7.14 (s, 1H), 3.60 (s, 3H), 3.39 (t, *J* = 7.3 Hz, 2H), 2.94 (t, *J* = 7.4 Hz, 2H); **^{13}C NMR** (126 MHz, MeOD): δ 159.6, 144.0, 135.1, 133.6, 129.6, 128.1, 127.2, 125.6, 125.1, 122.4, 118.0, 109.6, 109.4, 52.4, 43.0, 26.6; **HRMS** calcd. for $C_{18}H_{17}N_2O_3^-$ $[M - H]^-$ 309.1245, found 309.1241.

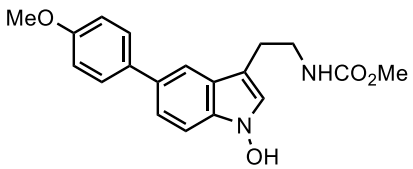
Methyl (2-(1-hydroxy-5-(naphthalen-2-yl)-1H-indol-3-yl)ethyl)carbamate (1d)



Following the **general procedure D** for 4 h, indoline **S2d** (75.0 mg, 0.216 mmol) afforded *N*-hydroxyindole **1d** (56.0 mg, 72%) as a brown oil and was used directly in the subsequent reaction without further purification.

R_f=0.24 (silica gel, hexanes:EtOAc = 7:3); **^{1}H NMR** (400 MHz, MeOD): δ 8.10 (s, 1H), 7.91 (d, *J* = 7.8 Hz, 3H), 7.87 – 7.83 (m, 2H), 7.59 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.50 – 7.42 (m, 3H), 7.17 (s, 1H), 3.61 (s, 3H), 3.42 (t, *J* = 7.3 Hz, 2H), 2.97 (t, *J* = 7.3 Hz, 2H); **^{13}C NMR** (126 MHz, MeOD): δ 159.7, 141.4, 135.4, 135.2, 133.7, 133.3, 129.2, 129.0, 128.6, 127.1, 127.1, 126.4, 126.1, 125.7, 125.2, 122.6, 118.4, 109.7, 109.5, 52.4, 43.1, 26.6; **HRMS** calcd. for $C_{22}H_{21}N_2O_3^+$ $[M + H]^+$ 361.1547, found 361.1545.

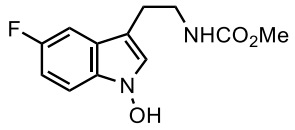
Methyl (2-(1-hydroxy-5-(4-methoxyphenyl)-1H-indol-3-yl)ethyl)carbamate (1e)



Following the **general procedure D** for 2 h, indoline **S2e** (75.0 mg, 0.230 mmol) afforded *N*-hydroxyindole **1e** (44.6 mg, 57%) as a pale yellow oil and was used directly in the subsequent reaction without further purification.

***R**f*=0.27 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, MeOD): δ 7.70 (s, 1H), 7.55 (d, *J* = 8.7 Hz, 2H), 7.38 (s, 2H), 7.12 (s, 1H), 6.97 (d, *J* = 8.7 Hz, 2H), 3.81 (s, 3H), 3.60 (s, 3H), 3.38 (t, *J* = 7.3 Hz, 2H), 2.92 (t, *J* = 7.4 Hz, 2H); **^{13}C NMR** (126 MHz, MeOD): δ 159.9, 159.6, 136.6, 134.9, 133.3, 129.1, 125.6, 125.0, 122.2, 117.4, 115.1, 109.5, 109.3, 55.7, 52.4, 43.0, 26.6; **HRMS** calcd. for $C_{19}H_{21}N_2O_4^+$ $[M + H]^+$ 341.1496, found 341.1504.

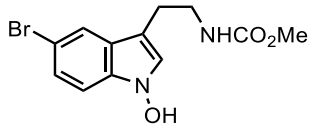
Methyl (2-(5-fluoro-1-hydroxy-1H-indol-3-yl)ethyl)carbamate (1f)



Following the **general procedure D** for 4 h, indoline **S2f** (50.0 mg, 0.210 mmol) afforded *N*-hydroxyindole **1f** (34.0 mg, 64%) as a pale yellow oil and was used directly in the subsequent reaction without further purification.

***R**f*=0.27 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, MeOD): δ 7.31 (dd, *J* = 8.9, 4.5 Hz, 1H), 7.22 (dd, *J* = 9.9, 2.4 Hz, 1H), 7.17 (s, 1H), 6.91 (td, *J* = 9.1, 2.4 Hz, 1H), 3.62 (s, 3H), 3.35 (t, *J* = 8.0 Hz, 2H), 2.85 (t, *J* = 7.4 Hz, 2H); **^{13}C NMR** (126 MHz, MeOD): δ 159.6, 158.9 (d, *J* = 232.4 Hz), 132.4, 126.1, 125.2 (d, *J* = 9.7 Hz), 110.9 (d, *J* = 26.7 Hz), 110.2 (d, *J* = 9.7 Hz), 108.7, 104.2 (d, *J* = 23.8 Hz), 52.4, 42.7, 26.5; **^{19}F NMR** (376 MHz, MeOD): δ –128.0 (td, *J* = 9.3, 4.2 Hz); **HRMS** calcd. for $C_{12}H_{12}FN_2O_3^-$ $[M – H]^-$ 251.0837, found 251.0832.

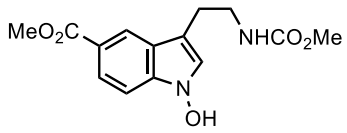
Methyl (2-(5-bromo-1-hydroxy-1H-indol-3-yl)ethyl)carbamate (1g)



Following the **general procedure D** for 2.5 h, indoline **S2g** (0.100 g, 0.334 mmol) afforded *N*-hydroxyindole **1g** (57.0 mg, 54%) as a pale yellow oil and was used directly in the subsequent reaction without further purification.

R_f=0.41 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, MeOD): δ 7.68 (s, 1H), 7.26 (d, *J* = 8.7 Hz, 1H), 7.21 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.14 (s, 1H), 3.61 (s, 3H), 3.33 (t, *J* = 7.3 Hz, 2H), 2.84 (t, *J* = 7.3 Hz, 2H); **^{13}C NMR** (126 MHz, MeOD): δ 159.6, 134.1, 126.7, 125.7, 125.4, 122.1, 112.8, 110.9, 108.6, 52.4, 42.8, 26.3; **HRMS** calcd. for $C_{12}H_{12}BrN_2O_3^-$ [M – H]$^-$ 311.0037, found 311.0033.

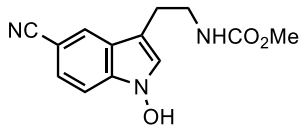
Methyl 1-hydroxy-3-(2-((methoxycarbonyl)amino)ethyl)-1H-indole-5-carboxylate (1h)



Following the **general procedure D** for 6 h, indoline **S2h** (70.0 mg, 0.252 mmol) afforded *N*-hydroxyindole **1h** (45.0 mg, 61%) as a pale yellow oil and was used directly in the subsequent reaction without further purification.

R_f=0.24 (silica gel, hexanes:EtOAc = 7:3); **^{1}H NMR** (500 MHz, MeOD): δ 8.32 (s, 1H), 7.83 (dd, *J* = 8.7, 1.4 Hz, 1H), 7.39 (d, *J* = 8.7 Hz, 1H), 7.23 (s, 1H), 3.90 (s, 3H), 3.62 (s, 3H), 3.37 (t, *J* = 7.2 Hz, 2H), 2.94 (t, *J* = 7.2 Hz, 2H); **^{13}C NMR** (126 MHz, MeOD): δ 170.0, 159.6, 137.4, 126.1, 124.5, 123.9, 122.9, 121.6, 110.9, 109.0, 52.4, 52.3, 42.8, 26.3; **HRMS** calcd. for $C_{14}H_{15}N_2O_5^-$ [M – H]$^-$ 291.0987, found 291.0985.

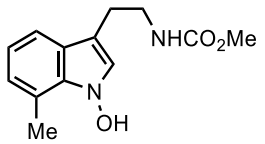
Methyl (2-(5-cyano-1-hydroxy-1H-indol-3-yl)ethyl)carbamate (1i)



Following the **general procedure D** for 6 h, indoline **S2i** (25.3 mg, 0.103 mmol) afforded *N*-hydroxyindole **1i** (17.1 mg, 64%) as a pale yellow oil and was used directly in the subsequent reaction without further purification.

R_f=0.24 (silica gel, hexanes:EtOAc = 7:3); **^{1}H NMR** (500 MHz, MeOD): δ 8.02 (s, 1H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.41 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.31 (s, 1H), 3.61 (s, 3H), 3.36 (t, *J* = 7.2 Hz, 3H), 2.92 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (126 MHz, MeOD): δ 159.6, 136.4, 126.9, 125.8, 125.3, 124.8, 121.8, 110.5, 110.3, 102.2, 52.4, 42.7, 26.2 ; **HRMS** calcd. for $C_{13}H_{14}N_3O_3^+$ $[M + H]^+$ 260.1030, found 260.1024.

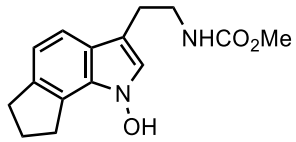
Methyl (2-(1-hydroxy-7-methyl-1H-indol-3-yl)ethyl)carbamate (1j)



Following the **general procedure D** for 2 h, indoline **S2j** (80.0 mg, 0.341 mmol) afforded *N*-hydroxyindole **1j** (39.6 mg, 47%) as a pale yellow oil and was used directly in the subsequent reaction without further purification.

R_f=0.24 (silica gel, hexanes:EtOAc = 7:3); **^{1}H NMR** (400 MHz, MeOD): δ 7.33 (d, *J* = 7.6 Hz, 1H), 7.03 (s, 1H), 6.90 – 6.80 (m, 2H), 3.62 (s, 3H), 3.35 (t, *J* = 7.5 Hz, 2H), 2.85 (t, *J* = 7.4 Hz, 2H), 2.67 (s, 3H); **^{13}C NMR** (101 MHz, MeOD): δ 159.6, 134.3, 125.7, 125.3, 124.7, 121.7, 120.0, 117.2, 108.8, 52.4, 42.7, 26.6, 18.3; **HRMS** calcd. for $C_{13}H_{17}N_2O_3^+$ $[M + H]^+$ 249.1234, found 249.1234.

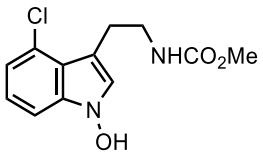
Methyl (2-(1-hydroxy-1,6,7,8-tetrahydrocyclopenta[g]indol-3-yl)ethyl)carbamate (1k)



Following the **general procedure D** for 2 h, indoline **S2k** (50.0 mg, 0.192 mmol) afforded *N*-hydroxyindole **1k** (40.5 mg, 77%) as a pale yellow oil and was used directly in the subsequent reaction without further purification.

***R*$_f$**=0.24 (silica gel, hexanes:EtOAc = 7:3); **^{1}H NMR** (500 MHz, MeOD): δ 7.29 (d, *J* = 8.1 Hz, 1H), 6.97 (s, 1H), 6.88 (d, *J* = 8.1 Hz, 1H), 3.61 (s, 3H), 3.35 – 3.27 (m, 4H), 2.94 (t, *J* = 7.4 Hz, 2H), 2.84 (t, *J* = 7.5 Hz, 2H), 2.14 (qui, *J* = 7.4 Hz, 2H); **^{13}C NMR** (126 MHz, MeOD): δ 159.6, 139.6, 132.9, 125.4, 124.1, 123.9, 117.6, 116.7, 109.2, 52.4, 42.7, 33.6, 31.4, 26.8, 26.5; **HRMS** calcd. for $C_{15}H_{19}N_2O_3^+$ $[M + H]^+$ 275.1390, found 275.1389.

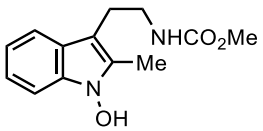
Methyl (2-(4-chloro-1-hydroxy-1H-indol-3-yl)ethyl)carbamate (1l)



Following the **general procedure D** for 5 h, indoline **S2l** (50.0 mg, 0.196 mmol) afforded *N*-hydroxyindole **1l** (37.1 mg, 70%) as a pale yellow oil and was used directly in the subsequent reaction without further purification.

***R*$_f$**=0.24 (silica gel, hexanes:EtOAc = 7:3); **^{1}H NMR** (500 MHz, MeOD): δ 7.30 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.17 (s, 1H), 7.05 (t, *J* = 7.9 Hz, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 3.61 (s, 3H), 3.40 (t, *J* = 7.3 Hz, 2H), 3.12 (t, *J* = 7.3 Hz, 2H); **^{13}C NMR** (126 MHz, MeOD): δ 159.6, 137.0, 127.1, 126.1, 123.1, 121.3, 120.6, 108.8, 108.3, 52.4, 43.8, 27.5; **HRMS** calcd. for $C_{12}H_{14}ClN_2O_3^+$ $[M + H]^+$ 269.0688, found 269.0685.

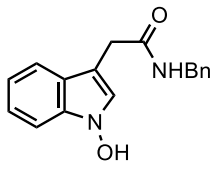
Methyl (2-(1-hydroxy-2-methyl-1H-indol-3-yl)ethyl)carbamate (1m)



Following the **general procedure D** for 2 h, indoline **S2m** (33.6 mg, 0.143 mmol) afforded *N*-hydroxyindole **1m** (23.7 mg, 67%) as a pale yellow oil and was used directly in the subsequent reaction without further purification.

R_f=0.60 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, MeOD): δ 7.46 (d, *J* = 7.4 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.96 (t, *J* = 7.4 Hz, 1H), 3.62 (s, 1H), 3.27 (t, *J* = 7.3 Hz, 2H), 2.87 (t, *J* = 7.2 Hz, 2H), 2.36 (s, 3H); **^{13}C NMR** (126 MHz, MeOD): δ 159.6, 135.3, 133.1, 124.9, 121.6, 119.7, 118.4, 108.6, 104.6, 52.3, 42.8, 25.8, 8.9; **HRMS** calcd. for $C_{13}H_{17}N_2O_3^+$ $[M + H]^+$ 249.1234, found 249.1233.

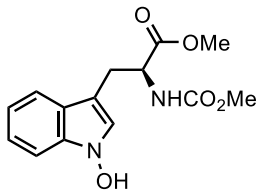
***N*-Benzyl-2-(1-hydroxy-1H-indol-3-yl)acetamide (1n)**



Following the **general procedure D** for 1.5 h, indoline **S2n** (40.8 mg, 0.153 mmol) afforded *N*-hydroxyindole **1n** (23.2 mg, 54%) as a pale yellow oil and was used directly in the subsequent reaction without further purification.

R_f=0.58 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, MeOD): δ 7.52 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.37 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.26 – 7.18 (m, 6H), 7.16 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 7.00 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1H), 4.35 (s, 2H), 3.66 (s, 2H); **^{13}C NMR** (126 MHz, MeOD): δ 174.6, 139.9, 135.6, 129.4, 128.5, 128.1, 125.6, 124.8, 122.9, 120.0, 119.7, 109.3, 104.8, 44.2, 33.7; **HRMS** calcd. for $C_{17}H_{17}N_2O_2^+$ $[M + H]^+$ 281.1285, found 281.1282.

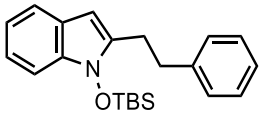
Methyl (S)-3-(1-hydroxy-1H-indol-3-yl)-2-((methoxycarbonyl)amino)propanoate (1o)



Following the **general procedure D** for 2 h, indoline **S2o** (70.0 mg, 0.252 mmol) afforded *N*-hydroxyindole **1o** (48.5 mg, 66%) as a pale yellow oil and was used directly in the subsequent reaction without further purification.

R_f=0.44 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (400 MHz, MeOD): δ 7.50 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.17 – 7.12 (m, 2H), 7.01 (t, *J* = 7.5 Hz, 1H), 4.47 (t, *J* = 6.7 Hz, 1H) 3.64 (s, 3H), 3.59 (s, 3H), 3.25 (dd, *J* = 14.6, 5.7 Hz, 1H), 3.10 (dd, *J* = 14.6, 7.9 Hz, 1H); **^{13}C NMR** (101 MHz, MeOD): δ 174.3, 159.0, 135.4, 125.2, 124.9, 122.8, 119.9, 119.3, 109.3, 106.1, 56.5, 52.7, 28.4; **HRMS** calcd. for $C_{14}H_{17}N_2O_5^+$ $[M + H]^+$ 293.1132, found 293.1138.

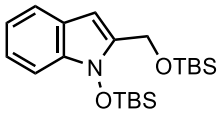
1-((*tert*-Butyldimethylsilyl)oxy)-2-phenethyl-1H-indole (1p')



Following the **general procedure D** for 1.5 h, indoline **S2p** (30.0 mg, 0.134 mmol) afforded *N*-hydroxyindole **1p** as a pale yellow oil and was used directly in the subsequent reaction without further purification. For characterization, crude *N*-hydroxyindole **1p** underwent TBS protection following the **general procedure E** to afford TBS-protected *N*-hydroxyindole **1p'** (27.4 mg, 0.0781 mmol, 58% for 2 steps) as a colorless oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 1:1).

R_f=0.24 (silica gel, hexanes:EtOAc = 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.8 Hz, 1H), 7.34 – 7.30 (m, 3H), 7.26 – 7.21 (m, 3H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.05 (t, *J* = 7.4 Hz, 1H), 6.16 (s, 1H), 3.06 (s, 4H), 1.14 (s, 9H), 0.27 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 141.5, 139.2, 134.8, 128.6, 128.5, 126.2, 124.1, 121.0, 120.0, 119.6, 109.0, 95.5, 34.6, 27.9, 26.1, 18.4, –3.7; **HRMS** calcd. for $C_{22}H_{30}NOSi^+$ $[M + H]^+$ 352.2091, found 352.2091.

1-((*tert*-Butyldimethylsilyl)oxy)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-1H-indole (1q')

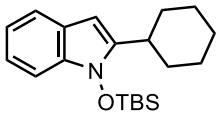


Following the **general procedure D** for 1.5 h, indoline **S2q** (70.0 mg, 0.266 mmol) afforded *N*-hydroxyindole **1q** as a pale yellow oil and was used directly in the subsequent reaction without

further purification. For characterization, crude *N*-hydroxyindole **1q** underwent TBS protection following the **general procedure E** to afford TBS-protected *N*-hydroxyindole **1q'** (71.9 mg, 0.190mmol, 72% for 2 steps) as a colorless oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 1:1).

R_f=0.24 (silica gel, hexanes:EtOAc = 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.06 (t, *J* = 7.4 Hz, 1H), 6.33 (s, 1H), 4.84 (s, 2H), 1.14 (s, 9H), 0.95 (s, 9H), 0.29 (s, 6H), 0.11 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 138.9, 135.3, 124.1, 121.5, 120.6, 119.8, 109.2, 96.9, 57.3, 26.1, 18.5, 18.5, –4.0, –5.1; **HRMS** calcd. for $C_{21}H_{38}NO_2Si_2^+$ $[M + H]^+$ 392.2436, found 392.2435.

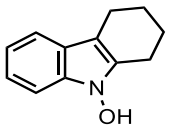
1-((*tert*-Butyldimethylsilyl)oxy)-2-cyclohexyl-1H-indole (1r')



Following the **general procedure D** for 1.5 h, indoline **S2r** (20.0 mg, 0.0993 mmol) afforded *N*-hydroxyindole **1r** as a pale yellow oil and was used directly in the subsequent reaction without further purification. For characterization, crude *N*-hydroxyindole **1r** underwent TBS protection following the **general procedure E** to afford TBS-protected *N*-hydroxyindole **1r'** (18.4 g, 0.0558 mmol, 56% for 2 steps) as a colorless oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 1:1).

R_f=0.24 (silica gel, hexanes:EtOAc = 7:3); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.48 (d, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 1H), 7.10 (td, *J* = 7.1, 0.9 Hz, 1H), 7.02 (td, *J* = 7.5, 0.8 Hz, 1H), 6.08 (s, 1H), 2.81 – 2.75 (m, 1H), 2.08 (d, *J* = 8.4 Hz, 2H), 1.86 – 1.84 (m, 2H), 1.76 (d, *J* = 11.7 Hz, 1H), 1.42 – 1.24 (m, 6H), 1.14 (s, 9H), 0.24 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 145.0, 134.1, 124.0, 120.6, 120.0, 119.3, 108.9, 92.8, 35.1, 32.8, 26.7, 26.3, 26.1, 18.4, –3.8; **HRMS** calcd. for $C_{20}H_{32}NOSi^+$ $[M + H]^+$ 330.2248, found 330.2246.

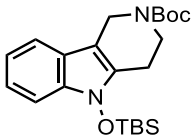
1,2,3,4-Tetrahydro-9H-carbazol-9-ol (1s)



Following the **general procedure D** for 1.5 h, indoline **S2s** (30.0 mg, 0.173 mmol) afforded *N*-hydroxyindole **1s** (25.0 mg, 77%) as a pale yellow oil and was used directly in the subsequent reaction without further purification.

***R*$_f$**=0.65 (silica gel, hexanes:EtOAc = 9:1); **^{1}H NMR** (400 MHz, MeOD): δ 7.30 (dd, *J* = 14.5, 7.9 Hz, 2H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.92 (t, *J* = 7.4 Hz, 1H), 2.69 (dt, *J* = 36.8, 4.8 Hz, 4H), 1.91 – 1.82 (m, 4H); **^{13}C NMR** (101 MHz, MeOD): δ 135.9, 135.15 124.6, 121.5, 119.4, 118.3, 108.6, 105.9, 24.5, 24.0, 21.9, 21.8; **HRMS** calcd. for $C_{12}H_{14}NO^+$ $[M + H]^+$ 188.1070, found 188.1067.

***tert*-Butyl 5-((*tert*-butyldimethylsilyl)oxy)-1,3,4,5-tetrahydro-2H-pyrido[4,3-b]indole-2-carboxylate (1v')**

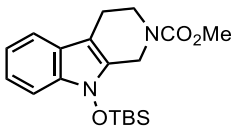


Following the **general procedure D** for 2 h, indoline **S2v** (50.0 mg, 0.182 mmol) afforded *N*-hydroxyindole **1v** as a pale yellow oil and was used directly in the subsequent reaction without further purification. For characterization, *N*-hydroxyindole **1v** underwent TBS protection following the **general procedure E** to afford TBS-protected *N*-hydroxyindole **1v'** (55.6 mg, 0.138 mmol, 76% for 2 steps) as a colorless oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3).

***R*$_f$**=0.24 (silica gel, hexanes:EtOAc = 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 4.61 (br s, 2H), 3.78 (br s, 2H), 2.79 (br s, 2H), 1.51 (s, 9H), 1.11 (s, 9H), 0.29 (s, 6H); **^{13}C NMR** (126 MHz,

$CDCl_3$): δ 136.6, 121.7, 119.9, 117.7, 109.5, 80.1, 41.4, 40.6, 28.7, 26.0, 22.7, 18.3, –4.0; **HRMS** calcd. for $C_{22}H_{35}N_2O_3Si^+$ $[M + H]^+$ 403.2412, found 403.2412.

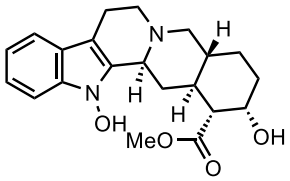
Methyl 9-((*tert*-butyldimethylsilyl)oxy)-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole-2-carboxylate (1w')



Following the **general procedure D** for 2 h, indoline **S2w** (50.0 mg, 0.215 mmol) afforded *N*-hydroxyindole **1w** as a pale yellow oil and was used directly in the subsequent reaction without further purification. For characterization, *N*-hydroxyindole **1w** underwent TBS protection following the **general procedure E** to afford TBS-protected *N*-hydroxyindole **1w'** (55.8 mg, 0.155 mmol, 72% for 2 steps) as a colorless oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 1:1).

R_f=0.24 (silica gel, hexanes:EtOAc = 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.09 (t, *J* = 7.4 Hz, 1H), 4.64 (d, *J* = 19.6 Hz, 2H), 3.83 – 3.76 (m, 2H), 3.77 (s, 3H), 2.79 (t, *J* = 5.8 Hz, 2H), 1.12 (s, 9H), 0.32 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 156.5, 136.9, 132.3, 123.8, 122.0, 120.0, 118.2, 109.6, 106.3, 105.7, 53.0, 42.2, 41.4, 26.0, 21.5, 21.0, 18.3, –3.9; **HRMS** calcd. for $C_{19}H_{29}N_2O_3Si^+$ $[M + H]^+$ 361.1942, found 361.1941.

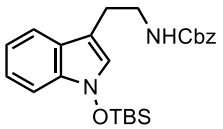
Methyl (1R,2S,4aR,13bS,14aS)-2,13-dihydroxy-1,2,3,4,4a,5,7,8,13,13b,14,14a-dodecahydroindolo [2',3':3,4]pyrido[1,2-b]isoquinoline-1-carboxylate (1x)



Following the **general procedure D** for 30 min, indoline **S2x** (40.0 mg, 0.112 mmol) afforded *N*-hydroxyindole **1x** (29.9 mg, 72%) as a pale yellow oil and was used directly in the subsequent reaction without further purification.The identity of synthesized product was confirmed based on reported NMR spectra.[13]

***R*$_f$**=0.39 (silica gel, CH_2Cl_2:MeOH = 9:1); **^{1}H NMR** (500 MHz, MeOD): δ 7.37 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.98 (t, *J* = 7.4 Hz, 1H), 4.23 (q, *J* = 2.9 Hz, 1H), 3.74 (s, 3H), 3.64 (d, *J* = 11.7 Hz, 1H), 3.17 – 3.10 (m, 1H), 2.98 – 2.91 (m, 3H), 2.76 – 2.65 (m, 2H), 2.41 (t, *J* = 11.2 Hz, 1H), 2.33 (dd, *J* = 11.7, 2.6 Hz, 1H), 2.00 (qd, *J* = 11.5, 3.1 Hz, 1H), 1.92 (dq, *J* = 14.3, 3.3 Hz, 1H), 1.71 – 1.63 (m, 1H), 1.60 – 1.44 (m, 2H), 1.41 – 1.34 (m, 1H), 1.21 (q, *J* = 11.8 Hz, 1H); **^{13}C NMR** (126 MHz, MeOD): δ 175.4, 137.3, 134.8, 123.8, 122.4, 120.2, 118.7, 109.3, 105.1, 68.6, 62.3, 60.9, 54.0, 52.7, 52.0, 40.3, 37.6, 33.6, 33.5, 24.4, 22.5; **HRMS** calcd. for $C_{19}H_{29}N_2O_3Si^+$ $[M + H]^+$ 361.1942, found 361.1941.

Benzyl (2-(1-((*tert*-butyldimethylsilyl)oxy)-1H-indol-3-yl)ethyl)carbamate (1a'')



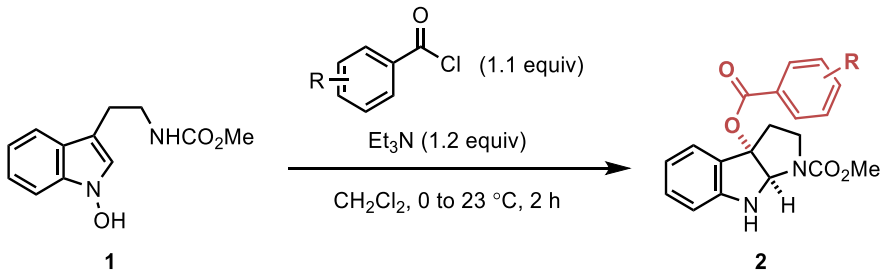
Following the **general procedure D** for 2 h, indoline **S2a'** (70.0 mg, 0.236 mmol) afforded *N*-hydroxyindole **1a'** as a pale yellow oil and was used directly in the subsequent reaction without further purification. For characterization, *N*-hydroxyindole **1a'** underwent TBS protection following the **general procedure E** to afford TBS-protected *N*-hydroxyindole **1a''** (66.2 mg,

0.156 mmol, 66% for 2 steps) as a colorless oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3).

***R*$_f$**=0.63 (silica gel, hexanes:EtOAc = 7:3); **^{1}H NMR** (500 MHz, MeOD): δ 7.56 (d, *J* = 8.0 Hz, 1H), 7.35 – 7.26 (m, 5H), 7.26 (d, *J* = 8.2 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.07 (s, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 5.06 (s, 2H), 3.39 (t, *J* = 7.1 Hz, 2H), 2.91 (t, *J* = 7.1 Hz, 2H), 1.10 (s, 9H), 0.22 (s, 6H); **^{13}C NMR** (126 MHz, MeOD): δ 158.9, 138.5, 136.0, 129.5, 128.9, 128.7, 125.1, 124.9, 123.1, 122.6, 120.2, 119.8, 110.0, 109.8, 67.3, 42.7, 26.4, 26.2, 18.8, –4.7; **HRMS** calcd. for $C_{24}H_{33}N_2O_3Si^+$ $[M + H]^+$ 425.2255, found 425.2269.

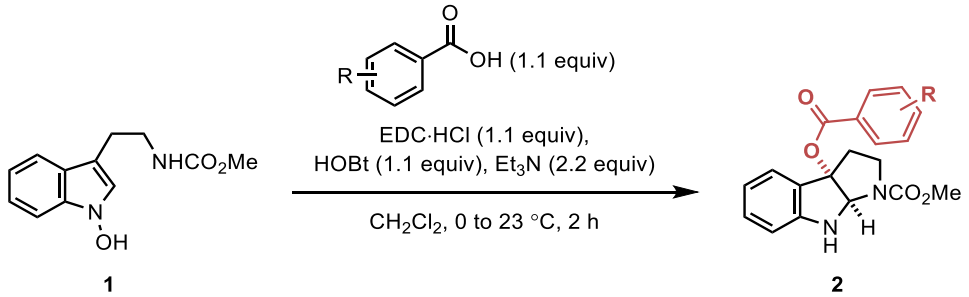
2.3.3. General Procedure for C3-Acyloxylation of Indole Scaffolds

General procedure F



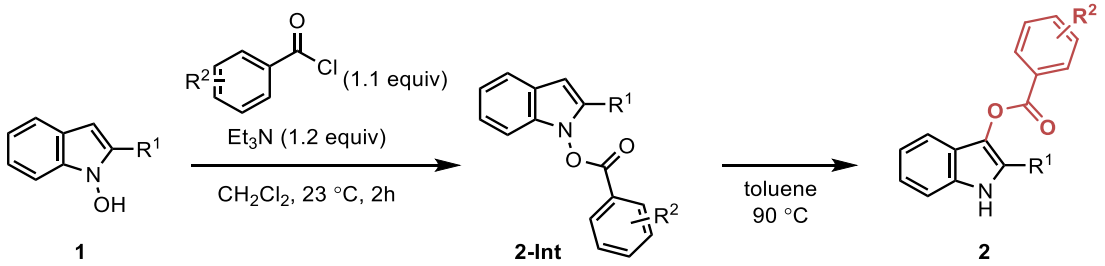
Reactions were performed in flame-dried round-bottom flask equipped with a magnetic stir bar and septum. Crude *N*-hydroxyindole **1** (1.0 equiv) and CH_2Cl_2 (0.05 M in **1**) were added to the flask at 23 °C, and benzoyl chloride (1.1 equiv) and Et_3N (1.2 equiv) were added to the solution at 0 °C. The reaction mixture was warm up to 23 °C and stirred for 2 h, then the reaction was quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo.* The crude product was purified by flash column chromatography to afford the product **2**.

General procedure G



Reactions were performed in flame-dried round-bottom flask equipped with a magnetic stir bar and septum. Crude *N*-hydroxyindole **1** (1.0 equiv) and CH_2Cl_2 (0.05 M in **1**) were added to the flask at 23 °C, and and benzoic acid (1.1 equiv), EDC·HCl (1.1 equiv), HOBt (1.1 equiv) and Et_3N (2.2 equiv) were successively added to the solution at 0 °C. The reaction mixture was warm up to 23 °C and stirred for 2 h, then the reaction was quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo.* The crude product was purified by flash column chromatography to afford the product **2**.

General procedure H

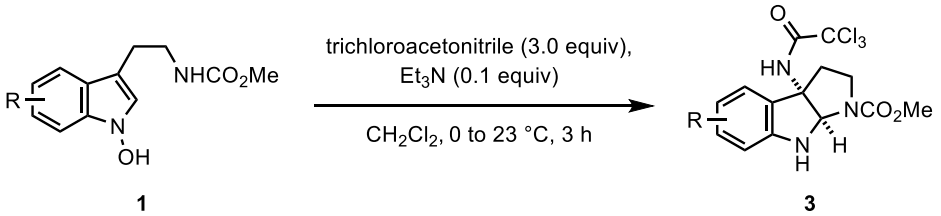


Reactions were performed in flame-dried round-bottom flask equipped with a magnetic stir bar and septum. Crude *N*-hydroxyindole **1** (1.0 equiv) and CH_2Cl_2 (0.05 M in **1**) were added to the flask at 23 °C, followed by benzoyl chloride (1.1 equiv) and Et_3N (1.2 equiv). The reaction mixture was stirred 2 h, then the reaction was quenched with saturated aqueous solution of $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layer was washed with $NaHCO_3$ (sat. aq.), dried over anhydrous Na_2SO_4, filtered, and

concentrated *in vacuo*. CH_2Cl_2 was added to the resulting residue and it was filtered through a silica gel plug, concentrated *in vacuo* and re-dissolved in toluene (0.05 M in **1**). Then the resulting solution was heated to 90 °C and stirred until TLC indicated complete conversion. Then the reaction mixture was cooled to 23 °C, then it was directly concentrated *in vacuo* and purified by column chromatography to afford the product **2**.

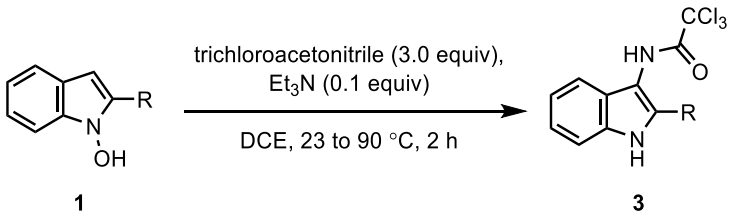
2.3.4. General Procedure for C3-Amidation of Indole Scaffolds

General procedure I



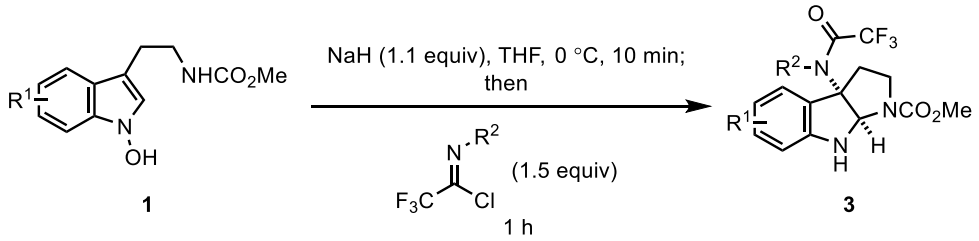
Reactions were performed in flame-dried round-bottom flask equipped with a magnetic stir bar and septum. Crude *N*-hydroxyindole **1** (1.0 equiv) and CH_2Cl_2 (0.05 M in **1**) were added to the flask at 23 °C, and trichloroacetonitrile (3.0 equiv) and Et_3N (0.1 equiv) were successively added to the solution at 0 °C. The reaction mixture was warmed up to 23 °C and stirred for 16 h, then the reaction was quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography to afford the desired product 3.

General procedure J



Reactions were performed in flame-dried round-bottom flask equipped with a magnetic stir bar and septum. Crude *N*-hydroxyindole **1** (1.0 equiv) and DCE (0.05 M in **1**) were added to the flask at 23 °C, followed by trichloroacetonitrile (3.0 equiv) and Et_3N (0.1 equiv). The reaction mixture was stirred for 2 h at 90 °C in an oil bath. Then the reaction mixture was cooled to 23 °C and quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo.* The crude product was purified by flash column chromatography to afford desired product **3**.

General procedure K

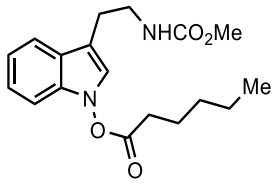


Reactions were performed in flame-dried round-bottom flask equipped with a magnetic stir bar and septum. Crude *N*-hydroxyindole **1** (1.0 equiv) and THF (0.05 M in **1**) were added to the flask at 23 °C, NaH (60% in mineral oil, 1.1 equiv) was added to the solution at 0 °C. After 10 min stirring, imidoyl chloride (1.5 equiv) was added to the solution. The reaction mixture was stirred for additional 1 h, then the reaction was quenched with brine. The aqueous layer was extracted with EtOAc (3x). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo.* The crude product was purified by flash column chromatography to afford the desired product 3.

2.3.5. Characterization Data of Synthesized Compounds

2.3.5.1. Characterization Data of Figure 1.3

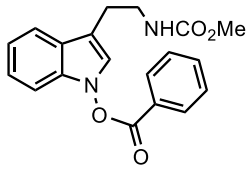
Methyl 3a-(hexanoyloxy)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (2a-Int)



Purified by silica gel column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3) to indolyl *N*-carboxylate **2a-Int** (41.1 mg, 62%) as a pale yellow oil.

***R*$_f$**=0.60 (silica gel, hexanes:EtOAc = 6:4); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 7.9 Hz, 1H), 7.28 – 7.22 (m, 1H), 7.19 – 7.13 (m, 2H), 6.98 (br s, 1H), 4.83 (s, 1H), 3.66 (s, 3H), 3.51 (q, *J* = 6.7 Hz, 2H), 2.94 (t, *J* = 6.8 Hz, 2H), 2.63 (t, *J* = 7.5 Hz, 2H), 1.82 (p, *J* = 7.4 Hz, 2H), 1.50 – 1.35 (m, 4H), 0.95 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.8, 157.2, 135.4, 124.7, 123.9, 123.5, 120.8, 119.3, 111.5, 108.9, 52.2, 41.1, 31.7, 31.3, 25.8, 24.7, 22.4; **HRMS** calcd. for $C_{18}H_{25}N_2O_4^+$ $[M + H]^+$ 333.1809, found 333.1810.

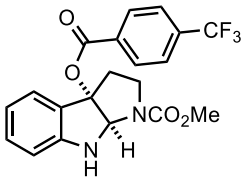
3-(2-((Methoxycarbonyl)amino)ethyl)-1H-indol-1-yl benzoate (2b-Int)



Purified by silica gel column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3) to indolyl *N*-carboxylate **2b-Int** (44.2 mg, 65%) as a pale yellow oil.

***R*$_f$**=0.31 (silica gel, hexanes:EtOAc = 7:3); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.22 (d, *J* = 7.2 Hz, 2H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 2H), 7.26 (d, *J* = 3.5 Hz, 2H), 7.18 (ddd, *J* = 8.1, 4.6, 3.5 Hz, 1H), 7.10 (s, 1H), 4.83 (s, 1H), 3.67 (s, 3H), 3.55 (q, *J* = 6.6 Hz, 2H), 2.98 (t, *J* = 6.8 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 164.9, 157.2, 135.9, 134.7, 130.4, 129.1, 126.6, 125.0, 124.2, 123.7, 121.1, 119.4, 112.0, 109.2, 52.2, 41.1, 25.9; **HRMS** calcd. for $C_{19}H_{19}N_2O_4^+$ $[M + H]^+$ 339.1339, found 339.1338.

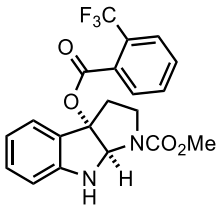
Methyl 3a-((4-(trifluoromethyl)benzoyl)oxy)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (2c)



Purified by silica gel column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3) to an inseparable mixture of indolyl *N*-carboxylate **2c-Int** and pyrroloindoline **2c** (53.1 mg, 12:1, overall 65%) as a pale yellow oil. For characterization, the pure sample of **2c** was obtained as a sole product by the reaction of **1a** at 90 °C (**general procedure H**, Section 3.3).

R_f =0.63 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$, 60:40 mixture of rotamers): δ 8.10 (d, *J* = 8.1 Hz, 2H), 7.67 (d, *J* = 8.1 Hz, 2H), 7.61 and 7.55 (d, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 7.7 Hz, 1H), 6.81 (q, *J* = 6.9 Hz, 1H), 6.69 (d, *J* = 7.9 Hz, 1H), 5.77 (s, 1H), 3.94 and 3.82 (t, *J* = 9.6 Hz, 1H), 3.80 and 3.73 (s, 3H), 3.26 – 3.20 (m, 1H), 3.09 and 2.99 (dd, *J* = 12.6, 5.9 Hz, 1H), 2.71 (q, *J* = 11.2 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 164.3, 155.7, 154.9, 151.1, 150.9, 134.8 (q, *J* = 32.5 Hz), 133.5, 131.4, 130.3, 126.7, 126.2, 125.5 (q, *J* = 4.2 Hz), 123.5 (q, *J* = 272.7 Hz), 119.8, 119.6, 110.6, 110.4, 95.1, 93.8, 80.4, 79.6, 53.0, 52.7, 45.6, 35.8, 35.7; **^{19}F NMR** (471 MHz, $CDCl_3$): δ −63.2; **HRMS** calcd. for $C_{20}H_{18}F_3N_2O_4^+$ $[M + H]^+$ 407.1213, found 407.1206.

Methyl 3a-((2-(trifluoromethyl)benzoyl)oxy)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (2d)

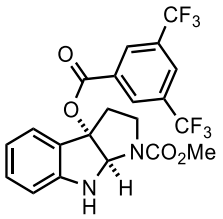


Purified by silica gel column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3) to an inseparable mixture of indolyl *N*-carboxylate **2d-Int** and pyrroloindoline **2d** (49.0 mg, 1:1, overall

60%) as a pale yellow oil. For characterization, the pure sample of **2d** was obtained as a sole product by the reaction of **1a** at 90 °C (**general procedure H**, Section 3.3).

***R*$_f$** =0.50 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$, 60:40 mixture of rotamers): δ 7.74 – 7.68 (m, 2H), 7.62 and 7.58 (d, *J* = 7.5 Hz, 1H), 7.60 – 7.54 (m, 2H), 7.21 (t, *J* = 7.8 Hz, 1H), 6.82 (q, *J* = 7.2 Hz, 1H), 6.68 (d, *J* = 7.9 Hz, 1H), 5.71 and 5.70 (s, 1H), 3.92 and 3.81 (t, *J* = 9.8 Hz, 1H), 3.80 and 3.73 (s, 3H), 3.25 – 3.19 (m, 1H), 3.05 and 2.96 (dd, *J* = 12.9, 6.3 Hz, 1H), 2.78 – 2.69 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 165.6, 155.7, 154.9, 151.1, 150.8, 131.9, 131.5, 131.3, 131.2, 130.7, 128.7 (q, *J* = 32.6 Hz), 126.8 (q, *J* = 5.6 Hz), 126.6, 126.2, 125.5, 125.4, 123.5 (q, *J* = 272.7 Hz), 119.8, 119.5, 110.5, 110.4, 95.5, 94.3, 80.0, 79.3, 53.0, 52.7, 45.6, 35.2, 35.1; **^{19}F NMR** (471 MHz, $CDCl_3$): δ –58.9; **HRMS** calcd. for $C_{20}H_{18}F_3N_2O_4^+$ $[M + H]^+$ 407.1213, found 407.1204.

Methyl 3a-((3,5-bis(trifluoromethyl)benzoyl)oxy)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (2e)

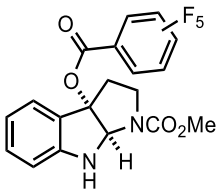


Purified by silica gel column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3) to an inseparable mixture of indolyl *N*-carboxylate **2e-Int** and pyrroloindoline **2e** (45.8 mg, 1:4, overall 48%) as a pale yellow oil. For characterization, the pure sample of **2e** was obtained as a sole product by the reaction of **1a** at 90 °C (**general procedure H**, Section 3.3).

***R*$_f$** =0.70 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$, 60:40 mixture of rotamers): δ 8.54 and 8.42 (s, 2H), 8.11 and 8.05 (s, 1H), 7.60 (dd, *J* = 20.2, 7.6 Hz, 1H), 7.22 (t, *J* = 7.7 Hz, 1H), 6.82 (q, *J* = 7.0 Hz, 1H), 6.71 (d, *J* = 7.9 Hz, 1H), 5.80 and 5.77 (s, 1H), 5.78 (d, *J* = 13.8 Hz, 1H), 3.96 and 3.86 (t, *J* = 9.5 Hz, 1H), 3.82 and 3.74 (s, 3H), 3.24 (tt, *J* = 11.5, 6.0 Hz, 1H), 3.13 and 3.07 (dd, *J* = 12.7, 6.2 Hz, 1H), 2.77 – 2.65 (m, 1H); **^{13}C NMR** (126 MHz,

$CDCl_3$): δ 162.8, 155.7, 154.8, 151.2, 151.0, 132.7, 132.4, 132.35 (q, *J* = 26.0 Hz), 131.7, 130.4, 130.0, 127.0, 126.8, 126.7, 126.4, 125.0, 125.0, 122.93 (q, *J* = 272.9 Hz), 120.0, 119.7, 110.6, 110.5, 95.8, 94.6, 80.4, 79.7, 53.1, 52.8, 45.7, 35.7; **^{19}F NMR** (471 MHz, $CDCl_3$): δ −63.0, −63.0; **HRMS** calcd. for $C_{21}H_{17}F_6N_2O_4^+$ $[M + H]^+$ 475.1087, found 475.1077.

Methyl 3a-((perfluorobenzoyl)oxy)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (2f)

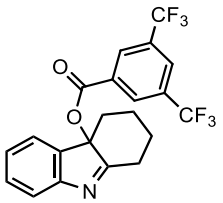


Purified by silica gel column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3) to pyrroloindoline **2f** (45.6 mg, 53%) as a pale yellow oil.

R$_f$ =0.56 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$, 60:40 mixture of rotamers): δ 7.56 and 7.53 (d, *J* = 8.7 Hz, 1H), 7.22 (t, *J* = 7.7 Hz, 1H), 6.83 (q, *J* = 7.2, 6.7 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 5.71 (d, *J* = 3.3 Hz, 1H), 3.92 and 3.82 (t, *J* = 9.7 Hz, 1H), 3.80 and 3.73 (s, 3H), 3.25 – 3.16 (m, 1H), 3.03 and 2.96 (dd, *J* = 12.6, 6.2 Hz, 1H), 2.70 (q, *J* = 10.7 Hz, 1H) ; **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.8, 155.6, 154.8, 151.2, 151.0, 147.2 – 144.0 (dm, *J* = 262.7 Hz), 145.1 – 141.9 (dm, *J* = 260.2 Hz), 139.5 – 136.1 (dm, *J* = 257.6 Hz), 131.7, 126.4, 126.1, 124.8, 124.7, 122.6, 120.5, 120.0, 119.7, 110.7, 110.5, 108.2 (t, *J* = 15.7 Hz), 96.6, 95.4, 80.1, 79.4, 53.0, 52.8, 45.5, 35.7, 35.6; **^{19}F NMR** (376 MHz, $CDCl_3$): δ −139.6 (dp, *J* = 17.0, 5.8 Hz), −149.6 (dtt, *J* = 57.4, 20.7, 4.8 Hz), −161.8 – −162.0 (m); **HRMS** calcd. for $C_{19}H_{14}F_5N_2O_4^+$ $[M + H]^+$ 429.0868, found 429.0873.

2.3.5.2. Characterization data for C3-Acyloxylation compounds

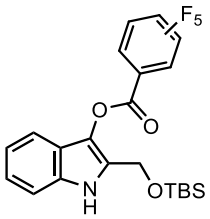
1,2,3,4-Tetrahydro-4aH-carbazol-4a-yl 3,5-bis(trifluoromethyl)benzoate (2g)



Following the **general procedure G**, *N*-hydroxyindole **1s** (86.6mg, 0.463 mmol) afforded indolenine **2i** (85.0 mg, 43%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 9:1).

R_f=0.27 (silica gel, hexanes:EtOAc = 9:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.45 (s, 2H), 8.08 (s, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.43 – 7.40 (m, 2H), 7.20 (t, *J* = 7.5 Hz, 1H), 3.00 (d, *J* = 15.0 Hz, 2H), 2.51 (td, *J* = 13.2, 5.9 Hz, 1H), 2.22 (br d, *J* = 10.9 Hz, 1H), 1.90 (tt, *J* = 13.3, 3.5 Hz, 1H), 1.85 – 1.81 (m, 1H), 1.62 – 1.49 (m, 1H), 1.36 (td, *J* = 14.1, 4.1 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 182.3, 161.7, 154.3, 137.2, 132.6 (q, *J* = 34.2 Hz), 131.7, 130.3, 130.0, 129.9, 126.9 (p, *J* = 3.8 Hz), 126.0, 122.9 (d, *J* = 273.0 Hz), 122.0, 121.2, 87.7, 38.4, 30.0, 28.6, 21.0; **^{19}F NMR** (471 MHz, $CDCl_3$): δ –63.0; **HRMS** calcd. for $C_{12}H_{16}N^+$ $[M + H]^+$ 174.1279, found 174.1277.

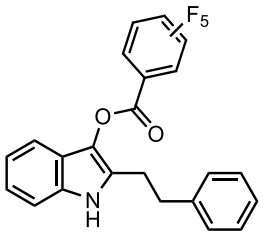
2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1H-indol-3-yl 2,3,4,5,6-pentafluorobenzoate (2h)



Following the **general procedure H for** 16 h, *N*-hydroxyindole **1q** (40.0 mg, 0.144 mmol) afforded indole **2p** (38.7 mg, 57%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 95:5).

R_f=0.52 (silica gel, hexanes:EtOAc = :2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.22 (br s, 1H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.22 (t, *J* = 8.2 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 4.87 (s, 2H), 0.94 (s, 9H), 0.12 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 157.2, 145.8 (dm, *J* = 244.4 Hz), 143.8 (dm, *J* = 261.0 Hz), 138.0 (dm, *J* = 256.0 Hz), 132.9, 127.0, 124.5, 122.8, 120.8, 120.6, 117.5, 111.6, 56.5, 26.0, –5.3; **^{19}F NMR** (376 MHz, $CDCl_3$): δ –137.2 (dt, *J* = 20.3, 6.0 Hz), –147.4 (tt, *J* = 20.9, 4.9 Hz), –159.6 – –159.8 (m); **HRMS** calcd. for $C_{22}H_{23}F_5NO_3Si^+$ [M + H]$^+$ 472.1362, found 472.1365.

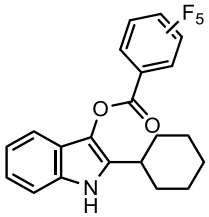
2-Phenethyl-1H-indol-3-yl 2,3,4,5,6-pentafluorobenzoate (2i)



Following the **general procedure H** for 16 h, *N*-hydroxyindole **1p** (27.8 mg, 0.117 mmol) afforded indole **2o** (28.8 mg, 55%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 95:5).

R_f=0.24 (silica gel, hexanes:EtOAc = 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.55 (br s, 1H), 7.41 (d, *J* = 6.6 Hz, 1H), 7.32 – 7.11 (m, 8H), 3.09 – 2.98 (m, 4H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 157.5, 145.7 (dm, *J* = 253.3 Hz), 143.7 (dm, *J* = 253.6 Hz), 140.8, 138.0 (dm, *J* = 255.9 Hz), 132.9, 128.8, 128.6, 127.8, 126.6, 126.2, 122.4, 120.8, 120.5, 117.1, 111.2, 108.5 – 107.5 (m), 35.1, 27.2; **^{19}F NMR** (376 MHz, $CDCl_3$): δ –137.3 (dp, *J* = 17.2, 5.6 Hz), –147.7 (tt, *J* = 20.9, 4.7 Hz), –159.8 (td, *J* = 20.1, 6.1 Hz); **HRMS** calcd. for $C_{23}H_{15}F_5NO_2^+$ [M + H]$^+$ 432.1018, found 432.1021.

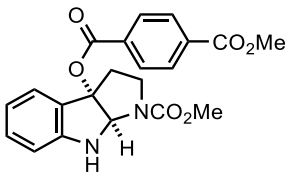
2-Cyclohexyl-1H-indol-3-yl 2,3,4,5,6-pentafluorobenzoate (2j)



Following the **general procedure H** for 16 h, *N*-hydroxyindole **1r** (28.8 mg, 0.134 mmol) afforded indole **2q** (43.3 mg, 76%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 95:5).

R_f=0.45 (silica gel, hexanes:EtOAc = 8:2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.83 (s, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.2 Hz, 1H), 2.85 (tt, *J* = 12.0, 3.5 Hz, 1H), 2.02 (dd, *J* = 12.5, 3.4 Hz, 2H), 1.88 (dt, *J* = 13.1, 3.3 Hz, 2H), 1.79 (dt, *J* = 13.1, 3.4 Hz, 1H), 1.54 – 1.37 (m, 4H), 1.29 (ddt, *J* = 12.3, 8.0, 3.6 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 157.8, 145.6 (dm, *J* = 257.0 Hz), 143.6 (d, *J* = 252.5 Hz), 138.0 (dddd, *J* = 250.9, 15.8, 12.6, 4.8 Hz), 133.1, 132.6, 124.8, 122.2, 121.0, 120.4, 116.9, 111.3, 108.2 (t, *J* = 16.7 Hz), 35.3, 32.2, 26.5, 26.0; **^{19}F NMR** (376 MHz, $CDCl_3$): δ −137.5 (dp, *J* = 16.9, 5.5, 5.1 Hz), −148.0 (tt, *J* = 21.1, 4.8 Hz), −159.7 – −159.9 (m); **HRMS** calcd. for $C_{21}H_{17}F_5NO_2^+$ $[M + H]^+$ 410.1174, found 410.1176.

1-(Methoxycarbonyl)-2,3,8,8a-tetrahydropyrrolo[2,3-b]indol-3a(1H)-yl methyl terephthalate (2k)

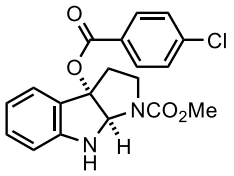


Following the **general procedure G**, *N*-hydroxyindole **1a** (91.2 mg, 0.389 mmol) afforded an inseparable mixture of pyrroloindoline **2j-Int** and indolyl *N*-carboxylate **2j** (122 mg, 2.7:1, overall 79%) as a pale yellow oil after purification by flash column chromatography (silica gel,

hexanes:EtOAc = 1:0 → 7:3). When following the **general procedure H** for 4 h, *N*-hydroxyindole **1a** (71.0 mg, 0.303 mmol) afforded pyrroloindoline **2j** (81.7 mg, 68%) as a sole product.

***R*$_f$** =0.27 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$, 60:40 mixture of rotamers): δ 8.06 (m, 1H), 7.62 and 7.56 (d, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 6.84 – 6.76 (m, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 5.78 (s, 1H), 3.96 – 3.91 and 3.85 – 3.80 (m, 1H), 3.94 (s, 3H), 3.80 and 3.73 (s, 3H), 3.27 – 3.20 (m, 1H), 3.08 and 2.99 (dd, *J* = 12.8, 6.2 Hz, 1H), 2.72 (q, *J* = 10.7 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.3, 164.7, 155.7, 154.9, 151.0, 150.7, 134.3, 134.0, 131.4, 129.9, 129.7, 126.7, 126.2, 125.8, 125.7, 122.4, 119.9, 119.7, 111.3, 110.6, 110.5, 94.9, 93.7, 80.4, 79.6, 53.0, 52.7, 52.6, 45.6, 35.8, 35.7; **HRMS** calcd. for $C_{21}H_{21}N_2O_6^+$ $[M + H]^+$ 397.1394, found 397.1383.

Methyl 3a-((4-chlorobenzoyl)oxy)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (2l)

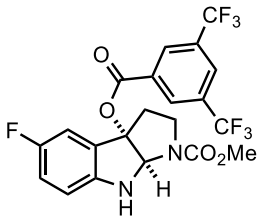


Following the **general procedure G**, *N*-hydroxyindole **1a** (88.0 mg, 0.376 mmol) afforded an inseparable mixture of pyrroloindoline **2k-Int** and indolyl *N*-carboxylate **2k** (109 mg, 7.7:1, overall 78%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3). When following the **general procedure H** for 16 h, *N*-hydroxyindole **1a** (70.9 mg, 0.303 mmol) afforded pyrroloindoline **2k** (68.8 mg, 61%) as a sole product.

***R*$_f$** =0.53 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$, 60:40 mixture of rotamers): δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.61 and 7.54 (d, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.20 (t, *J* = 7.8 Hz, 1H), 6.80 (q, *J* = 6.9 Hz, 1H), 6.68 (d, *J* = 7.9 Hz, 1H), 5.75 (s, 1H), 3.93 and 3.81 (t, *J* = 9.8 Hz, 1H), 3.79 and 3.72 (s, 3H), 3.25 – 3.19 (m, 1H), 3.06 and 2.96 (dd, *J* = 13.0, 6.3 Hz, 0H), 2.73 – 2.65 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 164.6, 155.7, 154.9, 151.0,

150.8, 139.8, 139.8, 131.3, 128.8, 128.7, 128.0, 128.0, 126.7, 126.1, 125.9, 125.7, 119.8, 119.5, 110.5, 110.3, 94.7, 93.5, 80.4, 79.6, 52.9, 52.7, 45.6, 45.6, 35.8, 35.7; **HRMS** calcd. for $C_{19}H_{18}ClN_2O_4^+$ $[M + H]^+$ 373.0950, found 373.0947.

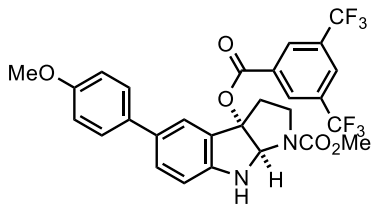
Methyl 3a-((3,5-bis(trifluoromethyl)benzoyl)oxy)-5-fluoro-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (2m)



Following the **general procedure H** for 8 h, *N*-hydroxyindole **1f** (43.0 mg, 0.170 mmol) afforded pyrroloindoline **2l** (52.8 mg, 63%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3).

R_f =0.57 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$, 55:45 mixture of rotamers): δ 8.42 (s, 2H), 8.06 (s, 1H), 7.35 and 7.31 (d, *J* = 8.2 Hz, 1H), 6.94 (t, *J* = 8.8 Hz, 1H), 6.64 and 6.62 (d, *J* = 4.2 Hz, 1H), 5.80 and 5.78 (s, 1H), 5.19 and 4.83 (s, 1H), 3.97 and 3.85 (t, *J* = 9.9 Hz, 1H), 3.81 and 3.74 (s, 3H), 3.29 – 3.21 (m, 1H), 3.11 – 3.01 (m, 1H), 2.73 – 2.65 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 162.8, 157.2 (d, *J* = 237.3 Hz), 157.1 (d, *J* = 237.0 Hz), 155.6, 154.7, 147.3, 147.1, 132.4 (q, *J* = 34.1 Hz), 132.2, 130.0 (d, *J* = 3.9 Hz), 126.8, 126.1 (br t, *J* = 9.4 Hz), 122.9 (q, *J* = 273.1 Hz), 118.4 (d, *J* = 24.0 Hz), 113.8 (d, *J* = 24.9 Hz), 113.5 (d, *J* = 24.6 Hz), 111.3 (d, *J* = 8.1 Hz), 111.2 (d, *J* = 7.8 Hz), 113.3, 111.4, 111.3, 111.2, 95.5, 94.3, 81.1, 80.4, 53.1, 52.8, 45.6, 45.6, 35.7, 31.0; **^{19}F NMR** (376 MHz, $CDCl_3$): δ −63.0, −124.1 (q, *J* = 4.5 Hz), −124.5 (q, *J* = 4.5 Hz); **HRMS** calcd. for $C_{21}H_{16}F_7N_2O_4^+$ $[M + H]^+$ 493.0993, found 493.0990.

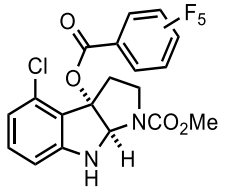
Methyl 3a-((3,5-bis(trifluoromethyl)benzoyl)oxy)-5-(4-methoxyphenyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (2n)



Following the **general procedure F**, *N*-hydroxyindole **1e** (51.0 mg, 0.150 mmol) afforded pyrroloindoline **2m** (47.8 mg, 55%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 8:2).

R_f =0.43 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$, 60:40 mixture of rotamers): δ 8.56 and 8.44 (s, 2H), 8.11 and 8.05 (s, 1H), 7.83 and 7.78 (s, 1H), 7.47 – 7.43 (m, 2H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 8.3 Hz, 1H), 5.86 and 5.83 (s, 1H), 4.00 and 3.88 (t, *J* = 8.2 Hz, 1H), 3.84 and 3.77 (s, 3H), 3.34 – 3.26 (m, 1H), 3.20 and 3.14 (dd, *J* = 12.7, 6.0 Hz, 1H), 2.79 – 2.70 (m, 1H) ; **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.9, 162.9, 158.8, 158.8, 155.8, 154.9, 150.2, 149.9, 133.7, 133.6, 133.2, 132.9, 132.8, 132.4, 132.4 (q, *J* = 34.0 Hz), 132.3 (q, *J* = 34.0 Hz), 130.4, 130.3, 130.2, 130.1, 130.0, 127.7, 126.7, 126.7, 127.1 – 126.8 (m), 126.3, 125.7, 125.6, 125.0, 124.6, 123.0 (q, *J* = 273.1 Hz), 122.91 (q, *J* = 273.1 Hz), 115.1, 114.3, 110.9, 110.7, 95.8, 94.6, 80.7, 80.0, 55.5, 53.2, 52.9, 45.7, 35.8, 35.8; **^{19}F NMR** (376 MHz, $CDCl_3$): δ –62.9, –63.0; **HRMS** calcd. for $C_{28}H_{23}F_6N_2O_5^+$ $[M + H]^+$ 581.1506, found 581.1499.

Methyl 4-chloro-3a-((perfluorobenzoyl)oxy)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (2o)

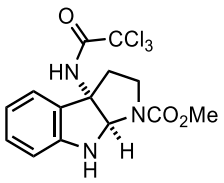


Following the **general procedure F**, *N*-hydroxyindole **1l** (75.0 mg, 0.279 mmol) afforded pyrroloindoline **2n** (58.1 mg, 45%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 8:2).

R_f =0.57 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$, 60:40 mixture of rotamers): δ 7.13 (t, *J* = 7.9 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 5.97 and 5.91 (s, 1H), 5.30 (s, 1H), 3.92 – 3.87 and 3.83 – 3.79 (m, 1H), 3.79 and 3.75 (s, 3H), 3.32 (q, *J* = 9.7 Hz, 1H), 2.88 – 2.72 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.7, 157.6, 155.8, 154.9, 152.2, 152.1, 145.9 (dm, *J* = 257.6 Hz), 143.6 (dm, *J* = 259.0 Hz), 137.8 (ddd, *J* = 256.1, 18.2, 12.4, 5.3 Hz), 132.5, 130.4, 121.9, 120.3, 120.0, 108.7, 108.6, 107.7 (t, *J* = 14.2 Hz), 96.7, 95.6, 79.8, 79.2, 53.0, 52.9, 44.3, 44.2, 35.8, 35.4; **^{19}F NMR** (376 MHz, $CDCl_3$): δ −137.1 (tt, *J* = 20.3, 6.0 Hz, 2F), −147.5 (t, *J* = 20.7 Hz), −147.8 (t, *J* = 20.7 Hz), −160.2 (dtd, *J* = 32.6, 20.2, 6.2 Hz, 2F); **HRMS** calcd. for $C_{19}H_{13}ClF_5N_2O_4^+$ $[M + H]^+$ 463.0479, found 463.0475.

2.3.5.3. Characterization Data for C3-Amidation Compounds

Methyl 3a-(2,2,2-trichloroacetamido)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (3a)

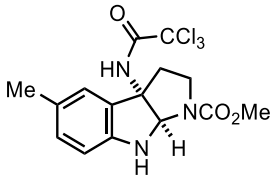


Following the **general procedure I**, *N*-hydroxyindole **1a** (133 mg, 0.568 mmol) afforded pyrroloindoline **3a** (168 mg, 78%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3).

R_f =0.51 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$, 60:40 mixture of rotamers): δ 7.34 and 7.30 (d, *J* = 7.5 Hz, 1H), 7.23 – 7.19 (m, 1H), 6.88 – 6.80 (m, 2H), 6.68 (d, *J* = 7.3 Hz, 1H), 5.70 and 5.68 (s, 1H), 3.88 and 3.78 (t, *J* = 9.9 Hz, 1H), 3.77 and 3.70 (s, 3H), 3.16 – 3.08 (m, 1H), 3.01 – 2.91 (m, 1H), 2.50 and 2.41 (dd, *J* = 12.5, 6.5 Hz, 1H); **^{13}C NMR**

(101 MHz, $CDCl_3$): δ 161.0, 155.5, 154.6, 149.9, 149.7, 131.1, 131.1, 127.0, 126.8, 123.8, 123.5, 120.0, 119.8, 110.5, 110.4, 92.3, 78.3, 78.2, 72.0, 70.9, 52.9, 52.6, 45.4, 45.3, 33.0; **HRMS** calcd. for $C_{14}H_{15}Cl_3N_3O_3^+$ $[M + H]^+$ 378.0174, found 378.0173.

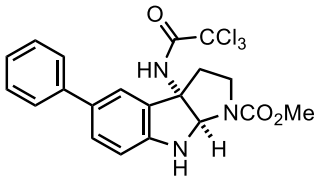
Methyl 5-methyl-3a-(2,2,2-trichloroacetamido)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (3b)



Following the **general procedure I,** *N*-hydroxyindole **1b** (72.0 mg, 0.290 mmol) afforded pyrroloindoline **3b** (77.2 mg, 68%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3).

R_f =0.56 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$, 55:45 mixture of rotamers): δ 7.14 and 7.10 (s, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.80 and 6.76 (s, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 5.69 and 5.67 (s, 1H), 3.89 and 3.77 (t, *J* = 9.7 Hz, 1H), 3.77 and 3.70 (s, 3H), 3.12 (tt, *J* = 10.9, 6.8 Hz, 1H), 3.01 – 2.91 (m, 1H), 2.47 and 2.39 (dd, *J* = 12.4, 6.1 Hz, 1H), 2.30 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 161.0, 155.6, 154.7, 147.7, 147.5, 131.8, 131.7, 129.7, 129.5, 127.2, 127.0, 124.2, 123.9, 110.7, 110.5, 92.3, 78.5, 72.1, 71.0, 52.9, 52.6, 45.5, 45.3, 32.7, 32.6, 21.0; **HRMS** calcd. for $C_{15}H_{17}Cl_3N_3O_3^+$ $[M + H]^+$ 392.0330, found 392.0330.

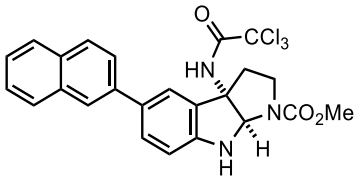
Methyl 5-phenyl-3a-(2,2,2-trichloroacetamido)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (3c)



Following the **general procedure J,** *N*-hydroxyindole **1c** (35.6 mg, 0.115 mmol) afforded pyrroloindoline **3c** (26.1 mg, 50%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3).

R_f =0.44 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$, 60:40 mixture of rotamers): δ 7.57 and 7.52 (s, 1H), 7.53 (d, *J* = 7.5 Hz, 2H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 1H), 6.87 and 6.84 (s, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 5.76 and 5.74 (s, 1H), 3.94 and 3.83 (t, *J* = 9.6 Hz, 1H), 3.80 and 3.72 (s, 3H), 3.20 (tt, *J* = 11.0, 5.6 Hz, 1H), 3.00 (dq, *J* = 21.9, 10.9 Hz, 1H), 2.57 and 2.49 (dd, *J* = 12.5, 6.5 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 161.2, 155.6, 154.7, 149.3, 149.2, 140.9, 140.8, 133.7, 133.5, 130.3, 130.2, 129.0, 127.9, 127.7, 126.9, 126.7, 122.5, 122.2, 110.9, 110.7, 92.3, 78.7, 72.1, 71.0, 53.0, 52.7, 45.5, 45.4, 33.0; **HRMS** calcd. for $C_{20}H_{19}Cl_3N_3O_3^+$ $[M + H]^+$ 454.0487, found 454.0487.

Methyl 5-(naphthalen-2-yl)-3a-(2,2,2-trichloroacetamido)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (3d)

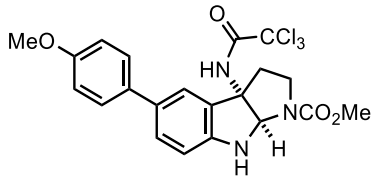


Following the **general procedure J**, *N*-hydroxyindole **1d** (47.2 mg, 0.131 mmol) afforded pyrroloindoline **3d** (29.7 mg, 45%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3).

R_f =0.41 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, MeOD, 60:40 mixture of rotamers): δ 7.98 (s, 1H), 7.87 (d, *J* = 8.2 Hz, 2H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.76 – 7.70 (m, 2H), 7.58 (d, *J* = 8.3 Hz, 1H), 7.44 (dt, *J* = 19.7, 7.1 Hz, 2H), 6.78 (d, *J* = 8.2 Hz, 1H), 5.84 and 5.83 (s, 1H), 3.83 (t, *J* = 10.3 Hz, 1H).3.80 and 3.74 (s, 3H), 3.22 (td, *J* = 10.9, 10.4, 6.9 Hz, 1H), 2.80 – 2.60 (m, 2H); **^{13}C NMR** (126 MHz, MeOD): δ 163.5, 157.2, 156.9, 151.4, 140.0, 135.4, 133.7, 133.5, 133.4, 130.4, 130.0, 129.9, 129.3, 129.0, 128.6, 127.2, 126.5, 126.2, 125.3, 123.7, 123.6,

111.3, 111.1, 93.9, 81.2, 80.7, 73.8, 72.8, 53.4, 53.2, 46.1, 46.0, 37.0, 36.6; **HRMS** calcd. for $C_{24}H_{21}Cl_3N_3O_3^+$ $[M + H]^+$ 504.0643, found 504.0648.

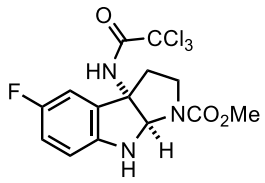
Methyl 5-(4-methoxyphenyl)-3a-(2,2,2-trichloroacetamido)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (3e)



Following the **general procedure I,** *N*-hydroxyindole **1e** (40.0 mg, 0.118 mmol) afforded pyrroloindoline **3e** (37.6 mg, 68%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3).

R_f =0.24 (silica gel, hexanes:EtOAc = 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$, 60:40 mixture of rotamers): δ 7.52 (s, 1H), 7.48 – 7.40 (m, 4H), 6.96 (d, *J* = 8.2 Hz, 2H), 6.87 and 6.84 (s, 1H), 6.74 (d, *J* = 8.2 Hz, 1H), 5.75 and 5.73 (s, 1H), 3.92 and 3.86 (t, *J* = 8.8 Hz, 1H), 3.84 (s, 3H), 3.79 and 3.72 (s, 3H), 3.20 (td, *J* = 10.2, 5.5 Hz, 1H), 3.00 (tt, *J* = 19.2, 9.8 Hz, 1H), 2.56 and 2.48 (dd, *J* = 12.4, 6.4 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 161.1, 158.9, 155.6, 154.7, 148.9, 148.7, 133.5, 133.5, 133.4, 133.2, 129.8, 129.8, 128.4, 127.8, 127.7, 122.0, 121.8, 114.4, 110.9, 110.7, 92.3, 78.6, 72.1, 71.0, 55.5, 53.0, 52.7, 45.5, 45.4, 33.0; **HRMS** calcd. for $C_{21}H_{21}Cl_3N_3O_4^+$ $[M + H]^+$ 484.0592, found 484.0595.

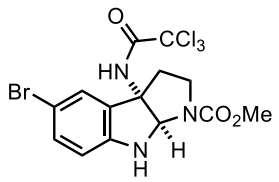
Methyl 5-fluoro-3a-(2,2,2-trichloroacetamido)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (3f)



Following the **general procedure J,** *N*-hydroxyindole **1f** (68.4 mg, 0.271 mmol) afforded pyrroloindoline **3f** (55.9 mg, 52%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 6:4).

***R*$_f$** =0.30 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$, 60:40 mixture of rotamers): δ 7.09 and 7.04 (dd, *J* = 7.9, 2.6 Hz, 1H), 6.94 – 6.85 (m, 2H), 6.62 (dd, *J* = 8.9, 4.2 Hz, 1H), 5.69 and 5.66 (s, 1H), 3.89 and 3.79 (t, *J* = 9.7 Hz, 1H), 3.77 and 3.70 (s, 3H), 3.16 (td, *J* = 10.7, 6.4 Hz, 1H), 2.93 – 2.80 (m, 1H), 2.55 and 2.45 (dd, *J* = 12.7, 6.5 Hz,1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 161.2, 160.2, 157.4 (d, *J* = 238.1 Hz), 157.3 (d, *J* = 238.1 Hz), 157.2, 155.5, 154.7, 146.0, 145.9, 128.2 (d, *J* = 7.6 Hz), 128.1 (d, *J* = 7.5 Hz), 117.7 (d, *J* = 22.5 Hz), 117.6 (d, *J* = 22.5 Hz), 111.3, 111.2 (d, *J* = 24.2 Hz), 110.8 (d, *J* = 24.2 Hz), 92.2, 79.6, 78.6, 72.1, 71.0, 53.0, 52.7, 45.4, 45.3, 33.6, 33.5; **^{19}F NMR** (376 MHz, $CDCl_3$): δ –123.6 (q, *J* = 8.1 Hz), –123.9 (td, *J* = 8.5, 4.1 Hz); **HRMS** calcd. for $C_{14}H_{14}Cl_3FN_3O_3^+$ $[M + H]^+$ 396.0079, found 396.0081.

Methyl 5-bromo-3a-(2,2,2-trichloroacetamido)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (3g)

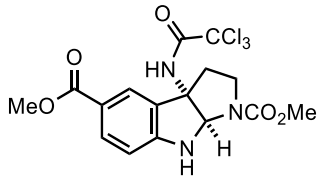


Following the **general procedure J,** *N*-hydroxyindole **1g** (63.1 mg, 0.201 mmol) afforded pyrroloindoline **3g** (58.0 mg, 63%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 6:4).

***R*$_f$** =0.35 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$, 60:40 mixture of rotamers): δ 7.45 and 7.40 (s, 1H), 7.31 (d, *J* = 6.2 Hz, 1H), 6.82 and 6.80 (s, 1H), 6.57 (d, *J* = 8.3 Hz, 1H), 5.70 and 5.67 (s, 1H), 5.29 and 4.88 (s, 1H), 3.90 and 3.80 (t, *J* = 9.6 Hz, 1H), 3.78 and 3.71 (s, 3H), 3.16 (td, *J* = 10.8, 6.5 Hz, 1H), 2.91 (ddd, *J* = 24.2, 13.1, 9.3 Hz, 1H), 2.50 and 2.42 (dd, *J* = 13.0, 6.4 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 161.2, 155.6, 154.6, 149.0, 134.0,

129.2, 129.0, 126.9, 126.7, 112.1, 111.9, 111.1, 92.2, 78.9, 78.0, 71.9, 70.7, 53.1, 52.8, 45.4, 45.3, 33.5, 33.4; **HRMS** calcd. for $C_{14}H_{14}BrCl_3N_3O_3^+$ $[M + H]^+$ 455.9279, found 455.9282.

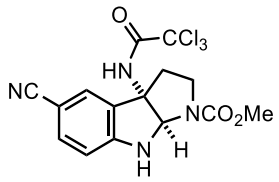
Dimethyl 3a-(2,2,2-trichloroacetamido)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1,5(2H)-dicarboxylate (3h)



Following the **general procedure J**, *N*-hydroxyindole **1h** (32.9 mg, 0.113 mmol) afforded pyrroloindoline **3h** (25.1 mg, 51%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 6:4).

R_f =0.30 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$, 60:40 mixture of rotamers): δ 8.00 and 7.98 (s, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 6.76 (s, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 5.80 and 5.79 (s, 1H), 3.92 and 3.81 (t, *J* = 9.8 Hz, 1H), 3.88 (s, 3H), 3.79 and 3.72 (s, 3H), 3.15 (td, *J* = 10.6, 7.0 Hz, 1H), 30.4 – 2.90 (m, 1H), 2.48 and 2.43 (dd, *J* = 12.8, 6.9 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 166.8, 161.1, 155.6, 154.5, 153.8, 153.6, 134.0, 126.9, 126.7, 125.8, 125.6, 121.6, 121.3, 109.2, 109.0, 92.2, 78.3, 71.5, 70.4, 53.1, 52.8, 52.1, 45.3, 45.2, 33.4, 33.4; **HRMS** calcd. for $C_{16}H_{17}Cl_3N_3O_5^+$ $[M + H]^+$ 436.0228, found 436.0227.

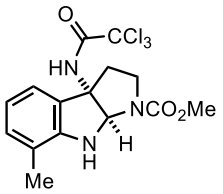
Methyl 5-cyano-3a-(2,2,2-trichloroacetamido)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (3i)



Following the **general procedure J**, *N*-hydroxyindole **1i** (30.1 mg, 0.116 mmol) afforded pyrroloindoline **3i** (25.8 mg, 55%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 1:1).

***R*$_f$** =0.22 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$, 60:40 mixture of rotamers): δ 7.61 and 7.55 (s, 1H), 7.49 (d, *J* = 8.3 Hz, 1H), 6.92 (s, 1H), 6.67 (d, *J* = 8.3 Hz, 1H), 5.78 and 5.75 (s, 1H), 3.93 and 3.83 (t, *J* = 9.8 Hz, 1H), 3.79 and 3.73 (s, 3H), 3.19 (td, *J* = 10.6, 6.5 Hz, 1H), 2.89 – 2.75 (m, 1H), 2.56 and 2.47 (dd, *J* = 12.9, 6.4 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 161.3, 155.6, 154.4, 153.1, 153.0, 136.0, 128.1, 127.9, 127.8, 119.6, 109.9, 109.7, 102.0, 101.7, 92.1, 79.2, 78.4, 71.5, 70.3, 53.2, 52.9, 45.1, 34.9, 34.7; **HRMS** calcd. for $C_{15}H_{14}Cl_3N_4O_3^+$ $[M + H]^+$ 403.0126, found 403.0125.

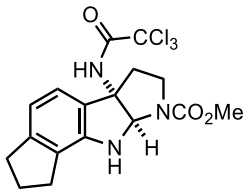
Methyl 7-methyl-3a-(2,2,2-trichloroacetamido)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (3j)



Following the **general procedure I**, *N*-hydroxyindole **1j** (57.0 mg, 0.230 mmol) afforded pyrroloindoline **3j** (42.3 mg, 47%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3).

***R*$_f$** =0.44 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$, 60:40 mixture of rotamers): δ 7.18 and 7.14 (d, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 7.4 Hz, 1H), 6.81 – 6.76 (m, 2H), 5.75 and 5.73 (s, 1H), 5.09 and 4.64 (s, 1H), 3.89 and 3.79 (t, *J* = 9.6 Hz, 1H), 3.79 and 3.71 (s, 3H), 3.13 (qd, *J* = 10.7, 6.3 Hz, 1H), 3.03 – 2.91 (m, 1H), 2.46 and 2.38 (dd, *J* = 12.2, 6.1 Hz, 1H), 2.16 and 2.15 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 161.0, 155.6, 154.8, 148.6, 148.5, 132.0, 131.9, 126.4, 126.1, 121.0, 120.8, 120.3, 120.1, 120.0, 119.9, 92.3, 78.1, 72.5, 71.4, 53.0, 52.6, 45.5, 45.3, 33.0, 32.9, 16.8; **HRMS** calcd. for $C_{15}H_{17}Cl_3N_3O_3^+$ $[M + H]^+$ 392.0330, found 392.0330.

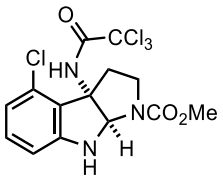
Methyl 5b-(2,2,2-trichloroacetamido)-1,2,3,5b,6,7,8a,9-octahydro-8H-cyclopenta[g]pyrrolo[2,3-b]indole-8-carboxylate (3k)



Following the **general procedure I**, *N*-hydroxyindole **1k** (41.0 mg, 0.149 mmol) afforded pyrroloindoline **3k** (34.4 mg, 55%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3).

R_f =0.48 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$, 60:40 mixture of rotamers): δ 7.12 and 7.09 (d, *J* = 7.6 Hz, 1H), 6.77 – 6.74 (m, 2H), 5.75 and 5.74 (s, 1H), 5.06 and 4.60 (s, 1H), 3.89 and 3.79 (t, *J* = 9.6 Hz, 1H), 3.79 and 3.71 (s, 3H), 3.19 – 3.09 (m, 1H), 3.00 (dtd, *J* = 20.0, 11.6, 8.6 Hz, 1H), 2.88 (m, 2H), 2.72 (m, 2H), 2.43 and 2.36 (dd, *J* = 12.1, 6.6 Hz, 1H), 2.11 (h, *J* = 7.4 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 161.0, 160.9, 155.6, 154.8, 148.5, 146.1, 145.9, 125.8, 125.6, 124.7, 124.5, 121.4, 121.2, 116.2, 115.9, 92.4, 78.6, 72.3, 71.2, 53.0, 52.6, 45.5, 45.4, 33.1, 32.9, 32.8, 29.5, 25.5, 25.4; **HRMS** calcd. for $C_{17}H_{19}Cl_3N_3O_3^+$ [M + H]$^+$ 418.0487, found 418.0494.

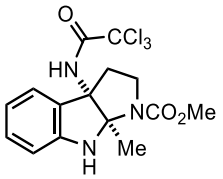
Methyl 4-chloro-3a-(2,2,2-trichloroacetamido)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (3l)



Following the **general procedure J**, *N*-hydroxyindole **1l** (31.7 mg, 0.118 mmol) afforded pyrroloindoline **3l** (27.8 mg, 57%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 6:4).

R_f =0.41 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$, 60:40 mixture of rotamers): δ 7.12 (t, *J* = 8.0 Hz, 1H), 1.12 and 7.07 (s, 1H), 6.74 (dd, *J* = 7.9, 3.6 Hz, 1H), 6.55 (d, *J* = 8.0 Hz, 1H), 5.87 and 5.86 (s, 1H), 5.35 and 4.99 (s, 1H), 3.95 – 3.91 and 3.86 – 3.82 (m, 1H), 3.78 and 3.73 (s, 3H), 3.24 (q, *J* = 8.4 Hz, 1H), 2.80 (dd, *J* = 8.6, 5.9 Hz, 1H), 2.84 – 2.78 and 2.71 – 2.65 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 161.0, 160.8, 155.7, 154.7, 151.9, 151.8, 132.3, 130.3, 130.2, 122.9, 122.6, 120.2, 119.9, 108.7, 108.5, 92.4, 78.5, 77.9, 73.0, 71.8, 53.0, 52.8, 44.8, 33.8, 31.1; **HRMS** calcd. for $C_{14}H_{14}Cl_4N_3O_3^+$ $[M + H]^+$ 411.9784, found 411.9789.

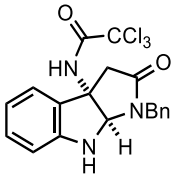
Methyl 8a-methyl-3a-(2,2,2-trichloroacetamido)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (3m)



Following the **general procedure I**, *N*-hydroxyindole **1m** (27.0 mg, 0.109 mmol) afforded pyrroloindoline **3m** (22.4 mg, 52%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3).

R_f =0.63 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$, 60:40 mixture of rotamers): δ 7.44 (d, *J* = 7.5 Hz, 1H), 7.18 (t, *J* = 7.7 Hz, 1H), 6.84 – 6.81 (m, 2H), 6.68 (d, *J* = 7.9 Hz, 1H), 5.87 (s, 1H), 3.64 (s, 3H), 3.09 – 3.03 (m, 1H), 2.95 (dd, *J* = 12.9, 6.6 Hz, 1H), 2.85 – 2.78 (m, 1H), 1.75 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 161.2, 154.8, 148.9, 130.7, 128.2, 124.6, 120.2, 110.8, 87.1, 71.5, 52.3, 45.5, 30.3, 19.5; **HRMS** calcd. for $C_{15}H_{17}Cl_3N_3O_3^+$ $[M + H]^+$ 392.0330, found 392.0333.

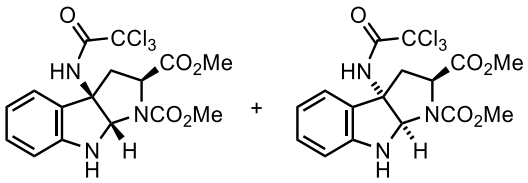
***N*-(1-Benzyl-2-oxo-2,3,8,8a-tetrahydropyrrolo[2,3-b]indol-3a(1H)-yl)-2,2,2-trichloroacetamide (3n)**



Following the **general procedure I**, *N*-hydroxyindole **1n** (95.1 mg, 0.339 mmol) afforded pyrroloindoline **3n** (87.8 mg, 61%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3).

R_f =0.50 (silica gel, hexanes:EtOAc = 6:4); **^{1}H NMR** (400 MHz, $CDCl_3$, 60:40 mixture of rotamers): δ 7.39 – 7.27 (m, 6H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.76 (s, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 5.43 and 5.42 (s, 1H), 4.95 (d, *J* = 15.4 Hz, 1H), 4.38 (d, *J* = 3.7 Hz, 1H), 4.31 (d, *J* = 15.4 Hz, 1H), 3.51 (d, *J* = 16.9 Hz, 1H), 3.03 (d, *J* = 16.8 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 170.6, 161.1, 148.4, 135.7, 131.6, 129.7, 129.1, 128.0, 127.8, 123.9, 121.7, 112.7, 92.0, 78.7, 65.3, 43.8, 40.1; **HRMS** calcd. for $C_{19}H_{17}Cl_3N_3O_2^+$ $[M + H]^+$ 424.0381, found 424.0383.

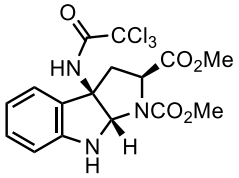
Dimethyl (2S)-3a-(2,2,2-trichloroacetamido)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1,2(2H)-dicarboxylate (3o)



3o-1 **3o-2**

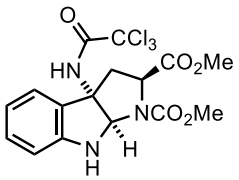
Following the **general procedure I**, *N*-hydroxyindole **1o** (108 mg, 0.369 mmol) afforded pyrroloindoline **3o** (77.4 mg, 48%, **3o-1**: **3o-2** = 1.3:1) as a pale yellow oil after purification by flash column chromatography (silica gel, CH_2Cl_2:acetone = 1:0 → 97:3). Both diastereomers were separated by preparative thin layer chromatography (silica gel, CH_2Cl_2:acetone = 95:5) and characterized respectively.

Dimethyl (2S,3aR,8aS)-3a-(2,2,2-trichloroacetamido)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1,2(2H)-dicarboxylate (3o-1)



***R**f* =0.72 (silica gel, CH_2Cl_2:acetone = 95:5); **^{1}H NMR** (500 MHz, $CDCl_3$, 60:40 mixture of rotamers): δ 7.39 and 7.30 (d, *J* = 7.5 Hz, 1H), 7.21 (q, *J* = 7.5 Hz, 1H), 7.05 and 6.93 (s, 1H), 6.84 (t, *J* = 7.4 Hz, 1H), 6.69 (t, *J* = 8.2 Hz, 1H), 5.86 and 5.79 (s, 1H), 5.45 and 5.00 (s, 1H), 4.37 and 4.30 (dd, *J* = 8.2, 5.8 Hz, 1H), 3.81 and 3.68 (s, 3H), 3.78 (s, 3H), 3.03 and 2.77 (dd, *J* = 13.5, 6.2 Hz, 1H), 2.96 – 2.88 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 172.2, 161.2, 155.3, 154.8, 148.7, 148.3, 131.0, 130.9, 127.6, 127.4, 124.0, 123.3, 120.3, 120.2, 110.9, 110.7, 92.2, 80.9, 80.5, 71.2, 69.8, 59.5, 59.1, 53.4, 53.0, 52.9, 52.9, 38.4, 37.8; **HRMS** calcd. for $C_{16}H_{17}Cl_3N_3O_5^+$ $[M + H]^+$ 436.0228, found 436.0240.

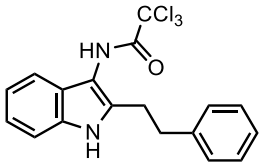
Dimethyl (2S,3aS,8aR)-3a-(2,2,2-trichloroacetamido)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1,2(2H)-dicarboxylate (3o-2)



***R**f*=0.70 (silica gel, CH_2Cl_2:acetone = 95:5); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.25 – 7.19 (m, 2H), 6.80 (dt, *J* = 14.9, 7.4 Hz, 1H), 6.74 – 6.65 (m, 1H), 5.77 (s, 1H), 4.75 and 4.63 (d, *J* = 9.3 Hz, 1H), 3.83 and 3.71 (s, 3H), 3.44 and 3.39 (dd, *J* = 12.8, 9.4 Hz, 1H), 3.22 and 3.21 (s, 3H), 2.79 (t, *J* = 12.1 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.2, 171.1, 161.2, 161.2, 155.2, 154.6, 150.8, 150.5, 131.8, 131.7, 126.0, 125.9, 124.1, 124.1, 119.9, 119.6, 110.6, 92.2, 78.3, 70.9, 69.7,

59.2, 59.0, 53.3, 53.0, 52.4, 36.2, 35.7; **HRMS** calcd. for $C_{16}H_{17}Cl_3N_3O_5^+$ $[M + H]^+$ 436.0228, found 436.0240.

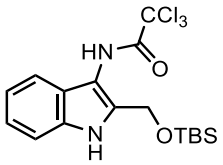
2,2,2-Trichloro-*N*-(2-phenethyl-1H-indol-3-yl)acetamide (3p)



Following the **general procedure J**, *N*-hydroxyindole **1p** (38.0 mg, 0.160 mmol) afforded indole **3p** (32.4 mg, 53%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 9:1).

R_f=0.27 (silica gel, hexanes:EtOAc = 9:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.78 (br s, 1H), 7.54 (s, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.29 – 7.22 (m, 3H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.14 – 7.11 (m, 3H), 3.01 (dq, *J* = 11.2, 6.0 Hz, 4H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 161.5, 140.8, 134.1, 133.9, 128.9, 128.7, 126.8, 124.3, 122.5, 120.6, 117.4, 111.1, 108.7, 92.9, 35.3, 28.2; **HRMS** calcd. for $C_{18}H_{16}Cl_3N_2O^+$ $[M + H]^+$ 381.0323, found 381.0323.

***N*-(2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1H-indol-3-yl)-2,2,2-trichloroacetamide (3q)**

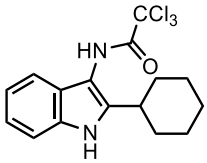


Following the **general procedure J**, *N*-hydroxyindole **1q** (89.8 mg, 0.324 mmol) afforded indole **3q** (62.8 mg, 46%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 9:1).

R_f=0.25 (silica gel, hexanes:EtOAc = 9:1); **^{1}H NMR** (500 MHz, MeOD): δ 7.39 (t, *J* = 8.3 Hz, 2H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 4.81 (s, 2H), 0.93 (s, 9H), 0.10 (s, 6H); **^{13}C**

NMR (126 MHz, MeOD): δ 164.0, 136.1, 134.0, 125.1, 123.0, 120.5, 118.6, 112.5, 109.3, 79.3, 57.9, 26.4, −5.2; **HRMS** calcd. for $C_{17}H_{24}Cl_3N_2O_2Si^+$ $[M + H]^+$ 421.0667, found 421.0682.

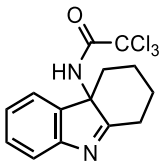
2,2,2-Trichloro-*N*-(2-cyclohexyl-1H-indol-3-yl)acetamide (3r)



Following the **general procedure J**, *N*-hydroxyindole **1r** (26.2 mg, 0.122 mmol) afforded indole **3r** (19.3 mg, 44%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 9:1).

R_f=0.26 (silica gel, hexanes:EtOAc = 9:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.92 (s, 1H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.19 – 7.12 (m, 2H), 2.82 (tt, *J* = 11.9, 3.5 Hz, 1H), 2.04 (d, *J* = 12.4 Hz, 2H), 1.88 (dt, *J* = 12.8, 3.2 Hz, 2H), 1.79 (d, *J* = 13.2 Hz, 1H), 1.51 – 1.38 (m, 4H), 1.33 – 1.24 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 161.6, 139.7, 133.6, 133.5, 124.7, 123.5, 122.3, 120.9, 120.6, 118.1, 117.1, 111.5, 111.2, 106.6, 56.9, 35.9, 32.4, 32.2, 26.6, 26.1, 25.6, 16.4; **HRMS** calcd. for $C_{16}H_{18}Cl_3N_2O^+$ $[M + H]^+$ 359.0479, found 359.0480.

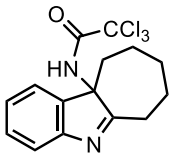
2,2,2-Trichloro-*N*-(1,2,3,4-tetrahydro-4aH-carbazol-4a-yl)acetamide (3s)



Following the **general procedure I**, *N*-hydroxyindole **1s** (126 mg, 0.673 mmol) afforded indolenine **3s** (129 mg, 58%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 1:1).

R_f=0.29 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.7 Hz, 1H), 7.41 – 7.36 (m, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 6.97 (s, 1H), 2.97 (d, *J* = 12.9 Hz, 1H), 2.70 (dd, *J* = 14.5, 2.8 Hz, 1H), 2.50 (td, *J* = 13.1, 5.7 Hz, 1H), 2.25 – 2.20 (m, 1H), 1.80 – 1.70 (m, 3H), 1.58 – 1.47 (m, 3H), 1.35 – 1.25 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 182.7, 160.1, 154.3, 139.1, 129.6, 126.0, 121.4, 121.0, 92.0, 67.9, 39.0, 29.5, 28.7, 21.1; **HRMS** calcd. for $C_{14}H_{14}Cl_3N_2O^+$ $[M + H]^+$ 331.0166, found 331.0167.

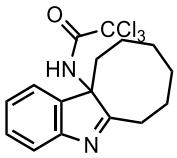
2,2,2-Trichloro-*N*-(7,8,9,10-tetrahydrocyclohepta[b]indol-10a(6H)-yl)acetamide (3t)



Following the **general procedure I**, *N*-hydroxyindole **1t** (105 mg, 0.523 mmol) afforded indolenine **3t** (136 mg, 75%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 1:1).

R_f=0.25 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 7.7 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.25 – 7.17 (m, 2H), 7.11 (s, 1H), 3.09 – 3.01 (m, 1H), 2.85 (dt, *J* = 17.2, 5.2 Hz, 1H), 2.37 (dt, *J* = 14.9, 3.8 Hz, 1H), 1.97 – 1.40 (m, 7H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 184.6, 159.7, 153.4, 139.9, 129.5, 126.2, 120.6, 120.5, 92.1, 71.8, 37.2, 32.5, 28.4, 26.0, 24.8; **HRMS** calcd. for $C_{15}H_{16}Cl_3N_2O^+$ $[M + H]^+$ 345.0323, found 345.0324.

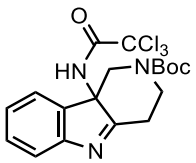
2,2,2-Trichloro-*N*-(6,7,8,9,10,11-hexahydro-11aH-cycloocta[b]indol-11a-yl)acetamide (3u)



Following the **general procedure I**, *N*-hydroxyindole **1u** (99.4 mg, 0.462 mmol) afforded indolenine **3u** (108 mg, 65%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 1:1).

***R*$_f$**=0.38 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 7.7 Hz, 1H), 7.37 (t, *J* = 7.3 Hz, 1H), 7.26 – 7.19 (m, 2H), 6.94 (s, 1H), 2.87 – 2.80 (m, 2H), 2.65 (ddd, *J* = 13.9, 8.3, 5.5 Hz, 1H), 2.43 – 2.37 (m, 1H), 2.19 – 2.14 (m, 1H), 2.08 – 1.92 (m, 2H), 1.63 – 1.42 (m, 5H), 1.02 – 0.93 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 184.8, 159.6, 154.2, 138.1, 129.7, 126.3, 121.1, 120.6, 92.0, 70.9, 34.3, 29.7, 27.4, 27.2, 24.7, 20.9; **HRMS** calcd. for $C_{16}H_{18}Cl_3N_2O^+$ $[M + H]^+$ 359.0479, found 359.0477.

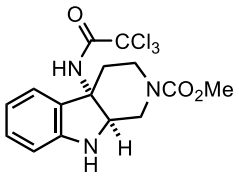
***tert*-Butyl 9b-(2,2,2-trichloroacetamido)-1,3,4,9b-tetrahydro-2H-pyrido[4,3-b]indole-2-carboxylate (3v)**



Following the **general procedure I**, *N*-hydroxyindole **1v** (121 mg, 0.420 mmol) afforded indolenine **3v** (87.2 mg, 48%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 6:4).

***R*$_f$**=0.36 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.38 (br s, 1H), 7.64 (d, *J* = 7.7 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.38 (d, *J* = 7.3 Hz, 1H), 7.26 (t, *J* = 7.3 Hz, 1H), 5.00 (d, *J* = 14.6 Hz, 1H), 4.51 (dd, *J* = 13.8, 5.9 Hz, 1H), 2.95 – 2.83 (m, 2H), 2.69 (td, *J* = 12.2, 6.2 Hz, 1H), 2.22 (d, *J* = 14.1 Hz, 1H), 1.54 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 179.0, 160.8, 157.0, 154.7, 135.1, 130.2, 126.4, 121.7, 121.5, 91.5, 82.3, 70.6, 53.8, 46.9, 30.9, 28.5; **HRMS** calcd. for $C_{18}H_{21}Cl_3N_3O_3^+$ $[M + H]^+$ 432.0643, found 432.0641.

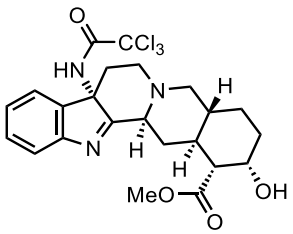
Methyl 4a-(2,2,2-trichloroacetamido)-1,3,4,4a,9,9a-hexahydro-2H-pyrido[3,4-b]indole-2-carboxylate (3w)



Following the **general procedure I**, *N*-hydroxyindole **1w** (50.6 mg, 0.205 mmol) afforded corresponding pyrroloindoline, which was then subsequently reduced due to its lability to afford indoline **3w** (32.2 mg, 40% for 2 steps) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 7:3).

***R**f*=0.25 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.31 (d, *J* = 7.6 Hz, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 6.83 (t, *J* = 7.4 Hz, 1H), 6.72 (d, *J* = 7.9 Hz, 1H), 4.84 (s, 1H), 3.88 (d, *J* = 10.4 Hz, 1H), 3.80 (d, *J* = 10.4 Hz, 1H), 3.64 (s, 3H), 3.35 – 3.11 (m, 2H), 2.55 – 2.49 (m, 1H), 2.30 – 2.23 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 161.1, 157.2, 150.7, 130.3, 129.0, 123.1, 119.6, 110.9, 92.7, 65.0, 58.1, 52.3, 37.1, 36.7, 31.1; **HRMS** calcd. for $C_{15}H_{17}Cl_3N_3O_3^+$ $[M + H]^+$ 392.0330, found 392.0325.

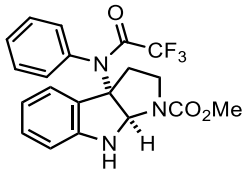
Methyl (1R,2S,4aR,8aS,13bS,14aS)-2-hydroxy-8a-(2,2,2-trichloroacetamido)-1,2,3,4,4a,5,7,8,8a,13b,14,14a-dodecahydroindolo[2',3':3,4]pyrido[1,2-b]isoquinoline-1-carboxylate (3x)



Following the **general procedure I**, *N*-hydroxyindole **1x** (40.0 mg, 0.108 mmol) afforded indolenine **3x** (24.5 mg, 44%) as a pale yellow oil after purification by flash column chromatography (silica gel, CH_2Cl_2:MeOH = 1:0 → 9:1).

***R*$_f$**=0.30 (silica gel, CH_2Cl_2:MeOH = 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 7.6 Hz, 1H), 7.43 – 7.37 (m, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 6.89 (s, 1H), 4.19 (s, 1H), 3.77 (s, 3H), 3.15 (s, 1H), 2.94 (ddd, *J* = 20.8, 10.9, 3.0 Hz, 2H), 2.83 (d, *J* = 12.0 Hz, 1H), 2.68 (d, *J* = 14.5 Hz, 1H), 2.60 (t, *J* = 12.9 Hz, 1H), 2.38 (d, *J* = 11.1 Hz, 1H), 2.18 (t, *J* = 10.8 Hz, 1H), 2.12 – 2.07 (m, 1H), 1.96 (ddd, *J* = 13.6, 10.6, 2.7 Hz, 2H), 1.93 – 1.81 (m, 2H), 1.64 – 1.35 (m, 5H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 178.7, 176.0, 160.1, 154.3, 138.7, 129.9, 126.7, 121.9, 121.7, 92.1, 66.9, 66.8, 61.6, 60.3, 52.2, 52.1, 50.1, 40.5, 36.5, 36.4, 31.4, 31.2, 23.2; **HRMS** calcd. for $C_{23}H_{27}Cl_3N_3O_4^+$ $[M + H]^+$ 514.1062, found 514.1053.

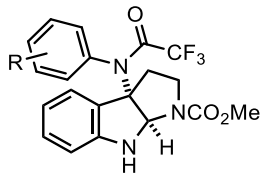
Methyl 3a-(2,2,2-trifluoro-*N*-phenylacetamido)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (3y)



Following the **general procedure K**, *N*-hydroxyindole **1a** (201 mg, 0.858 mmol) and imidoyl chloride **R1** (267 mg, 1.29 mmol) afforded pyrroloindoline **3y** (111 mg, 32%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 8:2).

***R*$_f$** =0.42 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$, 60:40 mixture of rotamers): δ 7.99 and 7.92 (s, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.40 – 7.37 (m, 2H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.02 (t, *J* = 6.8 Hz, 1H), 6.79 – 6.74 (m, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 5.46 and 5.41 (s, 1H), 5.21 and 4.78 (s, 1H), 3.92 and 3.80 (t, *J* = 9.1 Hz, 1H), 3.79 and 3.71 (s, 3H), 3.19 – 3.11 (m, 1H), 2.65 – 2.58 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 155.6, 154.87 (q, *J* = 37.5 Hz), 154.61, 149.0, 148.8, 142.1, 142.0, 134.1, 134.1, 131.9, 131.9, 129.0, 128.9, 126.9, 126.8, 124.0, 123.9, 120.9, 119.9, 119.6, 115.8 (q, *J* = 289.0 Hz), 110.3, 110.1, 83.0, 82.6, 61.2, 60.0, 52.9, 52.6, 46.5, 46.2, 36.2, 36.0; **^{19}F NMR** (471 MHz, $CDCl_3$): δ −75.7, −75.6; **HRMS** calcd. for $C_{20}H_{19}F_3N_3O_3^+$ $[M + H]^+$ 406.1373, found 406.1372.

Methyl 3a-(*N*-(2,6-dimethylphenyl)-2,2,2-trifluoroacetamido)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (3z)

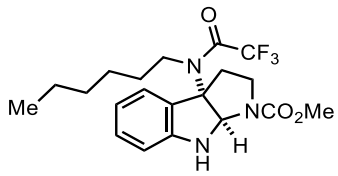


R= 2,6-Me_2

Following the **general procedure K**, *N*-hydroxyindole **1a** (63.0 mg, 0.269 mmol) and imidoyl chloride **R2** (95.1 mg, 0.404 mmol) afforded pyrroloindoline **3z** (19.1 mg, 16%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 8:2).

R_f =0.24 (silica gel, hexanes:EtOAc = 7:3); **^{1}H NMR** (500 MHz, $CDCl_3$, 60:40 mixture of rotamers): δ 7.53 and 7.50 (s, 1H), 7.12 – 7.10 (m, 3H), 7.04 (dd, *J* = 13.2, 7.4 Hz, 1H), 6.80 – 6.76 (m, 1H), 6.69 (d, *J* = 7.7 Hz, 1H), 5.48 and 5.43 (s, 1H), 3.89 and 3.79 (t, *J* = 8.8 Hz, 1H), 3.78 and 3.71 (s, 3H), 3.15 – 3.10 (m, 1H), 2.63 – 2.53 (m, 2H), 2.18 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 155.7 (q, *J* = 36.5 Hz), 155.5, 154.6, 149.0, 148.7, 144.3, 144.1, 135.6, 131.9, 131.8, 129.7, 128.9, 128.9, 126.1, 124.1, 123.9, 119.9, 119.6, 116.2 (q, *J* = 288.7 Hz), 110.3, 110.2, 83.0, 82.5, 61.2, 60.0, 52.9, 52.5, 46.5, 46.2, 36.5, 36.2, 18.4; **^{19}F NMR** (376 MHz, $CDCl_3$): δ –75.3; **HRMS** calcd. for $C_{22}H_{23}F_3N_3O_3^+$ $[M + H]^+$ 434.1686, found 434.1683.

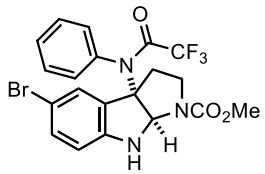
Methyl 3a-(2,2,2-trifluoro-*N*-hexylacetamido)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (3aa)



Following the **general procedure K**, *N*-hydroxyindole **1a** (129 mg, 0.551 mmol) and imidoyl chloride **R3** (178 mg, 0.825 mmol) afforded pyrroloindoline **3aa** (34.5 mg, 15%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 8:2).

R_f =0.65 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$, 60:40 mixture of rotamers): δ 7.34 and 7.30 (d, *J* = 7.4 Hz, 1H), 7.23 – 7.19 (m, 1H), 6.83 (q, *J* = 8.2 Hz, 1H), 6.66 (d, *J* = 7.9 Hz, 1H), 5.71 and 5.70 (s, 1H), 3.92 – 3.86 and 3.80 – 3.76 (m, 1H), 3.76 and 3.68 (s, 3H), 3.29 (dq, *J* = 11.2, 6.5, 4.8 Hz, 2H), 3.11 – 2.93 (m, 2H), 2.45 – 2.42 and 2.33 – 2.28 (m, 1H), 1.39 – 1.24 (m, 2H), 1.14 – 1.07 (m, 3H), 1.04 – 0.96 (m, 3H), 0.86 (t, *J* = 6.8 Hz, 1H), 0.78 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 157.6 (q, *J* = 35.6 Hz), 155.6, 154.7, 151.0, 150.9, 131.2, 131.1, 126.7, 126.6, 125.6, 125.1, 119.6, 119.3, 116.5 (q, *J* = 288.4 Hz), 110.6, 110.6, 78.3, 52.9, 52.6, 46.6, 46.5, 46.1, 45.8, 33.5, 32.6, 31.0, 30.4, 26.1, 26.0, 22.4, 14.0; **^{19}F NMR** (471 MHz, $CDCl_3$): δ –69.4; **HRMS** calcd. for $C_{20}H_{27}F_3N_3O_3^+$ $[M + H]^+$ 414.1999, found 414.1991.

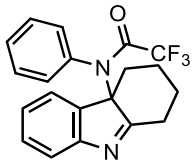
Methyl 5-bromo-3a-(2,2,2-trifluoro-*N*-phenylacetamido)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (3ab)



Following the **general procedure K**, *N*-hydroxyindole **1g** (0.150 g, 0.479 mmol) and imidoyl chloride **R1** (149 mg, 0.718 mmol) afforded pyrroloindoline **3ab** (48.7 mg, 21%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 8:2).

R_f =0.42 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$, 60:40 mixture of rotamers): δ 7.89 (br s, 1H), 7.51 (d, *J* = 8.7 Hz, 2H), 7.39 – 7.35 (m, 2H), 7.21 – 7.17 (m, 1H), 7.10 – 7.07 (m, 1H), 6.56 (d, *J* = 8.3 Hz, 1H), 5.47 and 5.42 (s, 1H), 3.94 and 3.81 (t, *J* = 9.3 Hz, 1H), 3.78 and 3.72 (s, 3H), 3.17 (td, *J* = 10.8, 5.9 Hz, 1H), 2.67 – 2.54 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 155.5, 154.9 (q, *J* = 38.7 Hz), 154.5, 148.1, 147.8, 141.4, 141.3, 134.5, 1345, 134.3, 134.3, 131.8, 131.7, 127.0, 126.9, 126.7, 126.7, 120.9, 115.8 (q, *J* = 288.8 Hz), 111.7, 111.5, 111.3, 111.0, 83.1, 82.7, 61.2, 60.0, 53.0, 52.7, 46.4, 46.1, 35.9, 35.7; **^{19}F NMR** (376 MHz, $CDCl_3$): δ –75.7; **HRMS** calcd. for $C_{20}H_{18}BrF_3N_3O_3^+$ $[M + H]^+$ 484.0478, found 484.0475.

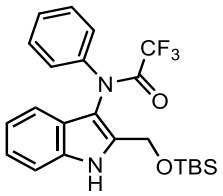
2,2,2-Trifluoro-*N*-phenyl-*N*-(1,2,3,4-tetrahydro-4aH-carbazol-4a-yl)acetamide (3ac)



Following the **general procedure K**, *N*-hydroxyindole **1s** (72.0 mg, 0.385 mmol) and imidoyl chloride **R1** (0.120 g, 0.578 mmol) afforded pyrroloindoline **3ac** (43.2 mg, 31%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 1:1).

***R*$_f$**=0.29 (silica gel, hexanes:EtOAc = 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.84 (br s, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.30 (td, *J* = 7.5, 1.4 Hz, 2H), 7.16 – 7.02 (m, 4H), 3.11 (d, *J* = 14.1 Hz, 1H), 2.96 (d, *J* = 13.1 Hz, 1H), 2.50 (td, *J* = 12.8, 5.9 Hz, 1H), 2.16 – 2.12 (m, 1H), 1.79 – 1.51 (m, 3H), 1.39 – 1.27 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 188.6, 154.1, 147.2, 136.9, 134.1, 127.9, 127.4, 125.6, 122.4, 121.4, 120.8, 118.5 (q, *J* = 251.0 Hz), 62.6, 36.6, 30.7, 29.4, 22.0; **^{19}F NMR** (376 MHz, $CDCl_3$): δ −75.7; **HRMS** calcd. for $C_{20}H_{18}F_3N_2O^+$ [M + H]$^+$ 359.1366, found 359.1366.

***N*-(2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1H-indol-3-yl)-2,2,2-trifluoro-*N*-phenylacetamide (3ad)**



Following the **general procedure K**, *N*-hydroxyindole **1q** (55.0 mg, 0.198 mmol) and imidoyl chloride **R1** (61.7 mg, 0.297 mmol) afforded pyrroloindoline **3ad** (45.3 mg, 51%) as a pale yellow oil after purification by flash column chromatography (silica gel, hexanes:EtOAc = 1:0 → 95:5).

***R*$_f$**=0.24 (silica gel, hexanes:EtOAc = 7:3); **^{1}H NMR** (400 MHz, MeOD): δ 7.90 – 7.86 (m, 1H), 7.49 – 7.43 (m, 3H), 7.38 (td, *J* = 7.4, 1.4 Hz, 1H), 7.19 – 7.14 (m, 2H), 7.01 (td, *J* = 7.5, 7.0, 1.1 Hz, 1H), 4.78 (d, *J* = 12.5 Hz, 1H), 4.71 (d, *J* = 12.5 Hz, 1H), 0.86 (s, 9H), 0.00 and −0.01 (s, 6H);

^{13}C NMR (126 MHz, MeOD): δ 154.7 (q, *J* = 37.3 Hz), 154.5, 136.3, 135.5, 134.1, 133.7, 131.8, 129.3, 128.6, 127.0, 126.0, 125.0, 123.1, 121.0, 119.0, 117.7, 115.7 (q, *J* = 288.8 Hz), 111.6, 107.0, 57.7, 26.0, 18.5, –5.4; **^{19}F NMR** (376 MHz, MeOD): δ –77.5; **HRMS** calcd. for $C_{23}H_{26}F_3N_2O_2Si^-$ $[M – H]^-$ 447.1721, found 447.1719.

2.3.6. References at Experimental Section

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Chapter 2. Indolyl 1,3-Heteroatom Transposition Reaction: Enantioselective C3-Heteroatom Functionalization of Indole Derivatives

2.1. Introduction

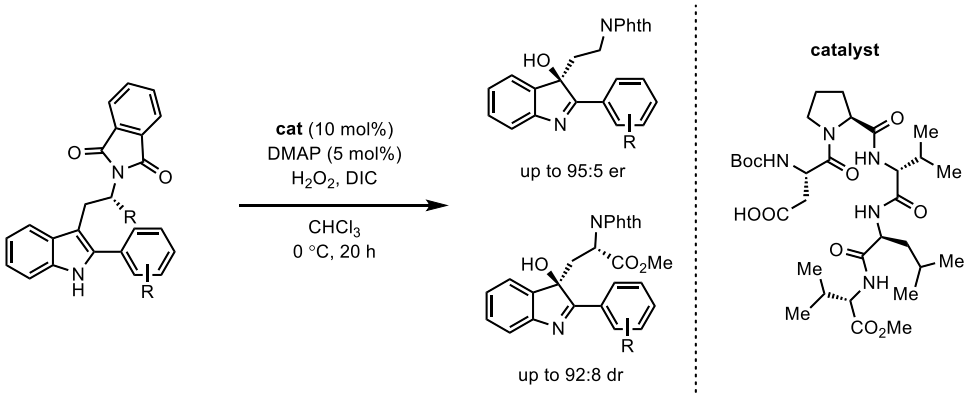
2.1.1. Enantioselective Indole C3-Hetero-Functionalization

Stereochemical differences significantly impact biochemical processes due to the chirality of the molecules involved. One of the tragic illustration is thalidomide, a sedative drug widely prescribed to pregnant women from the late 1950s to the 1960s. Unfortunately, one of the two enantiomers caused adverse drug reaction by inhibiting blood vessel formation, leading to foetus deformities.

Thus, the pursuit of obtaining enantiomerically pure compounds in the pharmaceuticals and agrochemicals sectors is of utmost significance and presents a formidable challenge.

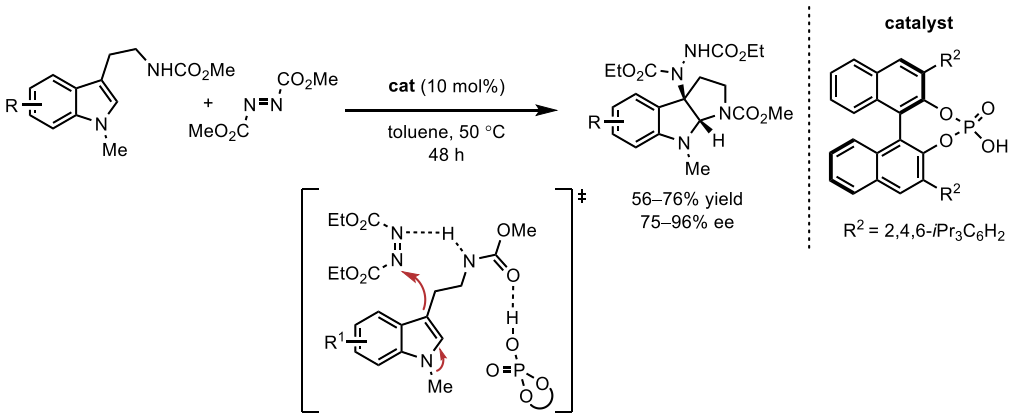
In 2011, Movassaghi and Miller developed a sophisticated method for the asymmetric indole oxidation of tryptamine analogues. This innovative approach employed a novel catalyst based on aspartyl peptides, as depicted in Scheme 2.1. This reaction system delivers 3-hydroxy-indolenines with good chemical yields and significant levels of enantio- and diastereoselectivity (up to 95:5 er and up to 92:8 dr).

Scheme 2.1. Enantioselective Formation of C3-Hydroxylation of Tryptamine with Peptide-based Catalysis



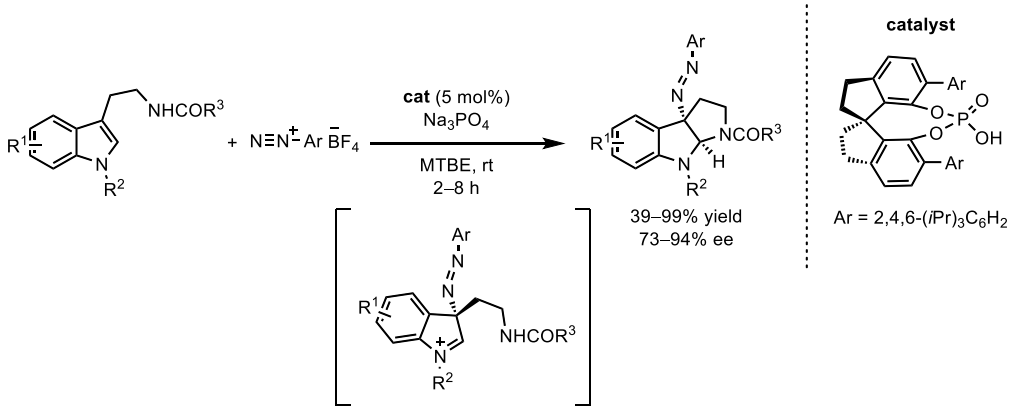
Antilla group reported a groundbreaking achievement in the chiral phosphoric acid-catalyzed formation of highly enantioselective carbon-nitrogen bonds in pyrroloindoline (Scheme 2.2).[2] Literatures and NMR studies have revealed that tryptamine engages in hydrogen bonding with both the electrophile dimethyl azodicarboxylate (DEAD) and the chiral phosphoric acid, which explains the high enantioselectivites observed. This newly developed method demonstrated that tryptamine substrate with methoxy, fluorine, chlorine, or bromine groups were capable of producing C3- aminated pyrroloindolines with yields of up to 76% and enantiomeric excesses of up to 96%.

Scheme 2.2. Enantioselective Formation of Pyrroloindolines Catalyzed by Chiral Phosphoric Acids



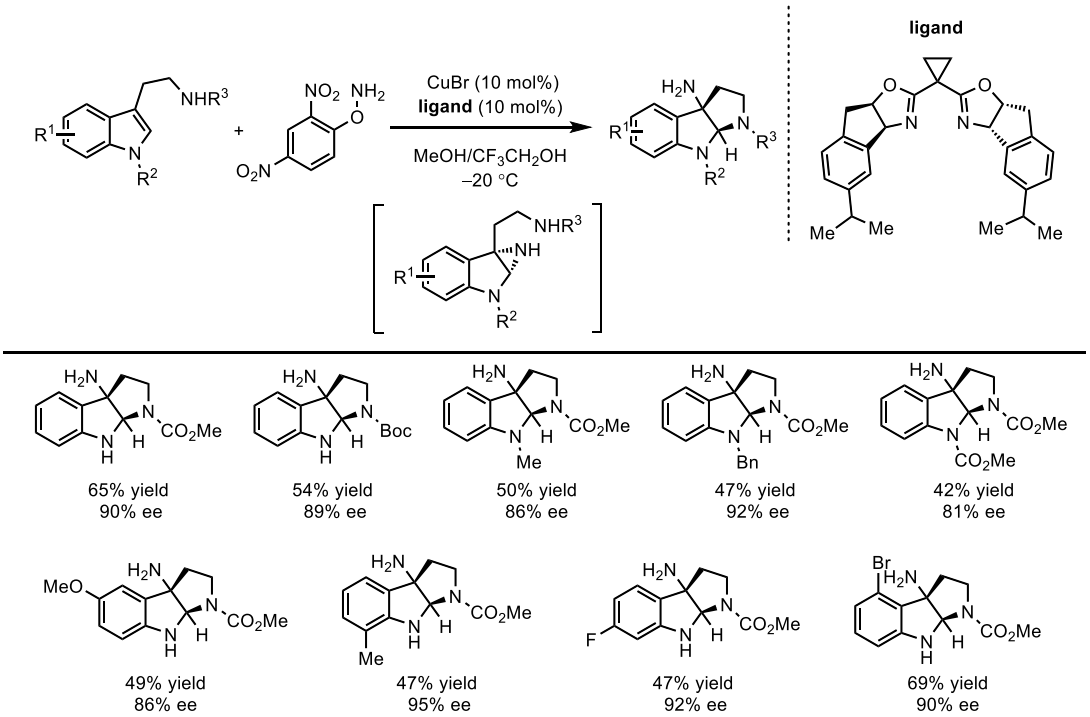
Toste group also reported similar organocatalytic strategy using chiral phosphoric acid (Scheme 2.3).[3] They utilized aryldiazonium tetrafluoroborates as an electrophilic nitrogen source to construct C3-diazenated pyrroloindolines. With 5 mol% of catalyst and additional Na_3PO_4 as a base, simple tryptamine derivatives were transformed into enantioenriched indolinium intermediates through chiral anion phase-transfer reaction. Subsequently, these indolenines were attacked by aliphatic chain's nitrogen atom facilitated pyrroloindoline formation.

Scheme 2.3. Enantioselective Formation of Pyrroloindolines Catalyzed by Chiral Phosphoric Acids



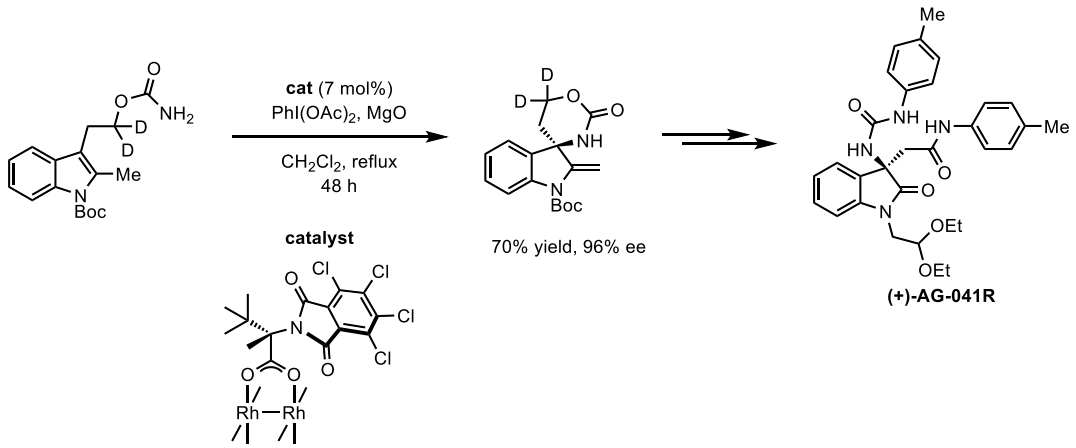
The enantioselective synthesis of 3a-amino-pyrroloindoline derivatives were also reported by Tang and You group in 2016 (Scheme 2.4).[4] They were able to access the protecting-group-free 3a-aminopyrroloindolines by direct asymmetric dearomative amination method. The amination reagent O-(2,4-dinitrophenyl)hydroxylamine (DPH) generates a Cu-nitrene intermediate with the CuBr-bisoxazoline complex, which is then inserted into tryptamine The resulting aziridine intermediates undergo intramolecular cyclization to yield the desired product. In this reaction system, N-protecting groups with electron-withdrawing properties on the side chain of tryptamine show good compatibility. Additionally, both electron-rich and electron-poor substituents on the indole nitrogen and indole core undergo smooth reactions, resulting in moderate yields with excellent enantioselectivity.

Scheme 2.4. Asymmetric Synthesis of Naked 3a-Amino-Pyrroloindolines Enabled by Cu Catalysis



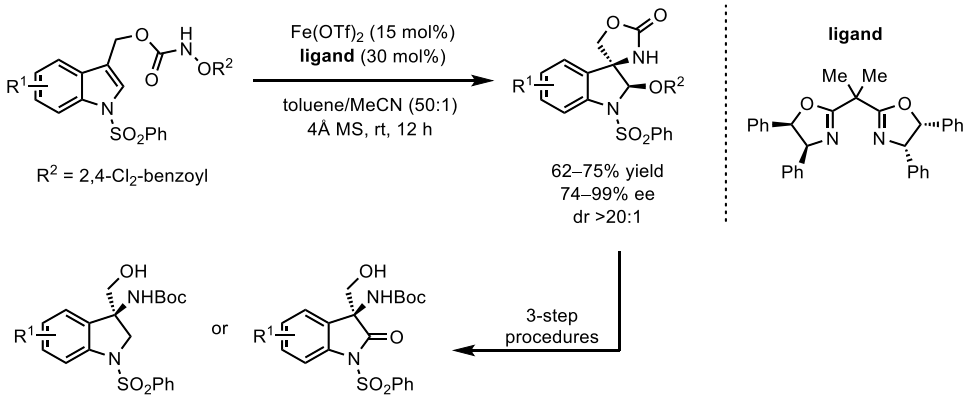
In 2009, Iwabuchi group reported enantioselective rhodium-catalyzed oxidative intramolecular aza-spirocyclization in indolyl carbamate with deuterium in the tethered chain in 70% yield with 96% ee (Scheme 2.5).[5] After obtaining this core structure, asymmetric synthesis of (+)-AG-041R, a potent gastrin/CCK-B receptor antagonist was accomplished through a 10-step series of reactions.

Scheme 2.5. Chiral Rh-catalyzed Aza-Spiroannulation Used in the Synthesis of (+)-AG-041R



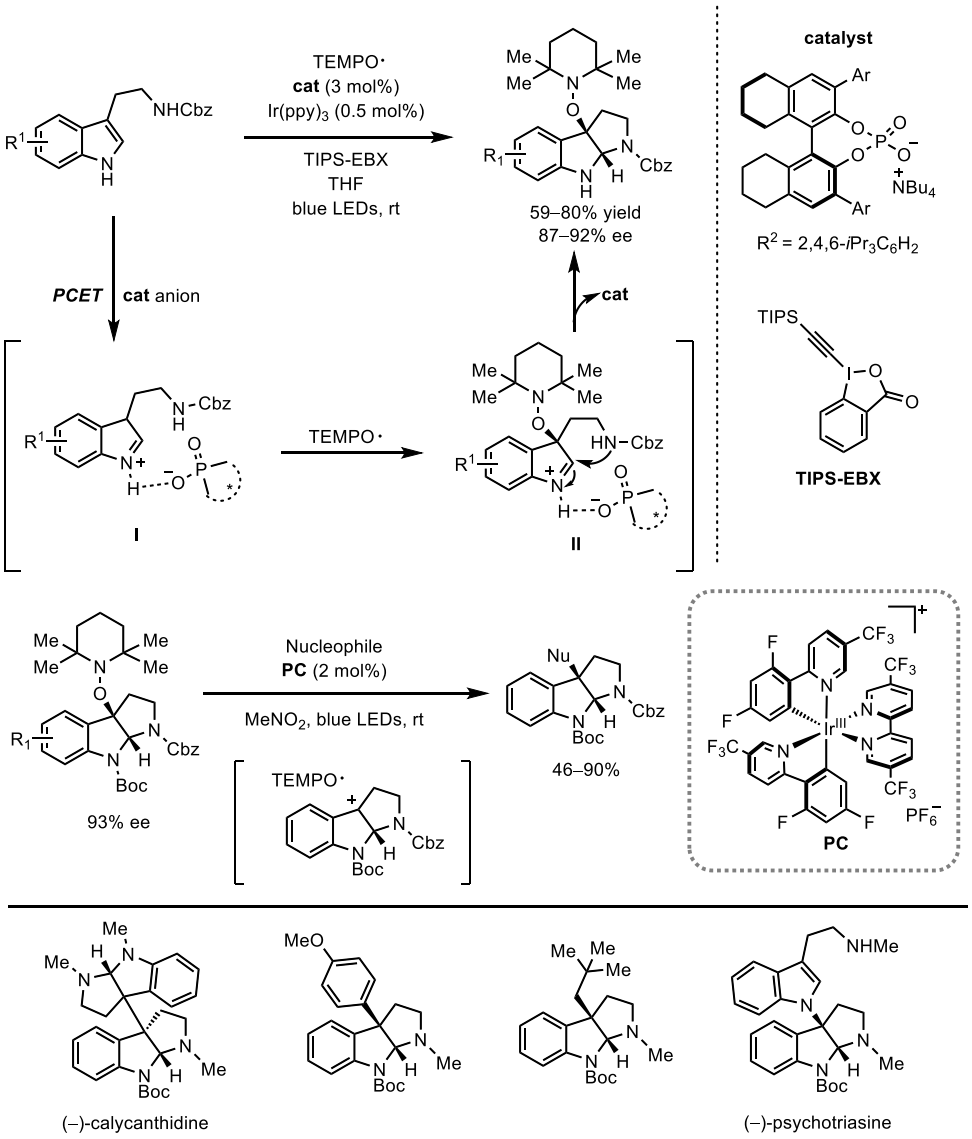
Fe(II)-chiral BOX complexes catalyzed asymmetric intramolecular indole aminohydroxylation was reported by Xu group in 2013(Scheme 2.6).[6] Through extensive screening of chiral ligands, benzoyl protecting groups with electronic tunings, solubility of iron sources in the solvent, and additives with bulky N-donor ability, optimal conditions were selected. With these reaction conditions in hand, enantio-enriched hydroxy oxazolidinones were successfully obtained in good yields. Furthermore, these hydroxy oxazolidinones can be easily transformed into a range of biologically active compounds, including 3-amino indolanes or 3-amino oxindoles, through a three-step procedure that maintains the enantiomeric excess.

Scheme 2.6. Asymmetric Spirocycled Indoline Synthesis via Fe Catalysis



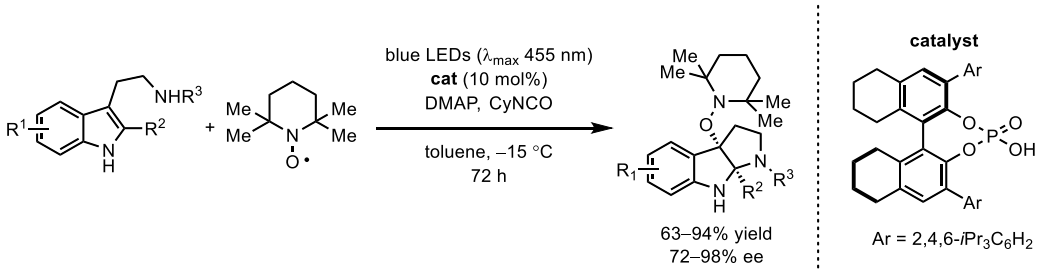
Knowles and coworkers presented the organo catalytic asymmetric dearomatization oxidation of tryptamines (Scheme 2.7).[7] This methodology enables the synthesis of C3-functionalized enantioselective pyrroloindolines. Firstly, oxidative proton-coupled electron transfer is promoted by hydrogen bonding stabilization of indole radical cation and chiral phosphate Subsequently, the indole radical cation effectively reacts with TEMPO radical, leading to cyclization to pyrroloindoline with high enantioselectivity. Moreover, the enantioenriched TEMPO-adducted pyrroloindoline can be attacked by a nucleophile after a single-electron oxidation/mesolytic cleavage reaction.

Scheme 2.7. Enantioselective Catalytic Dearomative Chiral Phosphoric Acid-assisted PCET Reaction of Indoles



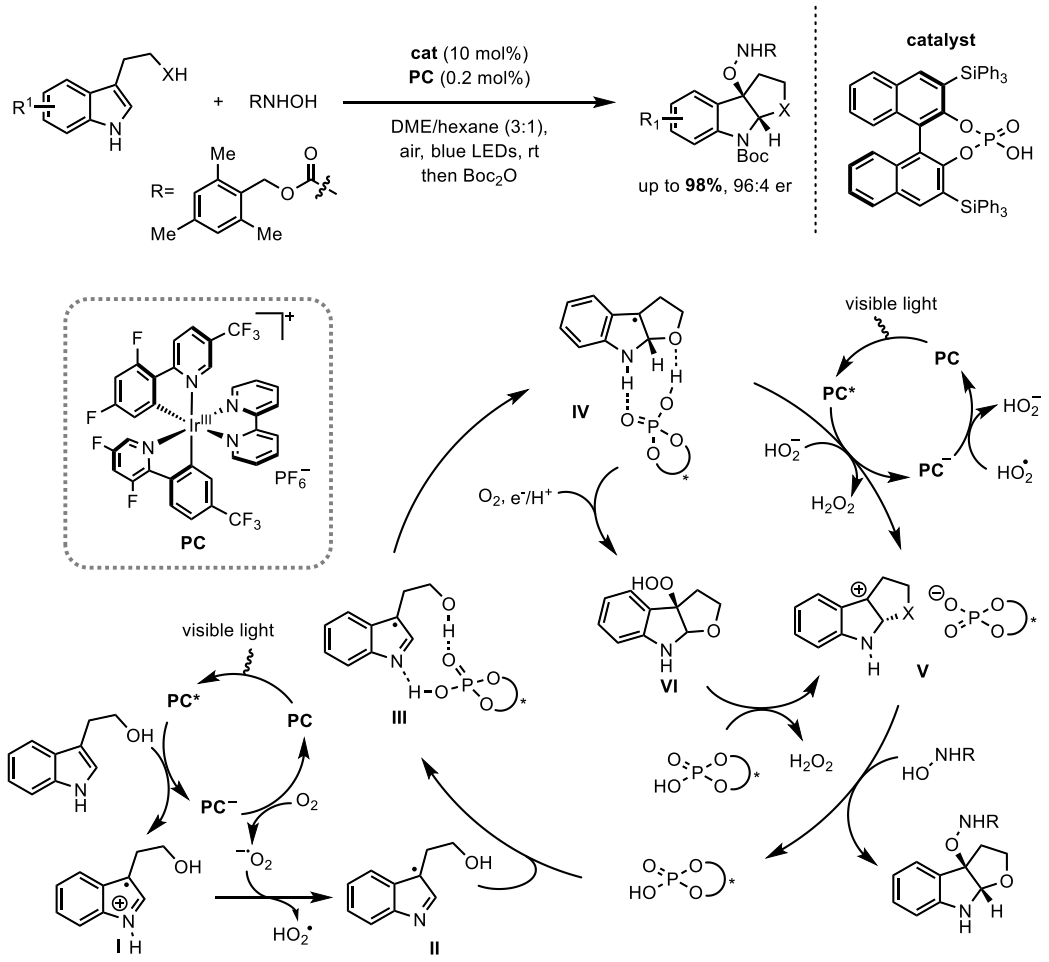
The Xia group also reported the enantioselective radical cyclization of tryptamines using visible-light irradiation (Scheme 2.8).[8] Unlike the Knowles group's work, this paper does not use iridium photocatalyst. Instead, TEMPO is directly exited by visible light, inducing n−π* transition of nitroxide. The resulting nitroxide *in situ* generates indole radical cation through hydrogen atom transfer (HAT), and subsequent chiral phosphoric acid-catalyzed cyclization affords TEMPO-trapped pyrroloindoline in high yield and enantioselectivity. To emphasize this strategy, a concise 5 step asymmetric total synthesis of natural product (−)-verrupyrroloindoline was accomplished.

Scheme 2.8. Enantioselective Synthesis of C3-TEMPO Pyrroloindoline



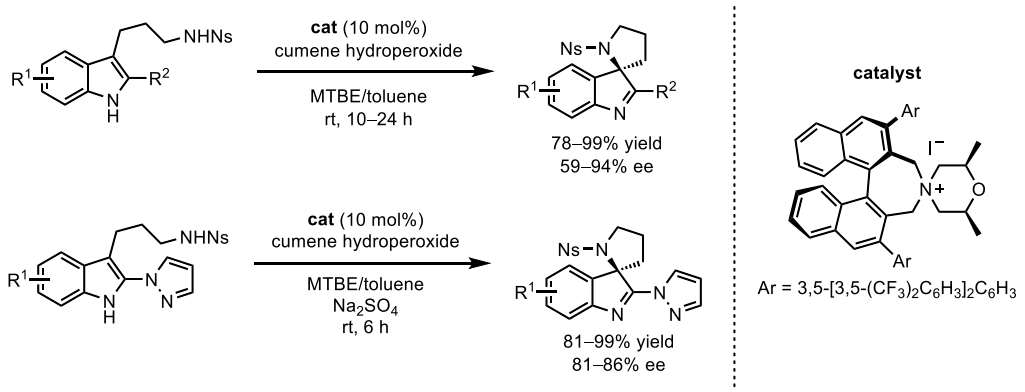
In 2019, Zhang and You group developed asymmetric dearomatizaton of indole derivatives using a combination of a chiral phosphoric acid and Ir photocatalyst (Scheme 2.9).[9] The previous approach by Knowles and Xia groups involved using chiral phosphoric acid as an oxidant to generate a tryptamine radical. However, in this paper, indole derivatives undergo two sequential electron loss to generate carbocation, which can be utilized as a nucleophile. Under the photochemical conditions, direct oxidation occurred, leading to the formation of radical cation **I**. Simultaneously, superoxide generated from the photocatalysis acted as a base, deprotonating radical cation **I** to produce radical **II**. Additionally, molecular oxygen, in the form of activated superoxide or hydroperoxyl radical, played a role not only in oxidizing indole but also in regenerating the catalyst, thereby completing the overall reaction cycle. This two-step oxidation process allowed tryptamine variants to readily form C3-cationic pyrroloindolines without the need for additional trapping and isolation of intermediates. Finally, the transient electrophilic species **V** would be trapped by electrophile, which might also invoke hydrogen-bonding interactions with the chiral phosphate anion, to furnish the optically enriched pyrroloindoline and complete the CPA catalytic cycle.

Scheme 2.9. Organo-Catalytic Asymmetric Dearomatization of Indoles via Photoredox Catalysis



Chiral ammonium hypoiodite-catalyzed enantioselective dearomative aza-spirocyclization of homo-tryptamine derivatives was developed by Uyanik and Ishihara group (Scheme 2.10).[10] They revealed a unique reactivity at C3 position of indoles by conducting N1 idoination. Various kinds of aza-spiroindolenines were gained under optimized reaction conditions with good to excellent yield and enantioselectivity. Furthermore, the synthesis of highly challenging enantioselective spiroazetidine products was accomplished with this reaction strategy, yielding up to 99% yield and enantiomeric excess of up to 86%. This was achieved by introducing an electron-deficient auxiliary pyrazole attached to the C2 position.

Scheme 2.10. Hypoiodite-catalyzed Oxidative Cyclization of Indoles



2.1.2. Organocatalysis

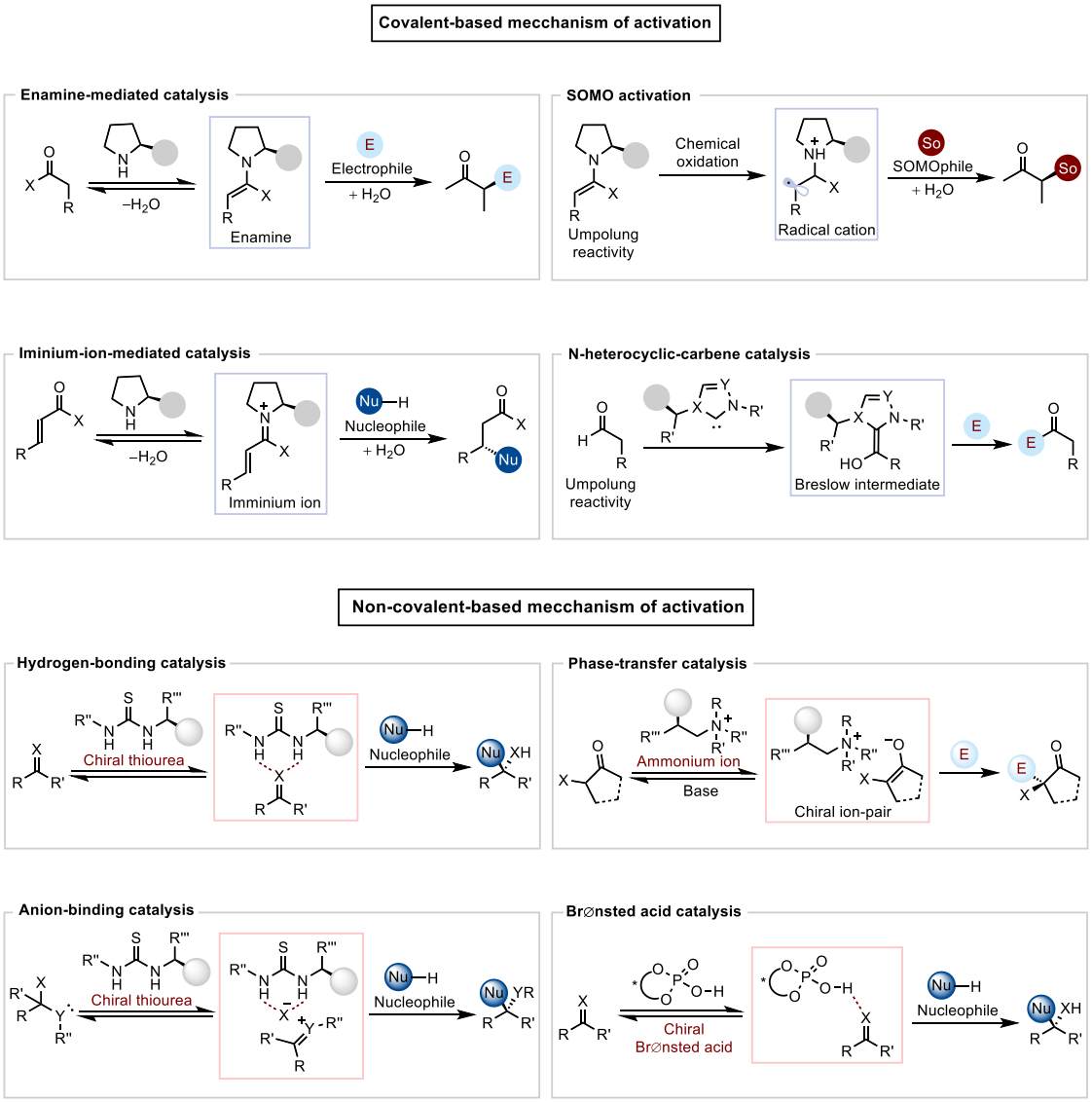
Organocatalysis utilizes small organic molecules without inorganic elements to act as catalysts for organic transformation. Organocatalysts are easy to handle in practical operations, exhibit resistance to air and moisture, are relatively inexpensive compared to metal catalysts, have non-toxic properties, and offer an extraordinary variety of small molecules that can be utilized as catalysts. Due to these inherent benefits of organocatalysts and ease of introducing chiral elements in catalysts, this field now plays an important role in asymmetric synthesis. Now organocatalysis is considered the third class of asymmetric catalysis with biocatalysis and transition metal catalysis.

Historically, asymmetric organocatalysis can be dated back to 1912. Bredig and Fiske reported the Cinchona alkaloid-catalyzed addition of HCN to benzaldehyde. Later, in 1960, Pracejus reported groundbreaking results with 1 mol% of O-acetal quinine-catalyzed methanloysis of ketene to afford an enantioenriched ester. Since then there has been continuous studies of different kinds of asymmetric organocatalyst such as carbenes, proline, cinchona alkaloid derivatives, thiourea, DMAP, ketone, phosphoramides, and quaternary ammonium salt. But these initial findings focused on developing individual transformations for each component, rather than conceptualizing organocatalysis as a general approach.

The term “Organocatalysis” came to be introduced as a generally applicable field in organic chemistry with the works of Benjamin List on iminium catalysis and David MacMillan on enamine catalysis in 2000.

Organocatalysis could be classified by its 'mode of activation': covalent organocatalysis and non-covalent organocatalysis (Figure 2.1). In the former case, the catalyst creates covalent binds with the substrate within the catalytic cycle. In the latter case, molecule's activation is due only to noncovalent interactions of the substrate and catalyst, such as hydrogen bonding (H-bonding) or the formation of ion pairs.

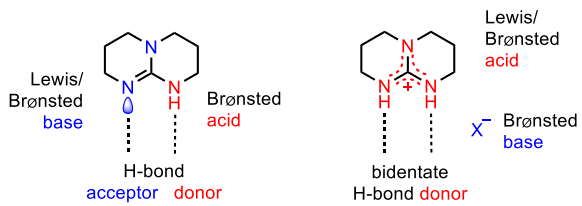
Figure 2.1. Organocatalysis Classification by 'Mode of Activation'



2.1.3. Guanidinium Ion Organocatalysis

Discovered over 150 years ago, guanidines are well known for very strong bases ('superbases'). However, wider range of useful chemical functionalities are possessed by guanidine and its corresponding salt (Figure 2.2). Free guanidine can serve as a Lewis/Bronsted base and hydrogen-bond donor and acceptor. On the other hand, guanidinium salt can be a weak Bronsted acid and function as a cationic bidentate hydrogen-bond donor, as well as a potential π-Lewis acid due to its delocalized guanidinium cation.

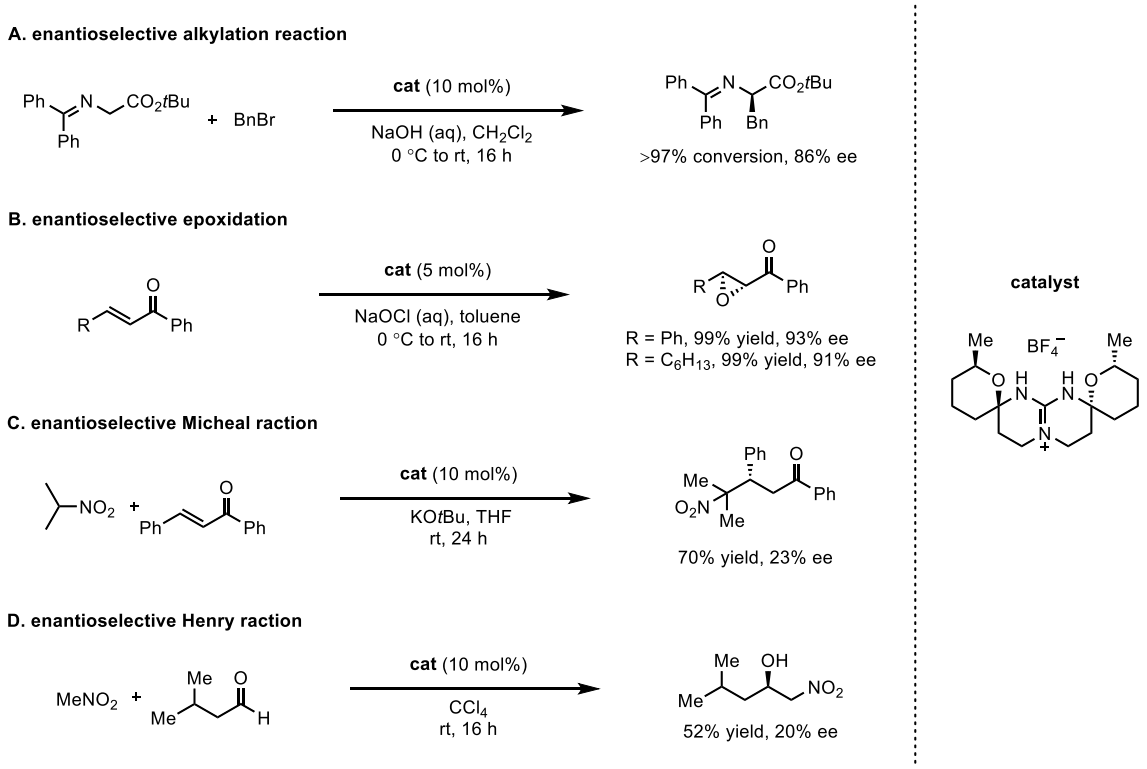
Figure 2.2. Guandine and Guanidinium Salt's Chemical Functionalities



Despite the diverse functionalities, guanidine is a recently researched area in asymmetric organocatalysis. Developing novel guanidine catalysts is quite demanding due to guanidine's high basicity and polarity, which makes the synthesis and purification generally more challenging compared to other organocatalysts such as thioureas or secondary amines.

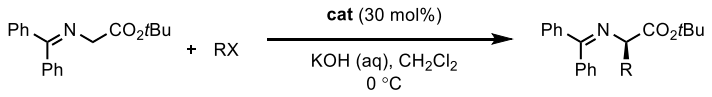
The Murphy group synthesized tetracyclic C2-symmetric guanidinium ion with the counter anion of tetrafluoroborate (BF_4^-) and applied it to enantioselective reactions (Scheme 2.11).[11] Enantioselective benzylation of glycinate Schiff's base was firstly reported in this paper (Schem A). Over 97% conversion of starting glycinate and 86% enantioselectivity value was introduced by 10 mol% of catalyst usage. Furthermore, epoxidation of chalcones also conducted in excellent yields and enantioselectivities under this phase-transfer conditions (Scheme B). Additionally, the catalyst was capable of facilitation the Michael addtion of 2- nitropropane to chalcone and Henry reaction of isovaleraldehyde, resulting in good yield but low enantiomeric excess, as demonstrated in Scheme 2.11C and D.

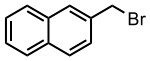
Scheme 2.11. Enantioselective Reactions Catalyzed by C_2-Symmetric Tetracyclic Guanidinium Salt



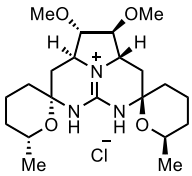
The Nagasawa group designed catalyst based on marine natural product ptilomycalin A and related compounds. And the catalyst has a C_2-symmetric chiral reaction cavity around the substrate activation site. They synthesized four different catalysts and analyzed them using X-ray crystallography.[12] They found that the catalyst shown in Table 2.1 has closed-type cavity around guanidinium component. Pleasingly, good enantioselectivity values in the range of 76 to 90% was observed in *t*-butyl glycinate alkylation reaction with various alkyl halides. This result revealed that the steric hinderance caused by the methyl groups on the spiro rings at the substrate-activation site. Although reaction time was quite long and the catalyst loading was 30 mol%, yields were generally good.

Table 2.1. Enantioselective Alkylation Reaction C_2-Symmetric Guanidinium Salt



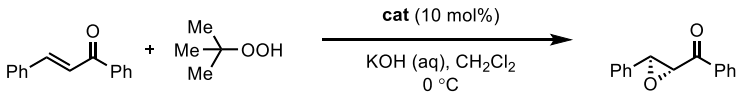
entry	RX	time (h)	yield (%)	ee(%)
1	BnBr	160	55	90
2	MeI	145	80	76
3	OctI	145	83	80
4	$H_2C{=}CHCH_2Br$	140	61	81
5	$H_2C{=}C(Me)CH_2Br$	145	85	81
6	*trans*-Me(H)C=$CHCH_2Br$	160	72	79
7	$CH^{o}CCH_2Br$	145	84	81
8	4-$NO_2C_6H_4CH_2Br$	40	80	82
10		95	81	90

catalyst



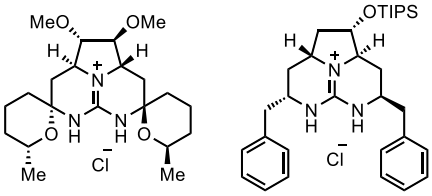
Tricyclic and pentacyclic guanidinium catalyst with additional potassium hydroxide base was also investigated by the Nagasawa group to generate epoxide from chalcones (Table 2.2).[13] When pentacyclic guanidinium was used, reaction time was over 110 hours, the yield range was 22 to over 99% and enantioselectivity value was moderate, up to 60%. Then tricyclic guanidinium catalyst was tested, considerable rate accelerations and excellent yields of over 99% were observed. Still enantioselectivities were similar to those of the pentacyclic guanidinium catalyst.

Table 2.2. Enantioselective Epoxidation Catalyzed by Tricyclic and Pentacyclic Guanidinium Salt



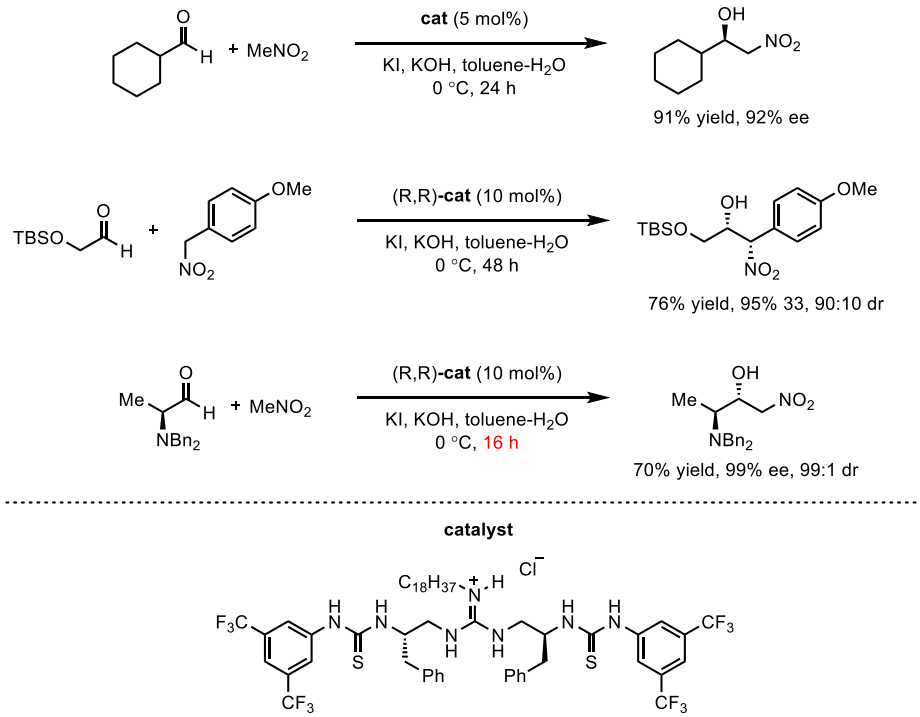
entry	cat.	R	time (h)	yield (%)	ee(%)
1	1	Ph	110	35	39
2	1	2-Nnaphthyl	140	51	50
3	1	1-naphthyl	140	77	60
4	1	9-anthracenyl	140	>99	35
5	1	4-$NO_2C_6H_4$	130	82	38
6	1	4-$MeOC_6H_4$	160	22	36
7	2	Ph	26	>99	52
8	2	2-Nnaphthyl	20	>99	52
9	2	1-naphthyl	20	>99	41
10	2	9-anthracenyl	24	>99	30

catalyst



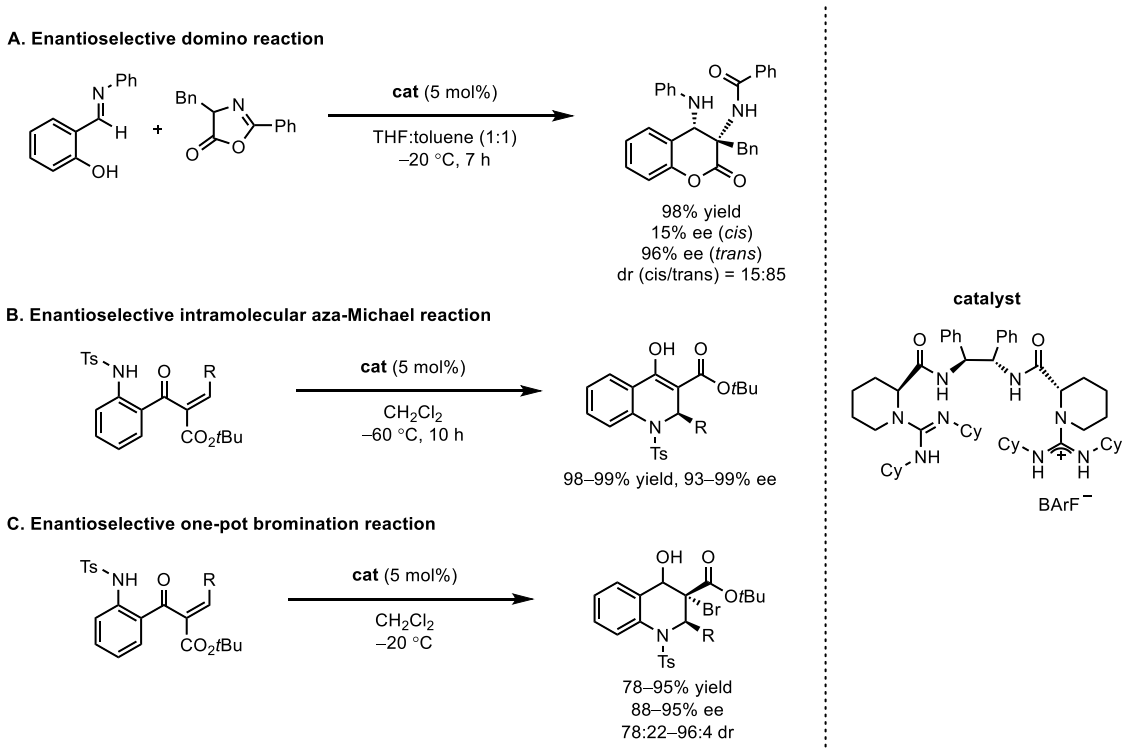
Nagasawa and co-workers identified that bifunctional C_2-symmetric bisthiourea-guanidinium ion catalyst could be effective in enantio- and diastereoselective catalysis for Henry reactions (Scheme 2.12).[14] The thiourea components interact strongly with aldehyde electrophile and guanidinium ion group activates nitroalkane nucleophile. Additionally, the long aliphatic chain of the guanidinium ion accelerates hydrophobic interactions in phase-transfer reaction.

Scheme 2.12. Asymmetric Henry reaction Catalyzed by C_2-Symmetric Bisthiourea-Guanidinium Salt



In 2011 and 2012, the Feng group reported a series of catalytic asymmetric reaction catalyzed by bisguanidium salt (Scheme 2.13).[15] It is assumned that bifunctional Brønsted base/ bidentate hydrogen-bond donor catalyst enhances the enantioselectivity in reported reactions.

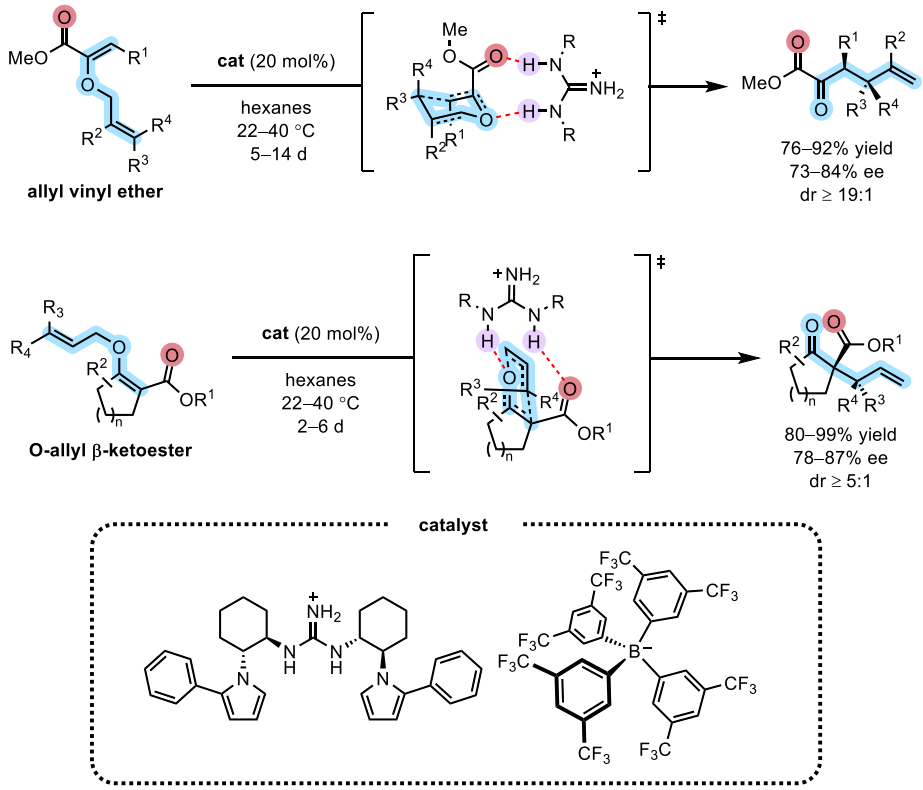
Scheme 2.13. Asymmetric Reactions Catalyzed by Bisguanidinium Salt



In 2008, Jacobsen and Uyeda developed a guanidinium catalyst based on the observation that chorismate, found in nature, undergoes [3,3]-sigmatropic rearrangement mediated by chorismate mutases enzymes possessing hydrogen-bond donating residues, leading to perphenate production (Scheme 2.14).[16,17] Through the design and evaluation of various catalysts, it was found that C_2-symmetric guanidinium ions derived from trans-1-pyrrolo-2-aminocyclohexane, which bear the non-coordinating BArF counterion, were particularly effective. This catalyst facilitated the reaction of a diverse range of electronically activated allyl vinyl ethers to afford the corresponding α-oxohex-5-enoates in high yields, excellent diastereoselectivities, and good to excellent enantioselectivities. The acceleration of this rearrangement is attributed to the catalyst's ability to stabilize the transition state through hydrogen bonding interactions with the oxygen atoms in both the ether and ester carbonyl groups. Additionally, in 2010, they reported wide-ranging method for synthesizing branched allylation products through the Claisen rearrangement of cyclic O-allyl β-ketoesters using the same chiral guanidinium catalyst. This innovative approach allows for simultaneous control over both enantioselectivity and diastereoselectivity. In both reports, the

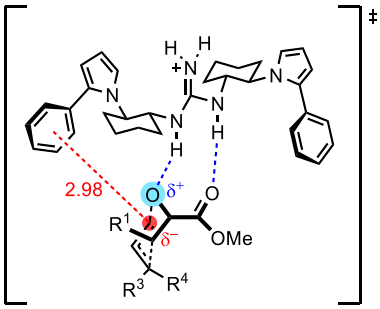
highest enantioselectivities were achieved in non-polar alkane solvents. However, toluene and dichloromethane also demonstrated usefulness, yielding products with only a slight reduction in enantiomeric excess.

Scheme 2.14. Asymmetric Clasien Rearrangement Catalyzed by C_2-symmetric Guanidinium Salt



In 2011, Jacobsen and Uyeda conducted in-depth theoretical investigations on this reaction system and revealed that the highly dipolar transition state is stabilized through the participation of multiple non-covalent interactions.[18] As can be seen in Figure 2.3, the C-H bond of the allyl fragment and the centroid of the phenyl ring are in close proximity, with a distance of 2.98 Å. This favorable distance allows for an electrostatic interaction to occur alongside the well-known bidentate hydrogen bonding.

Figure 2.3. Transition State of Asymmetric Claisen Rearrangement



2.2. Results and Discussion

2.2.1. Evaluation of Reaction Conditions

Initially, we started exploring the range of substrates. The proposed substrate candidates are shown in the Figure 2.4 below. In terms of bonding with the catalyst, **4a** to **4d** has a coordination site spanning 3 atoms, and **4f** to **4i** has a coordination site spanning 4 atoms. However, in the process of synthesizing them, there was a problem in the process of isolation by column chromatography. In the process of synthesizing **4b**, it was confirmed that the reaction immediately caused a 3,3-sigmatropic rearrangement. (Figure 2.5). The electronegative oxygen atom next to the carbonyl group is believed to produce an electron-withdrawing effect, causing further reactions after the synthesis of **4b**. Therefore, **4a** and **4c** were determined to be suitable candidates.

Figure 2.4. Substrate Scope Candidates

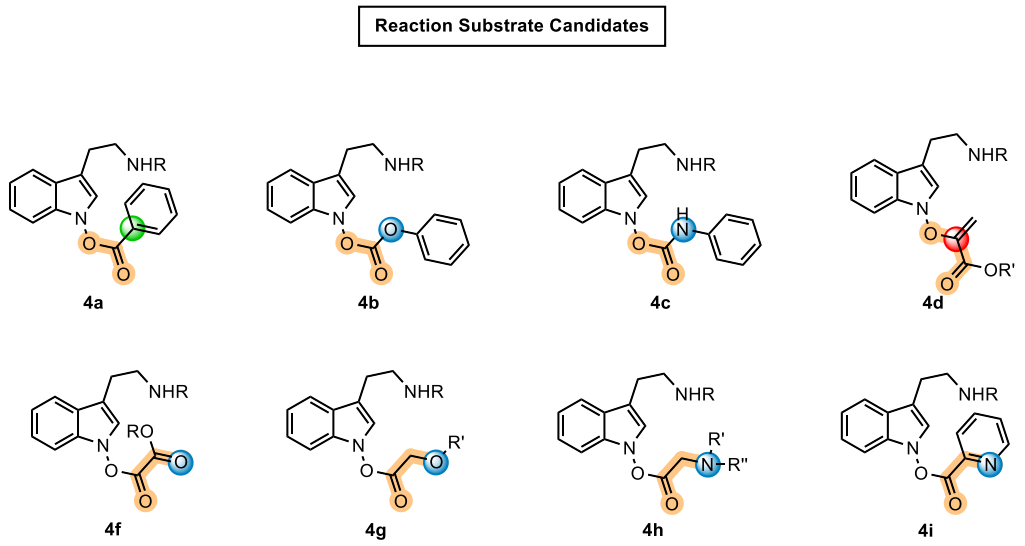
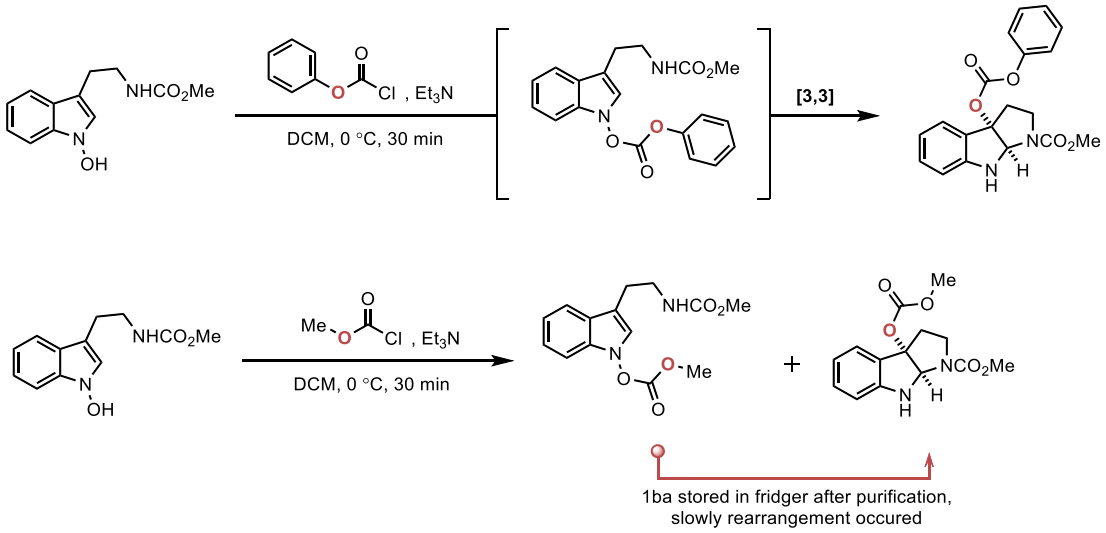


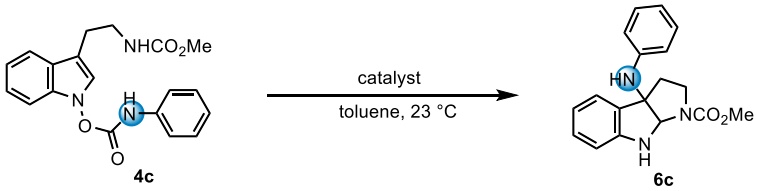
Figure 2.5. Unsuitable Substrate Candidates **4b**



The screening of hydrogen donor catalyst was carried out with the appropriate substrate **4c** (Table 2.3). Proline-derived catalyst **5a** and **5b**, cinchona alkaloid **5c**, BINOL **5d**, BINOL phosphoric acid **5e**, thioureas **5f** and **5g** were found to be not suitable for this reaction system. Subsequently, different guanidinium salts were tested and **5j** was emerged as the sole effective

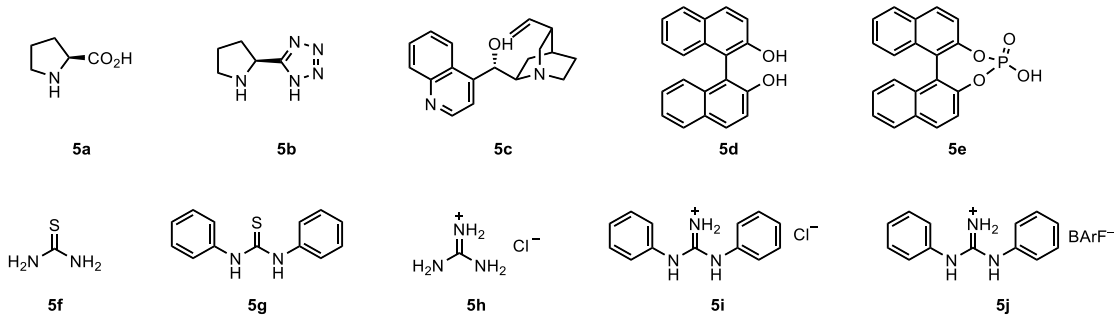
catalyst, providing 49% yield. The product was not a C3-oxygenation product but a C3-amidation product. This result indicates dissociative mechanism leads to the initial N–O bond cleavage, and rapid decarboxylation generates carbamate anion.

Table 2.3. Screen of Hydrogen Bond Donor Catalysts[a]



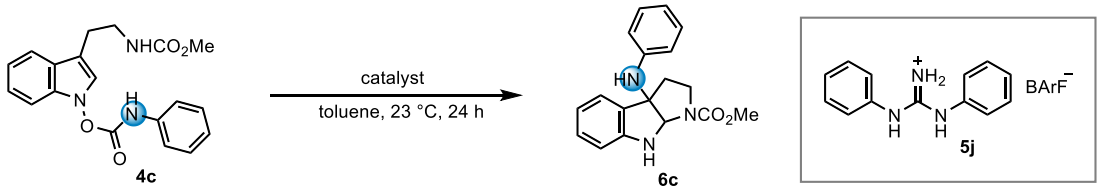
entry	catalyst	catalyst loading	time (h)	yield (%)[b]
1	5a	50 mol%	24	0
2	5b	50 mol%	24	0
3	5c	50 mol%	24	0
4	5d	50 mol%	24	0
5	5e	50 mol%	24	0
6	5f	50 mol%	24	0
7	5g	50 mol%	24	0
8	5h	50 mol%	24	0
9	5i	50 mol%	24	0
10	**5j**	**50 mol%**	**24**	**49**

[a]Reaction conditions: **1c** (0.056 mmol, 1.0 equiv) in toluene (0.05 M), 23 °C for 24 h. [b]The yield of product was determined by ^{1}H NMR analysis of the crude mixture using TCE as an internal standard.



Since bis(phenylamino)methaniminium BArF catalyst exhibited reactivity in our reaction system, we performed experiment to adjust the catalyst loading amount. (Table 2.4). When 50 mol% of catalyst was loaded and stirred for 24 h, yield was 49% (entry 1). The desired product was obtained in yields of 36% and 13% when 25 mol% and 10 mol% of catalyst were used, respectively (entry 2 and 3).

Table 2.4. Stoichiometric Experiment of Catalyst Loading[a]

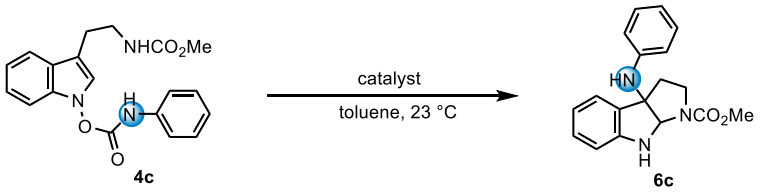


entry	catalyst	catalyst loading	time (h)	yield(%)[b]
1	5j	50 mol%	24	49
2	5j	25 mol%	24	36
3	5j	10 mol%	24	13

[a]Reaction conditions: **1c** (0.056 mmol, 1.0 equiv) in solvent (0.05 M), 23 °C for 24 h. [b]The yield of product was determined by ^{1}H NMR analysis of the crude mixture using TCE as an internal standard.

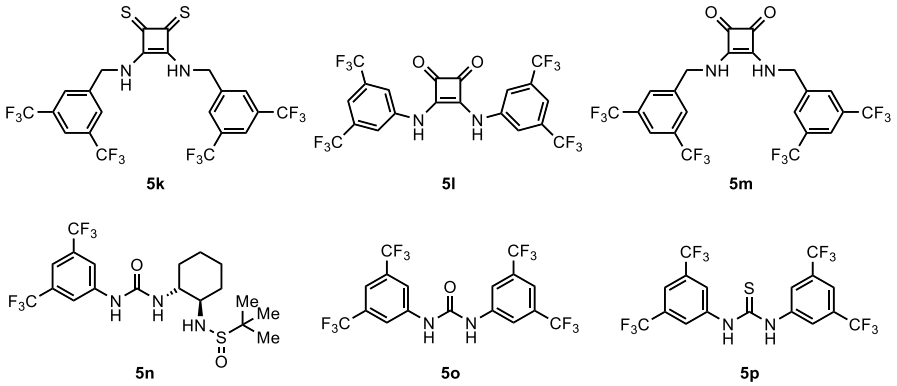
Then, we conducted screening of hydrogen bond donors with electron withdrawing group (Table 2.5). These catalysts were obtained from Professor Han-Yong Bae's laboratory at Sungkyunkwan University. Squaramides with electron withdrawing trifluoromethyl group (–CF_3) **5k, 5l, 5m** exhibited no activity in this reaction system. Urea with a unidirectional electron withdrawing group also didn't show reactivity. On the other hand, Schreiner's urea and thiourea were able to catalyzed the reaction with a 20 mol% catalyst loading, resulting in yields of 6% and 13% after 72 hours, respectively.

Table 2.5. Screen of Hydrogen Bond Donors with Electron Withdrawing Group[a]



entry	catalyst	catalyst loading	time (h)	yield (%)[b]
1	5k	20 mol%	72	0
2	5l	20 mol%	72	0
3	5m	20 mol%	72	0
4	5n	20 mol%	72	0
5	**5o**	**20 mol%**	**72**	**6**
6	**5p**	**20 mol%**	**72**	**13**

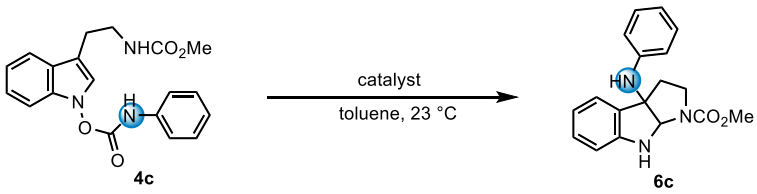
[a]Reaction conditions: **1c** (0.042 mmol, 1.0 equiv) in toluene (0.05 M), 23 °C for 72 h. [b]The yield of product was determined by ^{1}H NMR analysis of the crude mixture using TCE as an internal standard.



Based on the results of the previous screening, we utilized chiral guanidinium with BArF as the counterion to investigate the effect of introducing reactivity and enantioselectivity (Table 2.6). Initially, we investigated C_2-symmetric guanidinium salt derived from trans-1-pyrrolo-2-aminocyclohexane, which accelerated the Claisen rearrangement through hydrogen-bonding. After loading the catalyst **5aa** at a concentration of 50 mol% for 24 hours, 3c was obtained with a yield of 48% and an enantiomeric excess of 9.5% (entry 1). When we adjusted the catalyst by replacing one half with an amine derived from L-*tert*-Leucine, this catalyst was not suitable for this reaction system (entry 2). Additionally, when we used a catalyst with one half was being

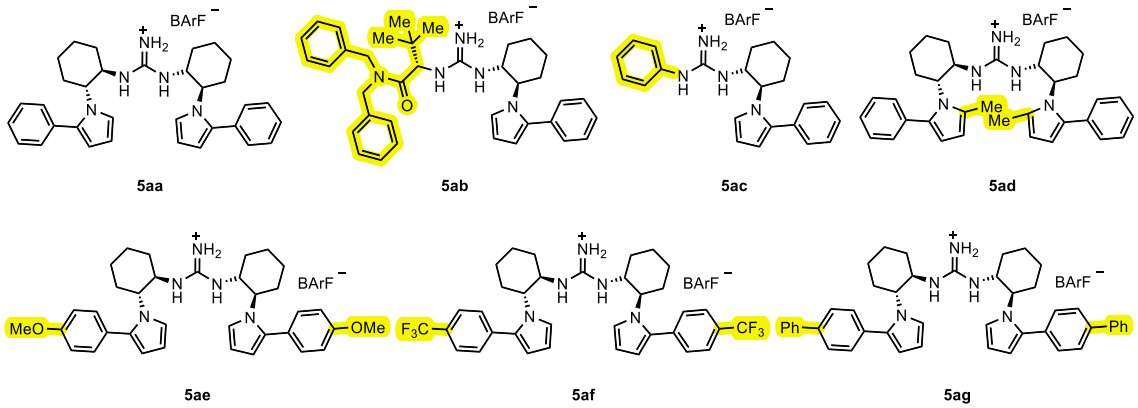
aniline, the yield increased but the enantioselectivity decreased (entry 3). These revealed that electron-withdrawing ability is crucial for yield, while a closed-type cavity around hydrogen donor components is important for enantioselectivity. Then, we introduced steric hindrance inside pyrrole ring with methyl group in **5ad** catalyst. With 25 mol% of catalyst loading and reaction time for 24 h, yield of 3c was 19% and enantioselectivity value was 4.7%, means that steric congestion in the reacting site inhibits the reaction (entry 4). Next, adjustment of electronics was examined by introducing an electron-donating methoxy group and electron-withdrawing trifluoromethyl group, respectively (entry 5 and 6). As we expected, the catalyst with the CF_3 group exhibited a higher yield, confirming our hypothesis. Also, better results were observed in terms of enantioselectivity. Finally, we tested with the catalyst with more aromatic groups, which we hoped would increase the π-cation interaction. Yield increased to 33%, but the enantiomeric excess was only 3.8% (entry7).

Table 2.6. Screen of Chiral Guanidinium BArF Catalysts[a]



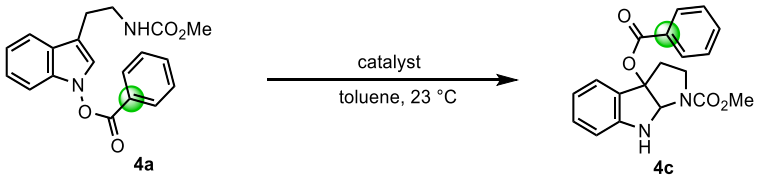
entry	catalyst	catalyst loading	time (h)	yield (%)[b]	ee (%)[c]
1	5aa	50 mol%	24	48	9.5
2	5ab	50 mol%	24	-	-
3	5ac	50 mol%	24	51	3.5
4	5ad	25 mol%	24	19	4.7
5	5ae	25 mol%	24	26	5.4
6	5af	25 mol%	24	30	11.6
7	5ag	25 mol%	24	33	3.8

[a]Reaction conditions: **1c** (0.056 mmol, 1.0 equiv) in toluene (0.05 M), 23 °C for 24 h. [b]The yield of product was determined by ^{1}H NMR analysis of the crude mixture using TCE as an internal standard. [c]Enantiomeric excess (%ee) was determined by HPLC analysis employing chiral stationary phase.



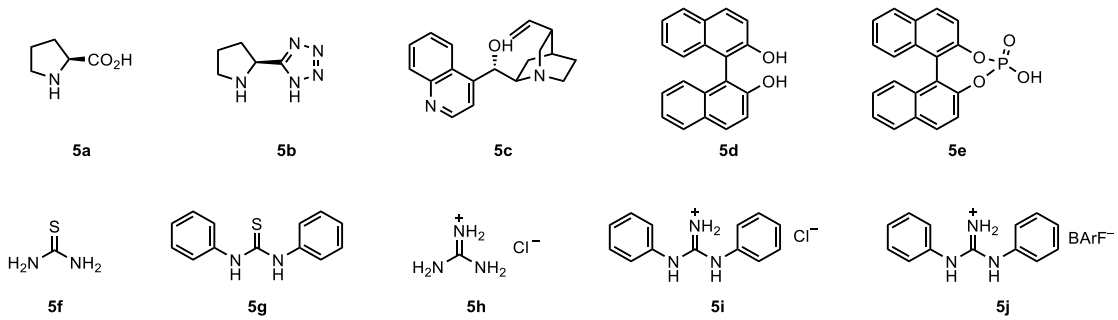
Investigation of hydrogen bond donors' reactivity was also carried out with the other appropriate substrate **4a** (Table 2.7). Screening result was same with the Table 2.3, only catalyst **5j** was able to proceeded the **IHT** reaction. However, the conversion rate was slower because the 2'-position was occupied by a carbon atom instead of an electron withdrawing nitrogen atom.

Table 2.7. Screen of Hydrogen Bond Donors[a]



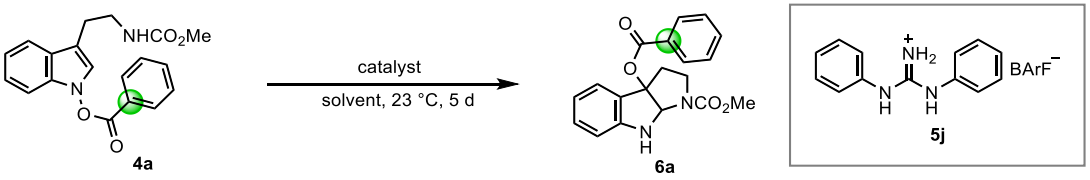
entry	catalyst	catalyst loading	time (d)	conv. (%)[b]
1	5a	50 mol%	3	0
2	5b	50 mol%	3	0
3	5c	50 mol%	3	0
4	5d	50 mol%	3	0
5	5e	50 mol%	3	0
6	5f	50 mol%	3	0
7	5g	50 mol%	3	0
8	5h	50 mol%	3	0
9	5i	50 mol%	3	0
10	**5j**	**50 mol%**	**3**	**33%**

[a]Reaction conditions: **1c** (0.059 mmol, 1.0 equiv) in toluene (0.05 M), 23 °C for 3 d. [b]The conversion of product was estimated from ^{1}H NMR spectroscopy.



With the effective bis(phenylamino)methaniminium BArF catalyst reaction time was adjusted (Table 2.8). When the reaction time was extended from 3 days to 5 days, the ratio of **4a** to **6a** increased from 1:0.50 to 1:1.85.

Table 2.8. Evaluation of Reacion Times[a]

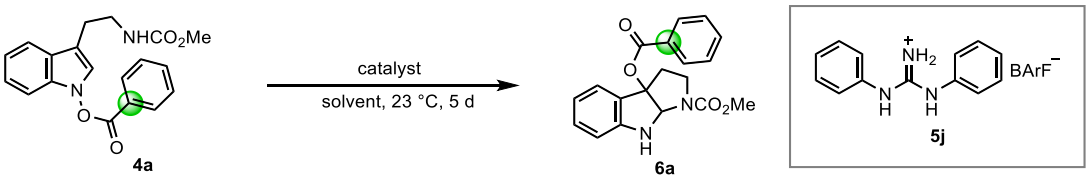


entry	catalyst	catalyst loading	time (d)	conversion SM : Pdt[b]
1	5j	50 mol%	3	1 : 0.50
2	5j	50 mol%	5	1 : 1.85

[a]Reaction conditions: **1c** (0.059 mmol, 1.0 equiv) in toluene (0.05 M), 2i (0.5 equiv), 23 °C. [b]The conversion ratios of product were determined by ^{1}H NMR analysis of the crude mixture.

Next, the solvent was also tested, and both nonpolar solvent hexane and Polar solvent CH_2Cl_2 showed similar results (Table 2.9).

Table 2.9. Evaluation of Solvents[a]

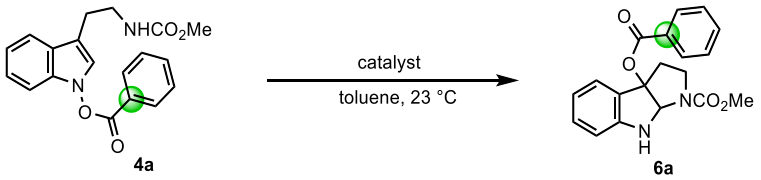


entry	catalyst	catalyst loading	solvent	yield (%)[b]
1	5j	50 mol%	toluene	16
2	5j	50 mol%	hexane	15
3	5j	50 mol%	CH_2Cl_2	16

[a]Reaction conditions: **1c** (0.059 mmol, 1.0 equiv) in solvent (0.05 M), 23 °C for 5 d. [b]The yield of product was determined by ^{1}H NMR analysis of the crude mixture using TCE as an internal standard.

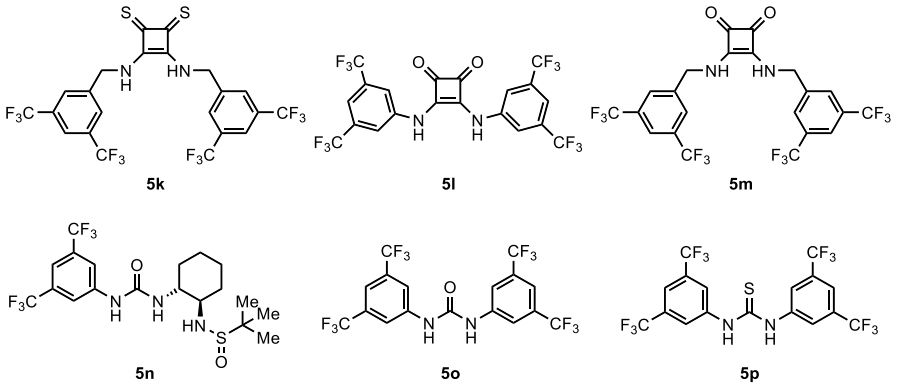
Then, we conducted screening of hydrogen bond donors with electron withdrawing group (Table 2.10). And it was discovered that indolyl benzoate requires more acidic conditions to activate the reaction.

Table 2.10. Screen of Hydrogen Bond Donors with Electron Withdrawing Group[a]



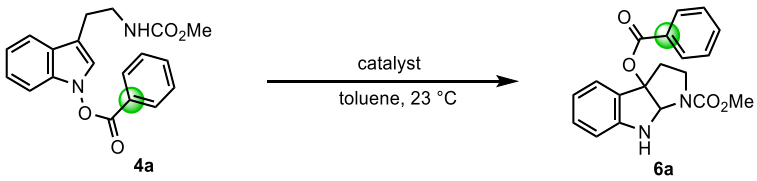
entry	catalyst	catalyst loading	time (d)	yield (%)[b]
1	5k	20 mol%	12	0
2	5l	20 mol%	12	0
3	5m	20 mol%	12	0
4	5n	20 mol%	12	0
5	5o	20 mol%	12	0
6	5p	20 mol%	12	0

[a]Reaction conditions: **1c** (0.044 mmol, 1.0 equiv) in toluene (0.05 M), 23 °C for 12 d. [b]The yield of product was determined by ^{1}H NMR analysis of the crude mixture using TCE as an internal standard.



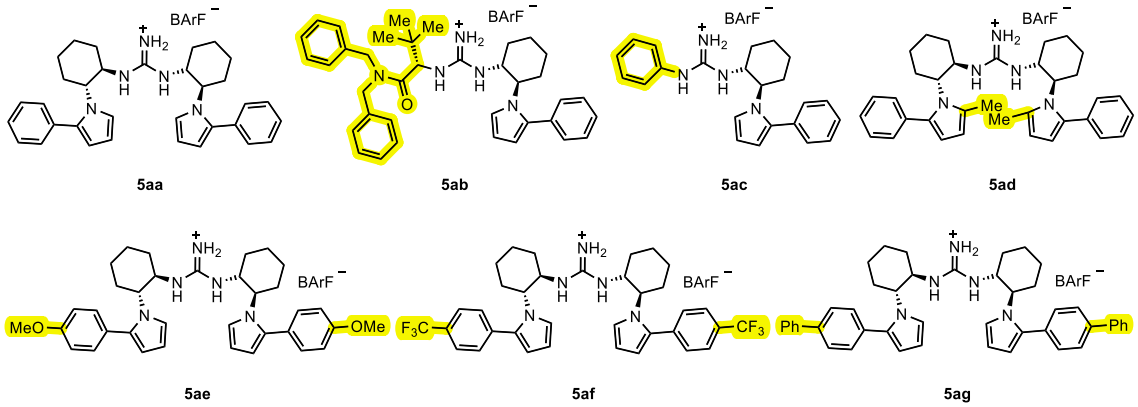
Finally, we utilized chiral guanidinium with BArF as the counterion to investigate the effect of introducing reactivity and enantioselectivity in indolyl benzoate system. And the results were similar to indolyl carbamate system. After loading the catalyst **5aa** at a concentration of 50 mol% for 12 days, 6a was obtained with a yield of 15.4% and an enantiomeric excess of 6.9% (entry 1). Catalyst **5ab** failed to initiate the reaction (entry 2). Additionally, when we used a catalyst with one half was being aniline, the yield increased but the enantioselectivity decreased (entry 3). Reaction with **5ad** catalyst provide yield of 9.6% and ee of 5.3% (entry 4). The catalyst with electron-withdrawing group, **5af** gave the better yield. However, in the indolyl benzoate system, the enantiomeric excess value was lower compared to the result obtained with **5aa** (entry 6). Lastly, we tested with the catalyst that could increase the π-cation interaction, **5ag**. The yield was 8.3%, and the enantiomeric excess was 13.2% (entry7).

Table 2.11. Screen of Chiral Guanidinium BArF Catalysts[a]



entry	catalyst	catalyst loading	time (d)	yield (%)[b]	ee (%)[c]
1	5aa	50 mol%	12	15.4	6.9
2	5ab	50 mol%	12	-	-
3	5ac	50 mol%	12	18.9	3.7
4	5ad	50 mol%	12	9.6	5.3
5	5ae	50 mol%	12	16.0	
6	5af	50 mol%	12	19.2	4.5
7	5ag	50 mol%	12	18.3	13.2

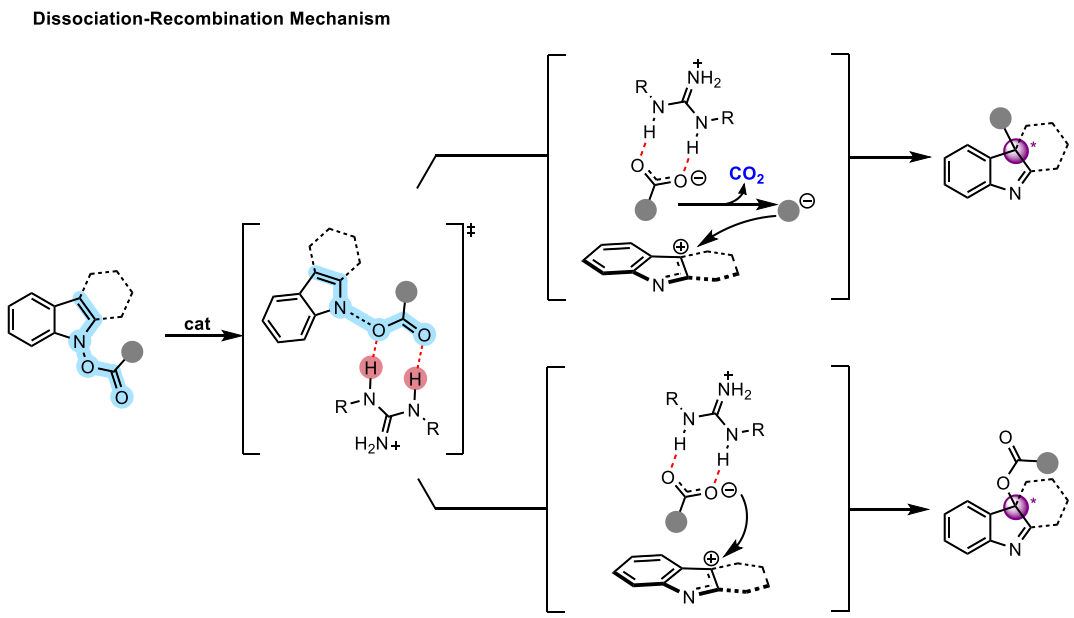
[a]Reaction conditions: **1c** (0.059 mmol, 1.0 equiv) in toluene (0.05 M), 23 °C for 12 d. [b]The yield of product was determined by ^{1}H NMR analysis of the crude mixture using TCE as an internal standard. [c]Enantiomeric excess (%ee) was determined by HPLC analysis employing chiral stationary phase.



2.2.2. Plausible Reaction Mechanism

Based on previous studies, a plausible reaction mechanism is proposed in Figure 2.6. The guanidinium catalyst with a non-coordinating BArF ion, first undergoes a transition state involving hydrogen bonding. Then, the labile N–O bond is cleaved. After such dissociation occurs, in the case of indolyl carbamate, decarboxylation of the detached fragment takes place, leading to the substitution of the amine anion at the C3 position of the umpolung-reactive indole. In the case of indolyl benzoate, recombination proceeds without the decarboxylation step. In conclusion, the guanidinium-catalyzed **IHT** reaction proceeds through a dissociative pathway.

Figure 2.6. Plausible Reaction Mechanism



2.3. Conclusion

Based on the electron-withdrawing effect at the 2'-position, an internal factor that enhances the **IHT** reaction, we aimed to develop an enantioselective approach by simultaneously inducing an external electron-withdrawing effect and creating a chiral environment. In the indolyl *N*-carbamate system, promising results were achieved with C3-amidation, exhibiting an enantiomeric excess of up to 11.6%. Also, C3-oxygenation was observed in the benzoate system,

with up to 13.2% of enantiomeric excess. This outcome suggests that the **IHT** reaction using the guanidinium organic catalyst proceeds through a dissociative pathway.

2.4. References

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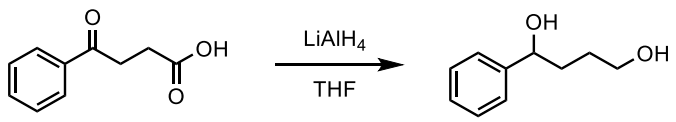
2.5. Experimental Section

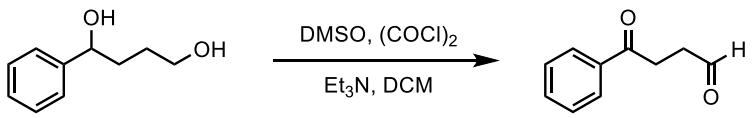
2.5.1. General Experimental Information

Unless stated, reactions were carried out in flame-dried glassware under an argon atmosphere with dry solvents under anhydrous conditions. Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), and *N,N*-Dimethylformamide (DMF) were were obtained from a PureSolv solvent purification system and toluene was dried over CaH_2 and distilled under N_2 atmosphere. Dimethyl sulfoxide (DMSO), 1,2-dichloroethane (DCE), acetonitrile (MeCN) were purchased in anhydrous form from Sigma Aldrich. Commercially available HPLC grade *n*-hexane and toluene were used without purification. Acetone, ethyl acetate (EtOAc), diethyl ether (Et_2O), CH_2Cl_2, *n*-hexane, and water (H_2O) were purchased from Samchun Chemical and used without further purification. Other reagents were purchased from Sigma Aldrich, Alfa Aesar, Acros Organics, and TCI with the and used as received. Thin-layers chromatography (TLC) analysis of reactions was performed on 0.25 mm E. Merck silica gel plates (60 F_{254}). TLC plates were visualized by UV light and treated with staining solution such as an acidic ethanolic anisaldehyde or potassium permanganate ($KMnO_4$). Flash column chromatography was performed on Intertec Silica gel (60–200 μm). ^{1}H, ^{11}B, ^{13}C and ^{19}F NMR spectra were recorded with Agilent 400-MR DD2 Magnetic Resonance System, Bruker 500 MHz instrument of Varian/Oxford As-500 instrument in solvents as indicated. Chemical shifts are quoted in parts per million (ppm) and referenced to residual un-deuterated solvent signal ($CHCl_3$ in $CDCl_3$: δ 7.26 ppm for ^{1}H, δ 77.16 ppm for ^{13}C; CH_3OH in MeOD: δ 3.31 ppm for ^{1}H, δ 49.00 ppm for ^{13}C). ^{11}B NMR spectra were referenced to external $BF_3{\cdot}OEt_2$ (δ 0.0 ppm). ^{19}F NMR spectra were calibrated to an external standard of neat $PhCF_3$ (δ –63.72 ppm). Coupling constants are reported in Hertz. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. The enantiomeric excess (*ee*) was determined using High-Performance Liquid Chromatography (HPLC) performed on Shimadzu C196-E061W (degassing unit: DGU-20A5R, pump: LC-20AD, auto sampler: SIL-20A, communication bus module: CBM-20A, UV/Vis detector: SPD-20A, and column oven: CTO-20A) using commercial Chiralcel OD (10 μm particle size, 4.6 mm vs. 250 mm).

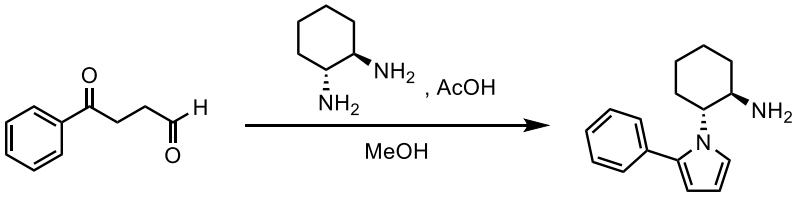
2.5.2. General Procedure for the Preparation of Guanidinium Catalysts[16]



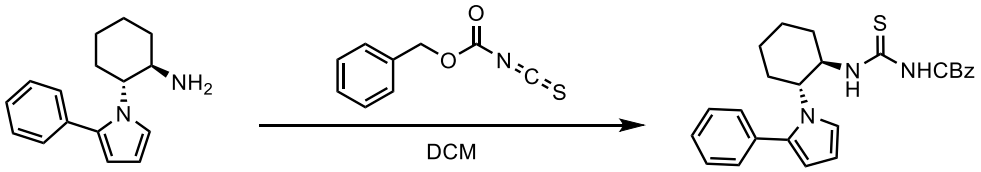
Reduction. To a stirred solution of $LiAlH_4$ (300 mg, 8.0 mmol, 4.0 eq) in 40 mL of THF was added dropwise benzoylpropionic acid (356 mg, 2.0 mmol, 1.0 eq, in 50 mL of THF) at 0 °C. The reaction mixture was warmed up to rt and stirred overnight. Then, reaction mixture was cooled to 0 °C and quenched by successive dropwise addition of 3 mL H_2O, 3 mL 15% NaOH (aq), and 9 mL H_2O. After stirring at rt for 20 min, $MgSO_4$ was added, and the mixture was filtered through a plug of celite (washing with THF). The filtrate was concentrated *in vacuo*. 270 mg of a white solid (80% yield) was used directly for the next step.



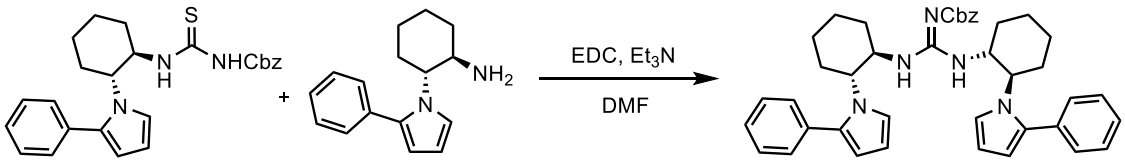
Swern Oxidation. To a stirred solution of DMSO (0.70 mL, 9.7 mmol, 6.0 eq) in 20 mL of CH_2Cl_2 was added dropwise oxalyl chloride (0.56 mL, 6.5 mmol, 4.0 eq) at −78 °C. The diol (270 mg, 1.6 mmol, 1.0 eq) in 100 mL of CH_2Cl_2 was added dropwise after 10 min stirring at −78 °C. Stirring was continued at −78 °C for 10 min. Et_3N (2.2 mL, 16 mmol, 10.0 eq) was added after 10 min stirring at −78 °C. The reaction mixture was warm up to rt and diluted with 40 mL of Et_2O. The organic layer was washed successively with water (3 × 20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (silica gel, hexanes:EtOAc = 4:1 → 2:1) to afford 267 mg of a clear oil.



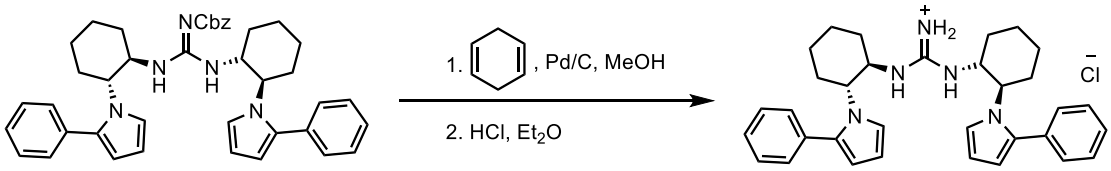
Paal-Knorr Pyrrole Synthesis. To a stirred solution of the keto-aldehyde (267 mg, 1.6 mmol, 1.0 eq) in 8 mL of MeOH was added (*R*,*R*)-1,2-*trans*-diaminocyclohexane (226 mg, 1.9 mmol, 1.2 eq). The reaction flask was evacuated and back-filled with N_2 gas three times. Acetic acid (0.1 mL, 1.9 mmol, 1.2 eq) was added, and the reaction mixture was stirred at 50 °C for 14 h. Then the reaction mixture was cooled to rt and poured into 40 mL of 15% aqueous NaOH. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (silica gel, CH_2Cl_2:MeOH = 95:5) to afford 211 mg of a pale brown oil.



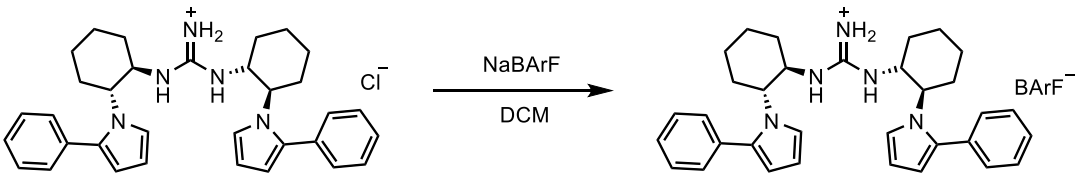
Thiourea Formation. To a stirred solution of amine (100 mg, 0.4 mmol, 1.0 eq) in 5 mL of CH_2Cl_2 was added dropwise NCS-Cbz (77 mg, 0.4 mmol, 1.0 eq) at ambient temperature. The reaction mixture was stirred for 15 min, then the solvent was evaporated *in vacuo*. The resulting residue was washed with hexanes (3 × 5 mL) to remove trace amounts of NCS-Cbz. Drying under vacuum gave in quantitative yield a light brown oil that used directly for the next step.



Guanidine Formation. To a stirred solution of the amine and thiourea in 50 mL of DMF were added Et_3N (0.3 mL, 2.2 mmol, 5.0 eq) and EDC (0.16 g, 0.8 mmol, 2.0 eq). The reaction mixture was stirred overnight at 50 °C. Then, the reaction solution was diluted with 250 mL of EtOAc and successively washed with 1M HCl (aq, 20mL), sat $NaHCO_3$ (aq, 20mL), and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to afford 257 mg of a pale brown solid that used directly for the next step.



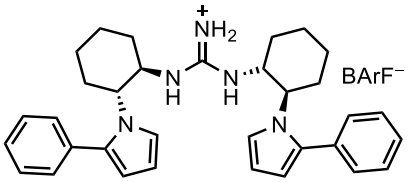
Transfer Hydrogenolysis. The Cbz-protected guanidine (257 mg, 0.4 mmol, 1.0 eq) was suspended in 16 mL of MeOH. The reaction flask was evacuated and back-filled with N_2 gas three times, and Pd/C (10 wt%, 500 mg, 200 wt% relative to SM) was added. 1,4-cyclohexadiene (0.76 mL, 8.0 mmol, 20.0 eq) was added dropwise to a reaction mixture in an ambient temperature. The reaction mixture was stirred at room temperature while the reaction was monitored by TLC. After 24 h, the reaction mixture was filtered through a celite plug (washing with MeOH). To a stirred solution of filtrate was addede dropwise 2M HCl in Et_2O (5 mL, 10.0 mmol, 2.5 eq) at −78 °C. The reaction mixture was allowed to warm up to rt, and the solvent and excess HCl were removed directly *in vacuo* to afford 173 mg of pale red solid, that used directly for the next step.



Counterion Metathesis. To a stirred solution of the guanidinium chloride (173 mg, 0.3 mmol, 1.0 eq) in 60 mL of CH_2Cl_2 was added NaBArF (319 mg, 0.3 mmol, 1.0 eq). The reaction mixture was stirred at rt for 15 min. The mixture was filtered through a plug of celite (washing with CH_2Cl_2), and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, CH_2Cl_2:MeOH = 95:5) to afford 300 mg of an off-white solid.

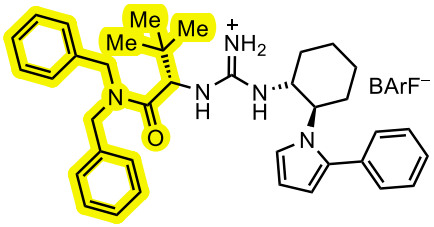
2.5.3. Characterization Data of Chiral Guanidinium Catalysts

bis(((1R,2R)-2-(2-phenyl-1H-pyrrol-1-yl)cyclohexyl)amino)methaniminium BArF (5aa)



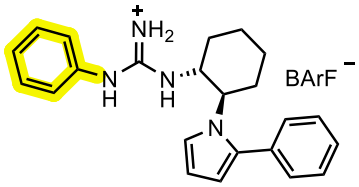
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (s, 8H), 7.52 (s, 4H), 7.30 (t, *J* = 7.3 Hz, 4H), 7.25 (t, *J* = 6.8 Hz, 2H), 7.00 (d, *J* = 7.3 Hz, 4H), 6.86 (s, 2H), 6.35 (t, *J* = 2.9 Hz, 2H), 6.06 (br s, 2H), 4.15 (br s, 2H), 3.91 (t, *J* = 9.5 Hz, 2H), 3.55 (br s, 2H), 3.00 (br m, 2H), 2.35 (br d, *J* = 13.2 Hz, 2H), 1.99 – 1.84 (m, 8H), 2.37 (m, 4H), 1.07 (br q, *J* =12.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 161.8 (q, $^1J_{B–C}$ = 49.3 Hz), 154.6, 136.9, 135.0, 132.2, 129.2, 129.0 (q, $^2J_{C–F}$ = 30.0 Hz), 128.7, 128.3, 124.7 (q, $^1J_{C-F}$ = 270.5 Hz), 117.6, 115.8, 112.4 110.5, 60.5, 59.2, 33.6, 31.6, 24.6, 24.4; **^{11}B NMR** (96 MHz, $CDCl_3$): δ –6.56 (s); **^{19}F NMR** (282 MHz, $CDCl_3$): δ –62.67 (s).

(((S)-1-(dibenzylamino)-3,3-dimethyl-1-oxobutan-2-yl)amino)(((1R,2R)-2-(2-phenyl-1H-pyrrol-1-yl)cyclohexyl)amino)methaniminium BArF (5ab)



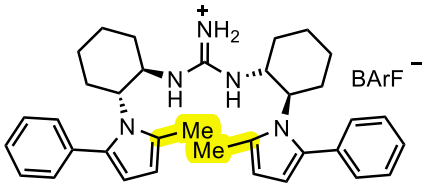
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (s, 8H), 7.52 (s, 4H), 7.41–7.27 (m, 10H), 7.17 (d, *J* = 7.1 Hz, 3H), 6.95 (s, 2H), 6.86 (s, 1H), 6.30 (s, 1H), 6.15 (s, 1H), 5.32 (d, *J* = 16.2 Hz, 1H), 4.66 (d, *J* = 18.5 Hz, 1H), 4.30 (d, *J* = 17.0 Hz, 1H), 3.89 – 3.81 (d, *J* = 14.8 Hz, 3H), 2.96 (br s, 1H), 2.30 (br d, *J* = 16.8 Hz, 1H), 1.89 – 1.64 (m, 4H), 1.37 – 1.31 (m, 2H), 1.07(br q, *J* =12.0 Hz, 1H), 0.88 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 161.8 (q, $^{1}J_{B–C}$ = 49.3 Hz), 154.6, 136.9, 135.0, 132.2, 129.2, 129.0 (q, $^{2}J_{C–F}$ = 30.0 Hz), 128.7, 128.3, 124.7 (q, $^{1}J_{C-F}$ = 270.5 Hz), 117.6, 115.8, 112.4 110.5, 60.5, 59.2, 33.6, 31.6, 24.6, 24.4; **^{11}B NMR** (128 MHz, $CDCl_3$): δ –6.63 (s); **^{19}F NMR** (471 MHz, $CDCl_3$): δ –62.30 (s).

(((1R,2R)-2-(2-phenyl-1H-pyrrol-1-yl)cyclohexyl)amino)(phenylamino)methaniminium BArF (5ac)



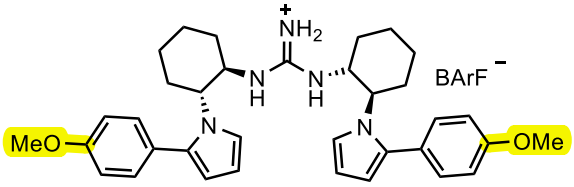
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (s, 8H), 7.54 (s, 4H), 7.46–7.40 (m, 6H), 7.28–7.24 (m, 2H), 7.00 (d, *J* = 13.2 Hz, 2H), 6.52 (s, 1H), 6.37 (s, 1H), 4.95–4.64 (m, 1H), 4.06 (s, 1H), 3.28 (d, *J* = 11.4 Hz, 1H), 2.44 (d, *J* = 8.3 Hz, 1H), 1.98 – 1.77 (m, 2H), 1.50 – 1.31 (m, 4H), 1.12 (d, *J* = 16.3 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 161.8 (q, $^{1}J_{B–C}$ = 50.3 Hz), 154.7, 137.7, 134.7, 132.3, 130.1, 129.1, 128.4 (q, $^{2}J_{C–F}$ = 28.8 Hz), 128.7, 128.3, 127.8, 125.7, 124.7 (q, $^{1}J_{C-F}$ = 275.8 Hz), 117.5, 115.8, 112.4 110.5, 60.2, 59.3, 32.9, 29.9, 24.6, 24.4; **^{11}B NMR** (128 MHz, $CDCl_3$): δ –6.63 (s); **^{19}F NMR** (471 MHz, $CDCl_3$): δ –62.29 (s).

bis(((1R,2R)-2-(2-methyl-5-phenyl-1H-pyrrol-1-yl)cyclohexyl)amino)methaniminium BArF (5ad)



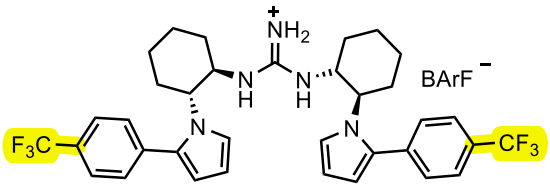
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (s, 8H), 7.55 (s, 4H), 7.40 (d, *J* = 4.4 Hz, 2H), 7.3–7.29 (m, 6H), 7.03 (d, *J* = 7.8 Hz, 2H), 6.03 (s, 2H), 5.95 (s, 2H), 4.53 (s, 2H), 4.04–3.92 (m, 2H), 3.86 (s, 2H), 3.62 – 3.45 (m, 2H), 3.29 (br m, 2H), 2.45 (s, 6H), 2.27 (br d, *J* = 12.0 Hz, 2H), 1.95 – 1.75 (d, *J* = 11.1 Hz, 8H), 1.34 – 1.27 (d, *J* = 14.9 Hz, 4H), 1.02 – 0.96 (2H, br q, *J* =12.0 Hz); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 161.8 (q, $^{1}J_{B–C}$ = 49.3 Hz), 154.6, 138.0, 135.0, 133.5, 133.1, 129.0 (q, $^{2}J_{C–F}$ = 32.0 Hz), 128.8, 128.2, 124.7 (q, $^{1}J_{C-F}$ = 270.5 Hz), 117.6, 116.2, 113.0, 109.6, 60.5, 57.0, 33.9, 30.7, 25.0, 24.4, 16.2; **^{11}B NMR** (128 MHz, $CDCl_3$): δ –6.67 (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ –62.31 (s).

bis(((1R,2R)-2-(2-(4-methoxyphenyl)-1H-pyrrol-1-yl)cyclohexyl)amino)methaniminium BArF (5af)



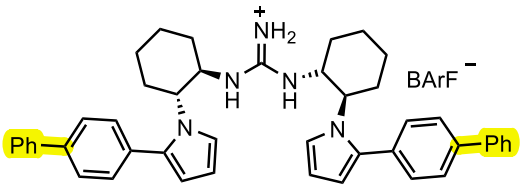
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (s, 8H), 7.53 (s, 4H), 6.94 (d, *J* = 8.3 Hz, 4H), 6.85 (s, 2H), 6.82 (d, *J* = 7.6 Hz, 4H), 6.33 (s, 2H), 6.01 (s, 2H), 4.52 (d, *J* = 6.5 Hz, 2H), 3.92–3.79 (m, 2H), 3.72 (s, 6H), 3.59 (br s, 2H), 3.09–2.92 (m, 2H), 2.30 (br d, *J* = 14.0 Hz, 2H), 1.99 – 1.81 (8H, m), 1.45 – 1.23 (m, 4H), 1.19 – 1.02 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 161.8 (q, $^{1}J_{B–C}$ = 49.2 Hz), 154.6, 136.7, 134.9, 132.2, 129.2, 129.0 (q, $^{2}J_{C–F}$ = 34.1 Hz), 128.8, 128.5, 124.9 (q, $^{1}J_{C-F}$ = 267.4 Hz), 117.6, 115.2, 112.2 110.0, 60.4, 59.0, 55.4, 33.6, 31.7, 24.6, 24.4; **^{11}B NMR** (161 MHz, $CDCl_3$): δ –6.61 (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ –62.31 (s).

bis(((1R,2R)-2-(2-(4-(trifluoromethyl)phenyl)-1H-pyrrol-1-yl)cyclohexyl)amino) methaniminium BArF (5ag)



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (s, 8H), 7.58 (d, *J* = 7.9 Hz, 4H), 7.53 (s, 4H), 7.15 (d, *J* = 7.8 Hz, 4H), 6.86 (s, 2H), 6.32 (s, 2H), 6.04 (s, 2H), 4.78 (br s, 2H), 3.86–3.66 (m, 2H), 3.00 (br d, *J* = 12.7 Hz, 2H), 2.31 (br d, *J* = 14.6 Hz, 2H), 1.91 – 1.79 (m, 6H), 1.36 – 1.23 (m, 6H), 1.18 – 1.00 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 161.8 (q, $^{1}J_{B–C}$ = 49.9 Hz), 155.0, 135.7, 135.1, 134.9, 130.4, 130.1, 129.0 (q, $^{2}J_{C–F}$ = 33.0 Hz), 128.7, 128.5, 124.7 (q, $^{1}J_{C-F}$ = 270.5 Hz), 117.6, 117.0, 112.7 111.6, 60.6, 59.5, 33.7, 31.9, 24.5, 24.2; **^{11}B NMR** (161 MHz, $CDCl_3$): δ –6.62 (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ –62.31 (s), –62.74 (s).

bis(((1R,2R)-2-(2-([1,1'-biphenyl]-4-yl)-1H-pyrrol-1-yl)cyclohexyl)amino)methaniminium (5ah)



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (s, 8H), 7.57 (d, *J* = 8.1 Hz, 4H), 7.53 (s, 6H), 7.51 (s, 2H), 7.42 (t, *J* = 7.5 Hz, 4H), 7.37 (d, *J* = 7.3 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 4H), 6.87 (s, 2H), 6.36 (t, *J* = 2.9 Hz, 2H), 6.10 (s, 2H), 4.63 (s, 2H), 3.98–3.93 (m, 2H), 3.65 (br s, 2H), 3.04 (br d, *J* = 7.4 Hz, 2H), 2.37 (br d, *J* = 11.8 Hz, 2H), 1.98 – 1.84(m, 8H), 1.40 – 1.34 (m, 4H), 1.14 – 1.00 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 161.8 (q, $^{1}J_{B–C}$ = 49.8 Hz), 154.8, 136.5, 134.9, 131.1, 129.2, 129.2, 128.9 (q, $^{2}J_{C–F}$ = 34.1 Hz), 128.7, 128.3, 127.7, 126.9, 124.7 (q, $^{1}J_{C-F}$ = 274.5 Hz), 117.6, 116.1, 112.5 110.7, 60.4, 59.3, 33.7, 31.7, 24.6, 24.4; **^{11}B NMR** (128 MHz, $CDCl_3$): δ –6.37 (s); **^{19}F NMR** (471 MHz, $CDCl_3$): δ –62.29 (s).

국문초록

인돌릴-1,3-헤테로원자 전위: 메커니즘 조사와 적용

남윤승

서울대학교 자연과학대학 화학부

본문에서는 인돌 3번탄소-헤테로 작용기화에 대한 효과적이고 다용도적인 접근법으로서 질소-하이드록시인돌의 1,3-헤테로 원자 전위 반응을 소개합니다. 이 반응의 고유한 특성을 밝히기 위해 ^{18}O 표지 실험, 교차 실험, 라디칼 실험 등 다양한 관점에서 실험을 수행했습니다. 결과는 두 개의 독립적인 메커니즘의 동시적인 참여를 보여주었으며, 이는 반응의 독특한 이중성 특성을 강조합니다. 또한 내부 치환체의 전자적 특성이 반응의 주요 경로를 조절하고 각 경로의 활성화 에너지를 제어한다는 사실이 밝혀졌습니다. 또한, 수소 결합을 통해 IHT 반응을 촉진하는 외부 카이랄 구아니디니움 유기 촉매를 사용한 거울상 이성질 선택적 반응으로의 확장 가능성도 탐구하였습니다.

주요어: 질소-하이드록시인돌, 헤테로 원자, 메커니즘, 이중성, 구아니디니움 촉매, 수소 결합

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