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Stereodivergent and enantioselective total syntheses of chaetominine-type alkaloids and azaphilic radical cascade cyclization for the synthesis of imidazo-fused heteroaromatics and toward analogs of the 2-Carboxyl-6-HydroxyOctahydroIndole (CHOI) Unit

Zhongyi Mao

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**DOCTORAL THESIS OF
XIAMEN UNIVERSITY
UNIVERSITÉ PIERRE ET MARIE CURIE**

Department of Chemistry
Ecole Doctorale de Chimie Moléculaire / Equipe ROCS

Present by

Zhongyi Mao

Thesis title:

Stereodivergent and enantioselective total syntheses of chaetominine-type alkaloids and Azaphilic radical cascade cyclization for the synthesis of imidazo-fused heteroaromatics and Toward analogs of the 2-Carboxyl-6-HydroxyOctahydroIndole (CHOI) Unit

Ph.D. Supervisors: Professor Haichao Xu

Professor Giovanni Poli

Professor Peiqiang Huang

Members of Jury:

Prof. Hongli Bao	Fujian Institute of Research on the Structure	Rapporteur
Dr. Bruno Figadère	BioCIS	Rapporteur
Prof. Peiqiang Huang	Xiamen University	Examineur
Prof. Dongping Zhan	Xiamen University	Examineur
Prof. Giovanni Poli	Université Pierre et Marie Curie, Paris	Examineur
Dr. Cyril Ollivier	Université Pierre et Marie Curie, Paris	Examineur
Dr. Julie Oble	Université Pierre et Marie Curie, Paris	Examineur

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Abbreviation

Ac	acetyl
Allyl	propylene
aq.	aqueous solution
Ar	aryl
atm	atmosphere
Bn	benzyl
Boc	<i>t</i> -butoxycarbonyl
Bu	butyl
CAN	cericammomium nitrate
Cbz	benzyloxycarbonyl
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
DEPBT	3-(diethoxyphosphoryloxy)-1,2,3-benzotrizin-4(3 <i>H</i>)-one
DIBAL-H	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMAP	4- <i>N,N</i> -dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMDO	dimethyldioxirane

DMSO	dimethylsulfoxide
EtOAc	ethyl acetate
ESI	electrospray ionization
2-F-Py	2-fluoropyridine
HRMS	high-resolution mass spectroscopy
IR	infrared
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	bis(trimethylsilyl)amine lithium
MS	mass spectroscopy
mp	melting point
NaHMDS	bis(trimethylsilyl)amine sodium
NCS	<i>N</i> -chlorosuccinimide
NMM	<i>N</i> -methylmorpholine
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
PE	petroleum ether
Ph	phenyl
PMB	<i>p</i> -methoxybenzyl
Pyr	pyridine
TBAF	tetrabutylammonium fluoride

TBDPS	<i>t</i> -butyldiphenylsilyl
TBS	<i>t</i> -butyldimethylsilyl
TEA	triethylamine
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TES	triethylsilyl
TESOTf	triethylsilyl trifluoromethanesulfonate
TFA	trifluoroacetic acid
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	trimethylsilyl
TMSOTf	trimethylsilyl triflate
Troc	2,2,2-trichloroethoxycarbonyl
Ts	tosyl

Chapter 1 General Introduction

Many natural products are exist in extremely low concentration in nature and cannot be obtained in sufficient quantity for scientific exploration. The total synthesis of natural products has been demonstrated to be a valuable approach to obtain sufficient material for research and applications. In addition, natural product synthesis is also a useful avenue for determination of the structure of natural products. Moreover, we can design and synthesis analogues or substructures of natural products for structure-activity studies in order to obtain compounds with desired properties for applications in phamarceutical, agricultural, and food industries.

Traditionally, total synthesis of complex natural products and drugs was usually through target-oriented synthesis (TOS).¹ However, more and more examples revealed that many natural product coexist with different stereoisomers in nature.² Using traditional TOS method for the synthesis of different stereoisomers of natural products usually require the use of different raw materials and/or synthetic route.³ The vast majority of natural products have nonplanar spatial structure and different stereoisomers usually show different physiological activity. Therefore the development of efficient synthetic strategy that is applicable to all the stereoisomers of a class of natural product is crucial for the structure determiantion⁴ and investigation of structure-activity relationship.⁵

DOS is a concept that has been proposed during the development of combinatorial chemistry and is introduced to increase the synthetic efficiency of compound libraries.⁶ Compared with conventional TOS, DOS emphasis on the access of diverse structures from a set of starting materials.

Diversity oriented synthesis (DOS) based on the non-selective reaction strategy has received little attention because the production of two or more diastereomers from a single reaction is usually considered synthetically inefficient in organic synthesis.⁷ However, if the resulting diastereoisomers can be used for the synthesis of different target molecules, the non-selective reaction becomes beneficial to the stereodiversity

synthesis of a target scaffold. Of course, the success of this strategy requires that the stereoisomers formed can be easily separated.

Endophytic fungi are abundant source of natural products with diverse structures and important physiological properties.⁸ (-)-Chaetominine⁹ (Figure 1.1), the first member from these sources, was the first isolated by Tan *et al.* in 2006 from the solid-substrate culture of *Chaetomium* sp. IFB-E015, an endophytic fungus on apparently healthy *Adenophora axilliflora* leaves.^{9a} After the isolation of (-)-chaetominine, several homologues and diastereomers of (-)-chaetominine have been isolated from different fungi by many research groups, and characterized as (-)-pseudofischerine,¹⁰ (-)-aniquinazoline D,¹¹ (-)-isochaetominines A–C,¹² (+)-14-*epi*-isochaetominine C¹² and isochaetominine¹³, respectively. Interesting, except 11-*epi*-isochaetominine C, all other 2,3-*cis*-diastereomers of isochaetominine C and isochaetominine have been reported to be natural products.

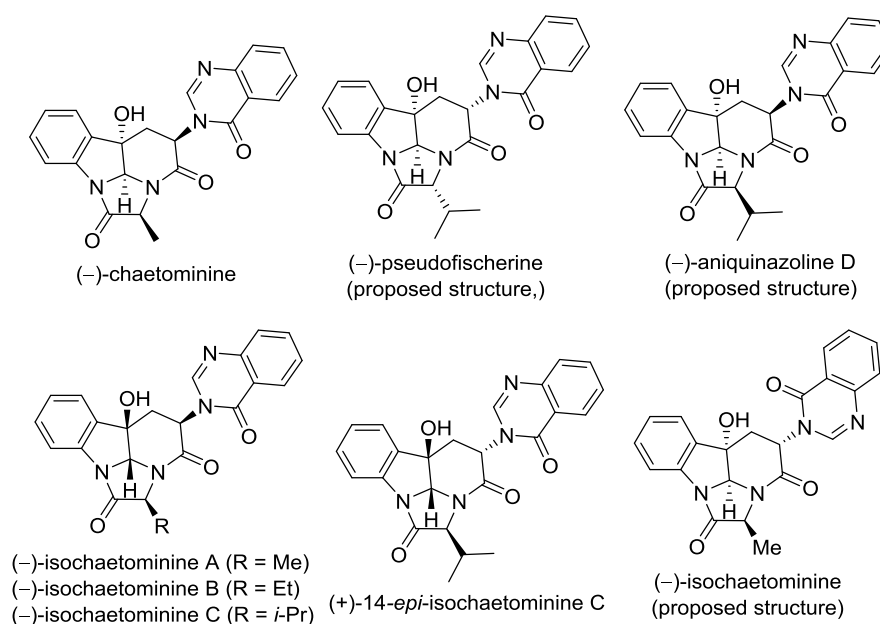


Figure 1.1

These alkaloids⁹⁻¹³ have a novel skeleton consisting of a tripeptide, they are also classified as quinazolinone alkaloids because of the quinazolinone ring present in these structures. Our group has reported in 2009 a concise four-step total synthesis of (-)-chaetominine starting from D-tryptophan^{14a} and later a five-step synthesis of (-)-chaetominine from L-tryptophan.^{14b}

The first goal of this thesis: based on the previous results from our group's research for the synthesis of (-)-chaetominine,¹⁴ in combination with the critical indole epoxidation step in the synthesis route, two roughly equal amounts diastereoisomers were obtained and several homologues and diastereomers of (-)-chaetominine have been reported, we aim to develop a concise, efficient and stereodivergent synthesis of (-)-aniquinazoline D,¹¹ (-)-isochaetominines C¹² and (+)-14-*epi*-isochaetominine C,¹² as well as the total synthesis of (-)-pseudofischerine,¹⁰ (-)-isochaetominines A, B¹² and (-)-isochaetominine.¹³

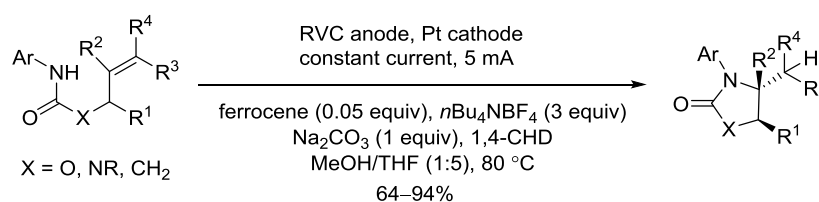
Further increase the efficiency and sustainability of organic synthesis is among the major goals of modern synthetic organic chemistry. These discoveries allow more flexible disconnections of a target molecule and thus streamline the synthetic sequence and increase the atom-¹⁵ and step-economy.¹⁶ The high reactivity of many radical intermediates allow radical reaction to become more and more important and useful synthetic tool.¹⁷ Relative to the widely studied carbon radicals, research on nitrogen radicals is relatively rare due to the lack of knowledge on their reactivities shortage of convenient methods for their preparation.¹⁸

Nitrogen radicals are potentially powerful intermediates for C–N bond formation due to their high reactivity. Particularly, the electrophilic amidyl radicals have received more and more attention due to its facile reaction with unsaturated systems such as aromatic rings and alkenes.¹⁹

Nitrogen radicals are traditionally generated through homolytic cleavage of a weak N–X bond (X = halogen, N, O, S, etc.). In recent years, the oxidative activation of N–H bond has been emerged as a more powerful method due to the availability of the starting materials and the inherent high atom- and step economy.²⁰ Nicolaou,^{20a} Chiba,^{20b} Zheng,^{20c} Li,^{20d} Xiao^{20e} and Knowles^{20f} have reported that the activation N–H bond method for the generation of amidyl radicals through the use of chemical oxidants or photoredox catalysis. These methods usually require the use of stoichiometric chemical oxidants or noble metal catalysts, which bring safety and/or cost issues to large scale production. In addition, reported methods are usually limited redox neutral transformations and net oxidation reactions remain rare.

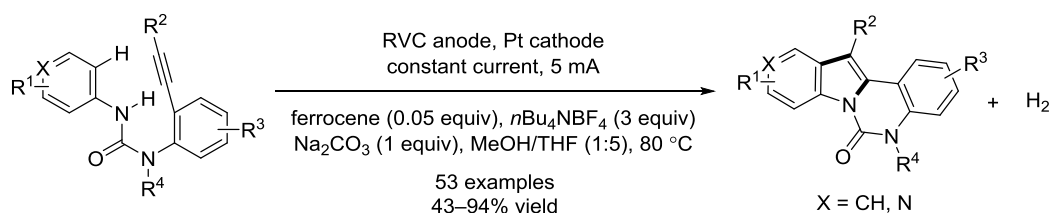
Electrochemical synthesis has been recognized as a "green synthetic tool" because electrons are used to replace stoichiometric chemical oxidants.²¹ Electrochemical oxidation of amide N–H bonds can be achieved by direct electrolysis or indirect electrolysis. The direct electrolysis is that the reactant directly oxidized or reduced on the surface of the electrode to obtain the final product. The indirect electrolysis rely on a kind of "media" with redox property, which is first oxidized or reduced on the surface of the electrode, and then the medium reacts with the organic substrate to obtain the product. While in the process of electrolysis reaction the medium can be regenerated by oxidation or reduction, which can participate in chemical reactions in the next time, until the completion of the electrolytic reaction, the "media" act as an electron transfer catalyst role. Compared with direct electrolysis, indirect electrolysis has the advantages of avoiding electrode passivation, eliminating kinetic inhibition and high selectivity .²²

Our group has involved in the development of sustainable redox reactions for organic synthesis using organic electrochemistry.²³ In 2016, our group reported the generation of amidyl radicals by electrocatalytic oxidation of N–H bonds and applied this method for the development of alkene hydroamination reactions (Scheme 1.1).^{23b} The electrochemical method is characterized by its mild conditions, broad substrate scope, high compatibility with many common functional groups.



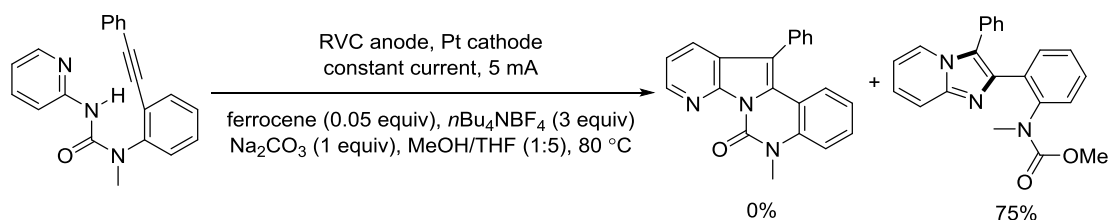
Scheme 1.1

Later on, a similar catalytic system was applied for the intramolecular coupling of aryl amines with alkynes to synthesize highly functionalized indoles and azaindoles (Scheme 1.2).^{23c}



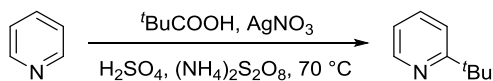
Scheme 1.2

In the course of these studies, unexpected results were obtained when Mr. Zhong-Wei Hou studied the cyclization of a 2-aminopyridine-derived substrate. The cyclization of this compound did not afford any of the azaindole product. Instead, imidazo[1,2-*a*]pyridine compound was formed in 75% yield.



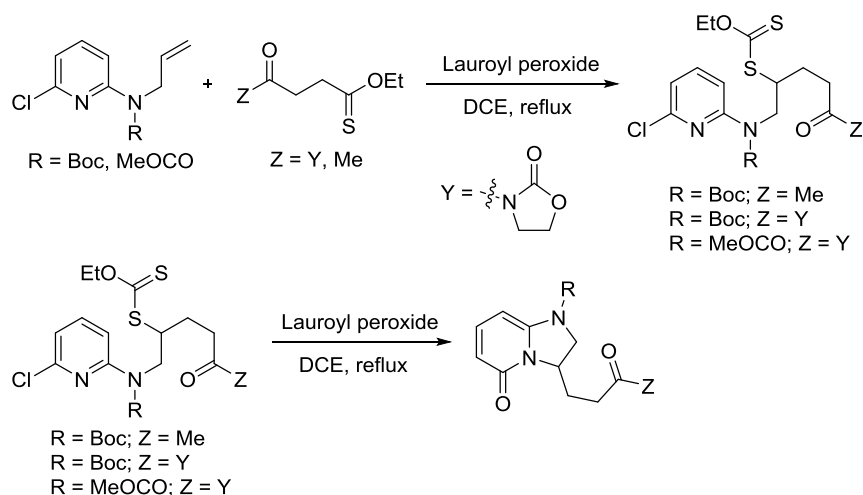
Scheme 1.3

Six-membered heteroaromatics such as pyridine and diazine are among the most important heterocyclic compounds in chemistry, biology and materials science. Derivatization of these heteroaromatics through the addition of carbon radicals to the pyridine ring were first reported by F. Minisci in 1970.²⁴ This type of carbon radical mediated aromatic C–H functionalization reaction is now known as the Minisci reaction (Scheme 1.4)



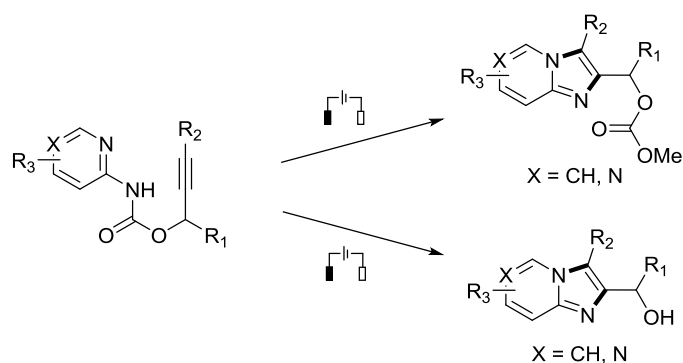
Schem 1.4

The addition of carbon radicals to the nitrogen atom of pyridine rings has remained elusive. In 2006, Zard's group observed isolated examples of alkyl radical addition to the nitrogen atom of pyridine.²⁵



Scheme 1.5

The second goal of this thesis is to develop synthesis of imidazo[1,2-*a*]pyridines and imidazo[1,2-*d*]pyridines through intramolecular oxidative alkyne annulation (Scheme 1.6).

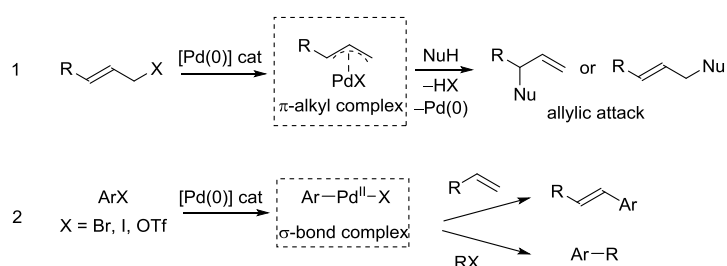


Scheme 1.6

Palladium catalyzed reactions are a kind of very important synthetic reactions, which play an important role in the development of organic synthesis chemistry. The 2010 Nobel Prize in chemistry was assigned to Professors Heck, Suzuki and Negishi in recognition of their significant contribution in Pd-catalyzed cross coupling reactions. Because of its usefulness, Pd-catalyzed chemistry has attracted extensive interest and has been widely used in organic synthesis.²⁶

Palladium is cheap, non-toxic and harmless, relatively stable, and palladium chemistry is often easy to perform. Probably, the two most fundamental features of palladium chemistry are the possibility of catalysis with high turnover numbers and the extreme functional group tolerance of the reactions associated to this chemistry.

We can distinguish two main types of Pd(0)-catalyzed chemistry, according to the type of organopalladium complex involved. In the first case, an allylic system (allylic acetate for example) can allylate a soft nucleophile in the presence of catalytic Pd(0) species, while in the latter case an aryl halide (Ar-X) or a vinyl halide (vinyl-X) and a main organometallic (or semimetallic nucleophile) (R'-M) can interact to provide the coupled organic product Ar-R' or vinyl-R'. While the former case is characterized by the involvement of a transient η^3 -allylpalladium intermediate (Scheme 1.7 top reaction), in the second case the reaction passes through a σ -aryl or a σ -vinylpalladium intermediate (Scheme 1.7 bottom reaction).²⁷



Scheme 1.7

The 2-carboxyl-6 α -hydroxy-octahydroindole (CHOI) bicyclic structure is the core structure in aeruginosins (Figure 1.2),²⁸ which are marine natural products isolated from sponges and cyanobacterial water blooms (blue-green algae). CHOI hydroxylated at positions 5 and/or 6 show potent in vitro inhibition of various serine proteases, including thrombin and trypsin. Since the discovery of their potent anticoagulant action, structure-activity relationship (SAR) studies on aeruginosin family are constantly and intensively pursued. Therefore, it is significant to develop new, efficient and concise methods for constructing CHOI core structure and their analogues.

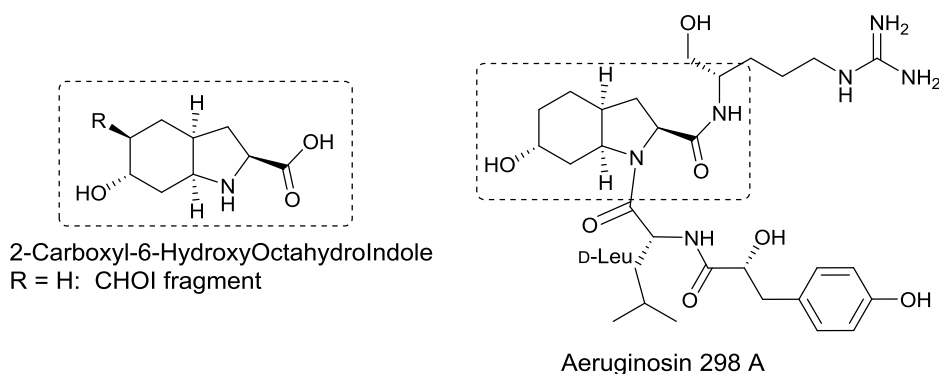
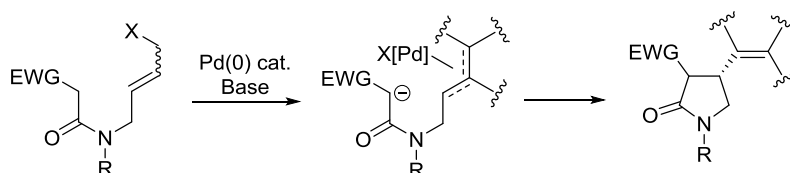


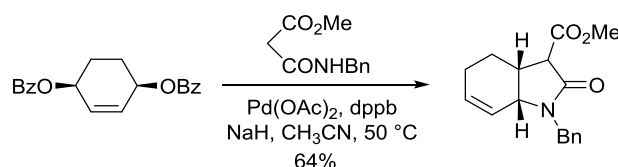
Figure 1.2

In recent years, Poli's group is committed to the study of intramolecular Pd-catalyzed allylations wherein the nucleophile and the electrophile are tethered by either an amide or an ester moiety, to produce γ -lactams and γ -lactones, and further explored on the synthesis of natural products (Scheme 1.8).²⁹



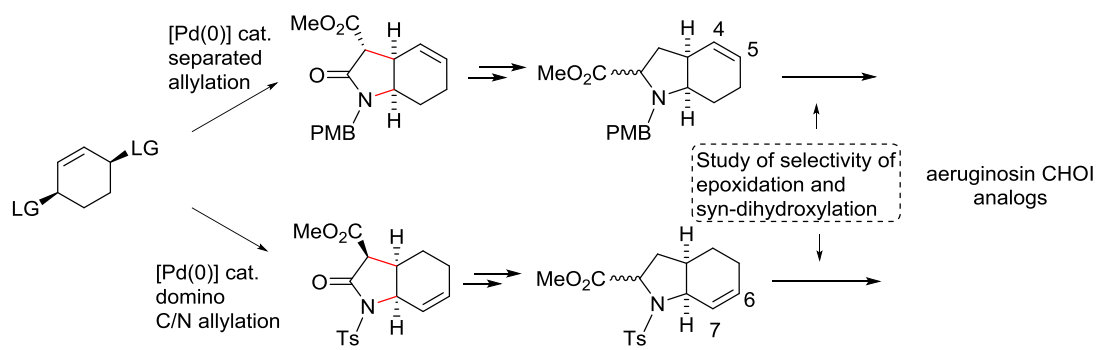
Scheme 1.8

On the other hand, in 1995, Mori's group³⁰ reported the double Pd-catalyzed allylation of a malonamide with a cyclohexenyl bis-allylic system, according to a C-allylation/N-allylation *pseudo-domino* sequence, to obtain bicyclic compound (Scheme 1.9).



Scheme 1.9

The third goal of this thesis: on the basis of the previous results of intramolecular Pd-catalyzed allylic alkylation to give γ -lactams reported by Poli's group²⁹ and the Pd-catalyzed C-allylation / N-allylation domino sequence reported by Mori's group,³⁰ we aim to develop two new approaches toward analogues of the CHOI unit. In particular, two different Pd-catalyzed approaches are expected to generate hexahydroindoles with unsaturations at different positions. Therefore, after a one-carbon homologation, epoxidation and *syn*-dihydroxylation of the two advanced intermediates are expected to afford the CHOI analogs and allow for a comparative analysis (Scheme 1.10).



Scheme 1.10

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Chapter 2 Stereodivergent and enantioselective total syntheses of chaetominine-type alkaloids

Alkaloids are alkaline nitrogenous organic compounds, which are widely existed in nature (mainly in plants, but also in animals).¹ A variety of nitrogenous metabolites from marine organisms, microbes, fungi and insects are also called alkaloids. Since the isolation of morphine from opium in 1806, more than 20 thousand kinds of alkaloids have been isolated for more than 200 years, which are classified up to 59 according to the structure. However, with more and more alkaloid discovered and isolated, the classification has also considerably increased. Among these alkaloids, the indole alkaloids are the most common alkaloids found so far.

Indole alkaloids are mainly distributed in flowering plants, consisting of the families Strychnaceae, Apocynaceae and Rubiaceae. They can also exist in Rutaceae, Simarubaceae, Annonaceae, Acanthaceae and other plants. Indole alkaloids have complex structure, and most of them have important biological activity, such as famous indole alkaloids: reserpine, vinblastine, ergometrine and strychnine (Figure 2.1). Due to the unique skeleton structure and diverse biological and pharmacological activities of this kind of alkaloids, a great deal of interest for their synthesis has been attracted by many organic chemists and pharmaceutical scientists.

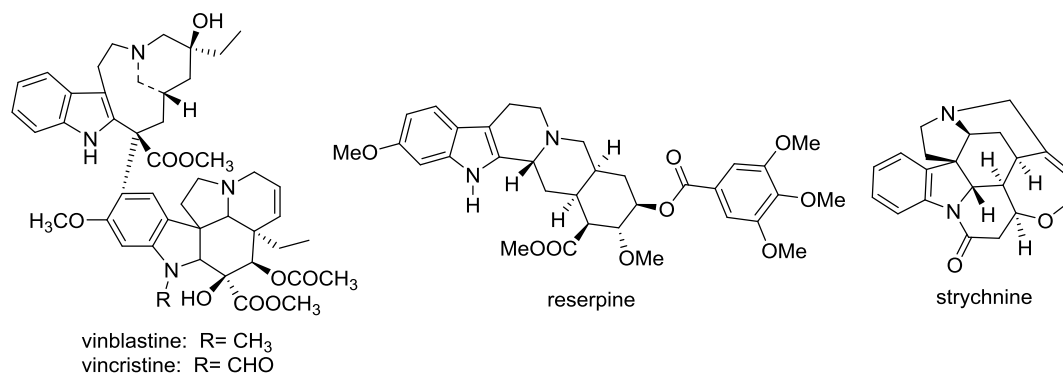


Figure 2.1 Several famous indole alkaloids

Endophytic fungi are abundant source of of bioactive indole alkaloids.² The first member, (-)-chaetominine³ (**2.1**, Figure 2.2) was the first isolated by Tan *et al.* in 2006 from the solid-substrate culture of *Chaetomium* sp. IFB-E015, an endophytic fungus on apparently healthy *Adenophora axilliflora* leaves.^{3a} After the first isolation of (-)-chaetominine, several homologues and diastereomers of (-)-chaetominine have been isolated from different fungi by many research groups, and characterized as (-)-pseudofischerine (**2.2**),⁴ (-)-aniquinazoline D (**2.3**),⁵ (-)-isochaetominines A–C (**2.4–2.6**),⁶ (+)-14-*epi*-isochaetominine C (**2.7**)⁶ and isochaetominine (**2.9**),⁷ respectively (Figure 2.2). Interesting, except 11-*epi*-isochaetominine C, all other 2,3-*cis*-diastereomers of isochaetominine C and isochaetominine have been reported to be natural products.

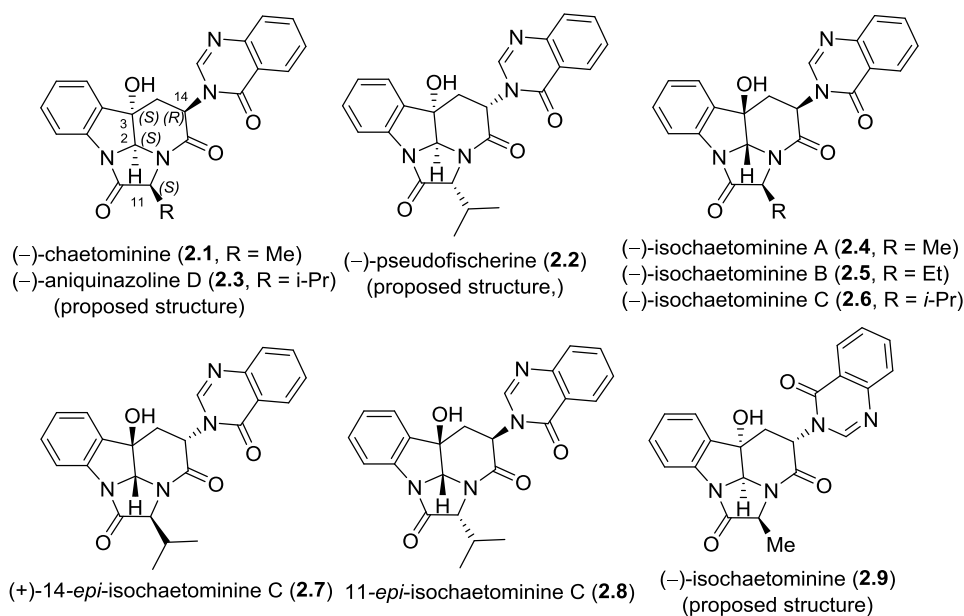


Figure 2.2

This type of quinazolinone alkaloids feature the same singular hexacyclic structure and differ from each other on the stereochemistry and/or the substituent at C-11. Because of the unique skeleton structure and diverse biological activities of chaetominine-type alkaloids, since their isolations many organic chemists have studied the development of novel synthetic approaches. However, up to date, only the

total syntheses of (–)-chaetominine (**2.1**) have been reported⁸ and synthetic studies on other members of isochaetominine-type alkaloids (**2.2–2.9**) have not appeared.

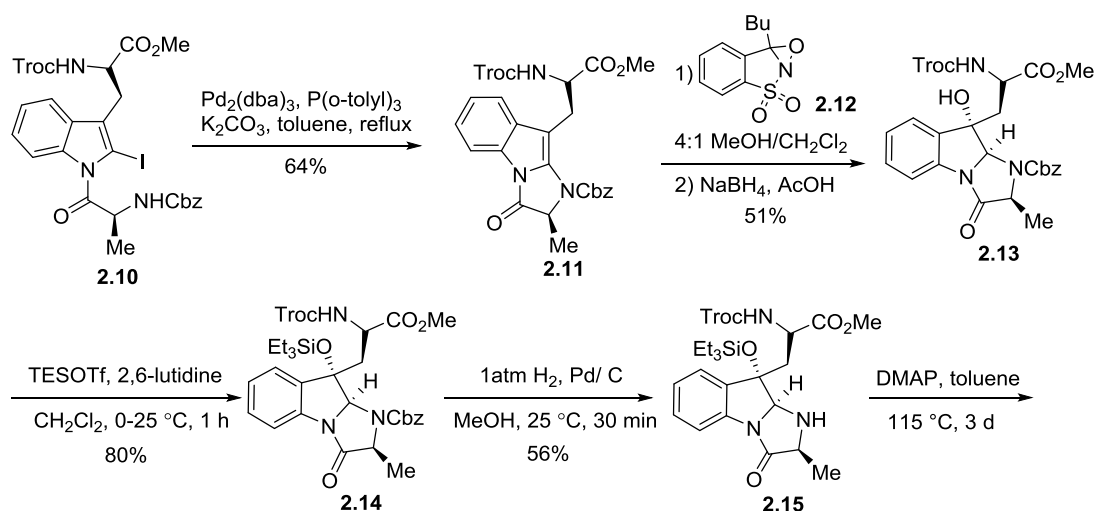
Huang's group has reported in 2009 a concise total synthesis of (–)-chaetominine (**2.1**), involving four steps starting from D-tryptophan.^{8f} Through in-depth study of this method, we further developed the five-step synthesis of (–)-chaetominine (**2.1**) from L-tryptophan.^{8g} Up to date, these two routes are the shortest step syntheses with the highest overall yield among all the synthesis of chaetominine. Based on these previous researches of our group, we have extended the existing synthetic method, which can be used to stereodivergent total synthesis of several chaetominine-type alkaloids.

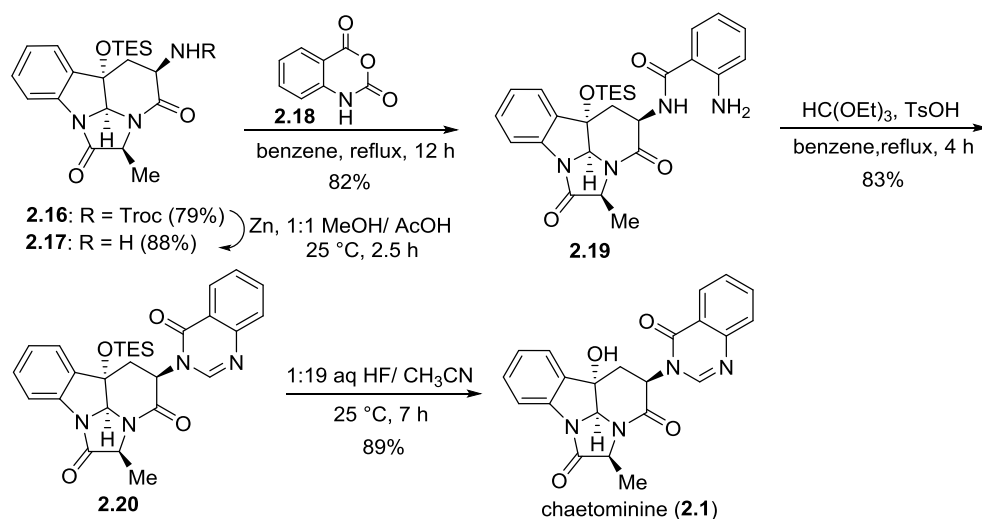
2.1 Review of the Reported Methods

The unprecedented framework makes chaetominine an idea target for exploring novel synthetic strategies. Many research groups have explored on the total synthesis of chaetominine.⁸

2.1.1 Snider's synthesis of chaetominine

In 2007, Snider group^{8a} reported the first total synthesis of chaetominine (Scheme 2.1). Starting from iodocarbamate **2.10**, a Buchwald Pd(0)-catalyzed cyclization afforded tricycle **2.11**. Then, epoxidation with oxaziridine **2.12** followed by NaBH₄ reduction led to hydroxy imidazolidinone **2.13**. TES protection and catalytic hydrogenolysis of Cbz protecting group of compound **2.13** afforded the amino ester **2.15**. Lactamization of **2.15** in the presence of DMAP provided the key compound **2.16** which contained the skeleton of chaetaminine. Troc deprotection followed by construction of quinazolinone ring and removal of the TES group completed the first asymmetric total synthesis of chaetominine (**2.1**) in 10 steps, 6.2% overall yield.

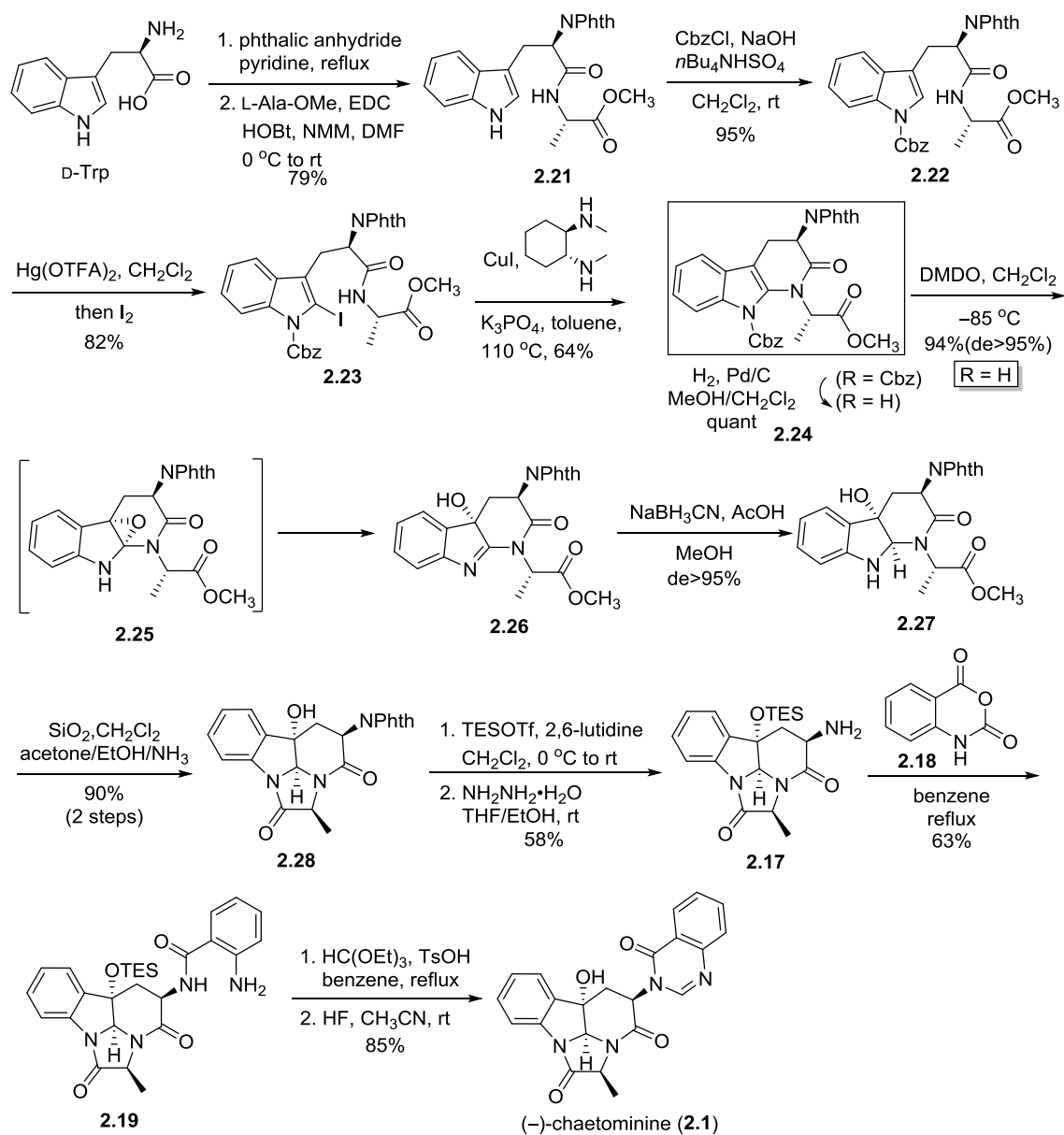




Scheme 2.1 Snider's synthesis of chaetominine.

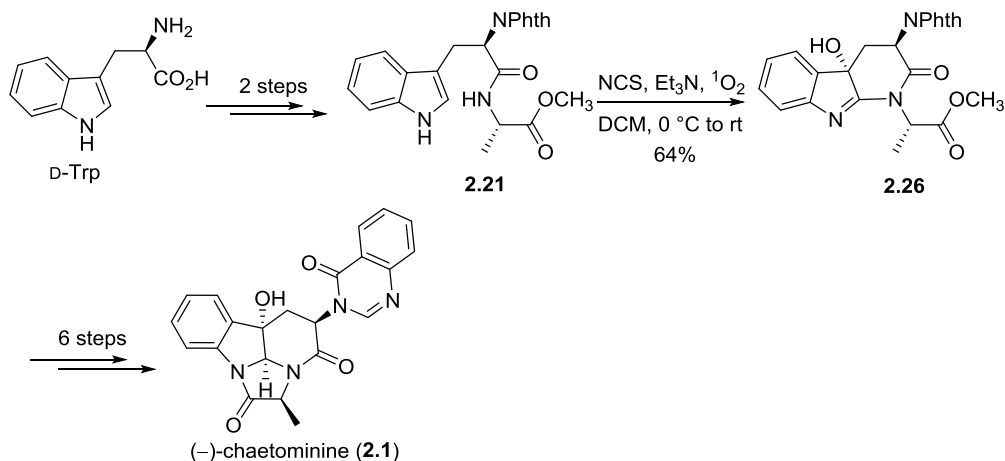
2.1.2 Evano's synthesis of chaetominine

In 2008, Evano's group^{8b} reported a total synthesis of (–)-chaetominine (**2.1**) (Scheme 2.2), starting from the D-tryptophan. The synthesis of dipeptide compound **2.21** was achieved through two intermolecular amide coupling reactions. Protection of the indole nitrogen with a Cbz group afforded **2.22**, which was treated with Hg(OTA)₂ and I₂ to afford compound **2.23**. Copper catalyzed intramolecular amination afforded compound **2.24** without epimerization. Deprotection of Cbz group, followed by DMDO epoxidation at –85 °C gave an extremely unstable epoxy intermediate **2.25**, which directly rearranges to the hydroxyl imine **2.26**. Due to the steric effect between Phth protecting group and DMDO, the epoxidation took place with a high diastereoselectivity (de>95%). Reduction of the hydroxyl imine **2.26** with NaBH₃CN provided an unstable compound **2.27**, which was transformed into compound **2.28** during silica gel purification. The subsequent steps are similar to the method of Snider (Scheme 2.1). This total synthesis of chaetominine was achieved in 10% overall yield over 14 steps.



Scheme 2.2 Evano's synthesis of (-)-chaetominine.

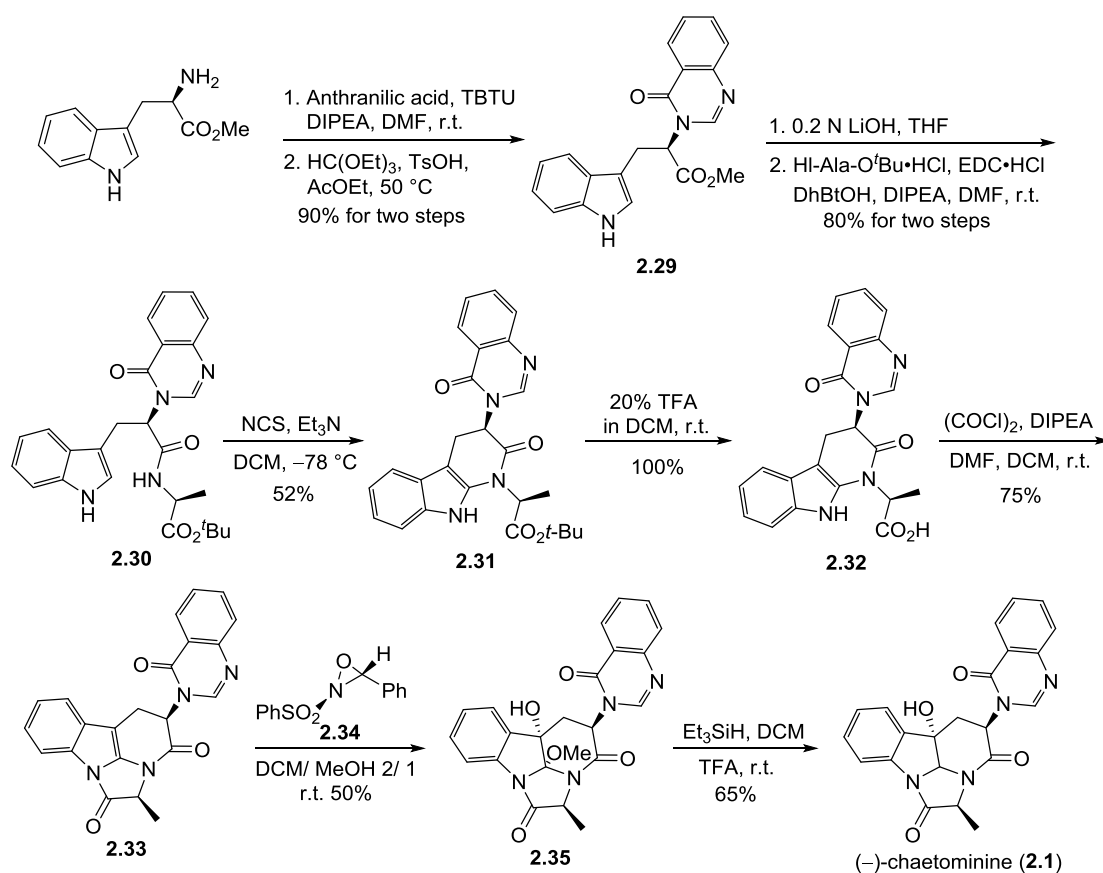
In 2009, Evano's group^{8e} reported an improved synthesis of **2.26** from **2.21** employing singlet oxygen oxidation (Scheme 2.3).



Scheme 2.3 Evano's second generation synthesis of (-)-chaetominine.

2.1.3 Papeo's synthesis of chaetominine

In 2009, Papeo's group^{8d} reported a novel method for the synthesis of chaetominine (Scheme 2.4). In this work, the quinazoline ring was constructed at an early stage to reduce the steps of protection and deprotection. Specifically, the commercial available D-tryptophan methyl ester was condensed with anthranilic acid followed by reaction with ethyl formate in the presence of TsOH to give quinazolinone **2.29**. The methyl ester was then hydrolyzed and coupled with alanine *tert*-butyl ester hydrochloride to afford di-peptide **2.30**. Oxidative cyclization in the presence of NCS and Et₃N at -78 °C led to **2.31**, which was converted to **2.33** through removal of the *tert*-butyl group of the ester followed by intramolecular amide formation. Oxidation the indole moiety with **2.34** afforded deoxygenated compound **2.35**. Reductive removal of the methoxyl group afforded the natural product chaetominine in 9.3% overall yield over nine steps.

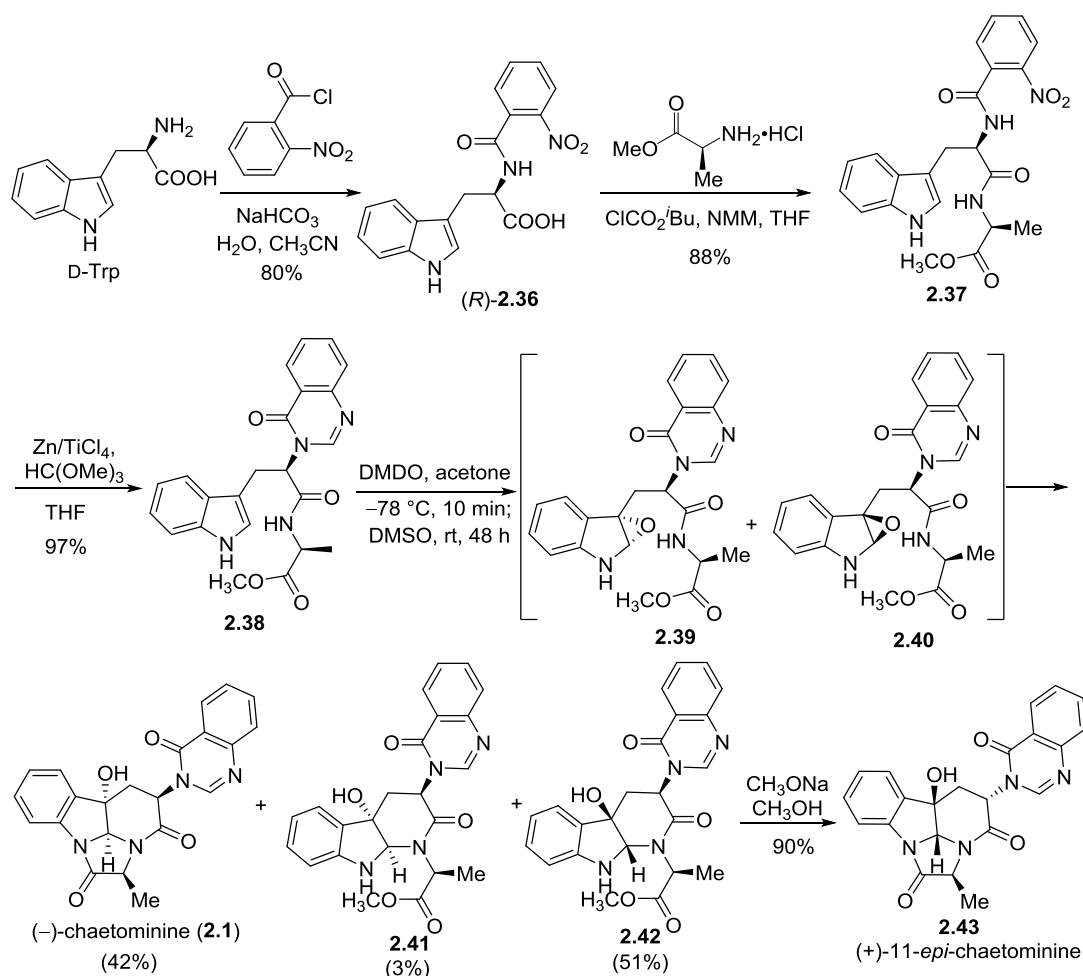


Scheme 2.4 Papeo's synthesis of (-)-chaetominine

2.1.4 Huang group's synthesis of chaetominine

In 2009, Huang group developed its first strategy for the total synthesis of chaetominine (Scheme 2.5).^{8c,8f} This short synthesis has high redox economy which is protecting group-free. First, D-tryptophan was reacted with 2-nitrobenzoyl chloride to form compound **2.36** through amide condensation reaction. The carboxyl group was then activated with isobutyl chloroformate and reacted with L-alanine methyl ester hydrochloride at low temperature to afford the dipeptide **2.37**. Subsequently, Following the method developed by Shi's group,⁹ compound **2.37** was reacted with HC(OEt)₃ in the presence of Zn/TiCl₄ to afford the quinazolinone derivative **2.38**. Epoxidation with DMDO followed by biscyclization in DMSO (which have been treated with CaH₂) afforded (-)-chaetominine (**2.1**) in 42% yield, along with monocyclized compound **2.41** in 3% yield and **2.42** in 51% yield. The compound **2.42**

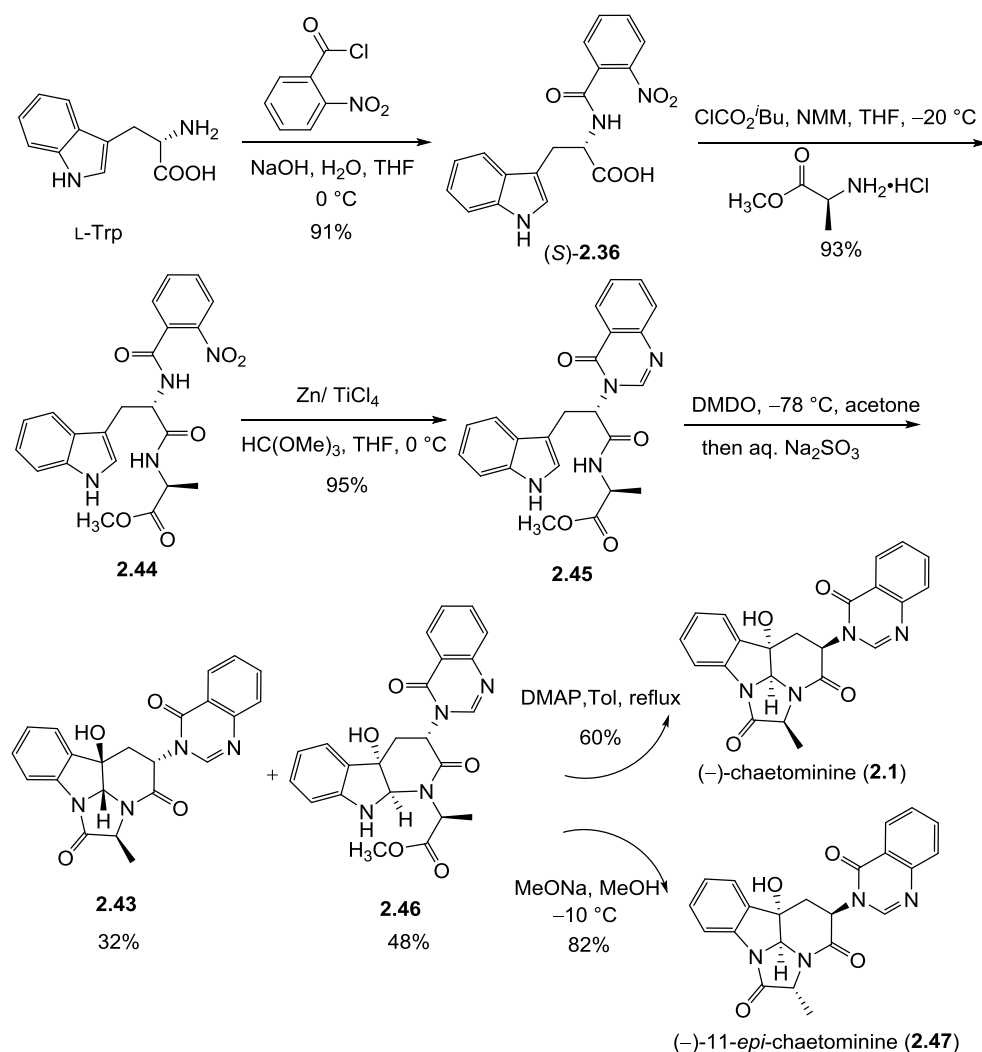
was cyclized by treating with CH_3ONa to provide (+)-11-*epi*-chaetominine (**2.43**) in 90% yield.



Scheme 2.5 Huang's first strategy for the synthesis of (-)-chaetominine and (+)-11-*epi*-chaetominine.

Soon after, Huang's group developed the second generation total synthesis of (-)-chaetominine (Scheme 2.6).^{8g} The synthesis of (-)-chaetominine (**2.1**) and (-)-11-*epi*-chaetominine (**2.47**) was achieved in 23.2% yield and 31.6% yield, respectively, starting from L-tryptophan. For the synthesis of compound **2.46**, a similar previously reported route was adopted. The compound **2.46** was refluxed in toluene for 3 days in the presence of a catalytic amount of DMAP to furnish (-)-chaetominine by selective epimerization. Compound **2.46** can also be bis-epimerized in the presence of CH_3ONa under low temperature to give (-)-11-*epi*-chaetominine in 82% yield.

These results suggested that the biosynthetic pathway of chaetominine may start from L-tryptophan.

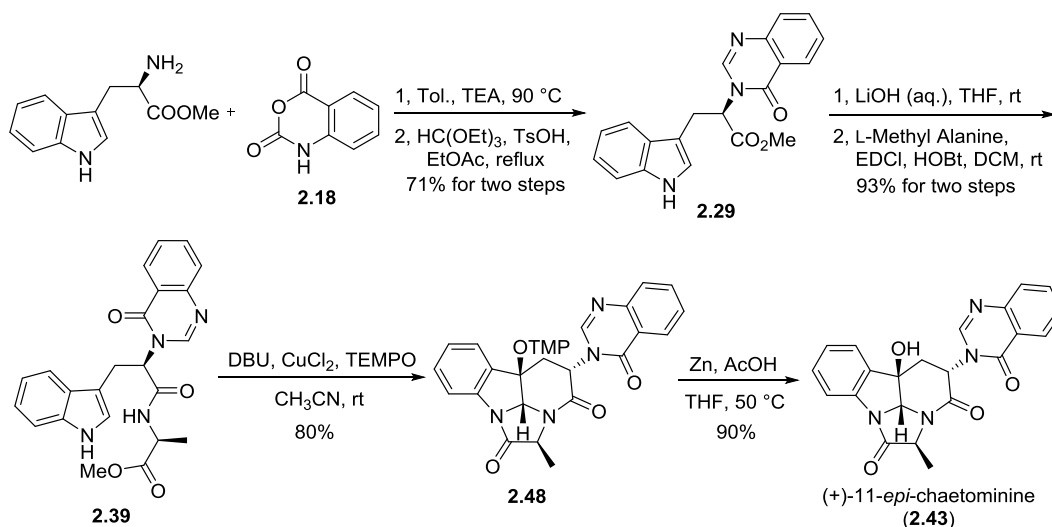


Scheme 2.6 Huang's second strategy for the synthesis of (-)-chaetominine.

2.1.5 Xia's synthesis of (+)-11-*epi*-chaetominine

Xia's group reported the synthesis of (+)-11-*epi*-chaetominine by employing a route similar to the Huang synthesis.⁸ⁱ They prepared the compound **2.29** by following papeo's method. The methyl ester **2.29** was converted to dipetide **2.39** through ester hydrolysis and amide formation. The key copper-catalyzed radical cyclization of **2.39** afforded compound **2.48**, which was converted to (+)-11-*epi*-chaetominine (**2.43**) in

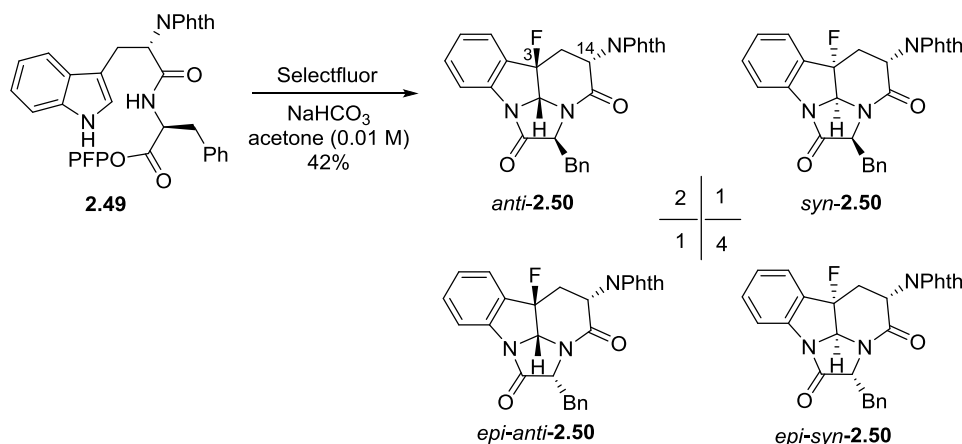
93% yield by treating with Zn/ AcOH. Total synthesis of (+)-11-*epi*-chaetominine (**2.43**) was completed in 48% overall yield over 6 steps.



Scheme 2.7 Xia's synthesis of (+)-11-*epi*-chaetominine.

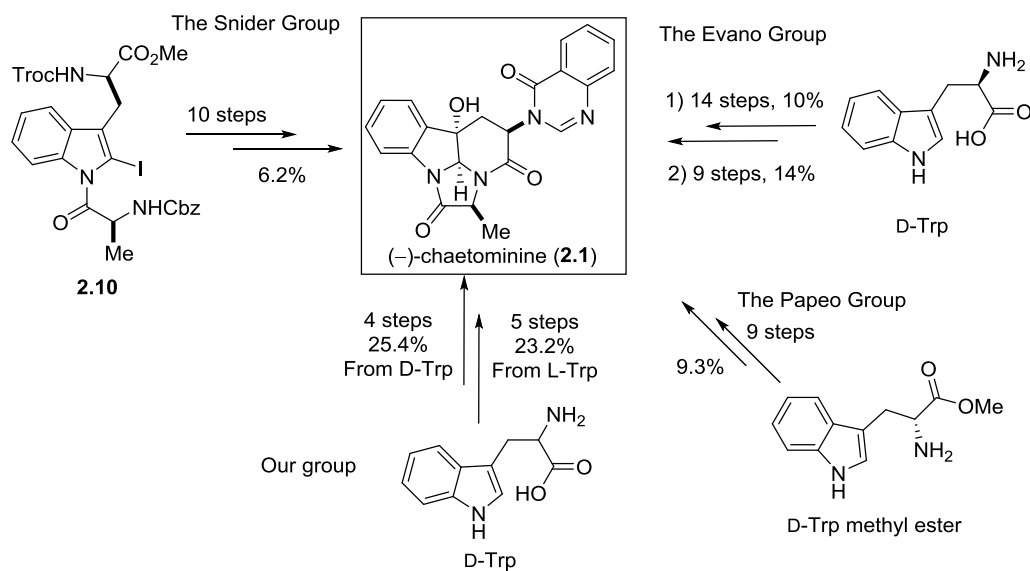
2.1.6 Roche's synthesis of 2-fluoro-chaetominine

Roche and Tréguier used a 1:1 epimeric mixture of *N*-Phth-Trp-Phe-OC₆F₅ (**2.49**) in their synthesis of 2-fluoro-chaetominine due to the ease of epimerization of compound **2.49** during the synthesis.^{8j} Then Selectfluor-triggered double cyclization cascade reaction with compound **2.49** afforded the tetracyclic core **2.50** as a mixture of four diastereomers in a ratio of 2:1:1:4 (combined yield: 42%), from which the overall C3-C14 *cis/trans* ratio was 5:3 (Scheme 2.8).



Scheme 2.8 Roche's cascade reaction to produce the tetracyclic core **2.50**

Although four research groups have completed the synthesis of chaetominine (Scheme 2.9), but the synthesis of other members of chaetominine-type alkaloids have not been reported, especially (-)-isochaetominines A–C (2.4–2.6), which feature a unique all-*cis*-stereochemistry that is different from chaetominine.

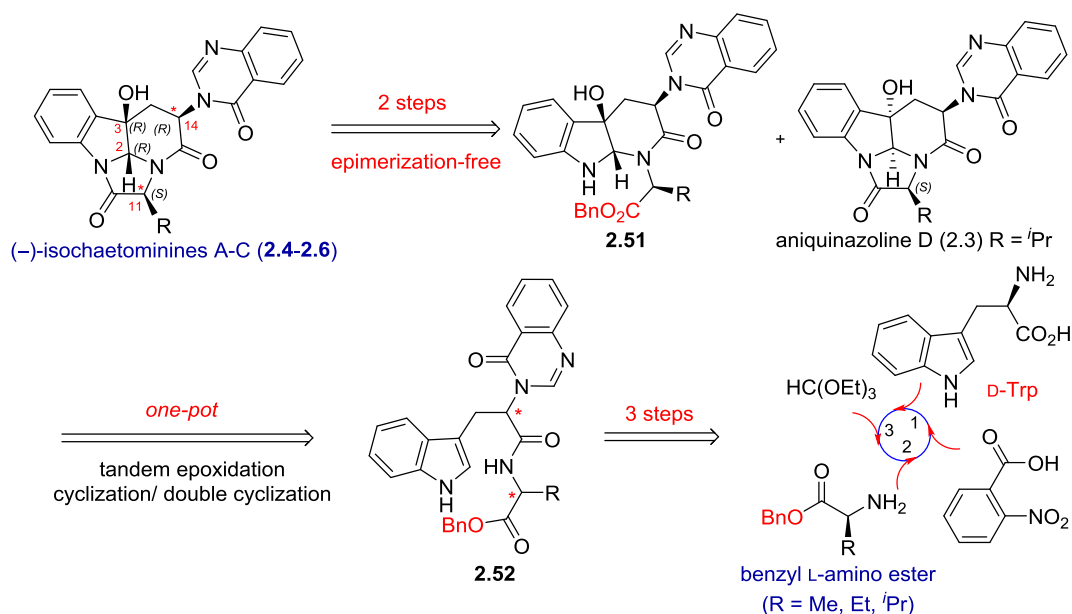


Scheme 2.9 All the approach to (-)-chaetominine (2.1)

2.2 Research Plan

The proposed retrosynthetic analysis of isochaetominine A–C (**2.4–2.6**) was shown in Scheme **2.10**. Previous results gained from the synthesis of (–)-chaetominine (**2.1**)^{8c,f-h} revealed that only when the *anti*-dispose of hydroxyl group at C-3 and the quinazolinonyl group at C-14 in compound **2.51** can the final lactamization occur spontaneously. In addition, the stereocenter at C-14 is prone to epimerization.^{8f-h} Hence, the key issue in this project is the epimerization-free approach to the all-*cis*-stereochemistry existed in (–)-pseudofischerine (**2.2**), (–)-isochaetominines A–C (**2.4–2.6**) and isochaetominine (**2.9**).

First of all, we choose isochaetominine A–C (**2.4–2.6**) as our first targets. The imidazolinone ring of **2.4–2.6** could be formed from the corresponding carboxylic acid under mild lactamization conditions using a racemization-free method.^{10,11} Thus benzyl valinate was chosen as an amino acid component to avoid emimerization during ester to acid conversion. Non-diastereoselective epoxidation of quinazolinonyl dipeptide **2.52** would yield two diastereomeric expoxides (no shown) and one of them is expected to convert spontaneously to the proposed structure of aniquinazoline D (**2.3**) when R is the isopropyl group, the other expoxide will form the monocyclization product **2.51**, which is an ideal precursor for isochaetominines C (**2.6**). The dipeptide **2.52** could be prepared from D-Trp with L-benzyl valinate through 3 steps.



Scheme 2.10 Retrosynthetic analysis.

We also plan to use the stereodivergent strategy for the synthesis of all other members of chaetominine-type alkaloids. Through the combination of D or L-tryptophan and different benzyl valinate or alaninate, a similar route may be employed for the synthesis of all eight 2,3-*cis*-stereoisomers of (-)-isochaetominine C and isochaetominine (Figure 2.2).

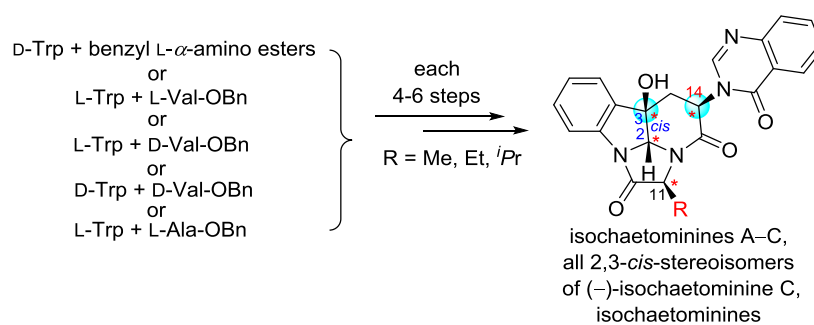


Figure 2.3

2.3 Results and discussion

2.3.1 Stereodivergent and enantioselective total syntheses of (–)-isochaetominines A–C and eight diastereomers of (–)-isochaetominine C

2.3.1.1 The development of method for diastereodivergent synthesis of the proposed structure of (–)-aniquinazoline D (2.3) and (–)-isochaetominine C (2.6)

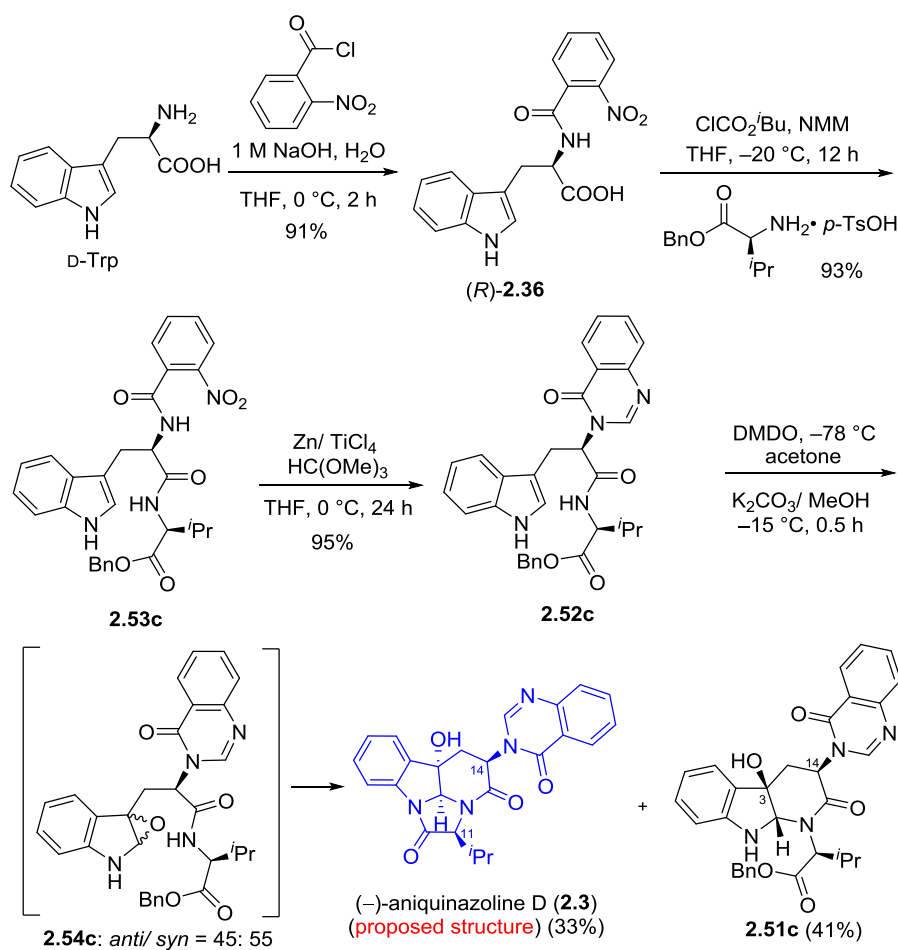
We start our research by developing a diastereodivergent synthesis of the proposed structure of (–)-aniquinazoline D (2.3) and (–)-isochaetominine C (2.6).

In 2013, Wang and co-workers reported the isolation of (–)-aniquinazoline D from the culture of *Aspergillus nidulans* MA-143, an endophytic fungus obtained from the leaves of marine mangrove plant *Rhizophora stylosa*.⁵ The relative stereochemistry was determined by NOESY technique, HMBC and ¹H–¹H COSY, the absolute configuration of C-11 was elucidated by Marfey's method, which led them to assume the absolute configuration of (–)-aniquinazoline D (2.3) as 2*S*,3*S*,11*S*,14*R*. The authors also showed that aniquinazoline D exhibited potent lethality against brine shrimp (LD₅₀ = 3.42 μM), which was stronger than the positive control colchicine (LD₅₀ = 88.4 μM).

Very recently, Oh, Shin and co-workers reported the isolation of (–)-isochaetominines A–C (2.4–2.6) and (+)-14-*epi*-isochaetominine C (2.7) from the solid-substrate culture of an *Aspergillus* sp. fungus collected from marine-submerged decaying wood from Korea.⁶ Their structures were determined by a combination of spectroscopic and chemical analyses. These alkaloids showed weak inhibition against Na⁺/K⁺-ATPase (IC₅₀ = 78, 20, 38, and 57 μM, respectively).

The synthesis started from D-tryptophan by *N*-arylation with 2-nitrobenzoyl chloride to give compound (*R*)-2.36^{8f} (Scheme 2.11). Then, coupling of the resulting (*R*)-2.36 with benzyl L-valinate *p*-toluenesulfonic acid salt produced the dipeptide derivative

2.53c in 93% yield. Treatment of **2.53c** with Zn/TiCl₄ and HC(OEt)₃ in THF⁹ at 0 °C afforded quinazolinone derivative **2.52c** in 95% yield.^{8f} The key oxidative cyclization of **2.52c** with DMDO¹² in acetone at -78 °C, followed by work-up of the resulting unstable epoxide intermediates *anti*-**2.54c** and *syn*-**2.54c** with K₂CO₃ in MeOH at -15 °C, produced the proposed structure of (-)-aniquinazoline D (**2.3**) in 33% yield and the monocyclization product **2.51c** in 41% yield.



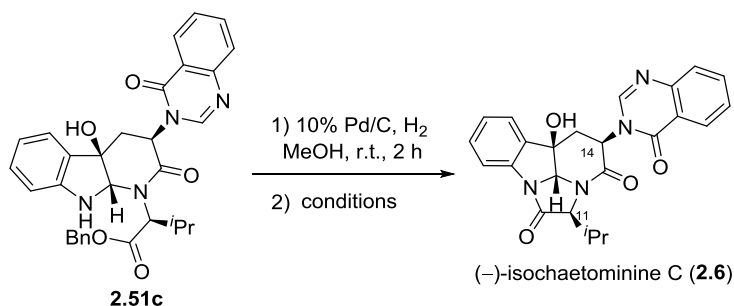
Scheme 2.11 Total synthesis of the proposed structure of (-)-aniquinazoline D (**2.2**).

Since compound **2.51c** is prone to epimerization due to the *cis*-stereochemistry of the OH group at C-3 and the quinazolinonyl group at C-14,^{8f-h} a careful selection of reaction conditions for the following transformations is required to avoid epimerization on C-14.

The removal of the benzyl group of **2.51c** under catalytic hydrogenation conditions (H_2 , 10% Pd/ C, MeOH, r.t., 2 h) was achieved smoothly. The high purity of carboxylic acid product without epimerization can be obtained after the Pd/C catalyst was filtered, and the obtained carboxylic acids directly put into the subsequent reaction without column chromatography purification.

Thus we next focused on the key lactamization reaction. A survey of literature¹¹ showed that Ye's peptide coupling reagent (DEPBT) is very efficiency and low tendency of racemization and epimerization for amide condensation. Hence, we selected DEPBT reagent for the lactamization first. To our delight, (-)-isochaetominine C (**2.6**) can be smoothly obtained in 77% yield (Table 2.1, entry 1). It is encouraging that no epimerization occurred in this transformation. Interestingly, **2.6** was also observed when reacted with another classical amide condensation condition, which is $(COCl)_2$, DIPEA and a catalytic amount of DMF (entry 2). When $(COCl)_2$ was decreased to 1.5 equiv, less than DIPEA, the yield was increased significantly, and no epimerization was observed (entry 3). When the reaction was not promoted by a catalytic amount of DMF, the reaction time was longer and the yield was decreased (entry 4). If the reaction was carried out in 25 °C, the yield was decreased significantly, it indicated that the high temperature will also cause negative effects on the reaction (entry 5).

Table 2.1



Entry	Conditions	Yield ^a (%)
1	DEPBT (2.0 equiv), DIPEA (2.0 equiv), DCM (0.04 M), 25 °C, 8 h	77

2	(COCl) ₂ (3.0 equiv), DIPEA (2.0 equiv), cat. DMF, DCM (0.04 M), -10 °C, 45 min	9
3	(COCl) ₂ (1.5 equiv), DIPEA (2.0 equiv), cat. DMF, DCM (0.04 M), -10 °C, 45 min	81
4	entry 2 but no cat. DMF	72
5	entry 2 but reaction at rt	51

a: Isolated yield of **2.6** from **2.51c**.

The spectral data (¹H and ¹³C NMR) and the sign of the optical rotation of our synthetic product **2.6** are in full agreement with those reported for the natural product. However, our product was obtained in high purity as colorless crystals, displayed a lower value of specific rotation compared with that reported for the natural product (Table 2.2). These differences could be attributed to the minute quantities isolated from the natural source and relatively low purity of the isolated sample as indicated by the reported ¹H and ¹³C NMR spectra.⁶

Table 2.2 A comparison of some data of synthetic **2.6** and natural **2.6**

	Synthetic 2.6	Natural 2.6
[α]	[α] _D ²⁵ -71.0 (c 1.0, MeOH)	[α] _D ²⁵ -90 (c 0.6, MeOH) ⁶
Physical state	Colorless crystals	Amorphous solid

A careful comparison of the ¹H and ¹³C NMR data of our synthetic **2.3** with those reported for the natural (-)-aniquinazoline D (**2.3**) showed that they are different (the comparison of NMR data can see experiment section pages 95). To make sure the structure of our synthetic **2.3** was correct, it was confirmed by single-crystal X-ray diffraction analysis (Figure 2.4). Thus, the structure assigned by Wang *et al.*⁶ for natural (-)-aniquinazoline D was incorrect.

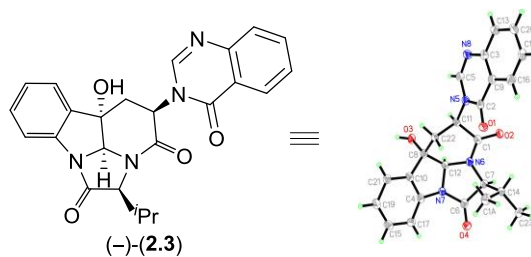
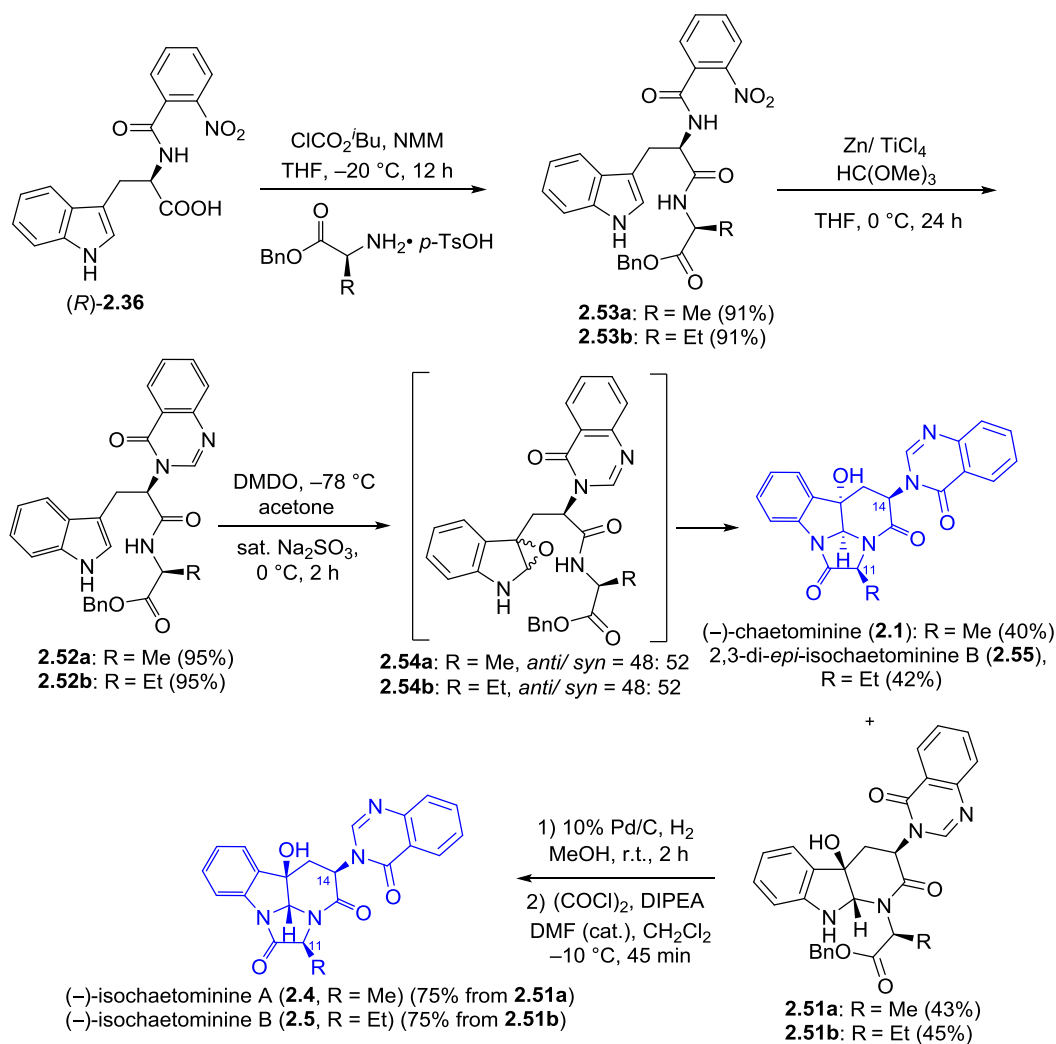


Figure 2.4 X-ray crystal structure of synthetic (-)-**2.3**.

Interestingly, the ^1H and ^{13}C NMR data of natural (-)-aniquinazoline D (**2.3**) fully matched those of both natural⁵ and our synthetic (-)-isochaetominine C (**2.6**). Based on these results, we concluded that the structure of the natural (-)-aniquinazoline D should be revised as that shown for (-)-isochaetominine C (**2.6**).

2.3.1.2 Diastereodivergent synthesis of (-)-isochaetominine A (**2.4**) and B (**2.5**), (-)-chaetominine (**2.1**), and 2,3-di-*epi*-isochaetominine B (**2.55**)

With the mild epimerization-free and diastereodivergent route established for the synthesis of the proposed structure of (-)-aniquinazoline D (**2.3**) and (-)-isochaetominine C (**2.6**), we next chose isochaetominines A, B (**2.4**, **2.5**) as our next targets (Scheme **2.12**). Thus, by substituting the benzyl L-valinate *p*-toluenesulfonic acid salt with its ethyl or methyl homologues, and following a similar five-step synthetic sequence, except that the epoxide intermediates (**2.54a**, **2.54b**) were quenched with a saturated solution of Na_2SO_3 , 2,3-di-*epi*-isochaetominine B (**2.55**), isochaetominine B (**2.5**), chaetominine (**2.1**), and isochaetominine A (**2.4**) were obtained smoothly as colorless crystals.



Scheme 2.12 Diastereodivergent syntheses of (-)-isochaetominines A, B (**2.4**, **2.5**) and (-)-chaetominine (**2.1**), 2,3-di-*epi*-isochaetominine B (**2.55**).

The ¹H and ¹³C NMR spectral data and the sign of the specific rotation of our synthetic products fully matched those reported for the natural products. The same circumstances with isochaetominine C, our synthetic product **2.5** and **2.4** displayed a lower value of specific rotation compared with the corresponding value reported for the natural isochaetominine B (**2.5**) and isochaetominine A (**2.4**), respectively. Such differences are probably caused by the relatively low purity of the isolated samples alike (-)-isochaetominine C (**2.6**).

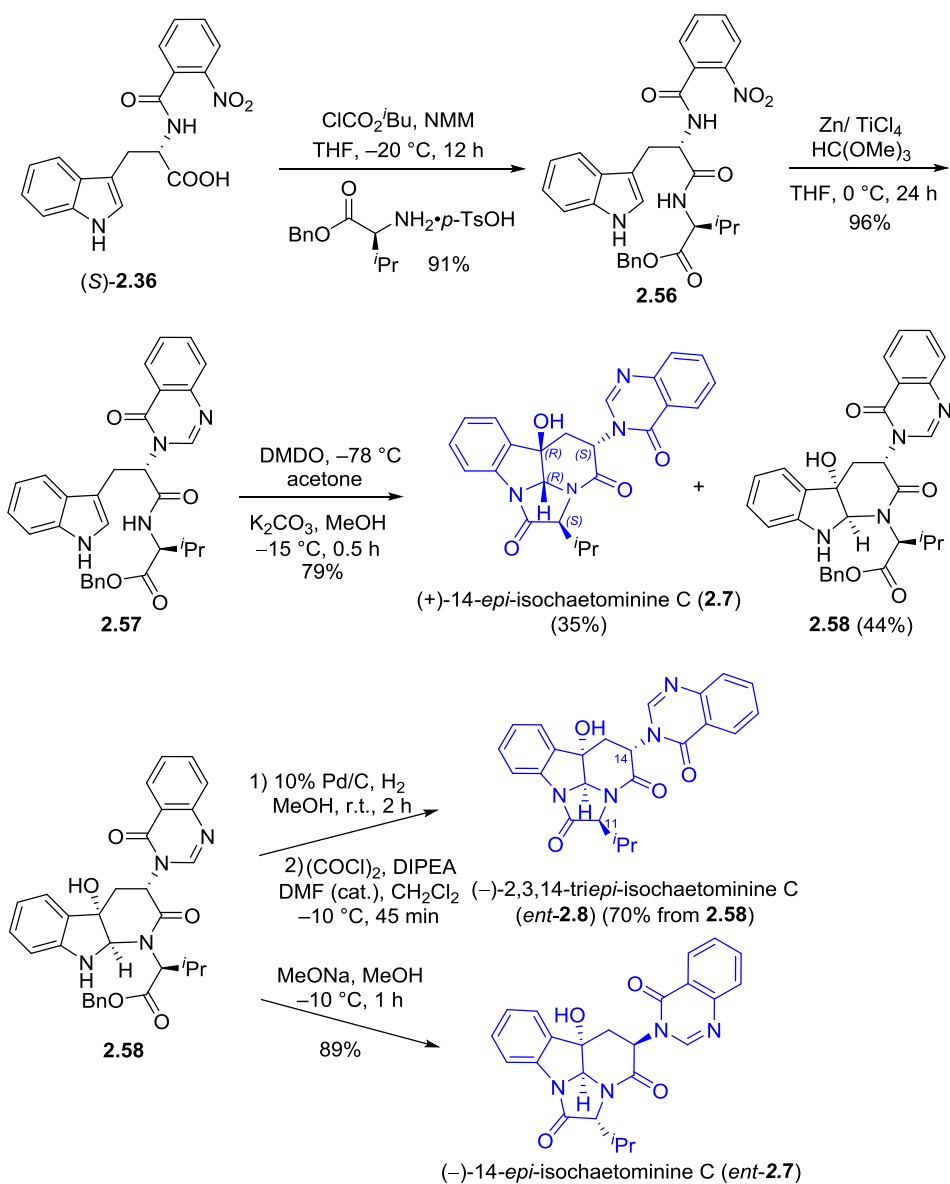
Table 2.3 A comparison of specific rotation data of synthetic **2.4**, **2.5** and natural **2.4**, **2.5**

	Synthetic	Natural
$[\alpha]$ of 2.4	$[\alpha]_D^{25} -23.0$ (<i>c</i> 1.0, MeOH)	$[\alpha]_D^{25} -63$ (<i>c</i> 0.5, MeOH) ⁶
$[\alpha]$ of 2.5	$[\alpha]_D^{25} -49.0$ (<i>c</i> 1.0, MeOH)	$[\alpha]_D^{25} -73$ (<i>c</i> 0.6, MeOH) ⁶

2.3.1.3 Enantio- and diastereo-divergent synthesis of (+)-14-*epi*-isochaetominine (**2.7**), *ent*-**2.7** and 2,3,14-*tri-epi*-isochaetominine C (*ent*-**2.8**)

To further demonstrate the versatility of our stereodivergent strategy, we turned to focus on the enantiodivergent synthesis of 14-*epi*-isochaetominine C (**2.7**) and *ent*-**2.7**, as well as 2,3,14-*tri-epi*-isochaetominine C (*ent*-**2.8**). To this end, natural L-Trp was 2-nitro-benzoylated^{8g} and the resulting L-Trp-derivative (*S*)-**2.36** was coupled with benzyl L-valinate *p*-toluenesulfonic acid salt to give **2.56** in 91% yield (Scheme **2.13**). Reductive condensation of **2.56** with HC(OEt)₃ in THF at 0 °C provided quinazolinone dipeptide **2.57** in 96% yield. Epoxidation of **2.57** with DMDO followed by work-up with K₂CO₃ in MeOH at -15 °C afforded the double cyclization product (+)-14-*epi*-isochaetominine C (**2.7**) in 35% yield along with the monocyclization product **2.58** in 44% yield. Debenzylation of **2.58** followed by lactamization through classical condition, (COCl)₂ and DIPEA as well as a catalytic amount of DMF led to 2,3,14-*tri-epi*-isochaetominine C (*ent*-**2.8**) in 70% yield over two steps. On the other hand, treatment of **2.62** with MeONa in MeOH at -10 °C for 1 h led to *ent*-**7** in 89% yield via bis-epimerization at C-11 and C-14 and lactamization.

This approach thus constitutes an enantio- and diastereo-divergent synthesis of three diastereomers/enantiomers of isochaetominine C.



Scheme 2.13 Enantio- and diastereo-divergent synthesis of (+)-14-epi-isochaetominine (**2.7**), *ent*-**2.7** and 2,3,14-tri-epi-isochaetominine C (*ent*-**2.8**).

The structure of our synthetic product **2.7** was confirmed by single-crystal X-ray diffraction analysis (Figure 2.5). The ^1H and ^{13}C NMR spectral data of our synthetic product matched those reported for the natural product.

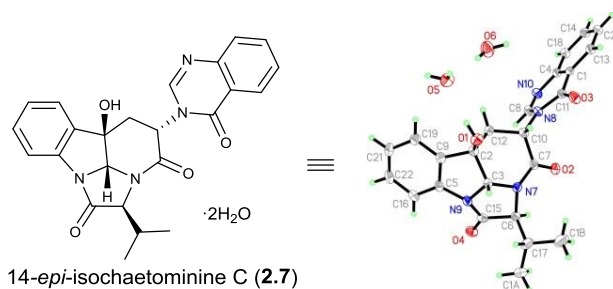
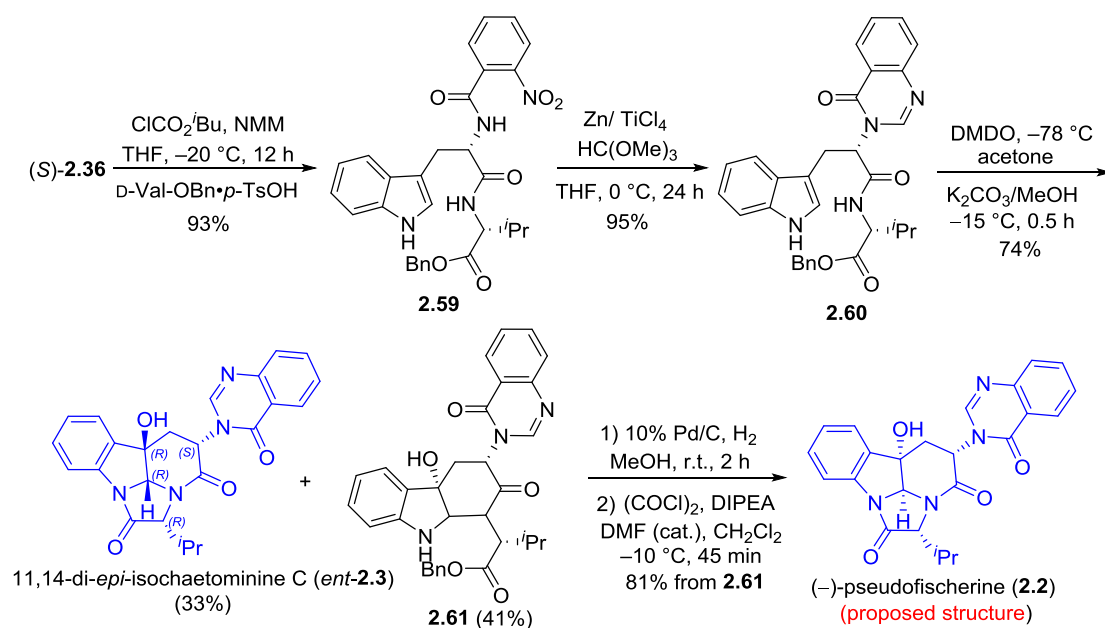


Figure 2.5 X-ray crystal structure of synthetic **2.7**.

2.3.1.4 Diastereodivergent synthesis of 11,14-di-*epi*-isochaetominine C (*ent*-**2.3**) and the proposed structure of (–)-pseudofischerine (**2.2**).

We next focused on (–)-pseudofischerine (**2.2**). In 2012, Eamvijarn, Kijjoa and co-workers reported the isolation of (–)-pseudofischerine from a culture of the fungus *Neosartorya pseudofischeri* S. W. Peterson obtained from agricultural soil collected in Thailand.⁴ The relative stereochemistry was determined by NOESY technique, although the absolute configuration has not been determined experimentally. The authors proposed that **2.2** was biosynthesized from L-tryptophan, anthranilic acid, and D-valine.

Therefore we chose L-Trp and D-Val-OBn for the synthesis of (–)-pseudofischerine (**2.2**). The dipeptide derivative **2.59** was easily prepared from (*S*)-**2.36** (Scheme **2.14**). Treatment of **2.59** with Zn/TiCl₄ and HC(OEt)₃ in THF⁹ at 0 °C^{8f} afforded quinazolinone derivative **2.60** in 95% yield. The DMDO-initiated tandem reaction of **2.60** produced 11,14-di-*epi*-isochaetominine C (*ent*-**2.3**) in 33% yield, along with **2.61** in 41% yield. Successive debenzoylation of **2.61** followed by lactamization reaction gave the proposed structure of (–)-pseudofischerine (**2.2**) in 81% yield, namely, the antipode of the alkaloid isochaetominine C.



Scheme **2.14** Diastereodivergent synthesis of 11,14-di-epi-isochaetominine C (*ent*-**2.3**) and the proposed structure of (-)-pseudofischerine (**2.2**).

The ¹H and ¹³C NMR spectrum data of our synthetic **2.2** are identical with those reported for both (-)-pseudofischerine (**2.2**) and isochaetominine C (**2.6**). However, the sign and magnitude of the specific rotation of our synthetic **2.2** are different from those reported for the natural (-)-pseudofischerine.⁴ Because the reported optical rotation data of natural (-)-pseudofischerine and natural (-)-isochaetominine C (**2.6**) have been tested in different solvents, which cannot lead a direct comparison of those data to determine their enantiomeric relationship. To clarify this issue, we measured the optical rotations of our two synthetic enantiomers **2.2** (*ent*-**2.6**) and **2.6** in both MeOH and CHCl₃ (Table **2.4**).

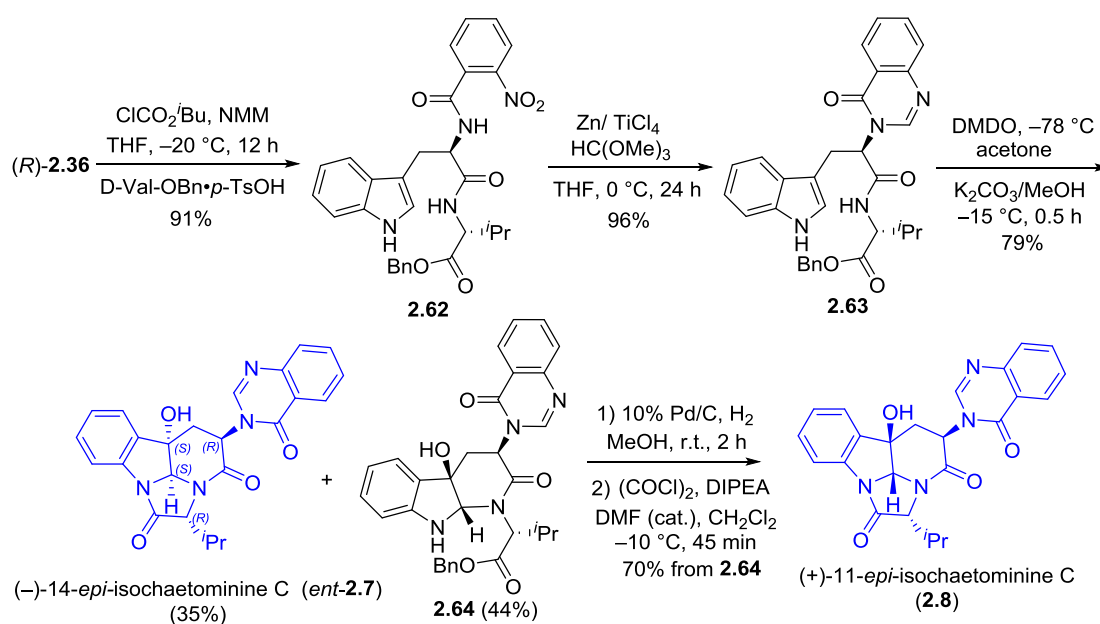
We can see that the sign of the specific rotation of natural **2.2** was the same with our synthetic **2.6** and natural **2.6**. These results allowed us to conclude that natural (-)-pseudofischerine and (-)-isochaetominine C (**2.6**) are the same. The structure of (-)-pseudofischerine should be revised to that shown for (-)-isochaetominine C (**2.6**).

Table 2.4 A comparison of specific rotation data of synthetic **2.2**, **2.6** and natural **2.2**, **2.6**

	Synthetic	Natural
$[\alpha]$ of 2.2	$[\alpha]_D^{25} +71.0$ (<i>c</i> 1.0, MeOH)	-
$[\alpha]$ of 2.2	$[\alpha]_D^{20} +76.8$ (<i>c</i> 1.0, CHCl ₃)	$[\alpha]_D^{25} -16.9$ (<i>c</i> 0.18, CHCl ₃) ⁴
$[\alpha]$ of 2.6	$[\alpha]_D^{25} -71.0$ (<i>c</i> 1.0, MeOH)	$[\alpha]_D^{25} -90$ (<i>c</i> 0.6, MeOH) ⁶
$[\alpha]$ of 2.6	$[\alpha]_D^{20} -76.8$ (<i>c</i> 1.0, CHCl ₃)	-

2.3.1.5 Diastereodivergent synthesis of (-)-14-*epi*-isochaetominine C (*ent*-**2.7**) and (+)-11-*epi*-isochaetominine C (**2.8**).

Finally, the D-Trp and D-Val-OBn combination was investigated, which led to a four-steps synthesis of (-)-14-*epi*-isochaetominine C (*ent*-**2.7**) and compound **2.64** from the same tryptophan derivative (*R*)-**2.36** (Scheme **2.15**). Compound **2.64** was converted to (+)-11-*epi*-isochaetominine C (**2.8**) in 70% yield.



Scheme **2.15** Diastereodivergent synthesis of (-)-14-*epi*-isochaetominine C (*ent*-**2.7**) and (+)-11-*epi*-isochaetominine C (**2.8**).

2.3.1.6 Determine the enantiopurities of four pair of 2, 3-*cis*-isochaetominine C enantiomers

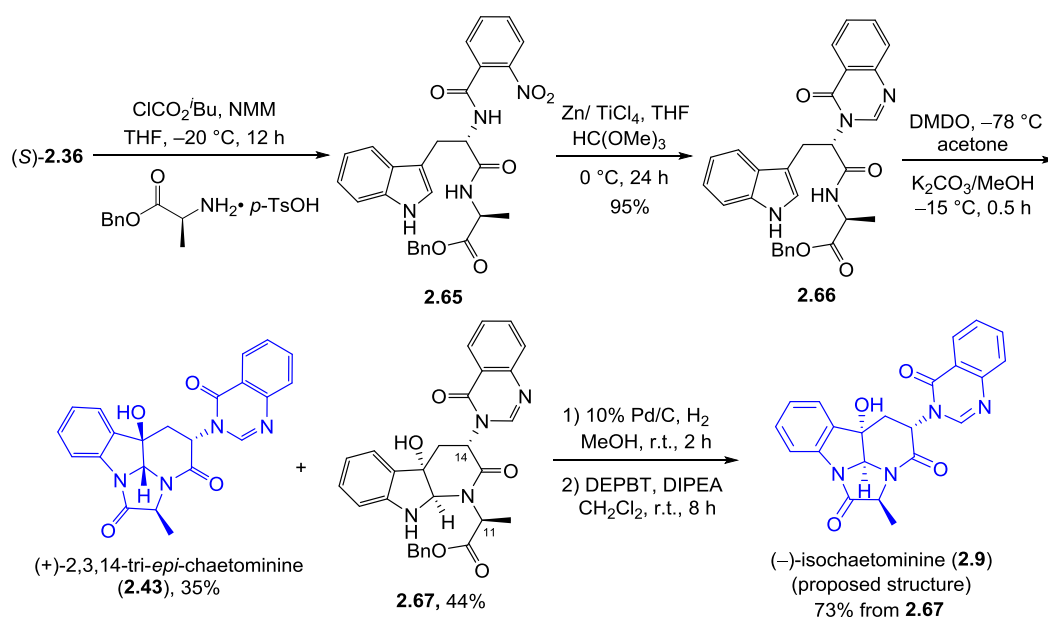
With all four pair of 2,3-*cis*-diastereomers/ enantiomers of isochaetominine C in hand,

and due to the magnitudes of specific rotation of all our synthetic products are significant different from those reported for the natural products, it was necessary to determine the enantiopurities of the synthetic samples. HPLC analyses on a chiral stationary phase (see the experiment section pages 88) of the synthetic samples, namely, (–)-isochaetominine A (**2.6**), (+)-14-*epi*-isochaetominine C (**2.7**), the proposed structures of (–)-pseudofischerine (**2.2** = *ent*-**2.6**) and (–)-aniquinazoline D (**2.3**), unnatural diastereomer 11-*epi*-isochaetominine C (**2.8**), *ent*-**2.3**, *ent*-**2.7**, and *ent*-**2.8**, showed that the enantiomeric excesses of all compounds are >99%.

2.3.2 Enantioselective total synthesis and structural revision of the proposed structure of (–)-isochaetominine (**2.9**)

In 2015, Lou's group⁷ reported the isolation of chaetominine (**2.1**) and its diastereoisomer isochaetominine (**2.9**), as well as other natural products from the culture of an endophytic strain of *aspergillus fumigatus* obtained from the liverwort *Heteroscyphus tener* (STEPH.) SCHIFFN from China. The preliminary biological activity test showed that these compounds have weak cytotoxic activity against the PC3 cell lines. From their biosynthetic standpoint, in combination with comparison of the CD spectrum of chaetominine (**2.1**) and isochaetominine (**2.9**), assumed that the isochaetominine is the stereoisomer of chaetominine and the absolute configuration of **2.9** was speculated as 2*S*,3*S*,11*S*,14*S*.

Due to the 3,14-*cis*-stereochemistry of the proposed structure of (–)-isochaetominine, this synthesis required the new synthetic strategy. Thus, the method features the use of L-tryptophan and L-alanine benzyl ester as starting materials (Scheme **2.16**). After similar steps as described before, the compound **2.66** was obtained. Thus, epoxidation of **2.66** with DMDO followed by work-up with K₂CO₃ in MeOH at –15 °C afforded the double cyclization product (+)-2,3,14-*tri-epi*-chaetominine (**2.43**) in 35% yield along with the monocyclized product **2.67** in 44% yield. Debenzylation of **2.67** followed by lactamization with Ye's peptide coupling reagent¹¹ led to the proposed structure of (–)-isochaetominine in 73% yield over two steps.



Scheme 2.16 Total synthesis of the proposed structure of isochaetominine (**2.9**) and diastereomers

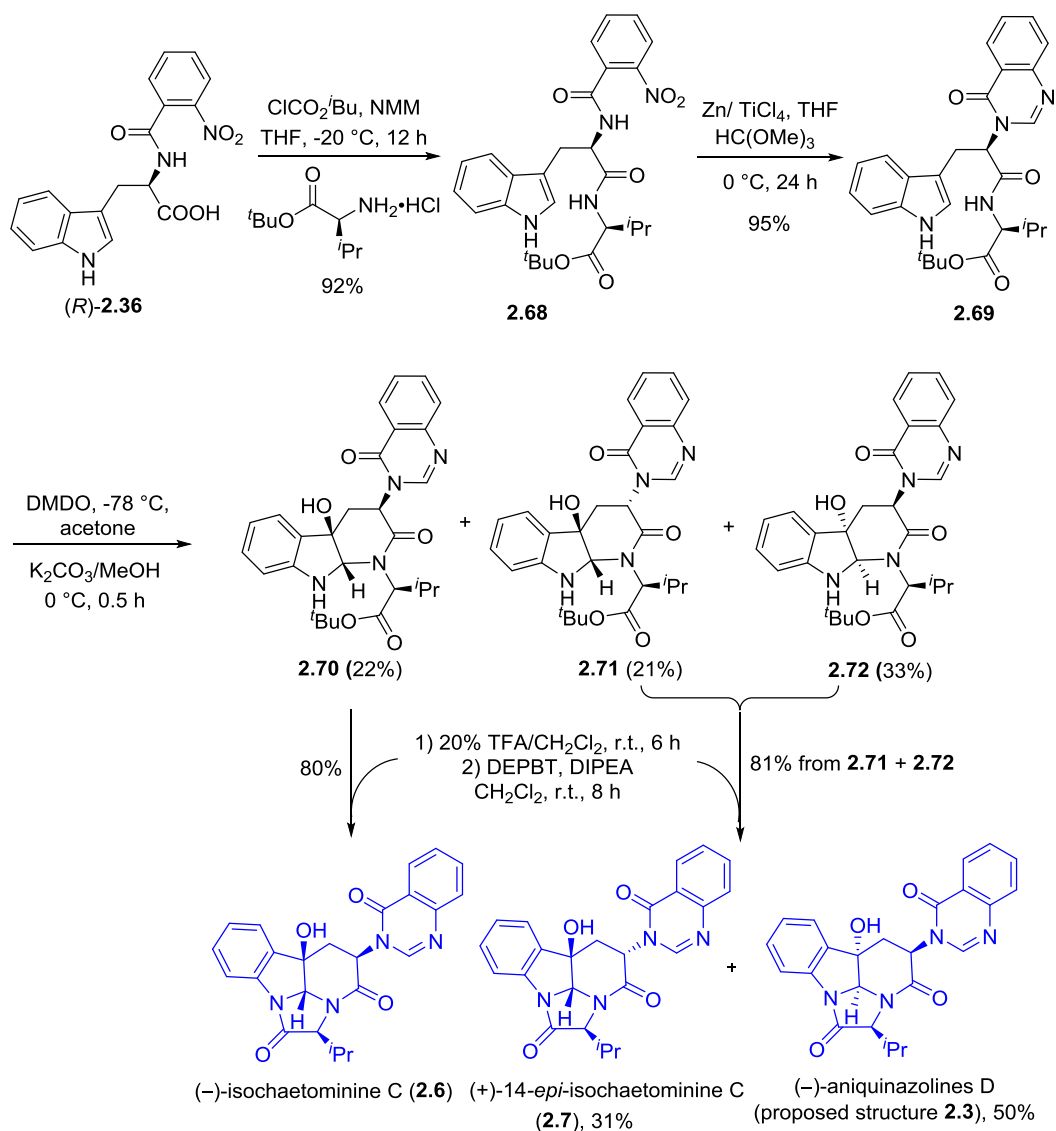
A careful comparison of the ^1H and ^{13}C NMR data of our synthetic **2.9** with those reported for the natural isochaetominine⁷ showed that they are different (the comparison of NMR data can see experiment section pages 97). The value of specific rotation of our synthetic product also displayed a big difference with the corresponding value reported for the natural isochaetominine.

On the basis of the diastereodivergent strategy developed by our laboratories, we have achieved many diastereomers from the stereodivergent synthesis of chaetominine (**2.1**). A comparison of the physical and spectral data of the natural isochaetominine with those of the diastereomers, showed that the ^1H and ^{13}C NMR spectrum data of natural (-)-isochaetominine fully matched those of our synthetic (-)-11-*epi*-chaetominine (**2.50**), which our laboratories have completed the first enantioselective total synthesis of this natural product previously.^{8g} The specific rotation are also similar.

Based on these results, we concluded that the structure of the natural (-)-isochaetominine should be revised as that shown for (-)-11-*epi*-chaetominine (**2.47**).

2.3.3 Stereodivergent synthesis of three diastereomers of isochaetominine C-type alkaloids

We turned to investigate another synthetic strategy for the synthesis of the chaetominine-type alkaloids basing on the combination of tryptophan and α -amino *tert*-butyl ester (Scheme 2.17). To this end, (*R*)-**2.36** was coupled with valine *tert*-butyl ester hydrochloride to give dipeptide derivative **2.68**. Reductive condensation of **2.68** with HC(OEt)₃ in THF at 0 °C provided quinazolinone **2.69** in 95% yield. Surprisingly, epoxidation of **2.69** with DMDO followed by work-up with K₂CO₃ in MeOH at -15 °C did not afford the expected epoxy-ring opening products **2.70** and **2.72**. Epoxidation of **2.69** with DMDO followed by work-up with K₂CO₃ in MeOH at 0 °C (ice-bath) for 30 minutes afforded three products, **2.70**, **2.71** and **2.72**. The diastereoisomer of **2.71** and **2.72** were inseparable by column chromatography. Based on our previous results,^{8f} 3,14-*trans*-diastereoisomers (methyl ester and benzyl ester) should cyclize spontaneously to give the corresponding bicyclic products. However, the mixture of **2.71** and **2.72** did not yield the bicyclic product **2.7** even at room temperature. The low reactivity of the *tert*-butyl ester can be attributed to the large steric hindrance of *tert*-butyl ester, which prevented the formation of lactam. Deprotection of the *tert*-butyl group of **2.70** with TFA followed by treatment with Ye's peptide coupling reagent¹¹ afforded compound **2.6** in 80% yield. Similarly, the mixture of **2.71** and **2.72** were transformed into **2.7** and **2.3**. Attempt to separate these two by silica gel column chromatography also failed.

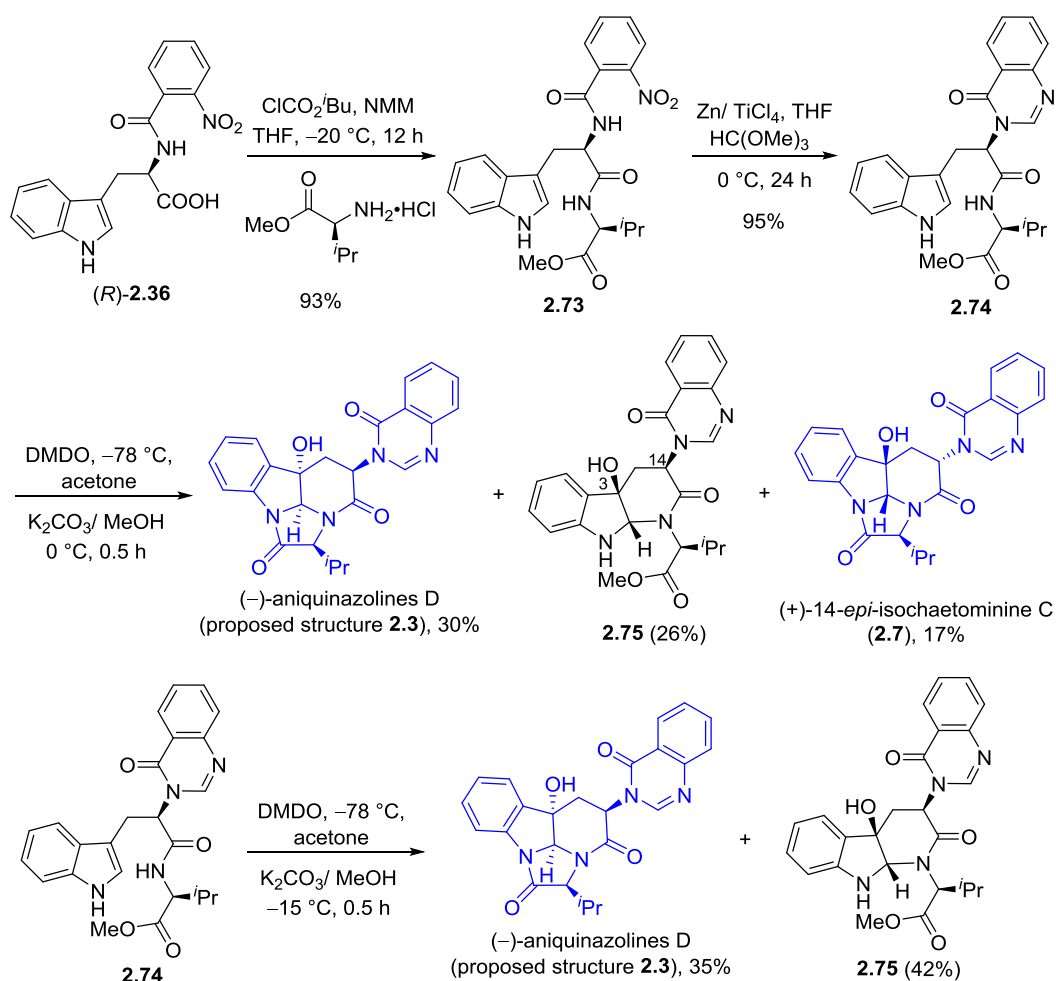


Scheme 2.17 Stereodivergent synthesis of three diastereomers of isochaetominine C-type alkaloids

The epoxidation/cyclization reaction of previous dipeptide **2.52c** (Scheme 2.11) and **2.66** (Scheme 2.16) produced two diastereoisomers. However, but epoxidation of **2.69** with DMDO followed by work-up with K_2CO_3 in MeOH gave three diastereoisomers (**2.70–2.72**). This was probably due to partial C14 epimerization during the base treatment at $0\text{ } ^\circ\text{C}$ instead of $-15\text{ } ^\circ\text{C}$ as in the cases of **2.52c** and **2.66**.

In order to check if this epimerization occurs for other dipeptides, we synthesized quinazolinone derivative **2.74** through the same synthetic route (Scheme 2.18). Epoxidation of **2.74** with DMDO followed by work-up with K_2CO_3 in MeOH at $0\text{ } ^\circ\text{C}$

also afforded three products **2.3**, **2.7** and **2.75**. The two *anti*-C3/ C14 stereoisomers transformed to bicyclic products **2.3** and **2.7** through further cyclization. The formation of compound **2.7** showed that only the *syn*-C3/ C14 stereoisomer was prone to C14 epimerized. Treating the reaction mixture after epoxidation with $K_2CO_3/MeOH$ at $-15\text{ }^\circ\text{C}$ afforded only two products **2.3** and **2.75** without epimerization.



Scheme 2.18

2.4 Conclusion

Through the work of this chapter, we achieved the following results:

A unified strategy has been developed for the highly enantioselective total syntheses of the proposed structures of (–)-pseudofischerine (**2.2**), (–)-aniquinazoline D (**2.3**) and (–)-isochaetominine (**2.9**), (–)-isochaetominines A–C (**2.4–2.6**), (+)-14-*epi*-isochaetominine C (**2.7**), as well as other four hitherto unknown stereoisomers of isochaetominine C. The non-diastereoselective epoxidation reaction led to the formation of two diastereomers for each of the six-step synthetic sequence. In addition, in combination with a regioselective epimerization reaction, three diastereomers were obtained in a seven-step route. The sensitive 3,14-*cis*-stereochemistry of isochaetominines A–C and the proposed structure of (–)-isochaetominine has been established through the use of a mild and epimerization-free protocol involving the use of benzyl α -amino esters (e.g. Val-OBn) and a lactamization reaction. It is worth noting that Ye's peptide coupling reagent afford advantages of operational simplicity in the lactamization step. Importantly, the structures of natural (–)-pseudofischerine (**2.2**), (–)-aniquinazoline D (**2.3**) have been revised both to (–)-isochaetominine C (**2.6**) and the structure of the natural (–)-isochaetominine (**2.9**) have been revised to (–)-11-*epi*-chaetominine (**2.47**) based on our synthetic efforts.

In addition, investigation on the synthesis of isochaetominine C (**2.6**) from L-tryptophan and L-valine *tert*-butyl ester led to the discovery of another stereodivergent synthesis of three diastereomers of isochaetominine C alkaloids.

2.5 Experimental Section

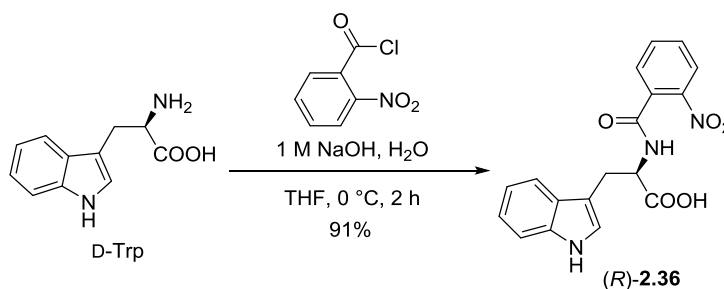
General Information

^1H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 or Bruker 500 ($^1\text{H}/400$ or 500 MHz, $^{13}\text{C}/100$ or 125 MHz) spectrometers. Chemical shifts are expressed in parts per million (δ) relative to an internal standard of residual chloroform (7.26 ppm for ^1H NMR and 77.0 ppm for ^{13}C NMR). Data for ^1H NMR are reported as chemical shift (multiplicity, coupling constant, number of proton). ESI-Mass spectra were recorded on a Bruker Dalton ESquire 3000 plus LC-MS apparatus. Optical rotations were measured with a Perkin-Elmer 341 automatic polarimeter or an Anton Paar MCP 500 polarimeter. Melting points were determined on a Büchi M560 Automatic Melting Point apparatus. Infrared spectra were recorded with a Nicolet Avatar 330 FT-IR spectrometer using film or KBr pellet technique.

Silica gel (300-400 mesh) was used for flash column chromatography, eluting (unless otherwise stated) with ethyl-acetate/ petroleum ether (PE) (60-90 °C) mixture. THF was distilled over sodium benzophenone ketyl under N_2 . Dichloromethane was distilled over calcium hydride under N_2 .

General Procedure for the Step 1

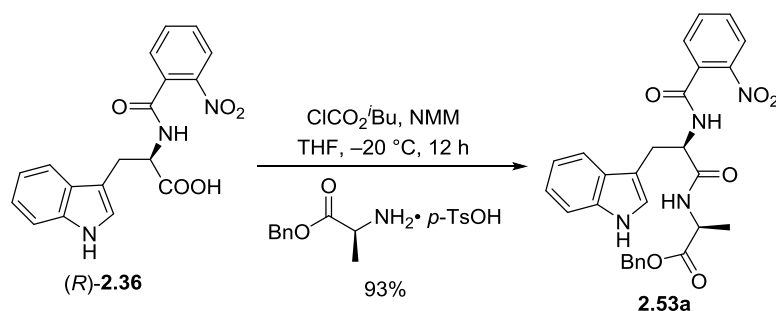
The preparations of (*R*)-**2.36** from D-tryptophan and (*S*)-**2.36** from L-tryptophan by *N*-arylation have been described in our previous reports.^{8f,8g}



General Procedure for the Step 2 (General Procedure 2)

To a stirring solution of **2.36** (5.09 mmol) in THF (20 mL) at $-20\text{ }^{\circ}\text{C}$ were added successively *N*-methylmorpholine (0.84 mL, 7.63 mmol) and i BuOCOC1 (0.74 mL, 5.60 mmol). After being stirred at $-20\text{ }^{\circ}\text{C}$ under N_2 for 15 min, the resulting suspension was added slowly to a solution of an amino acid benzyl ester *p*-toluenesulfonic acid salt (10.18 mmol) and *N*-methylmorpholine (1.68 mL, 15.28 mmol) in THF (36 mL) at $-78\text{ }^{\circ}\text{C}$. The mixture was stirred for 12 h at $-20\text{ }^{\circ}\text{C}$ before quenching with a saturated aqueous solution of NH_4Cl (20 mL). The mixture was diluted with water (100 mL) and the phases separated. The aqueous phase was extracted with EtOAc ($3 \times 20\text{ mL}$). The combined organic phases were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc: PE = 3:2) to give the dipeptide derivative.

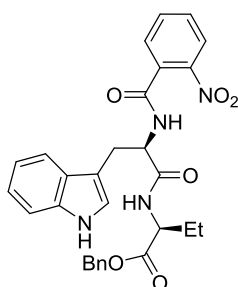
Benzyl (S)-2-((R)-3-(1*H*-indol-3-yl)-2-(2-nitrobenzamido)propanamido)propanoate (2.53a).



Following the general procedure 2, the coupling of (*R*)-**2.36** (1.80 g, 5.09 mmol) with L-alanine benzyl ester *p*-toluenesulfonic acid salt (3.57 g, 10.18 mmol) gave compound **2.53a** (2.38 g, yield: 91%) as a yellow solid. Mp $129\text{--}131\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{20} -36.9$ (c 1.1, CHCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.22 (s, 1H), 8.00–7.96 (m, 1H), 7.64 (d, $J = 7.8\text{ Hz}$, 1H), 7.56–7.46 (m, 2H), 7.36–7.26 (m, 6H), 7.20–7.13 (m, 2H), 7.12–7.04 (m, 2H), 6.60 (d, $J = 8.0\text{ Hz}$, 1H), 6.56 (d, $J = 8.0\text{ Hz}$, 1H), 5.12 (d, $J = 12.0\text{ Hz}$, 1H), 5.07 (d, $J = 12.0\text{ Hz}$, 1H), 5.00 (dd, $J = 14.8, 7.2\text{ Hz}$, 1H), 4.52 (dq, $J = 7.2, 7.3\text{ Hz}$, 1H), 3.49 (dd, $J = 14.8, 6.0\text{ Hz}$, 1H), 3.30 (dd, $J = 14.8, 7.2\text{ Hz}$, 1H), 1.23

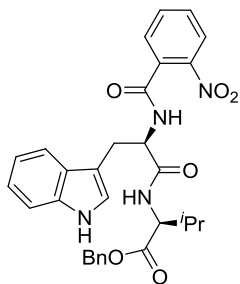
(d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.4, 170.3, 166.3, 146.3, 136.1, 135.4, 133.7, 132.4, 130.6, 128.6, 128.5, 128.3, 128.1, 127.7, 124.6, 123.3, 122.3, 119.8, 118.6, 111.3, 110.3, 67.0, 54.3, 48.4, 27.2, 17.5; IR (neat, cm^{-1}): 3415, 1738, 1646, 1529, 1455, 1349, 1198, 1140; HRMS (ESI, m/z) calcd for $\text{C}_{28}\text{H}_{26}\text{N}_4\text{O}_6\text{Na}$ ($\text{M}+\text{Na}^+$): 537.1745, found: 537.1750.

Benzyl (S)-2-((R)-3-(1H-indol-3-yl)-2-(2-nitrobenzamido)propanamido)butanoate (2.53b).



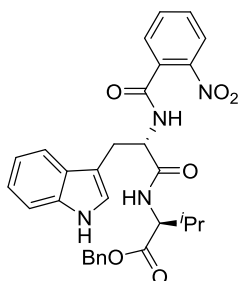
Following the general procedure 2, the coupling of (*R*)-**2.36** (1.80 g, 5.09 mmol) with L-2-aminobutyricbenzyl ester *p*-toluenesulfonic acid salt (3.72 g, 10.18 mmol) gave compound **2.53b** (2.45 g, yield: 91%) as a yellow solid. Mp 142–144 °C (EtOAc); $[\alpha]_{\text{D}}^{20} -35.9$ (c 0.5, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.15 (s, 1H), 8.02–7.97 (m, 1H), 7.66 (d, $J = 7.8$ Hz, 1H), 7.56–7.47 (m, 2H), 7.37–7.26 (m, 6H), 7.20–7.14 (m, 2H), 7.13–7.06 (m, 2H), 6.57 (d, $J = 7.7$ Hz, 1H), 6.52 (d, $J = 7.7$ Hz, 1H), 5.13 (d, $J = 12.5$ Hz, 1H), 5.07 (d, $J = 12.5$ Hz, 1H), 5.07–5.01 (m, 1H), 4.55–4.45 (m, 1H), 3.50 (dd, $J = 14.8, 6.0$ Hz, 1H), 3.32 (dd, $J = 14.8, 7.2$ Hz, 1H), 1.77–1.56 (m, 2H), 0.73 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.8, 170.5, 166.3, 146.4, 136.2, 135.5, 133.7, 132.4, 130.6, 128.6, 128.6, 128.4, 128.2, 127.6, 124.6, 123.2, 122.4, 119.9, 118.6, 111.3, 110.3, 67.0, 54.3, 53.8, 27.3, 25.2, 9.5; IR (neat, cm^{-1}): 3421, 1734, 1642, 1530, 1457, 1349, 1196, 1139; HRMS (ESI, m/z) calcd for $\text{C}_{29}\text{H}_{28}\text{N}_4\text{O}_6\text{Na}$ ($\text{M}+\text{Na}^+$): 551.1901, found: 551.1908.

Benzyl (S)-2-((R)-3-(1H-indol-3-yl)-2-(2-nitrobenzamido)propanamido)-3-methylbutanoate (2.53c).



Following the general procedure 2, the coupling of (*R*)-**2.36** (1.80 g, 5.09 mmol) with benzyl L-valinate *p*-toluenesulfonic acid salt (3.86 g, 10.18 mmol) gave compound **2.53c** (2.57 g, yield: 93%) as a yellow solid. Mp 148–150 °C (EtOAc); $[\alpha]_D^{20}$ –25.6 (*c* 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.33 (s, 1H), 7.97–7.91 (m, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.50–7.42 (m, 2H), 7.34–7.24 (m, 6H), 7.18–7.10 (m, 2H), 7.10–7.02 (m, 2H), 6.69 (d, *J* = 8.4 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 5.14–5.02 (m, 3H), 4.44 (dd, *J* = 8.4, 5.3 Hz, 1H), 3.44 (dd, *J* = 14.9, 6.4 Hz, 1H), 3.26 (dd, *J* = 14.9, 6.4 Hz, 1H), 2.07–1.95 (m, 1H), 0.74 (d, *J* = 6.8 Hz, 3H), 0.71 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 171.4, 170.8, 166.5, 146.2, 136.2, 135.3, 133.7, 132.2, 130.5, 128.6, 128.5, 128.3, 128.3, 127.5, 124.4, 123.2, 122.2, 119.7, 118.6, 111.3, 110.2, 66.9, 57.8, 54.2, 30.8, 27.5, 18.6, 17.7; IR (neat, cm⁻¹): 3420, 1733, 1643, 1530, 1459, 1349, 1195, 1143; HRMS (ESI, *m/z*) calcd for C₃₀H₃₀N₄O₆Na (M+Na⁺): 565.2058, found: 565.2063.

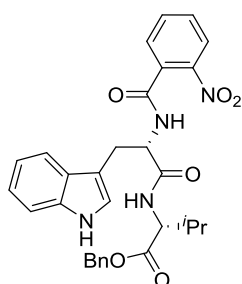
Benzyl (*S*)-2-((*S*)-3-(1*H*-indol-3-yl)-2-(2-nitrobenzamido)propanamido)-3-methylbutanoate (2.56**).**



Following the general procedure 2, the coupling of compound (*S*)-**2.36** (1.80 g, 5.09 mmol) with benzyl L-valinate *p*-toluenesulfonic acid salt (3.86 g, 10.18 mmol) gave compound **2.56** (2.51 g, yield: 91%) as a yellow solid. Mp 83–85 °C (EtOAc); $[\alpha]_D^{20}$

+11.4 (*c* 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.21 (s, 1H), 7.97 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.56–7.45 (m, 2H), 7.39–7.26 (m, 7H), 7.15 (ddd, *J* = 7.2, 7.2, 1.0 Hz, 1H), 7.10–7.02 (m, 2H), 6.93 (d, *J* = 7.7 Hz, 1H), 6.40 (d, *J* = 7.7 Hz, 1H), 5.08 (d, *J* = 12.2 Hz, 1H), 5.04 (d, *J* = 12.2 Hz, 1H), 4.98 (m, 1H), 4.40 (dd, *J* = 8.3, 5.3 Hz, 1H), 3.46 (dd, *J* = 14.9, 5.8 Hz, 1H), 3.23 (dd, *J* = 14.9, 8.1 Hz, 1H), 2.10–2.00 (m, 1H), 0.80 (d, *J* = 6.9 Hz, 3H), 0.74 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 170.9, 170.9, 166.2, 146.2, 136.2, 135.4, 133.6, 132.3, 130.5, 128.7, 128.6, 128.4, 128.3, 127.4, 124.4, 123.5, 122.1, 119.7, 118.8, 111.2, 110.2, 66.9, 57.7, 54.4, 31.0, 28.0, 18.7, 17.7; IR (neat, cm⁻¹): 3420, 1736, 1652, 1527, 1351, 1191, 1140, 1079; HRMS (ESI, *m/z*) calcd. for C₃₀H₃₀N₄O₆Na (M+Na⁺): 565.2058, found: 565.2059.

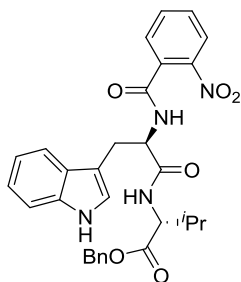
Benzyl (*R*)-2-((*S*)-3-(1*H*-indol-3-yl)-2-(2-nitrobenzamido)propanamido)-3-methylbutanoate (2.59**).**



Following the general procedure 2, the coupling of compound (*S*)-**2.36** (1.80 g, 5.09 mmol) with D-valinate *p*-toluenesulfonic acid salt (3.86 g, 10.18 mmol) gave compound **2.59** (2.57 g, yield: 93%) as a yellow solid. Mp 148–150 °C (EtOAc); [α]_D²⁰ +25.6 (*c* 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.33 (s, 1H), 7.97–7.91 (m, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.50–7.42 (m, 2H), 7.34–7.24 (m, 6H), 7.18–7.10 (m, 2H), 7.10–7.02 (m, 2H), 6.69 (d, *J* = 8.4 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 5.14–5.02 (m, 3H), 4.44 (dd, *J* = 8.4, 5.3 Hz, 1H), 3.44 (dd, *J* = 14.9, 6.4 Hz, 1H), 3.26 (dd, *J* = 14.9, 6.4 Hz, 1H), 2.07–1.95 (m, 1H), 0.74 (d, *J* = 6.8 Hz, 3H), 0.71 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 171.4, 170.8, 166.5, 146.2, 136.2, 135.3, 133.7, 132.2, 130.5, 128.6, 128.5, 128.3, 128.3, 127.5, 124.4, 123.2, 122.2, 119.7, 118.6,

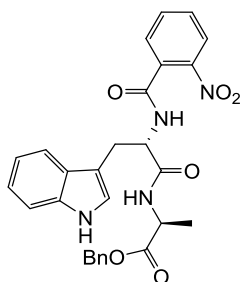
111.3, 110.2, 66.9, 57.8, 54.2, 30.8, 27.5, 18.6, 17.7; IR (neat, cm^{-1}): 3414, 1736, 1640, 1534, 1454, 1354, 1194, 1143; HRMS (ESI, m/z) calcd for $\text{C}_{30}\text{H}_{30}\text{N}_4\text{O}_6\text{Na}$ ($\text{M}+\text{Na}^+$): 565.2058, found: 565.2056.

Benzyl (*R*)-2-((*R*)-3-(1*H*-indol-3-yl)-2-(2-nitrobenzamido)propanamido)-3-methylbutanoate (2.62).



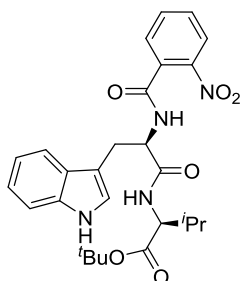
Following the general procedure for the step 2, the coupling of compound (*R*)-**2.36** (1.80 g, 5.09 mmol) with D-valinate *p*-toluenesulfonic acid salt (3.86 g, 10.18 mmol) gave compound **2.62** (2.51 g, yield: 91%) as a yellow solid. Mp 83–85 °C (EtOAc); $[\alpha]_{\text{D}}^{20}$ -11.4 (c 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.21 (s, 1H), 7.97 (dd, $J = 7.6, 1.3$ Hz, 1H), 7.70 (d, $J = 7.9$ Hz, 1H), 7.56–7.45 (m, 2H), 7.39–7.26 (m, 7H), 7.15 (ddd, $J = 7.2, 7.2, 1.0$ Hz, 1H), 7.10–7.02 (m, 2H), 6.93 (d, $J = 7.7$ Hz, 1H), 6.40 (d, $J = 7.7$ Hz, 1H), 5.08 (d, $J = 12.2$ Hz, 1H), 5.04 (d, $J = 12.2$ Hz, 1H), 4.98 (m, 1H), 4.40 (dd, $J = 8.3, 5.3$ Hz, 1H), 3.46 (dd, $J = 14.9, 5.8$ Hz, 1H), 3.23 (dd, $J = 14.9, 8.1$ Hz, 1H), 2.10–2.00 (m, 1H), 0.80 (d, $J = 6.9$ Hz, 3H), 0.74 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.9, 170.9, 166.2, 146.2, 136.2, 135.4, 133.6, 132.3, 130.5, 128.7, 128.6, 128.4, 128.3, 127.4, 124.4, 123.5, 122.1, 119.7, 118.8, 111.2, 110.2, 66.9, 57.7, 54.4, 31.0, 28.0, 18.7, 17.7; IR (neat, cm^{-1}): 3420, 1736, 1652, 1527, 1351, 1191, 1140, 1079; HRMS (ESI, m/z) calcd for $\text{C}_{30}\text{H}_{30}\text{N}_4\text{O}_6\text{Na}$ ($\text{M}+\text{Na}^+$): 565.2058, found: 565.2062.

Benzyl (*S*)-2-((*S*)-3-(1*H*-indol-3-yl)-2-(2-nitrobenzamido)propanamido)propanoate (2.65):



Following the general procedure 2, the coupling of (*S*)-**2.36** (1.80 g, 5.09 mmol) with L-alanine benzyl ester *p*-toluenesulfonic acid salt (3.57 g, 10.18 mmol) gave compound **2.65** (2.38 g, yield: 91%) as a yellow solid. Mp 134–135 °C (AcOEt); $[\alpha]_D^{20} +21.3$ (*c* 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 8.22 (s, 1H), 7.97 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.55–7.45 (m, 2H), 7.40–7.28 (m, 6H), 7.25–7.22 (m, 1H), 7.14 (dd, *J* = 7.2, 7.0 Hz, 1H), 7.09–7.03 (m, 2 H), 6.88 (d, *J* = 7.8 Hz, 1H), 6.55 (d, *J* = 7.9 Hz, 1H), 5.10 (d, *J* = 12.2 Hz, 1H), 5.07 (d, *J* = 12.2 Hz, 1H), 4.97–4.90 (m, 1H), 4.49–4.41 (m, 1H), 3.45 (dd, *J* = 14.8, 5.9 Hz, 1H), 3.24 (dd, *J* = 14.8, 7.6 Hz, 1H), 1.30 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 172.1, 170.4, 166.2, 146.3, 136.1, 135.3, 133.6, 132.3, 130.5, 128.6, 128.6, 128.4, 128.1, 127.5, 124.5, 123.5, 122.1, 119.6, 118.7, 111.2, 110.2, 67.1, 54.2, 48.5, 27.7, 17.9; IR (neat, cm⁻¹): 3409, 3605, 2926, 1740, 1646, 1531, 1455, 1350, 1198, 1153, 741; HRMS (ESI, *m/z*) calcd for C₂₈H₂₆N₄O₆Na (M+Na⁺):537.1745; found: 537.1748.

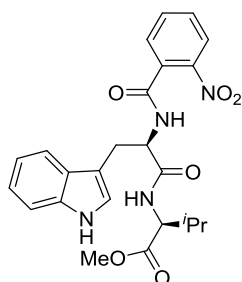
***tert*-Butyl (*S*)-2-((*R*)-3-(1*H*-indol-3-yl)-2-(2-nitrobenzamido)propanamido)-3-methylbutanoate (**2.68**):**



Following the general procedure 2, the coupling of (*R*)-**2.36** (1.80 g, 5.09 mmol) with benzyl L-valine *tert*-butyl ester hydrochloride (2.13 g, 10.18 mmol) gave compound **2.68** (2.40 g, yield: 92%) as a yellow solid. Mp 78–80 °C (AcOEt); $[\alpha]_D^{20} -16.2$ (*c* 1.0,

CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.32 (s, 1H), 8.04–7.97 (m, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.57–7.46 (m, 2H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.22–7.14 (m, 2H), 7.13–7.07 (m, 2H), 6.66 (d, *J* = 7.8 Hz, 1H), 6.48 (d, *J* = 8.3 Hz, 1H), 5.08 (dd, *J* = 14.3, 7.4 Hz, 1H), 4.33 (dd, *J* = 8.0, 5.1 Hz, 1H), 3.47 (dd, *J* = 14.8, 6.4 Hz, 1H), 3.32 (dd, *J* = 14.8, 7.6 Hz, 1H), 2.05–1.93 (m, 1H), 1.42 (s, 9H), 0.76 (d, *J* = 6.6 Hz, 3H), 0.75 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 170.6, 170.5, 166.3, 146.3, 136.3, 133.7, 132.4, 130.5, 128.6, 127.5, 124.5, 123.0, 122.3, 119.8, 118.8, 111.3, 110.5, 82.0, 58.0, 54.3, 31.1, 28.0, 27.8, 18.5, 17.6; IR (neat, cm⁻¹): 3410, 2965, 1736, 1656, 1527, 1354, 1262, 1149, 1076, 797; HRMS (ESI, *m/z*) calcd for C₂₇H₃₂N₄O₆Na (M+Na⁺): 531.2214; found: 531.2218.

Methyl (*S*)-2-[(*R*)-3-(1*H*-indol-3-yl)-2-(2-nitrobenzamido)-propanamido]-3-methylbutanoate (2.73**):**



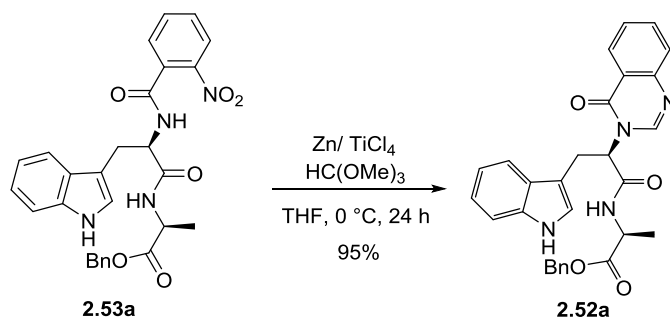
Following the general procedure 2, the coupling of (*R*)-**2.36** (1.80 g, 5.09 mmol) with benzyl L-valine methyl ester hydrochloride (2.13 g, 10.18 mmol) gave compound **2.73** (2.19 g, yield: 93%) as a yellow solid. Mp 78–81 °C (AcOEt); [α]_D²⁰ –24.8 (*c* 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.45 (s, 1H), 7.99–7.92 (m, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.54–7.44 (m, 2H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.19–7.11 (m, 2H), 7.10–7.03 (m, 2H), 6.69 (d, *J* = 7.9 Hz, 1H), 6.66 (d, *J* = 8.3 Hz, 1H), 5.10 (ddd, *J* = 7.8, 7.1, 6.5 Hz, 1H), 4.38 (dd, *J* = 8.0, 5.4 Hz, 1H), 3.65 (s, 3H), 3.42 (dd, *J* = 14.8, 6.7 Hz, 1H), 3.32 (dd, *J* = 14.8, 7.3 Hz, 1H), 2.06–1.92 (m, 1H), 0.75 (d, *J* = 6.6 Hz, 3H), 0.73 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 172.0, 170.8, 166.5, 146.2, 136.2, 133.7, 132.3, 130.5, 128.6, 127.5, 124.4, 123.2, 122.2, 119.7, 118.6, 111.3, 110.2, 57.7, 54.2, 52.0, 30.8, 27.6, 18.6, 17.8; IR (neat, cm⁻¹): 3300, 1757,

1634, 1530, 1456, 1435, 1348, 1210, 746; HRMS (ESI, m/z) calcd for $C_{24}H_{26}N_4O_6Na$ ($M+Na^+$): 489.1745; found: 489.1750.

General Procedure for the Step 3 (General Procedure 3)

To a mixture of zinc powder (776 mg, 11.94 mmol) and THF (50 mL) was added $TiCl_4$ (0.66 mL, 5.98 mmol). The resulting mixture were stirred for 1 h at 50 °C. After cooling to 0 °C, a THF (10 mL) solution of a tryptophan-derived dipeptide (1.50 mmol) and trimethylorthoformate (0.66 mL, 5.98 mmol) were added. The resulting mixture was stirred for 24 h at 0 °C. To the reaction mixture was added brine (10 mL) and the resulting mixture was stirred for 2 h. After separating the phases, the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic phases were dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc: PE = 1:3 to DCM: MeOH = 40:1) to give the corresponding quinazolino-dipeptide derivative.

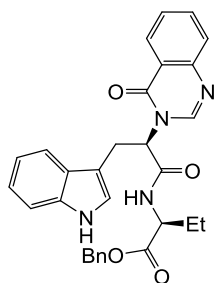
Benzyl (*S*)-2-((*R*)-3-(1*H*-indol-3-yl)-2-(4-oxoquinazolin-3(4*H*)-yl)propanamido)-propanoate (**2.52a**).



Following the general procedure 3, the reaction of compound **2.53a** (771 mg, 1.50 mmol) gave compound **2.52a** (704 mg, yield: 95%) as a white solid. Mp 161–163 °C (EtOAc); $[\alpha]_D^{20} +58.6$ (c 1.0, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.22–8.16 (m, 2H), 7.74–7.60 (m, 3H), 7.42 (ddd, J = 8.1, 6.8, 1.4 Hz, 1H), 7.31–7.24 (m, 4H), 7.22–7.18 (m, 2H), 7.15 (ddd, J = 8.0, 7.2, 1.1 Hz, 1H), 7.07 (ddd, J = 8.0, 7.9, 1.1 Hz, 1H), 6.99 (d, J = 2.4 Hz, 1H), 6.93 (d, J = 7.2 Hz, 1H), 5.83 (dd, J = 8.5, 7.2 Hz, 1H), 5.05 (d, J = 12.3 Hz, 1H), 5.01 (d, J = 12.3 Hz, 1H), 4.51 (dq, J = 7.3, 7.2

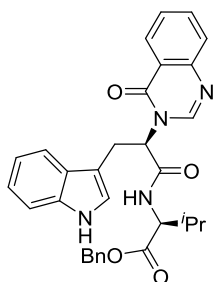
Hz, 1H), 3.72 (dd, $J = 14.5, 8.7$ Hz, 1H), 3.41 (dd, $J = 14.5, 7.1$ Hz, 1H), 1.20 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.9, 168.4, 161.1, 147.5, 144.2, 136.2, 135.2, 134.4, 128.5, 128.3, 128.0, 127.5, 127.2, 126.9 (2C), 123.2, 122.4, 121.4, 119.9, 118.4, 111.3, 109.7, 67.1, 56.5, 48.5, 27.2, 17.6; IR (neat, cm^{-1}): 3318, 2928, 1741, 1662, 1607, 1455, 1327, 1196, 1153; HRMS (ESI, m/z) calcd for $\text{C}_{29}\text{H}_{26}\text{N}_4\text{O}_4\text{Na}$ ($\text{M}+\text{Na}^+$): 517.1846, found: 517.1850.

Benzyl (S)-2-((R)-3-(1H-indol-3-yl)-2-(4-oxoquinazolin-3(4H)-yl)propanamido)-butaneate (2.52b).



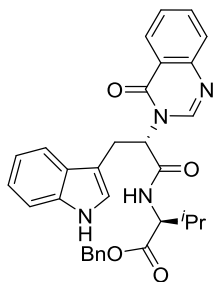
Following the general procedure 3, the reaction of compound **2.53b** (792 mg, 1.50 mmol) gave compound **2.52b** (724 mg, yield: 95%) as a white solid. Mp 185–187 °C (EtOAc); $[\alpha]_{\text{D}}^{20} +47.6$ (c 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.40 (s, 1H), 8.24 (br. s, 1H), 8.20 (dd, $J = 8.2, 0.9$ Hz, 1H), 7.72–7.61 (m, 3H), 7.41 (ddd, $J = 8.1, 6.8, 1.4$ Hz, 1H), 7.30–7.26 (m, 4H), 7.21–7.17 (m, 2H), 7.14 (ddd, $J = 7.9, 6.8, 0.9$ Hz, 1H), 7.06 (ddd, $J = 7.9, 7.8, 0.8$ Hz, 1H), 6.99 (d, $J = 2.2$ Hz, 1H), 6.91 (d, $J = 8.1$ Hz, 1H), 5.88 (dd, $J = 8.5, 7.2$ Hz, 1H), 5.04 (d, $J = 12.2$ Hz, 1H), 4.99 (d, $J = 12.2$ Hz, 1H), 4.51–4.44 (m, 1H), 3.73 (dd, $J = 14.5, 8.7$ Hz, 1H), 3.41 (dd, $J = 14.5, 7.1$ Hz, 1H), 1.76–1.63 (m, 1H), 1.61–1.49 (m, 1H), 0.61 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.3, 168.7, 161.2, 147.5, 144.3, 136.2, 135.2, 134.4, 128.5, 128.3, 128.1, 127.5, 127.2, 126.9 (2C), 123.2, 122.4, 121.5, 119.8, 118.4, 111.3, 109.6, 67.0, 56.6, 53.8, 27.3, 25.0, 9.2; IR (neat, cm^{-1}): 3422, 2968, 1738, 1659, 1610, 1477, 1328, 1195, 1140; HRMS (ESI, m/z) calcd for $\text{C}_{30}\text{H}_{28}\text{N}_4\text{O}_4\text{Na}$ ($\text{M}+\text{Na}^+$): 531.2003, found: 531.2000.

Benzyl (S)-2-((R)-3-(1H-indol-3-yl)-2-(4-oxoquinazolin-3(4H)-yl)propanamido)-3-methylbutanoate (2.52c).



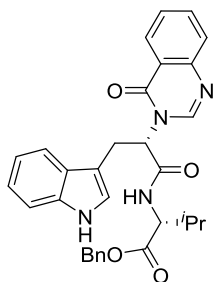
Following the general procedure 3, the reaction of compound **2.53c** (813 mg, 1.50 mmol) gave compound **2.52c** (744 mg, yield: 95%) as a white solid. Mp 165–167 °C (EtOAc); $[\alpha]_D^{20} +55.6$ (c 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.41 (s, 1H), 8.30 (s, 1H), 8.22 (dd, $J = 8.1, 1.0$ Hz, 1H), 7.72–7.62 (m, 3H), 7.41 (ddd, $J = 8.1, 6.8, 1.5$ Hz, 1H), 7.28 (d, $J = 8.1$ Hz, 1H), 7.26–7.17 (m, 5H), 7.14 (ddd, $J = 7.9, 6.8, 0.9$ Hz, 1H), 7.07 (ddd, $J = 7.9, 7.9, 0.9$ Hz, 1H), 7.00 (d, $J = 2.3$ Hz, 1H), 6.94 (d, $J = 8.1$ Hz, 1H), 5.94 (dd, $J = 7.6, 7.6$ Hz, 1H), 5.03 (d, $J = 12.2$ Hz, 1H), 4.98 (d, $J = 12.2$ Hz, 1H), 4.46 (dd, $J = 8.5, 5.0$ Hz, 1H), 3.74 (dd, $J = 14.5, 8.7$ Hz, 1H), 3.44 (dd, $J = 14.5, 7.1$ Hz, 1H), 2.04–1.96 (m, 1H), 0.68 (d, $J = 6.8$ Hz, 3H), 0.64 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.8, 168.8, 161.2, 147.5, 144.3, 136.2, 135.1, 134.4, 128.4, 128.3, 128.2, 127.4, 127.1, 126.9, 126.8, 123.2, 122.3, 121.4, 119.8, 118.4, 111.3, 109.4, 66.9, 57.7, 56.6, 30.8, 27.4, 18.6, 17.5; IR (neat, cm^{-1}): 3417, 2965, 1738, 1659, 1610, 1477, 1328, 1195, 1143; HRMS (ESI, m/z) calcd for $\text{C}_{31}\text{H}_{30}\text{N}_4\text{O}_4\text{Na}$ ($\text{M}+\text{Na}^+$): 545.2159, found: 545.2161.

Benzyl (S)-2-((S)-3-(1H-indol-3-yl)-2-(4-oxoquinazolin-3(4H)-yl)propanamido)-3-methylbutanoate (2.57).



Following the general procedure 3, the reaction of compound **2.56** (813 mg, 1.50 mmol) gave compound **2.57** (752 mg, yield: 96%) as a white solid. Mp 81–83 °C (EtOAc); $[\alpha]_D^{20}$ -31.5 (c 1.0, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 8.44 (s, 1H), 8.21 (dd, $J = 8.0, 1.2$ Hz, 1H), 8.12 (s, 1H), 7.75–7.66 (m, 2H), 7.50 (d, $J = 8.1$ Hz, 1H), 7.43 (ddd, $J = 8.2, 6.8, 1.3$ Hz, 1H), 7.38–7.30 (m, 5H), 7.21 (d, $J = 7.2$ Hz, 1H), 7.13 (d, $J = 8.6$ Hz, 1H), 6.93 (ddd, $J = 8.1, 6.8, 0.9$ Hz, 1H), 6.90 (d, $J = 2.3$ Hz, 1H), 5.96 (dd, $J = 7.9, 7.9$ Hz, 1H), 5.13 (d, $J = 12.2$ Hz, 1H), 5.07 (d, $J = 12.2$ Hz, 1H), 4.52 (dd, $J = 8.6, 5.1$ Hz, 1H), 3.67 (dd, $J = 14.9, 8.0$ Hz, 1H), 3.40 (dd, $J = 14.9, 7.9$ Hz, 1H), 2.12–2.04 (m, 1H), 0.75 (d, $J = 6.9$ Hz, 3H), 0.71 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.1, 169.3, 161.3, 147.4, 144.5, 136.1, 135.3, 134.5, 128.6, 128.4, 128.3, 127.4, 127.2, 127.0, 126.7, 123.2, 122.2, 121.3, 119.6, 118.2, 111.3, 109.3, 67.0, 57.6, 56.5, 31.0, 27.2, 18.8, 17.6; IR (neat, cm^{-1}): 3440, 2965, 1729, 1656, 1607, 1556, 1457, 1194, 1137; HRMS (ESI, m/z) calcd for $\text{C}_{31}\text{H}_{30}\text{N}_4\text{O}_4\text{Na}$ ($\text{M}+\text{Na}^+$): 545.2159, found: 545.2151.

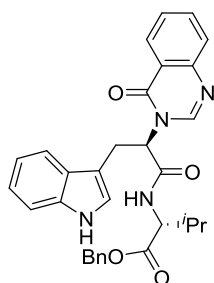
Benzyl (*R*)-2-((*S*)-3-(1*H*-indol-3-yl)-2-(4-oxoquinazolin-3(4*H*)-yl)propanamido)-3-methylbutanoate (2.60**).**



Following the general procedure 3, the reaction of compound **2.59** (813 mg, 1.50 mmol) gave compound **2.60** (744 mg, yield: 95%) as a white solid. Mp 165–167 °C

(EtOAc); $[\alpha]_D^{20} -55.6$ (*c* 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.41 (s, 1H), 8.30 (s, 1H), 8.22 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.72–7.62 (m, 3H), 7.41 (ddd, *J* = 8.1, 6.8, 1.5 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 7.26–7.17 (m, 5H), 7.14 (ddd, *J* = 7.9, 6.8, 0.9 Hz, 1H), 7.07 (ddd, *J* = 7.9, 7.9, 0.9 Hz, 1H), 7.00 (d, *J* = 2.3 Hz, 1H), 6.94 (d, *J* = 8.1 Hz, 1H), 5.94 (dd, *J* = 7.6, 7.6 Hz, 1H), 5.03 (d, *J* = 12.2 Hz, 1H), 4.98 (d, *J* = 12.2 Hz, 1H), 4.46 (dd, *J* = 8.5, 5.0 Hz, 1H), 3.74 (dd, *J* = 14.5, 8.7 Hz, 1H), 3.44 (dd, *J* = 14.5, 7.1 Hz, 1H), 2.04–1.96 (m, 1H), 0.68 (d, *J* = 6.8 Hz, 3H), 0.64 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 170.8, 168.8, 161.2, 147.5, 144.3, 136.2, 135.1, 134.4, 128.4, 128.3, 128.2, 127.4, 127.1, 126.9, 126.8, 123.2, 122.3, 121.4, 119.8, 118.4, 111.3, 109.4, 66.9, 57.7, 56.6, 30.8, 27.4, 18.6, 17.5; IR (neat, cm⁻¹): 3417, 2965, 1738, 1659, 1610, 1477, 1328, 1195, 1143; HRMS (ESI, *m/z*) calcd for C₃₁H₃₀N₄O₄Na (M+Na⁺): 545.2159, found: 545.2161.

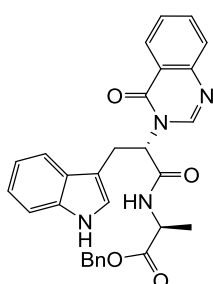
Benzyl (R)-2-((R)-3-(1*H*-indol-3-yl)-2-(4-oxoquinazolin-3(4*H*)-yl)propanamido)-3-methylbutanoate (2.63).



Following the general procedure 3, the reaction of compound **2.62** (813 mg, 1.50 mmol) gave compound **2.63** (752 mg, yield: 96%) as a white solid. Mp 81–83 °C (EtOAc); $[\alpha]_D^{20} +31.5$ (*c* 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 8.44 (s, 1H), 8.21 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.12 (s, 1H), 7.75–7.66 (m, 2H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.43 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.38–7.30 (m, 5H), 7.21 (d, *J* = 7.2 Hz, 1H), 7.13 (d, *J* = 8.6 Hz, 1H), 6.93 (ddd, *J* = 8.1, 6.8, 0.9 Hz, 1H), 6.90 (d, *J* = 2.3 Hz, 1H), 5.96 (dd, *J* = 7.9, 7.9 Hz, 1H), 5.13 (d, *J* = 12.2 Hz, 1H), 5.07 (d, *J* = 12.2 Hz, 1H), 4.52 (dd, *J* = 8.6, 5.1 Hz, 1H), 3.67 (dd, *J* = 14.9, 8.0 Hz, 1H), 3.40 (dd, *J* = 14.9, 7.9 Hz, 1H), 2.12–2.04 (m, 1H), 0.75 (d, *J* = 6.9 Hz, 3H), 0.71 (d, *J* = 6.9 Hz, 3H); ¹³C

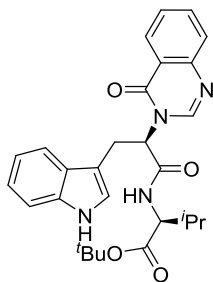
NMR (125 MHz, CDCl₃) δ 171.1, 169.3, 161.3, 147.4, 144.5, 136.1, 135.3, 134.5, 128.6, 128.4, 128.3, 127.4, 127.2, 127.0, 126.7, 123.2, 122.2, 121.3, 119.6, 118.2, 111.3, 109.3, 67.0, 57.6, 56.5, 31.0, 27.2, 18.8, 17.6; IR (neat, cm⁻¹): 3440, 2965, 1729, 1656, 1607, 1556, 1457, 1194, 1137; HRMS (ESI, m/z) calcd for C₃₁H₃₀N₄O₄Na (M+Na⁺): 545.2159, found: 545.2156.

Benzyl (S)-2-((S)-3-(1H-indol-3-yl)-2-(4-oxoquinazolin-3(4H)-yl)propanamido)-propanoate (2.66).



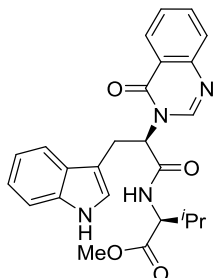
Following the general procedure 3, the reaction of compound **2.65** (771 mg, 1.50 mmol) gave compound **2.66** (704 mg, yield: 95%) as a white solid. Mp 114–115 °C (EtOAc); $[\alpha]_D^{20}$ -23.6 (*c* 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 8.40 (s, 1H), 8.22 (dd, *J* = 7.9, 0.9 Hz, 1H), 8.04 (s, 1H), 7.76–7.66 (m, 2H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.45 (ddd, *J* = 7.5, 7.4, 0.9 Hz, 1H), 7.39–7.28 (m, 5H), 7.25–7.22 (m, 1H), 7.12 (t, *J* = 7.1 Hz, 1H), 7.02 (t, *J* = 7.1 Hz, 1H), 6.95 (d, *J* = 2.1 Hz, 1H), 6.92 (d, *J* = 7.2 Hz, 1H), 5.85 (dd, *J* = 7.8, 7.8 Hz, 1H), 5.12 (d, *J* = 12.2 Hz, 1H), 5.08 (d, *J* = 12.2 Hz, 1H), 4.57–4.48 (m, 1H), 3.68 (dd, *J* = 14.8, 8.2 Hz, 1H), 3.42 (dd, *J* = 14.8, 7.6 Hz, 1H), 1.29 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 172.0, 168.6, 161.2, 147.5, 144.5, 136.1, 135.3, 134.5, 128.6, 128.5, 128.1, 127.5, 127.2, 126.9, 126.8, 123.2, 122.3, 121.4, 119.7, 118.3, 111.3, 109.4, 67.1, 56.4, 48.6, 27.3, 17.8; IR (neat, cm⁻¹): 3416, 2084, 1658, 1610, 1456, 1327, 1197, 1160, 1076, 741; HRMS (ESI, m/z) calcd for C₂₉H₂₆N₄O₄Na (M+Na⁺): 517.1846; found: 517.1851.

***tert*-Butyl (S)-2-((R)-3-(1H-indol-3-yl)-2-(4-oxoquinazolin-3(4H)-yl)propanamido)-3-methylbutanoate (2.69).**



Following the general procedure 3, the reaction of compound **2.68** (762 mg, 1.50 mmol) gave compound **2.69** (695 mg, yield: 95%) as a white solid. Mp 89–91 °C (EtOAc); $[\alpha]_D^{20} +55.7$ (*c* 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.42 (s, 1H), 8.36 (br s, 1H), 8.26 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.75–7.63 (m, 3H), 7.50–7.41 (ddd, *J* = 7.5, 7.4, 0.9 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.16 (ddd, *J* = 7.6, 7.3, 0.8 Hz, 1H), 7.10 (ddd, *J* = 7.6, 7.3, 0.8 Hz, 1H), 7.03 (d, *J* = 2.2 Hz, 1H), 6.75 (d, *J* = 7.3 Hz, 1H), 5.90 (dd, *J* = 8.4, 7.3 Hz, 1H), 4.29 (dd, *J* = 8.3, 5.0 Hz, 1H), 3.74 (dd, *J* = 14.5, 8.7 Hz, 1H), 3.45 (dd, *J* = 14.5, 7.1 Hz, 1H), 2.04–1.93 (m, 1H), 1.33 (s, 9H), 0.71 (d, *J* = 6.2 Hz, 3H), 0.69 (d, *J* = 6.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 169.9, 168.5, 161.1, 147.5, 144.3, 136.3, 134.4, 127.4, 127.1, 126.9, 126.8, 123.2, 122.3, 121.5, 119.8, 118.4, 111.3, 109.5, 82.0, 58.1, 56.7, 31.0, 27.8, 27.4, 18.5, 17.6; IR (neat, cm⁻¹): 3420, 2102, 1658, 1476, 1369, 1196, 1142, 1076, 742; HRMS (ESI, *m/z*) calcd for C₂₈H₃₂N₄O₄Na (M+Na⁺):511.2316; found: 511.2318.

Methyl (S)-2-[(R)-3-(1H-indol-3-yl)-2-(4-oxoquinazolin-3(4H)-yl)propanamido] -3-methylbutanoate (2.74)



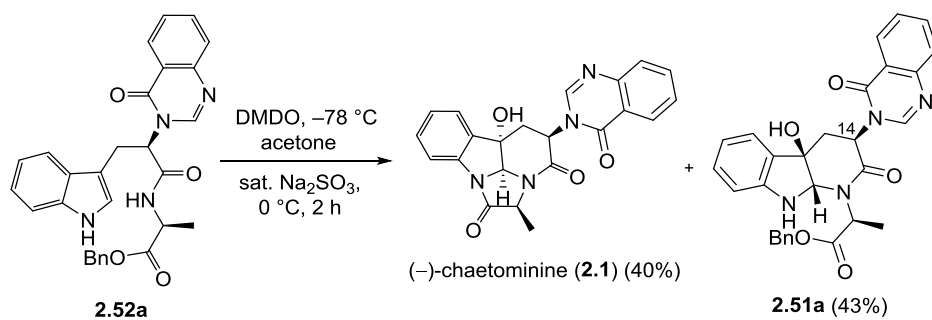
Following the general procedure 3, the reaction of compound **2.73** (700 mg, 1.50 mmol) gave compound **2.74** (634 mg, yield: 95%) as a white solid. Mp 202–204 °C (EtOAc); $[\alpha]_D^{20} +53.2$ (*c* 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.41 (s, 1H),

8.25 (dd, $J = 7.8, 0.9$ Hz, 1H), 8.22 (br s, 1H), 7.75–7.64 (m, 3H), 7.44 (ddd, $J = 7.6, 7.3, 1.0$ Hz, 1H), 7.31 (d, $J = 8.1$ Hz, 1H), 7.17 (ddd, $J = 7.6, 7.3, 0.8$ Hz, 1H), 7.09 (ddd, $J = 7.6, 7.3, 0.8$ Hz, 1H), 7.03 (d, $J = 2.2$ Hz, 1H), 6.84 (d, $J = 7.3$ Hz, 1H), 5.85 (dd, $J = 8.7, 7.3$ Hz, 1H), 4.42 (dd, $J = 8.3, 5.0$ Hz, 1H), 3.75 (dd, $J = 14.5, 8.7$ Hz, 1H), 3.57 (s, 3H), 3.45 (dd, $J = 14.5, 7.0$ Hz, 1H), 2.06–1.95 (m, 1H), 0.72 (d, $J = 6.3$ Hz, 3H), 0.70 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.5, 168.9, 161.2, 147.4, 144.3, 136.2, 134.5, 127.4, 127.2, 126.8 (2C), 123.2, 122.3, 121.4, 119.8, 118.4, 111.3, 109.4, 57.7, 56.4, 52.0, 30.8, 27.4, 18.6, 17.6; IR (neat, cm^{-1}): 3330, 1743, 1665, 1600, 1549, 1462, 1434, 1204, 1162, 749; HRMS (ESI, m/z) calcd for $\text{C}_{25}\text{H}_{26}\text{N}_4\text{O}_4\text{Na}$ ($\text{M}+\text{Na}^+$): 469.1846; found: 469.1851.

General Procedure A for the Step 4 (General Procedure 4-A)

To a solution of quinazolino-dipeptide derivative (0.38 mmol) in anhydrous acetone (2 mL) was added a solution of 0.04 M DMDO in acetone (19 mL, 0.76 mmol) at -78 °C. After being stirred for 1 h, Na_2SO_3 (sat., 10 mL) was added and the mixture was stirred for 2 h at 0 °C. To the resulting reaction mixture was added 10 mL NH_4Cl (sat.) and concentrated under reduced pressure. To the resulting residue was added H_2O (50 mL), and extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc: PE = 1:1) to give a chaetominine/isochaetominine-type compound and a monocyclization product.

(–)-(2*S*,3*S*,11*S*,14*R*)-Chaetominine (2.1) and benzyl (S)-2-((3*R*,4*aR*,9*aS*)-4*a*-hydroxy-2-oxo-3-(4-oxoquinazolin-3(4*H*)-yl)-2,3,4,4*a*,9,9*a*-hexahydro-1*H*-pyrido[2,3-*b*]indol-1-yl)propanoate (2.51a).

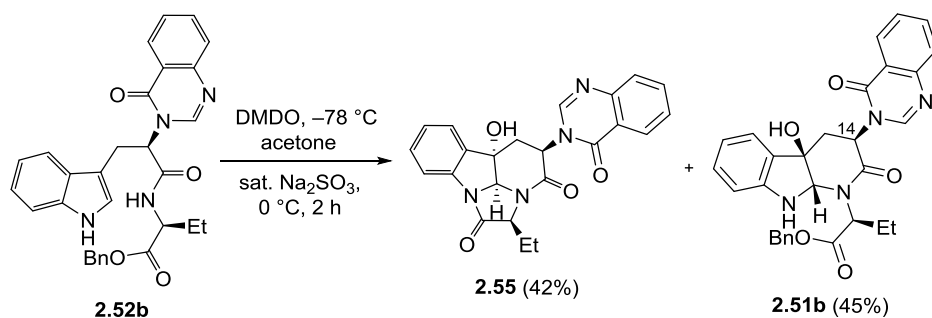


Following the general procedure 4-A, the reaction of compound **2.52a** (188 mg, 0.38 mmol) gave (-)-chaetominine (**2.1**) (61 mg, yield: 40%) and compound **2.51a** (83 mg, yield: 43%) (eluent: EtOAc:PE = 1:1).

(-)-Chaetominine (**2.1**): colorless crystals, Mp 301–302 °C (EtOAc) [lit. 161–163 °C,^{8a} 288–290 °C (MeOH)^{8f}]; [α]_D²⁰ -49.7 (*c* 0.5, MeOH) {lit. [α]_D²⁰ -70 (*c* 0.48, MeOH),^{3a} [α]_D²⁰ -49.4 (*c* 0.26, MeOH);^{8a} [α]_D²⁰ -49.7 (*c* 0.48, MeOH)^{8f}}; The IR, ¹H NMR, ¹³C NMR and MS data are identical with those reported previously.^{8f}

Compound **2.51a**: White solid. Mp 154–156 °C (EtOAc); [α]_D²⁰ -145.1 (*c* 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.18 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.69 (ddd, *J* = 8.4, 7.4, 1.2 Hz, 1H), 7.64–7.56 (m, 2H), 7.43 (ddd, *J* = 8.2, 7.8, 0.9 Hz, 1H), 7.38–7.30 (m, 5H), 7.27 (d, *J* = 7.2 Hz, 1H), 7.13 (ddd, *J* = 7.9, 7.8, 0.9 Hz, 1H), 6.78 (dd, *J* = 7.4, 7.3 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 5.36–5.05 (m, 6H), 4.10 (s, 1H), 2.88 (dd, *J* = 12.5, 12.5 Hz, 1H), 2.48 (dd, *J* = 12.5, 4.0 Hz, 1H), 1.53 (d, *J* = 7.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 172.7, 169.5, 160.6, 148.2, 147.2, 145.4, 135.1, 134.4, 130.8, 129.1, 128.7, 128.6, 128.2, 127.3, 127.1, 126.9, 123.6, 121.8, 120.2, 110.2, 80.5, 79.3, 67.3, 52.2, 40.7, 16.3 (one carbon was not observed due to slow rotation at the C14-N bond);^{8a} IR (neat, cm⁻¹): 3365, 2930, 1738, 1677, 1610, 1475, 1321, 1244, 1185, 1140, 751; HRMS (ESI, *m/z*) calcd for C₂₉H₂₆N₄O₅Na (M+Na⁺): 533.1795, found: 533.1795.

(-)-(2*S*,3*S*,11*S*,14*R*)-2,3-Di-*epi*-isochaetominine **B** (**2.55**) and benzyl (*S*)-2-((3*R*,4*aR*,9*aS*)-4*a*-hydroxy-2-oxo-3-(4-oxoquinazolin-3(4*H*)-yl)-2,3,4,4*a*,9,9*a*-hexahydro-1*H*-pyrido[2,3-*b*]indol-1-yl)butanoate (**2.51b**).



Following the general procedure 4-A, the reaction of compound **2.52b** (193 mg, 0.38 mmol) gave compound **2.55** (66 mg, yield: 42%) and compound **2.51b** (90 mg, yield: 45%) (eluent: EtOAc:PE = 1:1).

2,3-Di-*epi*-isochaetominine B (**2.55**): colorless crystals, Mp 302–304 °C (EtOAc); $[\alpha]_{\text{D}}^{20} -47.7$ (*c* 1.0, MeOH); $^1\text{H NMR}$ (500 MHz, DMSO-*d*₆) δ 8.30 (br. s, 1H), 8.17 (d, *J* = 1.3 Hz, 1H), 7.87 (ddd, *J* = 7.7, 7.6, 1.5 Hz, 1H), 7.71 (d, *J* = 6.9 Hz, 1H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.54–7.47 (m, 2H), 7.44 (td, *J* = 7.6, 1.2 Hz, 1H), 7.25 (td, *J* = 7.5, 1.0 Hz, 1H), 6.70 (br. s, 1H), 6.18–5.70 (br. s, 1H), 5.58 (s, 1H), 4.65 (t, *J* = 3.5 Hz, 1H), 2.90 (dd, *J* = 12.8, 12.8 Hz, 1H), 2.63 (dd, *J* = 12.8, 3.0 Hz, 1H), 2.49–2.38 (m, 1H), 1.97–1.80 (m, 1H), 0.69 (t, *J* = 7.1 Hz, 3H); $^{13}\text{C NMR}$ (125 MHz, DMSO-*d*₆) δ 172.2, 165.5 (br.), 160.3, 147.6, 146.6 (br.), 139.1, 136.5, 134.9, 130.2, 127.5, 127.4, 126.5, 125.6, 125.2, 121.5, 114.4, 82.5, 76.7, 64.1, 50.8 (br.), 38.1, 20.0, 8.8 (br.); IR (neat, cm^{-1}): 3443, 1732, 1656, 1476, 1277, 1191, 1137, 742; HRMS (ESI, *m/z*) calcd for C₂₃H₂₀N₄O₄Na (M+Na⁺): 439.1377, found: 439.1380.

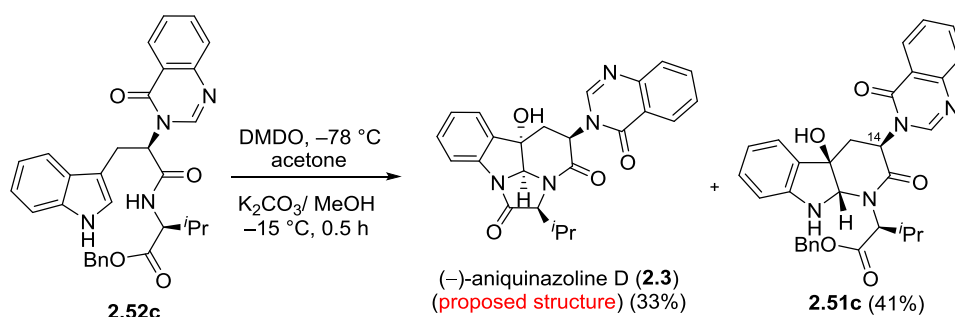
Compound **2.51b**: white solid, Mp 113–115 °C (EtOAc); $[\alpha]_{\text{D}}^{20} -146.7$ (*c* 1.0, CHCl₃); IR (neat, cm^{-1}): 3442, 2932, 1733, 1671, 1612, 1470, 1321, 1238, 1176, 751; $^1\text{H NMR}$ (400 MHz, CDCl₃) δ 8.18 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.68 (ddd, *J* = 8.2, 7.2, 1.5 Hz, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.50–7.39 (m, 2H), 7.38–7.30 (m, 5H), 7.25 (d, *J* = 7.4 Hz, 1H), 7.10 (ddd, *J* = 8.2, 7.8, 1.1 Hz, 1H), 6.74 (dd, *J* = 7.4, 7.2 Hz, 1H), 6.54 (d, *J* = 8.0 Hz, 1H), 5.40–5.10 (m, 6H), 4.30 (s, 1H), 2.88 (dd, *J* = 12.5, 12.5 Hz, 1H), 2.43 (dd, *J* = 12.5, 3.9 Hz, 1H), 2.10–1.98 (m, 1H), 1.85–1.71 (m, 1H), 1.08 (t, *J* = 7.3 Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl₃) δ 172.5, 170.4, 160.5, 148.2, 147.2, 145.3,

135.0, 134.3, 130.7, 129.3, 128.7, 128.6, 128.3, 127.2, 127.0, 127.0, 123.6, 121.8, 120.0, 110.0, 80.1, 79.5, 67.3, 57.1, 41.2, 23.6, 10.4 (one carbon was not observed due to slow rotation at the C14-N bond);^{8a} IR (neat, cm⁻¹): 3442, 2932, 1733, 1671, 1612, 1470, 1321, 1238, 1176, 751; HRMS (ESI, *m/z*) calcd for C₃₀H₂₈N₄O₅Na (M+Na⁺): 547.1952, found: 547.1954.

General Procedure B for the Step 4 (General Procedure 4-B)

To a solution of a quinazolino-dipeptide derivative in anhydrous acetone (2 mL) was added a solution of 0.04 M DMDO in acetone (19 mL, 0.76 mmol) at -78 °C. After being stirred for 1 h, K₂CO₃/ MeOH (94 mg/ 10 mL) was added and the mixture was warm up to -15 °C or 0 °C over 30 minutes. To the reaction mixture was added 10 mL NH₄Cl (sat.) and concentrated under reduced pressure. To the resulting residue was added H₂O (50 mL), and resulting mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc: PE = 1:1) to give an isochaetominine-type compound and a monocyclization product.

The proposed structure of (-)-aniquiazoline D [(2*S*,3*S*,11*S*,14*R*)-2.3], and benzyl (*S*)-2-((3*R*,4*aR*,9*aS*)-4*a*-hydroxy-2-oxo-3-(4-oxoquinazolin-3(4*H*)-yl)-2,3,4,4*a*,9,9*a*-hexahydro-1*H*-pyrido[2,3-*b*]indol-1-yl)-3-methylbutanoate (2.51c).



Following the general procedure 4-B, the reaction of compound **2.52c** (200 mg, 0.38 mmol) gave compound **2.3** (53 mg, yield: 33%) and compound **2.51c** (82 mg, yield: 41%) (eluent: EtOAc:PE = 1:1).

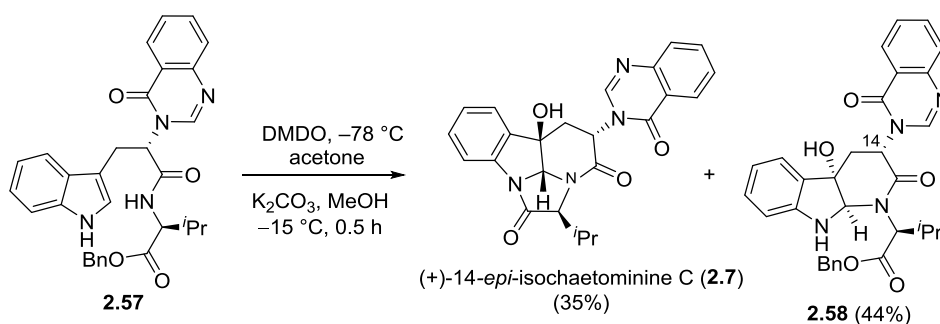
Compound **2.3** [the proposed structure⁵ of (-)-aniquiniazoline D]: colorless crystals. Mp 302–303 °C (EtOAc); $[\alpha]_D^{20}$ -50.7 (*c* 0.5, MeOH); ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.30 (br. s, 1H), 8.16 (d, *J* = 1.3 Hz, 1H), 7.86 (ddd, *J* = 7.7, 7.6, 1.5 Hz, 1H), 7.70 (d, *J* = 6.9 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.53–7.46 (m, 2H), 7.43 (td, *J* = 7.6, 1.2 Hz, 1H), 7.24 (td, *J* = 7.5, 1.0 Hz, 1H), 6.68 (br. s, 1H), 6.16–5.68 (br. s, 1H), 5.52 (s, 1H), 4.56 (d, *J* = 2.8 Hz, 1H), 3.17 (m, 1H), 2.91 (dd, *J* = 12.8, 12.8 Hz, 1H), 2.62 (dd, *J* = 12.8, 3.0 Hz, 1H), 1.13 (d, *J* = 7.3 Hz, 3H), 0.79 (d, *J* = 7.3 Hz, 3H); ¹³C NMR (125 MHz, DMSO-*d*₆) δ 171.9, 166.3 (br.), 160.6, 147.9, 146.6 (br.), 139.5, 136.5, 135.1, 130.5, 127.8, 127.7, 126.8, 125.8, 125.4, 121.8, 114.6, 82.6, 77.0, 68.0, 51.2 (br.), 38.6, 25.8, 18.3, 16.6 (br.); IR (neat, cm⁻¹): 3446, 2965, 1738, 1642, 1610, 1475, 1275, 1192, 1137, 742; HRMS (ESI, *m/z*) calcd for C₂₄H₂₂N₄O₄Na (M+Na⁺): 453.1533, found: 453.1536; chiral HPLC conditions: Chiralpak AD-H (*n*-hexane/EtOH, 30:70), flow rate = 0.8 mL/min, *R*_t = 9.9 min, respectively. The enantiomeric excess was determined to be >99%.

Crystallographic data for compound **2.3**: C₂₄N₄O₄H₂₂, M = 430.46 g mol⁻¹, crystal size 0.3 × 0.2 × 0.1 mm³, orthorhombic, space group P2₁2₁2₁, a = 7.6889(2) Å, b = 15.5382(5) Å, c = 16.4272(6) Å, α = 90.00°, β = 90.00°, γ = 90.00°, V = 1962.58(11) Å³, Z = 4, ρ_{calc} = 1.457 g cm⁻³, μ = 0.832 mm⁻¹, λ = 1.54184 Å, T = 99.8(5) K, θ range = 3.92–68.84°, reflections collected 4748, independent reflections 3186 (R_{int} = 0.0469, R_{sigma} = 0.0597), 292 parameters. The structure was solved by direct methods and refined by goodness-of-fit on F² (1.037); final R indices [I > 2σ(I)] R₁ = 0.0413 and wR₂ = 0.0982; Largest diff. peak/hole 0.18/-0.23 e Å⁻³. CCDC-1423418 contains the supplementary crystallographic data for this structure.

Compound **2.51c**: White solid, Mp 296–298 °C (EtOAc); $[\alpha]_D^{20}$ -180.1 (*c* 0.5, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.19 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.70 (ddd, *J* =

7.8, 7.6, 1.0 Hz, 1H), 7.62 (dd, $J = 8.0, 0.8$ Hz, 1H), 7.57 (br. s, 1H), 7.44 (ddd, $J = 7.7, 7.5, 0.9$ Hz, 1H), 7.39–7.31 (m, 5H), 7.27 (dd, $J = 7.2, 0.9$ Hz, 1H), 7.15 (ddd, $J = 7.6, 7.5, 0.8$ Hz, 1H), 6.79 (dd, $J = 7.4, 7.3$ Hz, 1H), 6.56 (d, $J = 7.8$ Hz, 1H), 5.47 (d, $J = 4.4$ Hz, 1H), 5.35–5.07 (m, 3H), 5.01 (d, $J = 10.4$ Hz, 1H), 4.93 (d, $J = 4.2$ Hz, 1H), 3.66 (s, 1H), 2.89 (dd, $J = 13.0, 13.0$ Hz, 1H), 2.47 (dd, $J = 13.0, 3.7$ Hz, 1H), 2.30–2.18 (m, 1H), 1.13 (d, $J = 6.7$ Hz, 3H), 0.98 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.6, 170.5, 160.5, 148.3, 147.2, 145.2, 134.9, 134.3, 130.8, 129.1, 128.7, 128.6, 128.5, 127.2, 127.1, 127.0, 123.7, 121.8, 120.2, 110.2, 80.1, 79.8, 67.2, 60.8, 41.2, 28.9, 19.4, 18.7 (one carbon was not observed due to slow rotation at the C14-N bond);^{8a} IR (neat, cm^{-1}): 3388, 2924, 1731, 1680, 1610, 1472, 1321, 1229, 1175, 749; HRMS (ESI, m/z) calcd for $\text{C}_{31}\text{H}_{30}\text{N}_4\text{O}_5\text{Na}$ ($\text{M}+\text{Na}^+$): 561.2108, found: 561.2115.

(+)-(2*R*,3*R*,11*S*,14*S*)-14-*epi*-Isochaetominine C (2.7), and benzyl (*S*)-2-((3*S*,4*aS*,9*aR*)-4*a*-hydroxy-2-oxo-3-(4-oxoquinazolin-3(4*H*)-yl)-2,3,4,4*a*,9,9*a*-hexahydro-1*H*-pyrido[2,3-*b*]indol-1-yl)-3-methylbutanoate (2.58)



Following the general procedure 4-B, the reaction of compound **2.57** (183 mg, 0.35 mmol) gave (+)-14-*epi*-isochaetominine C (**2.7**, 51 mg, yield: 35%) and compound **2.58** (83 mg, yield: 44%) (eluent: EtOAc:PE = 1:1).

(+)-14-*epi*-Isochaetominine C (**2.7**): white solid. Mp. 323–325 °C (EtOAc); $[\alpha]_{\text{D}}^{25} +48.0$ (c 1.0, MeOH) {lit. $[\alpha]_{\text{D}}^{25} +33$ (c 0.7, MeOH)⁶}; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.22 (br s, 1H), 8.19 (dd, $J = 7.9, 1.3$ Hz, 1H), 7.87–7.83 (ddd, $J = 7.8, 7.6, 1.2$ Hz, 1H), 7.70 (dd, $J = 7.8, 0.9$ Hz, 1H), 7.59 (ddd, $J = 7.9, 7.6, 0.9$ Hz, 1H), 7.50 (dd, $J =$

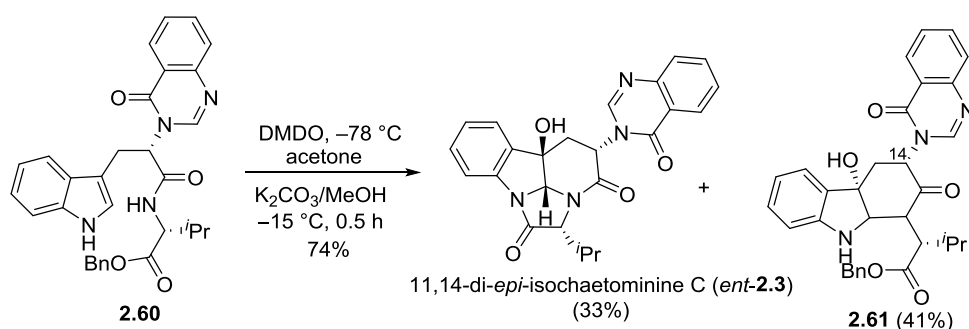
7.8, 1.2 Hz, 1H), 7.47 (dd, $J = 7.9, 0.9$ Hz, 1H), 7.42 (ddd, $J = 7.8, 7.4, 1.1$ Hz, 1H), 7.24 (ddd, $J = 7.5, 7.4, 1.0$ Hz, 1H), 6.74 (br s, 1H), 5.99 (dd, $J = 13.0, 2.9$ Hz, 1H), 5.78 (s, 1H), 4.38 (d, $J = 6.6$ Hz, 1H), 2.94 (dd, $J = 13.0, 13.0$ Hz, 1H), 2.49 (dd, $J = 13.0, 3.5$ Hz, 1H), 2.30–2.21 (m, 1 H), 1.09 (d, $J = 6.5$ Hz, 3H), 1.05 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (125 MHz, DMSO- d_6) δ 169.7, 167.2, 160.0, 147.3, 146.7, 137.6, 137.5, 134.7, 129.7, 127.2, 127.2, 126.4, 125.5, 124.5, 121.0, 114.7, 84.5, 76.7, 69.6, 49.1, 38.2, 30.3, 19.1, 19.0; IR (neat, cm^{-1}): 3406, 1716, 1690, 1603, 1443, 1325, 1267, 1224, 754; HRMS (ESI, m/z) calcd for $\text{C}_{24}\text{H}_{23}\text{N}_4\text{O}_4\text{Na}$ ($\text{M}+\text{Na}^+$): 453.1533, found: 453.1539; chiral HPLC conditions: Chiralpak AD-H (*n*-hexane/ EtOH, 30:70), flow rate = 0.8 mL/min, $R_t = 17.0$ min, respectively. The enantiomeric excess was determined to be >99%.

Crystallographic data for (+)-14-*epi*-isochaetominine C (**2.7**)·2H₂O: $\text{C}_{24}\text{N}_4\text{O}_6\text{H}_{26}$, $M = 466.50$ g mol⁻¹, crystal size 0.2 × 0.1 × 0.05 mm³, triclinic, space group P-1, $a = 9.3200(6)$ Å, $b = 10.5489(6)$ Å, $c = 12.1772(7)$ Å, $\alpha = 95.818(5)^\circ$, $\beta = 90.490(5)^\circ$, $\gamma = 111.805(6)^\circ$, $V = 1104.43(12)$ Å³, $Z = 2$, $\rho_{\text{calc}} = 1.4027$ g cm⁻³, $\mu = 0.849$ mm⁻¹, $\lambda = 1.54184$ Å, $T = 173.00(14)$ K, θ range = 3.65–60.18 °, reflections collected 5671, independent reflections 3246 ($R_{\text{int}} = 0.0442$, $R_{\text{sigma}} = 0.0662$), 315 parameters. The structure was solved by direct methods and refined by goodness-of-fit on F^2 (0.939); final R indices [$I > 2\sigma(I)$] $R_1 = 0.0380$ and $wR_2 = 0.0881$; Largest diff. peak/hole 0.27/-0.27 e Å⁻³. CCDC-1423426 contains the supplementary crystallographic data for this structure.

Compound **2.58**: White solid. Mp 121–122 °C (EtOAc); $[\alpha]_{\text{D}}^{20} +98.7$ (c 1.0, CHCl₃); ^1H NMR (500 MHz, CDCl₃) δ 8.19 (dd, $J = 8.0, 0.8$ Hz, 1H), 7.70 (ddd, $J = 7.8, 7.6, 1.0$ Hz, 1H), 7.62 (dd, $J = 8.0, 0.8$ Hz, 1H), 7.57 (br. s, 1H), 7.44 (ddd, $J = 7.7, 7.5, 0.9$ Hz, 1H), 7.39–7.31 (m, 5H), 7.27 (dd, $J = 7.2, 0.9$ Hz, 1H), 7.15 (ddd, $J = 7.6, 7.5, 0.8$ Hz, 1H), 6.79 (dd, $J = 7.4, 7.3$ Hz, 1H), 6.56 (d, $J = 7.8$ Hz, 1H), 5.47 (d, $J = 4.4$ Hz, 1H), 5.35–5.07 (m, 3H), 5.01 (d, $J = 10.4$ Hz, 1H), 4.93 (d, $J = 4.2$ Hz, 1H), 3.66 (s, 1H), 2.89 (dd, $J = 13.0, 13.0$ Hz, 1H), 2.47 (dd, $J = 13.0, 3.7$ Hz, 1H), 2.30–2.18

(m, 1H), 1.13 (d, $J = 6.7$ Hz, 3H), 0.98 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.1, 170.0, 160.1, 147.9, 147.3, 144.9, 135.0, 134.4, 130.8, 128.9, 128.7, 128.7, 128.6, 127.3, 127.2, 126.9, 123.8, 121.7, 120.9, 110.5, 82.4, 80.0, 67.6, 63.6, 41.9, 29.3, 20.1, 19.5 (one carbon was not observed due to slow rotation at the C14-N bond);^{8a} IR (neat, cm^{-1}): 3356, 2914, 2850, 1732, 1681, 1607, 1476, 1239, 1198, 1130, 749; HRMS (ESI, m/z) calcd for $\text{C}_{31}\text{H}_{30}\text{N}_4\text{O}_5\text{Na}$ ($\text{M}+\text{Na}^+$): 561.2108, found: 561.2108.

(+)-(2*R*,3*R*,11*R*,14*S*)-11,14-Di-*epi*-isochaetominine C (*ent*-2.3**) and benzyl (*R*)-2-((3*S*,4*aS*,9*aR*)-4*a*-hydroxy-2-oxo-3-(4-oxoquinazolin-3(4*H*)-yl)-2,3,4,4*a*,9,9*a*-hexahydro-1*H*-pyrido[2,3-*b*]indol-1-yl)-3-methylbutanoate (**2.61**)**



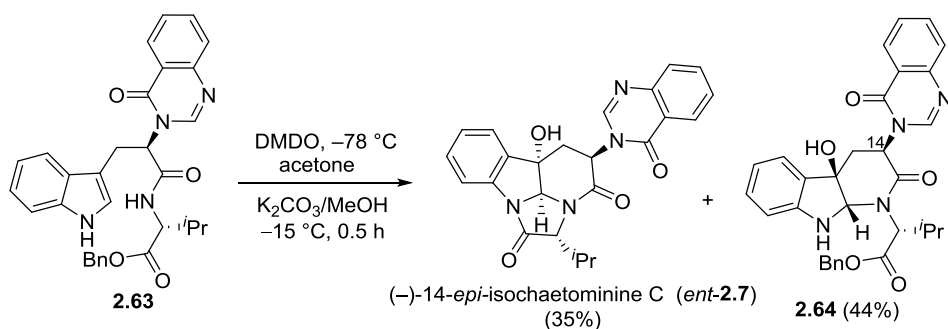
Following the general procedure 4-B, the reaction of compound **2.60** (183 mg, 0.35 mmol) gave compound *ent*-**2.3** (48 mg, yield: 33%) and compound **2.61** (77 mg, yield: 41%) (eluent: EtOAc: PE = 1:1).

11,14-Di-*epi*-isochaetominine C (*ent*-2.3**)**: colorless crystals. Mp 302–303 °C (EtOAc); $[\alpha]_{\text{D}}^{20} +50.7$ (c 0.5, MeOH); ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.30 (br. s, 1H), 8.16 (d, $J = 1.3$ Hz, 1H), 7.86 (ddd, $J = 7.7, 7.6, 1.5$ Hz, 1H), 7.70 (d, $J = 6.9$ Hz, 1H), 7.57 (t, $J = 7.4$ Hz, 1H), 7.53–7.46 (m, 2H), 7.43 (td, $J = 7.6, 1.2$ Hz, 1H), 7.24 (td, $J = 7.5, 1.0$ Hz, 1H), 6.68 (br. s, 1H), 6.16–5.68 (br. s, 1H), 5.52 (s, 1H), 4.56 (d, $J = 2.8$ Hz, 1H), 3.17 (m, 1H), 2.91 (dd, $J = 12.8, 12.8$ Hz, 1H), 2.62 (dd, $J = 12.8, 3.0$ Hz, 1H), 1.13 (d, $J = 7.3$ Hz, 3H), 0.79 (d, $J = 7.3$ Hz, 3H); ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$) δ 171.9, 166.3 (br.), 160.6, 147.9, 146.6 (br.), 139.5, 136.5, 135.1, 130.5, 127.8, 127.7, 126.8, 125.8, 125.4, 121.8, 114.6, 82.6, 77.0, 68.0, 51.2 (br.), 38.6, 25.8,

18.3, 16.6 (br.); IR (neat, cm^{-1}): 3407, 2962, 1732, 1655, 1613, 1476, 1198, 1133, 1076, 768; HRMS (ESI, m/z) calcd for $\text{C}_{24}\text{H}_{22}\text{N}_4\text{O}_4\text{Na}$ ($\text{M}+\text{Na}^+$): 453.1533, found: 453.1533; chiral HPLC conditions: Chiralpak AD-H (*n*-hexane/ EtOH, 30:70), flow rate = 0.8 mL/min, R_t = 11.8 min, respectively. The enantiomeric excess was determined to be >99%.

Compound **2.61**: White solid. Mp 296–298 °C (EtOAc); $[\alpha]_D^{20} +180.1$ (c 0.5, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.19 (dd, J = 8.0, 0.8 Hz, 1H), 7.70 (ddd, J = 7.8, 7.6, 1.0 Hz, 1H), 7.62 (dd, J = 8.0, 0.8 Hz, 1H), 7.57 (br/ s, 1H), 7.44 (ddd, J = 7.7, 7.5, 0.9 Hz, 1H), 7.39–7.31 (m, 5H), 7.27 (dd, J = 7.2, 0.9 Hz, 1H), 7.15 (ddd, J = 7.6, 7.5, 0.8 Hz, 1H), 6.79 (dd, J = 7.4, 7.3 Hz, 1H), 6.56 (d, J = 7.8 Hz, 1H), 5.47 (d, J = 4.4 Hz, 1H), 5.35–5.07 (m, 3H), 5.01 (d, J = 10.4 Hz, 1H), 4.93 (d, J = 4.2 Hz, 1H), 3.66 (s, 1H), 2.89 (dd, J = 13.0, 13.0 Hz, 1H), 2.47 (dd, J = 13.0, 3.7 Hz, 1H), 2.30–2.18 (m, 1H), 1.13 (d, J = 6.7 Hz, 3H), 0.98 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.6, 170.5, 160.5, 148.3, 147.2, 145.2, 134.9, 134.3, 130.8, 129.1, 128.7, 128.6, 128.5, 127.2, 127.1, 127.0, 123.7, 121.8, 120.2, 110.2, 80.1, 79.8, 67.2, 60.8, 41.2, 28.9, 19.4, 18.7 (one carbon was not observed due to slow rotation at the C14-N bond);^{8a} IR (neat, cm^{-1}): 3388, 2924, 1731, 1680, 1610, 1472, 1321, 1229, 1175, 749; HRMS (ESI, m/z) calcd for $\text{C}_{31}\text{H}_{30}\text{N}_4\text{O}_5\text{Na}$ ($\text{M}+\text{Na}^+$): 561.2108, found: 561.2110.

(-)-(2*S*,3*S*,11*R*,14*R*)-14-*epi*-Isochaetominine C (*ent*-2.7) and benzyl (*R*)-2-((3*R*,4*aR*,9*aS*)-4*a*-hydroxy-2-oxo-3-(4-oxoquinazolin-3(4*H*)-yl)-2,3,4,4*a*,9,9*a*-hexahydro-1*H*-pyrido[2,3-*b*]indol-1-yl)-3-methylbutanoate (**2.64**)



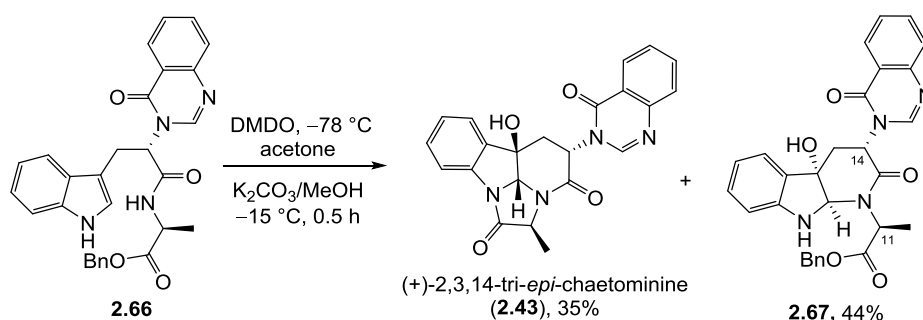
Following the general procedure 4-B, the reaction of compound **2.63** (183 mg, 0.35 mmol) gave compound *ent*-**2.7** (51 mg, yield: 35%) and compound **2.64** (83 mg, yield: 44%) (eluent: EtOAc:PE = 1:1).

14-*epi*-Isochaetominine C (*ent*-**2.7**): white solid. Mp 323–325 °C (EtOAc); $[\alpha]_D^{25}$ –48.0 (*c* 1.0, MeOH); $^1\text{H NMR}$ (500 MHz, DMSO- d_6) δ 8.22 (br s, 1H), 8.19 (dd, $J = 7.9, 1.3$ Hz, 1H), 7.87–7.83 (ddd, $J = 7.8, 7.6, 1.2$ Hz, 1H), 7.70 (dd, $J = 7.8, 0.9$ Hz, 1H), 7.59 (ddd, $J = 7.9, 7.6, 0.9$ Hz, 1H), 7.50 (dd, $J = 7.8, 1.2$ Hz, 1H), 7.47 (dd, $J = 7.9, 0.9$ Hz, 1H), 7.42 (ddd, $J = 7.8, 7.4, 1.1$ Hz, 1H), 7.24 (ddd, $J = 7.5, 7.4, 1.0$ Hz, 1H), 6.74 (br s, 1H), 5.99 (dd, $J = 13.0, 2.9$ Hz, 1H), 5.78 (s, 1H), 4.38 (d, $J = 6.6$ Hz, 1H), 2.94 (dd, $J = 13.0, 13.0$ Hz, 1H), 2.49 (dd, $J = 13.0, 3.5$ Hz, 1H), 2.30–2.21 (m, 1H), 1.09 (d, $J = 6.5$ Hz, 3H), 1.05 (d, $J = 6.5$ Hz, 3H); $^{13}\text{C NMR}$ (125 MHz, DMSO- d_6) δ 169.7, 167.2, 160.0, 147.3, 146.7, 137.6, 137.5, 134.7, 129.7, 127.2, 127.2, 126.4, 125.5, 124.5, 121.0, 114.7, 84.5, 76.7, 69.6, 49.1, 38.2, 30.3, 19.1, 19.0; IR (neat, cm^{-1}): 3406, 1716, 1690, 1603, 1443, 1325, 1267, 1224, 754; HRMS (ESI, m/z) calcd for $\text{C}_{24}\text{H}_{23}\text{N}_4\text{O}_4$ ($M+\text{Na}^+$): 453.1533, found: 453.1535; chiral HPLC conditions: Chiralpak AD-H (*n*-hexane/ EtOH, 30:70), flow rate = 0.8 mL/min, $R_t = 28.7$ min, respectively. The enantiomeric excess was determined to be >99%.

Compound **2.64**: White solid. Mp 121–122 °C (EtOAc); $[\alpha]_D^{20}$ –98.7 (*c* 1.0, CHCl_3); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.19 (dd, $J = 8.0, 0.8$ Hz, 1H), 7.70 (ddd, $J = 7.8, 7.6, 1.0$ Hz, 1H), 7.62 (dd, $J = 8.0, 0.8$ Hz, 1H), 7.57 (br s, 1H), 7.44 (ddd, $J = 7.7, 7.5, 0.9$ Hz, 1H), 7.39–7.31 (m, 5H), 7.27 (dd, $J = 7.2, 0.9$ Hz, 1H), 7.15 (ddd, $J = 7.6, 7.5, 0.8$ Hz, 1H), 6.79 (dd, $J = 7.4, 7.3$ Hz, 1H), 6.56 (d, $J = 7.8$ Hz, 1H), 5.47 (d, $J = 4.4$ Hz, 1H), 5.35–5.07 (m, 3H), 5.01 (d, $J = 10.4$ Hz, 1H), 4.93 (d, $J = 4.2$ Hz, 1H), 3.66 (s, 1H), 2.89 (dd, $J = 13.0, 13.0$ Hz, 1H), 2.47 (dd, $J = 13.0, 3.7$ Hz, 1H), 2.30–2.18 (m, 1H), 1.13 (d, $J = 6.7$ Hz, 3H), 0.98 (d, $J = 6.7$ Hz, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 171.1, 170.0, 160.1, 147.9, 147.3, 144.9, 135.0, 134.4, 130.8, 128.9, 128.7 (2C), 128.6, 127.3, 127.2, 126.9, 123.8, 121.7, 120.9, 110.5, 82.4, 80.0, 67.6, 63.6, 41.9, 29.3, 20.1, 19.5 (one carbon was not observed due to slow rotation at the C14-N

bond);^{8a} IR (neat, cm⁻¹): 3356, 2914, 2850, 1732, 1681, 1607, 1476, 1239, 1198, 1130, 749; HRMS (ESI, *m/z*) calcd for C₃₁H₃₀N₄O₅Na (M+Na⁺): 561.2108, found: 561.2112.

(+)-2,3,14-Tri-*epi*-chaetominine (2.43) and benzyl (S)-2-((3*S*,4*aS*,9*aR*)-4*a*-hydroxy-2-oxo-3-(4-oxo-quinazolin-3(4*H*)-yl)-2,3,4*a*,9,9*a*-hexahydro-1*H*-pyrido[2,3-*b*]indol-1-yl)propanoate (2.67)

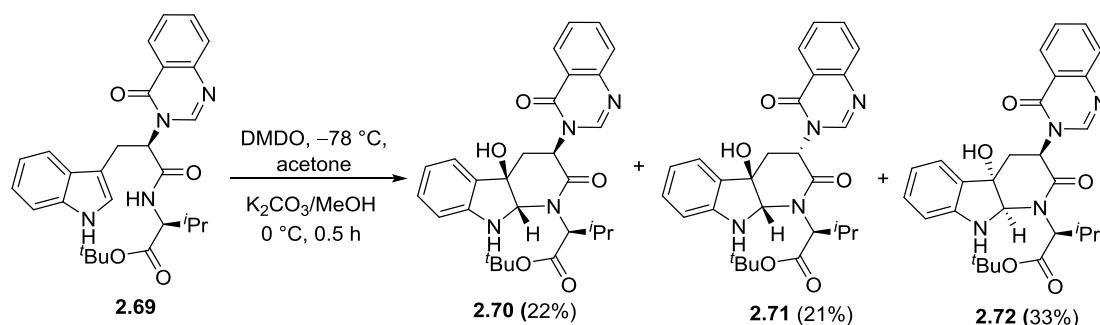


Following the general procedure 4-B, the reaction of compound **2.66** (173 mg, 0.35 mmol) gave compound **2.43** (46 mg, yield: 35%) and compound **2.67** (67 mg, yield: 44%) (eluent: EtOAc:PE = 1:1).

(+)-2,3,14-tri-*epi*-chaetominine (**2.43**): White solid. The IR, ¹H NMR, ¹³C NMR and MS data are identical with those reported previously.^{8f}

Compound **2.67**: White solid. [α]_D²⁰ +114.7 (*c* 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 8.18 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.74–7.60 (m, 3H), 7.44 (ddd, *J* = 8.2, 7.8, 0.9 Hz, 1H), 7.40–7.28 (m, 6H), 7.16 (td, *J* = 7.8, 0.9 Hz, 1H), 6.86 (t, *J* = 7.4 Hz, 1H), 6.60 (d, *J* = 7.8 Hz, 1H), 5.50–5.05 (m, 5H), 4.63–4.50 (m, 1H), 3.90 (s, 1H), 2.87 (dd, *J* = 12.5, 12.5 Hz, 1H), 2.58 (dd, *J* = 12.5, 4.0 Hz, 1H), 1.57 (d, *J* = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 172.1, 169.4, 160.6, 148.0, 147.4, 144.8, 135.1, 134.4, 130.8, 128.7, 128.7, 128.6, 128.4, 127.3, 127.3, 126.9, 123.9, 121.7, 120.8, 110.4, 81.9, 79.9, 67.8, 52.9, 41.8, 15.8 (one carbon was not observed due to slow rotation at the C14-N bond);^{8a} IR (neat, cm⁻¹): 3338, 2925, 1740, 1678, 1612, 1475, 1247, 753; HRMS (ESI, *m/z*) calcd for C₂₉H₂₆N₄O₅Na (M+Na⁺): 533.1795, found: 533.1795.

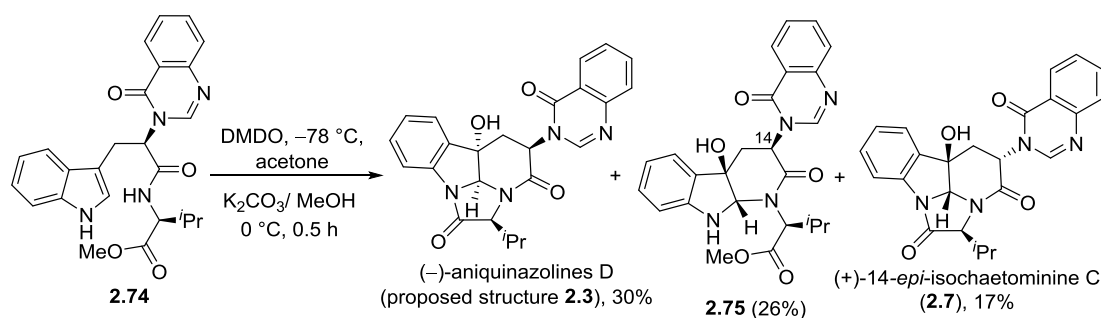
***tert*-Butyl(*S*)-2-((3*R*,4*aR*,9*aS*)-4*a*-hydroxy-2-oxo-3-(4-oxoquinazolin-3(4*H*)-yl)-2,3,4,4*a*,9,9*a*-hexahydro-1*H*-pyrido[2,3-*b*]indol-1-yl)-3-methylbutanoate (2.70).**



Following the general procedure 4-B, the reaction of compound **2.69** (244 mg, 0.5 mmol) gave compound **2.70** (55 mg, yield: 22%) and a mixture of compound **2.71** and compound **2.72** (135 mg, yield: 54%) (eluent: EtOAc:PE = 1:1).

Compound **2.70**: Mp $156\text{--}158\text{ }^{\circ}\text{C}$ (EtOAc); $[\alpha]_{\text{D}}^{20} -183.8$ (c 1.0, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 8.20 (dd, $J = 8.0, 0.9$ Hz, 1H), 7.74–7.58 (m, 3H), 7.47–7.42 (m, 1H), 7.30 (d, $J = 7.3$ Hz, 1H), 7.21–7.16 (m, 1H), 6.82 (t, $J = 7.2$ Hz, 1H), 6.68 (d, $J = 7.9$ Hz, 1H), 5.50 (d, $J = 4.3$ Hz, 1H), 5.34 (br s, 1H), 5.21 (d, $J = 4.1$ Hz, 1H), 4.86 (d, $J = 10.2$ Hz, 1H), 3.44 (s, 1H), 3.00–2.75 (m, 1H), 2.54 (dd, $J = 12.1, 3.8$ Hz, 1H), 2.29–2.16 (m, 1H), 1.49 (s, 9H), 1.14 (d, $J = 6.8$ Hz, 3H), 1.07 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.2, 170.4, 160.5, 148.4, 147.3, 145.2, 134.3, 130.9, 129.1, 127.2, 127.1, 127.0, 123.7, 121.8, 120.2, 110.2, 82.6, 80.2, 79.7, 61.4, 41.3, 29.1, 28.0, 19.4, 18.9 (one carbon was not observed due to slow rotation at the C14-N bond); $^{\text{a}}$ IR (neat, cm^{-1}): 3394, 2925, 1722, 1683, 1613, 1471, 1369, 1292, 1146, 1076, 756; HRMS (ESI, m/z) calcd for $\text{C}_{28}\text{H}_{32}\text{N}_4\text{O}_5\text{Na}$ ($\text{M}+\text{Na}^+$): 527.2265; found: 527.2267.

The proposed structure of (–)-aniquinazoline D [(2*S*,3*S*,11*S*,14*R*)-2.3] and methyl(*S*)-2-((3*R*,4*aR*,9*aS*)-4*a*-hydroxy-2-oxo-3-(4-oxoquinazolin-3(4*H*)-yl)-2,3,4,4*a*,9,9*a*-hexahydro-1*H*-pyrido[2,3-*b*]indol-1-yl)-3-methylbutanoate (**2.75**) and (+)-14-*epi*-isochaetominine C (**2.7**).



Following the general procedure 4-B, the reaction of compound **2.74** (224 mg, 0.5 mmol) gave the proposed structure of (-)-aniquinazoline D (**2.3**) (65 mg, yield: 30%) and compound **2.75** (61 mg, yield: 30%) and (+)-14-*epi*-isochaetominine C (**2.7**) (37 mg, yield: 17%) (eluent: EtOAc:PE = 1:1).

The proposed structure of (-)-aniquinazoline D (**2.3**): Colorless crystals. The IR, ¹H NMR, ¹³C NMR and MS data are identical with those reported above.

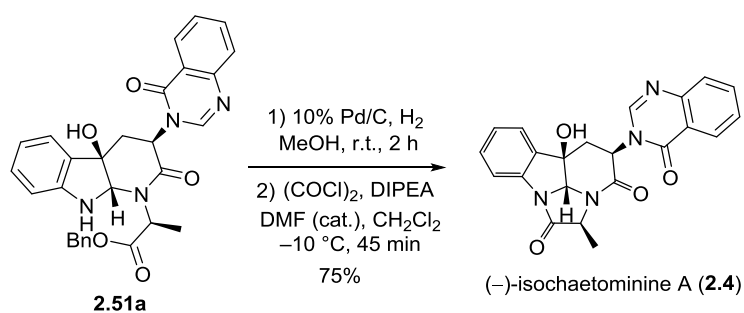
Compound **2.75**: White solid. Mp 128–130 °C (EtOAc); [α]_D²⁰ -392.8 (*c* 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.19 (d, *J* = 8.0 Hz, 1H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.56–7.40 (m, 2H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 6.79 (t, *J* = 7.4 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 5.49 (d, *J* = 4.3 Hz, 1H), 5.21 (br s, 1H), 5.15 (d, *J* = 4.0 Hz, 1H), 4.95 (d, *J* = 10.5 Hz, 1H), 4.00 (s, 1H), 3.76 (s, 3H), 2.91 (dd, *J* = 12.1, 12.1 Hz, 1H), 2.47 (dd, *J* = 12.1, 3.5 Hz, 1H), 2.29–2.13 (m, 1 H), 1.15 (d, *J* = 6.5 Hz, 3H), 1.02 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 173.5, 170.5, 160.5, 148.4, 147.2, 145.2, 134.3, 130.8, 129.2, 127.2, 127.0 (2C), 123.8, 121.8, 120.3, 110.2, 80.0, 79.7, 60.6, 52.2, 41.1, 28.7, 19.4, 18.7; (one carbon was not observed due to slow rotation at the C14-N bond);^{8a} IR (neat, cm⁻¹): 3391, 2930, 1732, 1684, 1611, 1470, 1223, 1201, 752; HRMS (ESI, *m/z*) calcd for C₂₅H₂₆N₄O₅Na (M+Na⁺): 485.1795; found:485.1799.

(+)-14-*epi*-isochaetominine C (**2.7**): White solid. The IR, ¹H NMR, ¹³C NMR and MS data are identical with those reported above.

General Procedure A for the Step 5 (General Procedure 5-A)

A suspension of a quinazolino-dipeptide derivative (0.10 mmol) and 10% Pd/C (8.00 mg) in methanol (2 mL) was stirred under an atmosphere of H₂ for 2 h at room temperature. The mixture was filtered through a Celite pad by washing with methanol. The solvent was removed under reduced pressure. Without separation, the residue was directly treated with (COCl)₂ (0.013 mL, 0.15 mmol) and a catalytic amount of DMF in anhydrous CH₂Cl₂ (3 mL) for 5 minutes at -10 °C. To the resulting mixture was added DIPEA (0.035 mL, 0.21 mmol) and the mixture was stirred for 45 min. The reaction was quenched with 5 mL of H₂O at -10 °C, and then extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc: PE = 1:1) to give the corresponding isochaetominine-type compound.

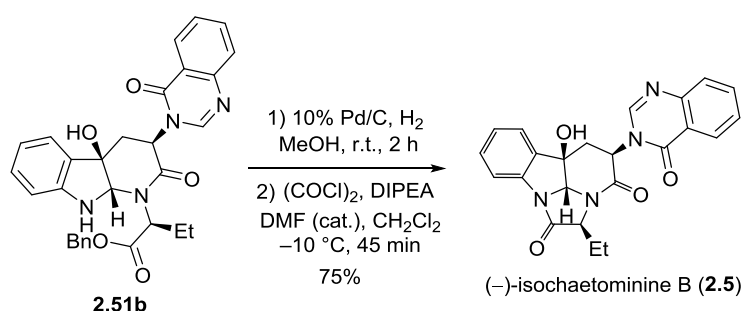
(-)-(2R,3R,11S,14R)-Isochaetominine A (2.4)



Following the general procedure 5-A, the reaction of compound **2.51a** (51 mg, 0.10 mmol), gave compound **2.4** (30 mg, yield: 75%) (eluent: EtOAc: PE = 1:1) as colorless crystals. Mp 184–186 °C (EtOAc); [α]_D²⁵ -23.0 (*c* 1.0, MeOH) {lit.⁶ [α]_D²⁵ -63 (*c* 0.5, MeOH)}; ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.28 (s, 1H), 8.18 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.87 (ddd, *J* = 7.8, 7.8, 1.3 Hz, 1H), 7.71 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.59 (ddd, *J* = 7.9, 7.9, 0.9 Hz, 1H), 7.51 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.44 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.42 (ddd, *J* = 7.6, 7.4, 1.0 Hz, 1H), 7.24 (ddd, *J* = 7.5, 7.4, 1.2 Hz, 1H), 6.29 (br. s, 1H), 5.92 (s, 1H), 4.91 (dd, *J* = 7.0, 5.0 Hz, 1H), 4.62 (q, *J* = 7.3 Hz, 1H), 2.98

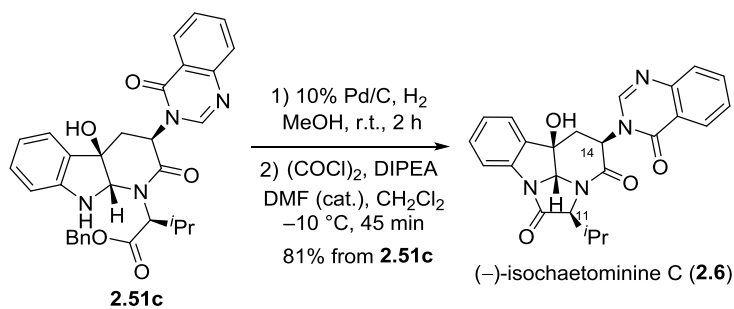
(dd, $J = 14.2, 7.0$ Hz, 1H), 2.73 (dd, $J = 14.2, 5.2$ Hz, 1H), 1.60 (d, $J = 7.3$ Hz, 3H); ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$) δ 174.4, 164.2, 159.9, 147.6, 146.7, 139.8, 135.8, 134.8, 130.1, 127.4, 127.2, 126.2, 125.3, 124.7, 121.5, 114.1, 82.9, 74.1, 59.7, 55.6, 34.7, 13.9; IR (neat, cm^{-1}): 3410, 2925, 1728, 1674, 1608, 1477, 1383, 1327, 1290, 1136, 768; HRMS (ESI, m/z) calcd for $\text{C}_{22}\text{H}_{18}\text{N}_4\text{O}_4\text{Na}$ ($\text{M}+\text{Na}^+$): 425.1220, found: 425.1224.

(-)-(2*R*,3*R*,11*S*,14*R*)-Isochaetominine B (2.5)



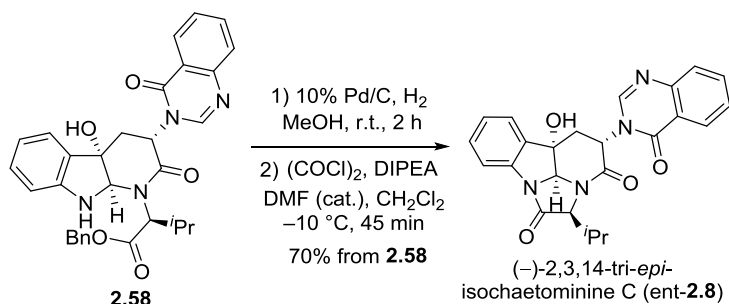
Following the general procedure 5-A, the reaction of compound **2.51b** (52 mg, 0.10 mmol) gave compound **2.5** (31 mg, yield: 75%) (eluent: EtOAc: PE = 1:1) as colorless crystals. Mp 173–175 °C (EtOAc); $[\alpha]_{\text{D}}^{25} -49.0$ (c 1.0, MeOH) {lit.⁶ $[\alpha]_{\text{D}}^{25} -73$ (c 0.6, MeOH)}; ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 8.30 (s, 1H), 8.18 (dd, $J = 7.9, 1.0$ Hz, 1H), 7.87 (ddd, $J = 7.8, 7.8, 1.3$ Hz, 1H), 7.71 (dd, $J = 7.9, 0.8$ Hz, 1H), 7.59 (ddd, $J = 7.9, 7.9, 0.9$ Hz, 1H), 7.52 (dd, $J = 7.6, 0.9$ Hz, 1H), 7.43 (dd, $J = 7.6, 1.0$ Hz, 1H), 7.42 (ddd, $J = 7.4, 7.2, 1.0$ Hz, 1H), 7.25 (ddd, $J = 7.5, 7.4, 1.2$ Hz, 1H), 6.28 (br. s, 1H), 5.86 (s, 1H), 4.90 (dd, $J = 7.3, 5.2$ Hz, 1H), 4.47 (dd, $J = 9.2, 5.9$ Hz, 1H), 2.98 (dd, $J = 14.2, 7.5$ Hz, 1H), 2.73 (dd, $J = 14.2, 5.3$ Hz, 1H), 2.11–1.93 (m, 2H), 1.11 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$) δ 174.0, 164.6, 159.8, 147.5, 146.7, 139.9, 135.4, 134.7, 130.0, 127.3, 127.2, 126.2, 125.2, 124.6, 121.4, 114.1, 83.3, 74.0, 65.3, 55.6, 34.4, 21.7, 10.9; HRMS (ESI, m/z) calcd for $\text{C}_{23}\text{H}_{20}\text{N}_4\text{O}_4\text{Na}$ ($\text{M}+\text{Na}^+$): 439.1377, found: 439.1381.

(-)-(2*R*,3*R*,11*S*,14*R*)-Isochaetominine C (2.6)



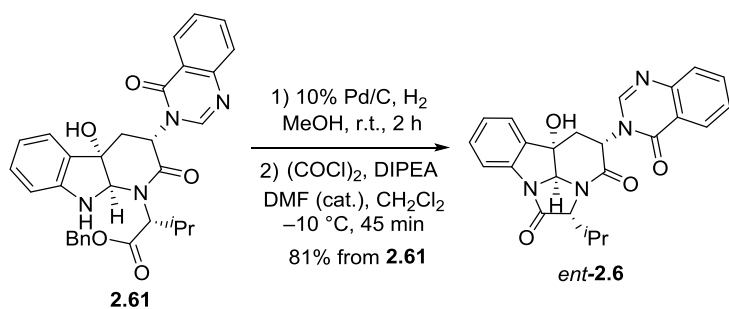
Following the general procedure 5-A, reaction of compound **2.51c** (54 mg, 0.10 mmol) gave compound **2.6** (34 mg, yield: 81%) (eluent: EtOAc: PE = 1:1) as colorless crystals. Mp 166–168 °C (EtOAc); $[\alpha]_D^{25}$ -71.0 (*c* 1.0, MeOH); $[\alpha]_D^{20}$ -76.8 (*c* 1.0, CHCl₃) {lit. $[\alpha]_D^{20}$ -33 (*c* 0.37, MeOH);⁵ $[\alpha]_D^{25}$ -90 (*c* 0.6, MeOH);⁶ $[\alpha]_D^{20}$ -16.9 (*c* 0.18, CHCl₃);⁴}; ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.30 (s, 1H), 8.18 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.87 (ddd, *J* = 7.7, 7.5, 1.5 Hz, 1H), 7.71 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.59 (ddd, *J* = 7.9, 7.6, 1.0 Hz, 1H), 7.54 (dd, *J* = 7.1, 1.0 Hz, 1H), 7.47 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.43 (ddd, *J* = 7.4, 7.2, 1.0 Hz, 1H), 7.26 (ddd, *J* = 7.4, 7.2, 1.0 Hz, 1H), 6.29 (br. s, 1H), 5.81 (s, 1H), 4.85 (dd, *J* = 8.0, 5.3 Hz, 1H), 4.21 (d, *J* = 9.3 Hz, 1H), 3.00 (dd, *J* = 14.0, 8.0 Hz, 1H), 2.77 (dd, *J* = 14.0, 5.3 Hz, 1H), 2.43–2.46 (m, 1H), 1.15 (d, *J* = 6.7 Hz, 3H), 1.12 (d, *J* = 6.7 Hz, 3H); ¹³C NMR (125 MHz, DMSO-*d*₆) δ 173.9, 164.9, 159.8, 147.5, 146.9, 140.3, 134.9, 134.7, 130.1, 127.4, 127.2, 126.2, 125.2, 124.6, 121.5, 114.2, 83.7, 73.8, 69.4, 55.7, 34.1, 28.2, 20.2, 18.7; IR (neat, cm⁻¹): 3404, 2962, 2917, 1732, 1684, 1607, 1476, 1325, 1197, 1181, 752; HRMS (ESI, *m/z*) calcd for C₂₄H₂₂N₄O₄Na (M+Na⁺): 453.1533, found: 453.1535; chiral HPLC conditions: Chiralpak AD-H (*n*-hexane/ isopropanol, 70:30), flow rate = 0.8 mL/min, *R*_t = 21.4 min, respectively. The enantiomeric excess was determined to be >99%.

(-)-(2*S*,3*S*,11*S*,14*S*)-2,3,14-Tri-*epi*-isochaetominine C (*ent*-2.8**)**



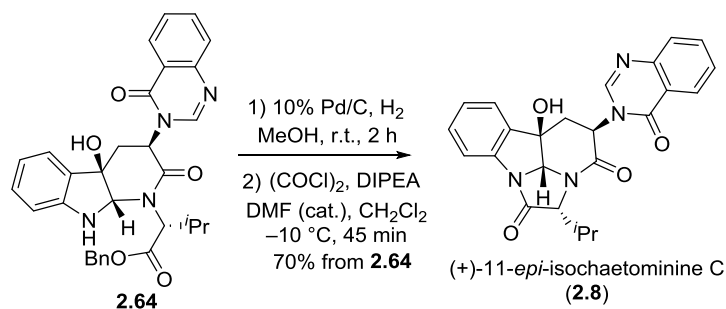
Following the general procedure 5-A, reaction of compound **2.58** (54 mg, 0.10 mmol) gave compound *ent*-**2.8** (29 mg, yield: 70%) (eluent: EtOAc: PE = 1:1) as a white solid. M.p. 179–181 °C (EtOAc); $[\alpha]_D^{20}$ -105.0 (*c* 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.25 (dd, *J* = 8.2, 1.1 Hz, 1H), 8.01 (s, 1H), 7.77 (ddd, *J* = 7.9, 7.7, 1.4 Hz, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.51 (ddd, *J* = 7.5, 7.4, 1.0 Hz, 1H), 7.40–7.30 (m, 2H), 7.16 (ddd, *J* = 7.6, 7.5, 0.7 Hz, 1H), 5.80 (s, 1H), 4.85 (d, *J* = 5.2 Hz, 1H), 4.49 (d, *J* = 3.0 Hz, 1H), 4.21 (s, 1H), 3.33–3.20 (m, 1H), 2.87 (dd, *J* = 15.4, 1.3 Hz, 1H), 2.46 (dd, *J* = 15.4, 6.3 Hz, 1H), 1.24 (d, *J* = 7.2 Hz, 3H), 0.83 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 170.2, 163.4, 162.1, 147.7, 145.5, 138.6, 135.9, 135.0, 130.7, 128.0, 127.5, 126.7, 125.7, 124.0, 121.7, 115.3, 84.2, 75.6, 68.6, 58.9, 39.2, 25.2, 17.8, 16.2; IR (neat, cm⁻¹): 3395, 2964, 1732, 1681, 1607, 1476, 1328, 1262, 1185, 756; HRMS (ESI, *m/z*) calcd for C₂₄H₂₂N₄O₄Na (M+Na⁺): 453.1533, found: 453.1534; Conditions for the chiral HPLC analysis: Chiralpak AD-H (*n*-hexane/ EtOH, 30:70), flow rate = 0.8 mL/min, *R*_t = 28.1 min, respectively. The enantiomeric excess was determined to be >99%.

(+)-(2*S*,3*S*,11*R*,14*S*)-Isochaetominine C (*ent*-**2.6**)



Following the general procedure 5-A, reaction of compound **2.61** (54 mg, 0.10 mmol) gave compound *ent*-**2.6** (34 mg, yield: 81%)(eluent: EtOAc: PE = 1:1) as colorless crystals. M.p. 166–168 °C (EtOAc); $[\alpha]_{\text{D}}^{25} +71.0$ (*c* 1.0, MeOH); $[\alpha]_{\text{D}}^{20} +76.8$ (*c* 1.0, CHCl₃); ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.30 (s, 1H), 8.18 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.87 (ddd, *J* = 7.7, 7.5, 1.5 Hz, 1H), 7.71 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.59 (ddd, *J* = 7.9, 7.6, 1.0 Hz, 1H), 7.54 (dd, *J* = 7.1, 1.0 Hz, 1H), 7.47 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.43 (ddd, *J* = 7.4, 7.2, 1.0 Hz, 1H), 7.26 (ddd, *J* = 7.4, 7.2, 1.0 Hz, 1H), 6.29 (br. s, 1H), 5.81 (s, 1H), 4.85 (dd, *J* = 8.0, 5.3 Hz, 1H), 4.21 (d, *J* = 9.3 Hz, 1H), 3.00 (dd, *J* = 14.0, 8.0 Hz, 1H), 2.77 (dd, *J* = 14.0, 5.3 Hz, 1H), 2.43–2.46 (m, 1H), 1.15 (d, *J* = 6.7 Hz, 3H), 1.12 (d, *J* = 6.7 Hz, 3H); ¹³C NMR (125 MHz, DMSO-*d*₆) δ 173.9, 164.9, 159.8, 147.5, 146.9, 140.3, 134.9, 134.7, 130.1, 127.4, 127.2, 126.2, 125.2, 124.6, 121.5, 114.2, 83.7, 73.8, 69.4, 55.7, 34.1, 28.2, 20.2, 18.7; IR (neat, cm⁻¹): 3404, 2962, 1732, 1684, 1607, 1476, 1198, 1181, 1076, 752; HRMS (ESI, *m/z*) calcd for C₂₄H₂₂N₄O₄Na (M+Na⁺):453.1533, found:453.1532; Conditions for the chiral HPLC analysis: Chiralpak AD-H (*n*-hexane/ isopropanol, 70:30), flow rate = 0.8 mL/min, *R*_t = 14.2 min, respectively. The enantiomeric excess was determined to be >99%.

(+)-(2*R*,3*R*,11*R*,14*R*)-11-*epi*-Isochaetominine C (2.8)



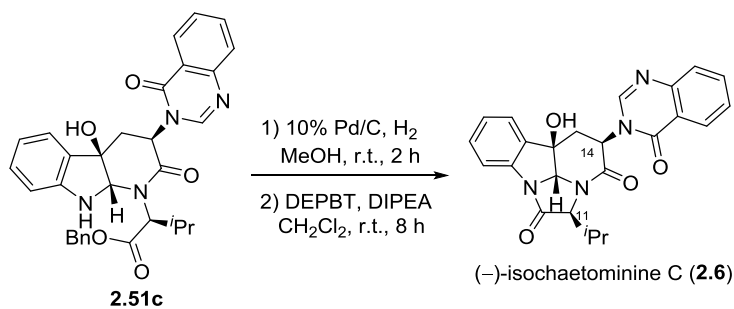
Following the general procedure 5-A, reaction of compound **2.64** (54 mg, 0.10 mmol) gave compound **2.8** (29 mg, yield: 70%) (eluent: EtOAc: PE = 1:1) as colorless crystals. M.p. 179–181 °C (EtOAc); $[\alpha]_{\text{D}}^{20} +105.0$ (*c* 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.25 (dd, *J* = 8.2, 1.1 Hz, 1H), 8.01 (s, 1H), 7.77 (ddd, *J* = 7.9, 7.7, 1.4 Hz, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.51 (ddd, *J* = 7.5, 7.4,

1.0 Hz, 1H), 7.40–7.30 (m, 2H), 7.16 (ddd, $J = 7.6, 7.5, 0.7$ Hz, 1H), 5.80 (s, 1H), 4.85 (d, $J = 5.2$ Hz, 1H), 4.49 (d, $J = 3.0$ Hz, 1H), 4.21 (s, 1H), 3.33–3.20 (m, 1H), 2.87 (dd, $J = 15.4, 1.3$ Hz, 1H), 2.46 (dd, $J = 15.4, 6.3$ Hz, 1H), 1.24 (d, $J = 7.2$ Hz, 3H), 0.83 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.2, 163.4, 162.1, 147.7, 145.5, 138.6, 135.9, 135.0, 130.7, 128.0, 127.5, 126.7, 125.7, 124.0, 121.7, 115.3, 84.2, 75.6, 68.6, 58.9, 39.2, 25.2, 17.8, 16.2; IR (neat, cm^{-1}): 3395, 2964, 1732, 1681, 1607, 1476, 1328, 1262, 1185, 756; HRMS (ESI, m/z) calcd for $\text{C}_{24}\text{H}_{22}\text{N}_4\text{O}_4\text{Na}$ ($\text{M}+\text{Na}^+$): 453.1533, found: 453.1535; Conditions for the chiral HPLC analysis: Chiralpak AD-H (*n*-hexane/ EtOH, 30:70), flow rate = 0.8 mL/min, $R_t = 47.0$ min, respectively. The enantiomeric excess was determined to be >99%.

General Procedure B for the Step 5 (General Procedure 5-B)

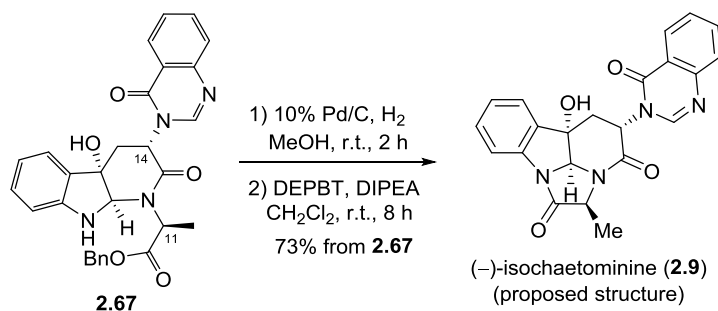
A suspension of a quinazolino-dipeptide derivative (0.10 mmol) and 10% Pd/C (8 mg) in methanol (2 mL) was stirred under an atmosphere of H_2 for 2 h at room temperature. The reaction mixture was filtered through a Celite pad and the residue was washed with methanol. The filtrate was concentrated under reduced pressure. Without further purification, the residue was directly treated with Ye's reagent (DEPBT) (63 mg, 0.21 mmol) and DIPEA (0.035 mL, 0.21 mmol) in anhydrous CH_2Cl_2 (3 mL) for 8 h at room temperature. The reaction was quenched with 5 mL of H_2O at 0 °C, and the resulting mixture was extracted with CH_2Cl_2 (3 \times 10 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc: PE = 1:1) to give the corresponding isochaetominine-type compound.

(–)-(2*R*,3*R*,11*S*,14*R*)-Isochaetominine C (2.6)



Following the general procedure 5-B, the reaction of compound **2.51c** (54 mg, 0.10 mmol) gave compound **2.6** (32 mg, yield: 77%) (eluent: EtOAc: PE = 1:1) as colorless crystals. The IR, ¹H NMR, ¹³C NMR and MS data are identical with those reported above.

The proposed structure of (-)-isochaetominine (**2.9**)



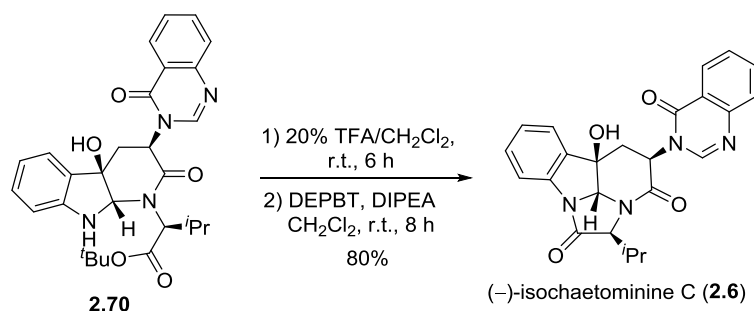
Following the general procedure 5-B, the reaction of compound **2.67** (51 mg, 0.10 mmol) gave compound **2.9** (30 mg, yield: 73%) (eluent: EtOAc: PE = 1:1) as colorless crystals. Mp 215–216 °C (EtOAc); [α]_D²⁵ -57.7 (*c* 1.0, CH₃OH); ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.39 (s, 1H), 8.22 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.89 (td, *J* = 7.5, 1.0 Hz, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.61 (td, *J* = 7.5, 1.0 Hz, 1H), 7.49–7.38 (m, 3H), 7.21 (td, *J* = 7.5, 1.0 Hz, 1H), 6.13 (s, 1H), 5.80 (s, 1H), 5.12 (br s, 1 H), 4.71 (q, *J* = 7.1 Hz, 1H), 2.77 (dd, *J* = 15.2, 3.2 Hz, 1H), 2.46 (dd, *J* = 15.2, 5.0 Hz, 1H), 1.60 (d, *J* = 7.1 Hz, 3H); ¹³C NMR (125 MHz, DMSO-*d*₆) δ 173.1, 163.5, 160.4, 148.0, 147.2, 139.2, 138.2, 135.1, 130.2, 127.8, 127.7, 126.7, 125.8, 125.1, 122.0, 114.8, 83.8, 75.3, 60.0, 57.6, 36.9, 13.9; IR (neat, cm⁻¹): 3445, 2089, 1651, 1478, 1329, 1137,

1076, 772; HRMS (ESI, m/z) calcd for $C_{22}H_{18}N_4O_4Na$ ($M+Na^+$): 425.1220, found: 425.1222.

General Procedure C for the Step 5 (General Procedure 5-C)

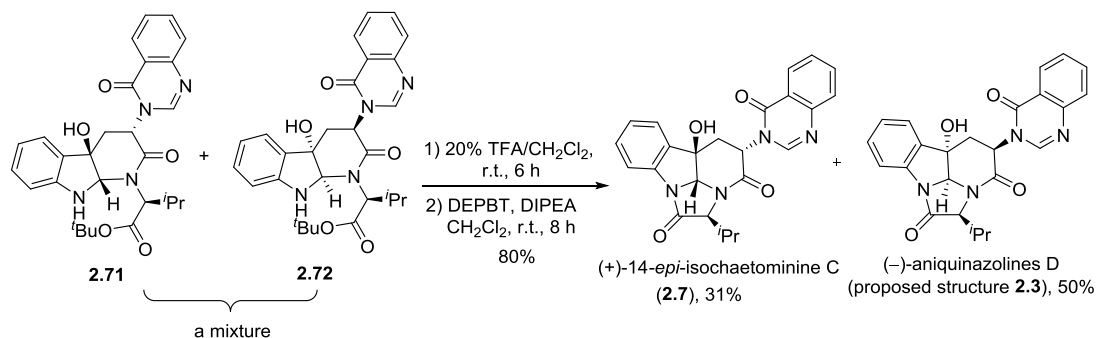
A suspension of a quinazolino-dipeptide derivative (0.10 mmol) in CH_2Cl_2 (2 mL) was added 0.4 mL TFA under an atmosphere of N_2 and then stirred for 6 h at room temperature. The filtrate was concentrated under reduced pressure. Without further purification, the residue was directly treated with Ye's reagent (DEPBT) (63 mg, 0.21 mmol) and DIPEA (0.035 mL, 0.21 mmol) in anhydrous CH_2Cl_2 (3 mL) for 8 h at room temperature. The reaction was quenched with 5 mL of H_2O at 0 °C, and the resulting mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc: PE = 1:1) to give the corresponding isochaetominine-type compound.

(-)-Isochaetominine C (2.6)



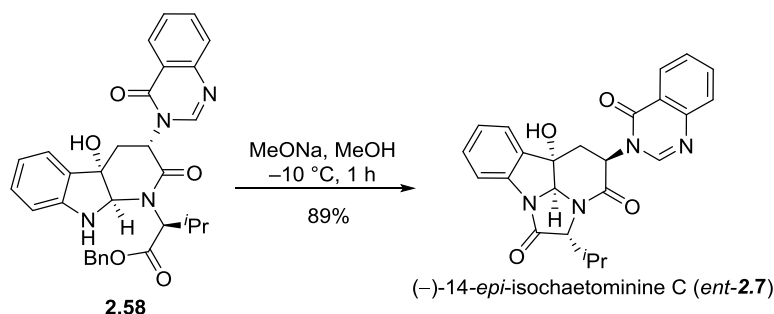
Following the general procedure 5-C, the reaction of compound **2.70** (54 mg, 0.10 mmol) gave compound **2.6** (34 mg, yield: 80%) (eluent: EtOAc: PE = 1:1) as colorless crystals. The IR, 1H NMR, ^{13}C NMR and MS data are identical with those reported above.

The proposed structure of (–)-aniquinazolines **D** (**2.3**) and (+)-(2*R*,3*R*,11*S*,14*S*)-14-*epi*-Isochaetominine **C** (**2.7**)



Following the general procedure 5-C, the reaction of a mixture of compound **2.71** and compound **2.72** (54 mg, 0.10 mmol) gave compound **2.7** (13 mg, yield: 31%) and compound **2.3** (22 mg, yield: 50%) (eluent: EtOAc: PE = 1:1) as colorless crystals. The IR, ¹H NMR, ¹³C NMR and MS data are identical with those reported above.

(–)-(2*R*,3*R*,11*S*,14*S*)-14-*epi*-Isochaetominine **C** (from compound **2.58**)



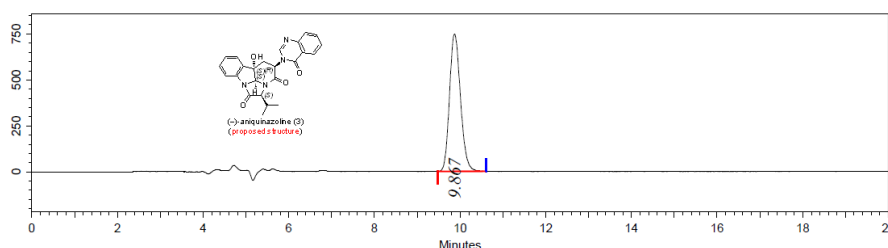
To a solution of compound **2.58** (54 mg, 0.1 mmol) in MeOH (1.5 mL) was added a solution of freshly prepared CH₃ONa (27 mg, 0.5 mmol) in CH₃OH (3.5 mL) at –10 °C. After being stirred for 1 h, the reaction mixture was acidified with 10% HCOOH to reach pH = 7. The solvent was removed under reduced pressure, and the residue was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (eluent: EtOAc: PE = 1:1) to give (–)-14-*epi*-isochaetominine **C** (*ent*-**2.7**) (38 mg, yield: 89%) as a white

solid. The physical and spectral data of *ent*-**2.7** thus obtained are in full agreement with those of *ent*-**2.7** prepared from **2.63**.

HPLC analysis of compound **2.3** and *ent*-**2.3**

Shimadzu CLASS-VP V6.13 SP2
 Column: Chiralpak AD-H
 Mobile Phase: Hex/EtOH=30/70(v/v)
 Flow Rate: 0.8mL/min
 CT: 40°C Sample Name: 3

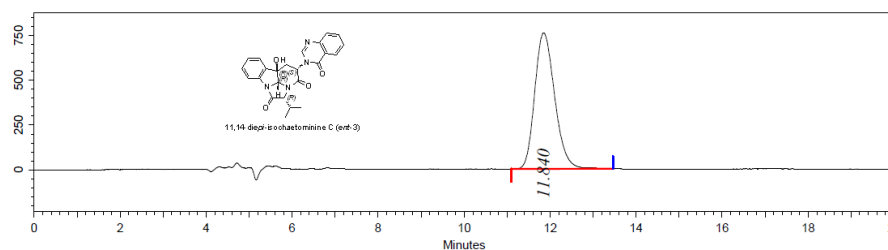
Area % Report



Detector A-230 nm			
Pk #	Retention Time	Area	Area Percent
1	9.867	13276112	100.00
Totals		13276112	100.00

Shimadzu CLASS-VP V6.13 SP2
 Column: Chiralpak AD-H
 Mobile Phase: Hex/EtOH=30/70(v/v)
 Flow Rate: 0.8mL/min
 CT: 40°C Sample Name: *ent*-3

Area % Report

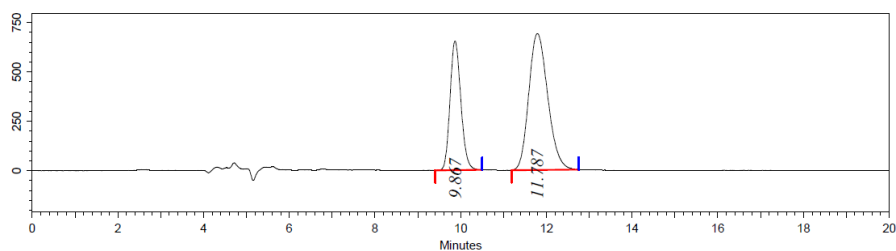


Detector A-230 nm			
Pk #	Retention Time	Area	Area Percent
1	11.840	24538507	100.00
Totals		24538507	100.00

HPLC analysis of the mixture of compound **2.3** and *ent*-**2.3**

Shimadzu CLASS-VP V6.13 SP2
 Column: Chiralpak AD-H
 Mobile Phase: Hex/EtOH=30/70(v/v)
 Flow Rate: 0.8mL/min
 CT: 40°C Sample Name: 3 +*ent*-3

Area % Report

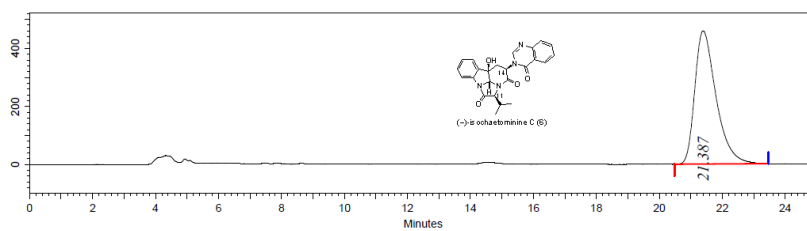


Detector A-230 nm				
PK #	Retention Time	Area	Area Percent	
1	9.867	11448715	35.02	
2	11.787	21239230	64.98	
Totals		32687945	100.00	

HPLC analysis of compound 2.6 and *ent*-2.6

Shimadzu CLASS-VP V6.13 SP2
 Column: Chiralpak AD-H
 Mobile Phase: Hex/IPA=70/30(v/v)
 Flow Rate: 0.8mL/min
 CT: 30°C Sample Name: 6

Area % Report

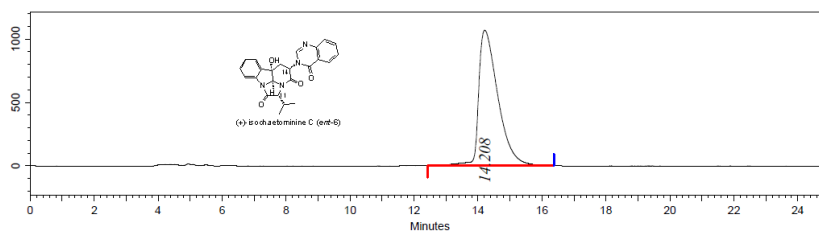


Detector A-230 nm				
PK #	Retention Time	Area	Area Percent	
1	21.387	21587527	100.00	
Totals		21587527	100.00	

Shimadzu CLASS-VP V6.13 SP2
Column: Chiralpak AD-H
Mobile Phase: Hex/IPA=70/30(v/v)
Flow Rate: 0.8mL/min
CT: 30°C

Area % Report

Sample Name: *ent-6*



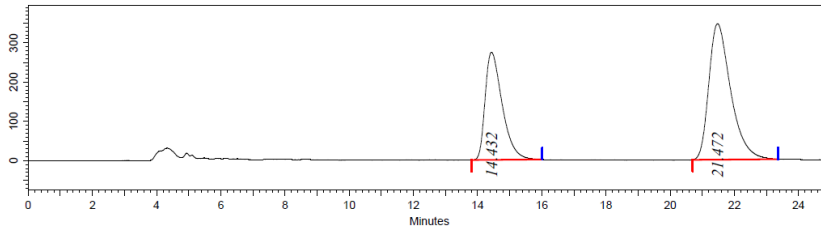
Detector A-230 nm

Pk #	Retention Time	Area	Area Percent
1	14.208	44695640	100.00
Totals		44695640	100.00

HPLC analysis of the mixture of compound **2.6** and *ent-2.6*

Shimadzu CLASS-VP V6.13 SP2
 Column: Chiralpak AD-H
 Mobile Phase: Hex/IPA=70/30(v/v)
 Flow Rate: 0.8mL/min
 CT: 30°C Sample Name: 6+ *ent*-6

Area % Report

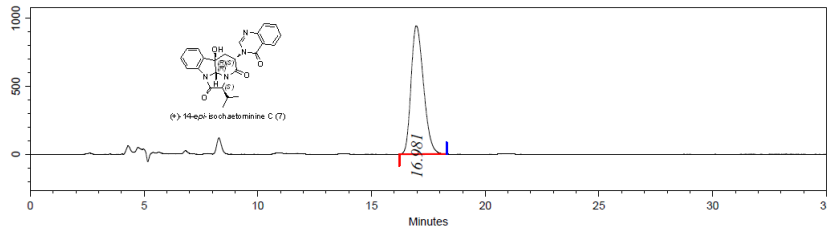


Detector A-230 nm			
Pk #	Retention Time	Area	Area Percent
1	14.432	10145140	38.21
2	21.472	16402704	61.79
Totals		26547844	100.00

HPLC analysis of compound 2.7 and *ent*-2.7

Shimadzu CLASS-VP V6.13 SP2
 Column: Chiralpak AD-H
 Mobile Phase: Hex/EtOH=30/70(v/v)
 Flow Rate: 0.8mL/min
 CT: 40°C Sample Name: (+)-14- *epi*-isochaetominine C (7)

Area % Report



Detector A-230 nm			
Pk #	Retention Time	Area	Area Percent
1	16.981	35841003	100.00
Totals		35841003	100.00

Shimadzu CLASS-VP V6.13 SP2

Area % Report

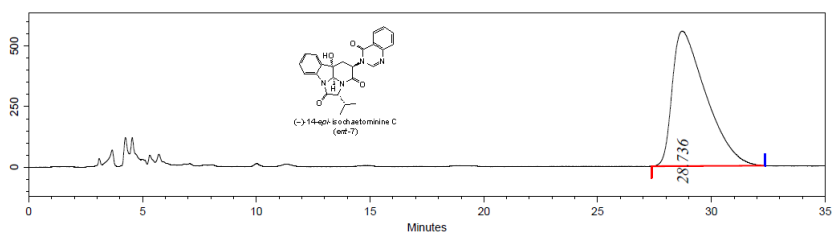
Column: Chiralpak AD-H

Mobile Phase: Hex/EtOH=30/70(v/v)

Flow Rate: 0.8mL/min

CT: 40°C

Sample Name: (-)-14- *epi*-isochaetominine C (*ent*-7)



Detector A-230 nm			
Pk #	Retention Time	Area	Area Percent
1	28.736	57425127	100.00
Totals		57425127	100.00

HPLC analysis of the mixture of compound **2.7** and *ent*-**2.7**

Shimadzu CLASS-VP V6.13 SP2

Area % Report

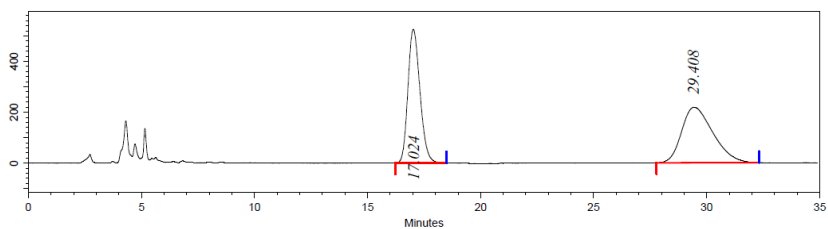
Column: Chiralpak AD-H

Mobile Phase: Hex/EtOH=30/70(v/v)

Flow Rate: 0.8mL/min

CT: 40°C

Sample Name: 7 + *ent*-7



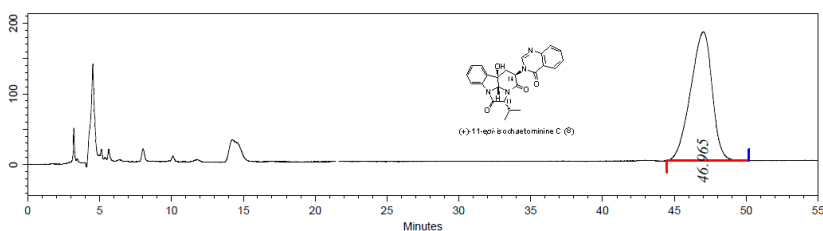
Detector A-230 nm			
Pk #	Retention Time	Area	Area Percent
1	17.024	19419077	48.09
2	29.408	20959002	51.91
Totals		40378079	100.00

HPLC analysis of compound **2.8** and *ent*-**2.8**

Shimadzu CLASS-VP V6.13 SP2
 Column: Chiralpak AD-H
 Mobile Phase: Hex/EtOH=30/70(v/v)
 Flow Rate: 0.8mL/min
 CT: 40°C

Area % Report

Sample Name: 8

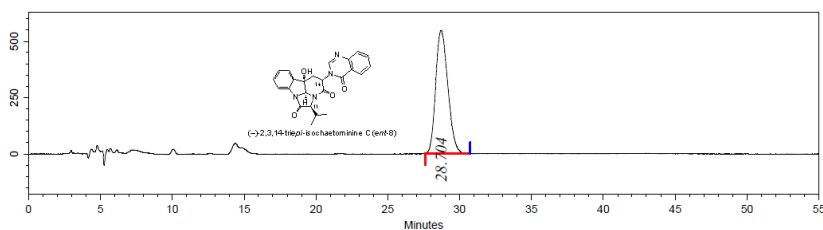


Detector A-230 nm			
Pk #	Retention Time	Area	Area Percent
1	46.965	19095447	100.00
Totals		19095447	100.00

Shimadzu CLASS-VP V6.13 SP2
 Column: Chiralpak AD-H
 Mobile Phase: Hex/EtOH=30/70(v/v)
 Flow Rate: 0.8mL/min
 CT: 40°C

Area % Report

Sample Name: ent-8

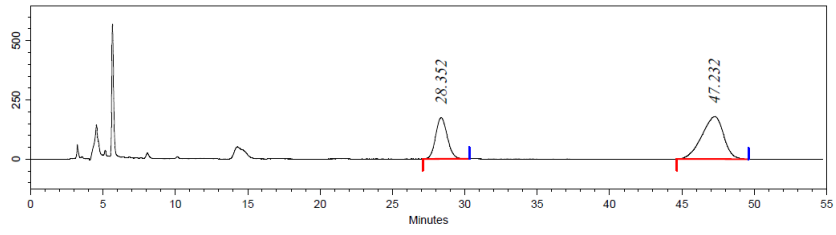


Detector A-230 nm			
Pk #	Retention Time	Area	Area Percent
1	28.704	32190413	100.00
Totals		32190413	100.00

HPLC analysis of the mixture of compound **2.8** and *ent-2.8*

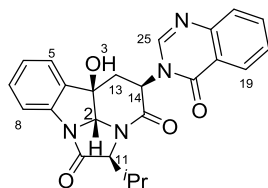
Shimadzu CLASS-VP V6.13 SP2
Column: Chiralpak AD-H
Mobile Phase: Hex/EtOH=30/70(v/v)
Flow Rate: 0.8mL/min
CT: 40°C Sample Name: 8+ent-8

Area % Report



Detector A-230 nm			
Pk #	Retention Time	Area	Area Percent
1	28.352	9705454	33.96
2	47.232	18869477	66.04
Totals		28574931	100.00

A comparison of ^1H NMR and ^{13}C NMR data of reported and synthetic of the proposed structure of isochaetomine C (2.6).



(-)-isochaetomine C (**2.6**)

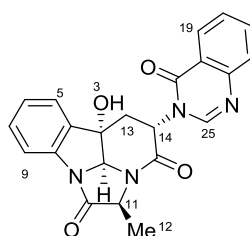
Position	Natural 2.6 (Shin, ^1H NMR 500 MHz)	aniquinazolines D (Wang, ^1H NMR 500 MHz)	Synthetic 2.6 (Huang, ^1H NMR 500 MHz)
2	5.81, s	5.82, s	5.81, s
5	7.54, dd (7.4, 0.9)	7.54, d (7.4)	7.54, dd (7.1, 1.0)
6	7.26, ddd (7.8, 7.5, 1.3)	7.26, td (7.4, 1.2)	7.26, ddd (7.4, 7.2, 1.0)
7	7.43, ddd (7.8, 7.5, 1.3)	7.43, td (7.4, 1.2)	7.43, ddd (7.4, 7.2, 1.0)
8	7.46, dd (7.5, 1.3)	7.47, d (7.4)	7.47, dd (7.6, 1.0)
11	4.21, d (9.3)	4.21, d (9.3)	4.21, d (9.3)
12	2.44, m	2.45, m	2.43-2.46, m
13	3.01, dd (14.0, 7.9) 2.77, dd (14.0, 5.3)	3.01, dd (14.0, 8.1) 2.77, dd (14.0, 5.3)	3.00, dd (14.0, 8.0) 2.77, dd (14.0, 5.3)
14	4.86, dd (7.9, 5.3)	4.86, dd (8.1, 5.3)	4.85, dd (8.0, 5.3)
19	8.18, dd (7.9, 1.3)	8.18, dd (7.9, 1.3)	8.18, dd (7.9, 1.2)
20	7.59, ddd (7.9, 7.5, 1.0)	7.59, td (7.9, 0.8)	7.59, ddd (7.9, 7.6, 1.0)
21	7.87, ddd (7.7, 7.5, 1.3)	7.87, td (7.9, 1.3)	7.87, ddd (7.7, 7.5, 1.5)
22	7.71, dd (7.7, 1.0)	7.71, d (7.9, 0.8)	7.71, dd (7.9, 0.9)
25	8.30, s	8.30, s	8.30, s
27	1.12, d (6.7)	1.12, d (6.7)	1.12, d (6.7)
28	1.15, d (6.7)	1.15, d (6.7)	1.15, d (6.7)

3-OH	6.30, brs	5.45, brs (detected in acetone-d ₆)	6.29, brs
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Position	Natural 2.6 (Shin, ¹³ C NMR 500 MHz)	Aniquinazolines D (Wang, ¹³ C NMR 500 MHz)	Synthetic 2.6 (Huang, ¹³ C NMR 500 MHz)
2	83.7, CH	83.7	83.7
3	73.9, C	73.8	73.8
4	134.9, C	134.9	134.9
5	124.6, CH	124.5	124.6
6	125.2, CH	125.1	125.2
7	130.1, CH	130.0	130.1
8	114.2, CH	114.2	114.2
9	140.3, C	140.2	140.3
10	173.9, C	173.8	173.9
11	69.4, CH	69.3	69.4
12	28.2, CH	28.2	28.2
13	34.1, CH ₂	34.1	34.1
14	55.7, CH	55.6	55.7
15	164.9, C	164.8	164.9
17	159.8, C	159.7	159.8
18	121.5, C	121.5	121.5
19	126.2, CH	126.1	126.2
20	127.4, CH	127.3	127.4
21	134.7, CH	134.6	134.7
22	127.2, CH	127.1	127.2

23	147.5, C	147.5	147.5
25	146.9, CH	146.7	146.9
27	20.2, CH ₃	20.1	20.2
28	18.7, CH ₃	18.6	18.7

A comparison of ¹H NMR and ¹³C NMR data of reported and synthetic of the proposed structure of isochaetomine (2.9)



(-)-isochaetomine (**2.9**)
(proposed structure)

Position	Natural 2.9 (Lou, ¹ H NMR 600 MHz)	Synthetic 2.9 (Huang, ¹ H NMR 500 MHz)	(-)-11- <i>epi</i> -chaetominine (2.50) (Huang, ¹ H NMR 400 MHz)
2	5.85, s	5.80, s	5.85, s
5	7.47	7.49-7.38 (m, 3H)	7.50-7.45 (m, 2H)
6	7.24, t (7.2)	7.21, td (7.5, 1.0)	7.24, td (7.5, 1.0)
7	7.42, t (7.2)	-	7.42, td (7.5, 1.0)
8	7.48	-	-
11	4.64	4.71, q (7.1)	4.65, q (7.3)
12	1.49, d (6.6)	1.6, d (7.1)	1.49, d (7.3)
13	2.93, t (12.2) 2.47	2.77, dd (15.2, 3.2) 2.46, dd (15.2, 5.0)	2.93, t (13.0) 2.51, dd (13.0, 3.4)
14	5.91, (br. s)	5.12, dd (8.0, 5.3)	5.98-5.88 (br. s)
19	8.19, d (7.2)	8.22, dd (8.0, 1.2)	8.21, dd (8.0, 1.0)

20	7.59, t (7.2)	7.61, td (7.5, 1.0)	7.58, td (7.5, 1.0)
21	7.87, t (7.2)	7.89, td (7.5, 1.0)	7.86, td (7.5,1.0)
22	7.70, d (7.2)	7.74, d (7.9)	7.69, d (8.0)
25	8.23, s	8.39, s	8.23, s
3-OH	6.78, brs	6.13, brs	6.76, brs

Position	Natural 2.9 (Lou, ¹³ C NMR 150 MHz)	Synthetic 2.9 (Huang, ¹³ C NMR 125 MHz)	(-)-11- <i>epi</i> -chaetomine (2.50) (Huang, ¹³ C NMR 100 MHz)
2	82.9	83.8	82.9
3	76.6	75.3	76.6
4	137.6	138.2	137.5
5	124.7	125.1	124.6
6	125.6	125.8	125.4
7	129.8	130.2	129.7
8	114.5	114.8	114.5
9	137.7	139.2	137.7
10	170.9	173.1	170.8
11	59.7	60.0	59.6
12	15.1	13.9	15.0
13	38.4	36.9	38.3
14	49.0	57.6	49.3
15	160.0	160.4	159.9
17	166.3	163.5	166.2
18	121.0	122.0	121.0

19	126.5	126.7	126.4
20	127.3	127.8	127.2
21	134.8	135.1	134.6
22	127.2	127.7	127.2
23	146.7	147.2	146.6
25	147.4	148.0	147.3

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Chapter 3 Azaphilic Radical Cascade Cyclization for the Synthesis of Imidazo-Fused Heteroaromatics

Imidazo[1,2-*a*]pyridines and imidazo[1,2-*d*]azines are important heteroaromatics¹ because they are widely used in drug, pesticides, materials and dyes industries.² Imidazo[1,2-*a*]pyridine scaffolds are found in many pharmacologically important compounds that exhibit antiviral, antimicrobial, antitumor, anti-inflammatory, antiparasitic, and hypnotic activities.³ Because of such appealing benefits, many commercially available drugs containing this scaffold have been developed (Figure 3.1), including Alpidem (anti anxiety),⁴ Zolpidem (hypnotic),⁵ Zolimidine (for the treatment of gastric ulcer),⁶ Saripidem (sedative and anti anxiety),⁷ Olprinone (cardiac drugs, vasodilators),⁸ Minodronicacid (for the treatment of anxiety, cardiac failure and osteoporosis),⁹ Necopidem (anesthetic) and optically active GSK812397 (for the treatment of HIV infection).¹⁰

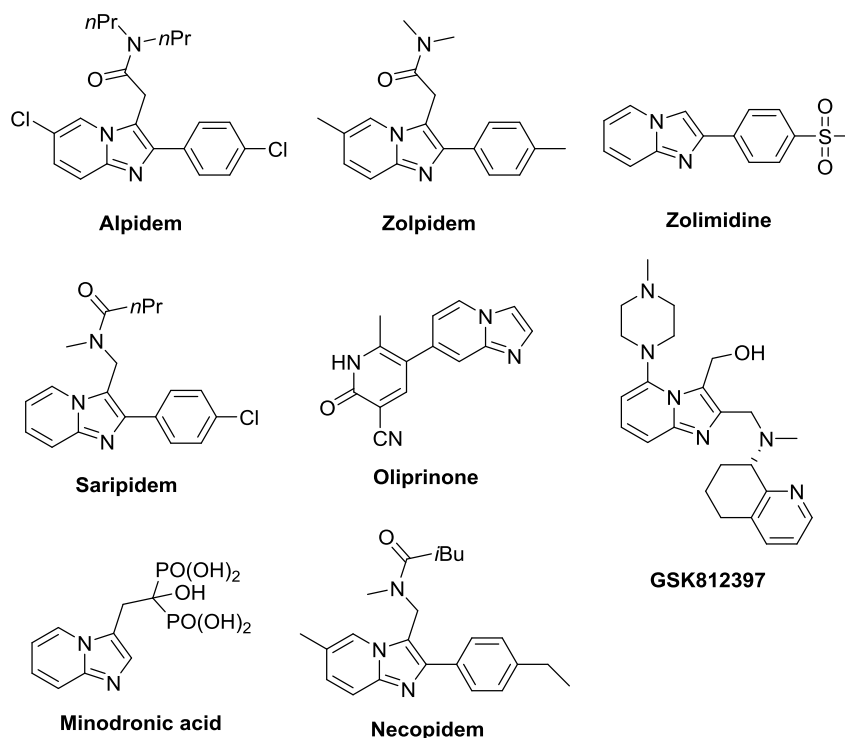


Figure 3.1

Heteroaromatics containing imidazo[1,2]diazine structures also have a wide range of applications. This skeleton exists in many bioactive compounds (Figure 3.2). For example, LY2784544 with an imidazo[1,2-*b*]pyridazine skeleton has been conducting clinical trials for myeloproliferative disorders, and Fasiplon is an anxiolytic drug with an imidazo[1,2-*a*]pyrimidine core structure. In addition, ZAP-70 is a kinase inhibitor that has an imidazo[1,2-*c*]pyrimidine skeleton.¹¹

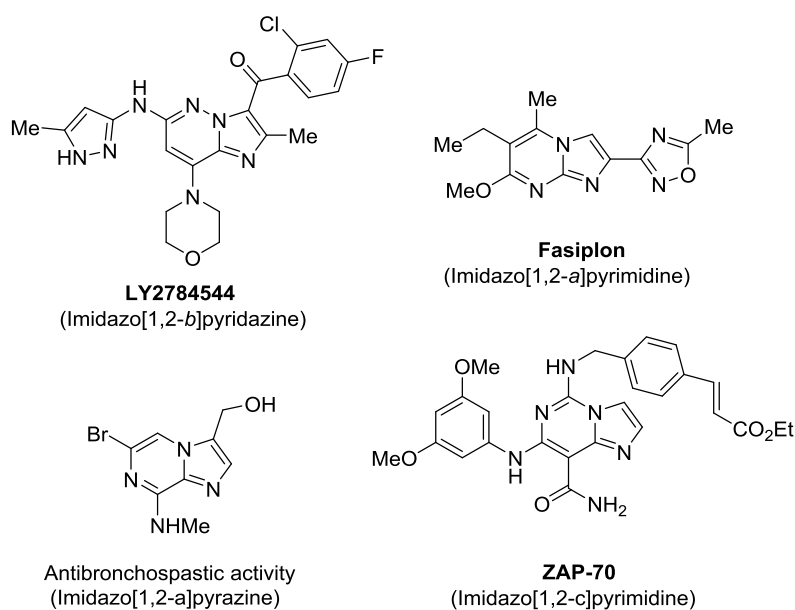


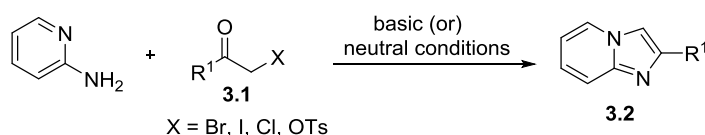
Figure 3.2

The importance of heteroaromatics containing imidazo[1,2-*a*]pyridine and imidazo[1,2]diazine structures have spurred the development efficient methods for their synthesis.

3.1 Review of the Reported Synthetic Methods

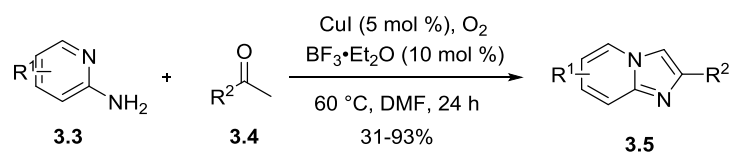
The redox neutral condensation of 2-aminopyridines and per-functionalized carbonyl compounds has been extensively studied for the synthesis of imidazo[1,2-*a*]pyridine (Scheme 3.1).¹²

Classical routes:



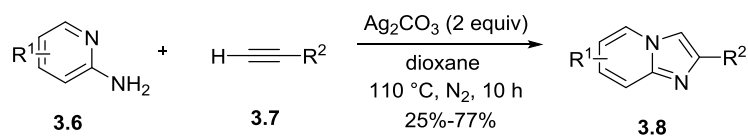
Scheme 3.1

To develop methods with increased atom-economy from easily available starting materials, several groups have reported the formation of imidazo[1,2-*a*]pyridines through metal-catalyzed oxidative coupling of 2-aminopyridines and methyl ketones (Scheme 3.2).¹³ For example, Adimurthy's group^{13b} reported in 2013 an operationally simple method of the synthesis of 2-substituted imidazo[1,2-*a*]pyridines derivatives through copper-catalyzed aerobic coupling of 2-aminopyridines with methyl ketones.



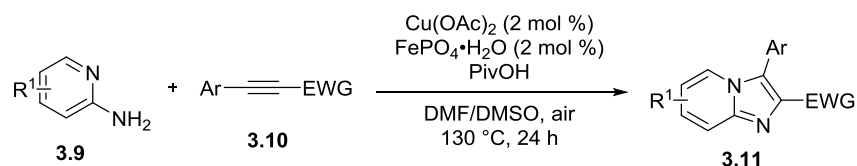
Scheme 3.2

In 2012, Lei's group¹⁴ reported a novel approach for constructing 2-substituted imidazo[1,2-*a*]pyridines from 2-aminopyridines **3.6** and terminal alkynes **3.7** promoted by stoichiometric amount of Ag_2CO_3 (Scheme 3.3).



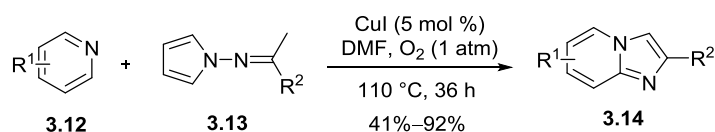
Scheme 3.3

In 2012, Liu's group¹⁵ reported a Cu(II) and Fe(III) co-catalyzed strategy for the synthesis of 2,3-disubstituted imidazo[1,2-*a*]pyridines through aerobic coupling of activated internal alkynes with 2-aminopyridines (Scheme 3.4). This method needed high temperature and long reaction time and the scope of substrates was narrow.



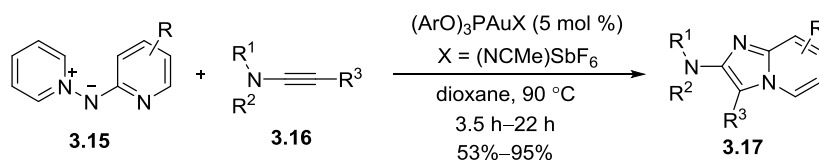
Scheme 3.4

In 2013, Fu's group¹⁶ reported the synthesis of 2-substituted imidazo[1,2-*a*]pyridines derivatives through Cu-catalyzed coupling of pyridines and hydrazones (Scheme 3.5). This reaction demonstrated for the first time that simple pyridines could be used as starting material to construct the imidazo[1,2-*a*]pyridine structures.



Scheme 3.5

While many methods have been reported for the synthesis of imidazo[1,2-*a*]pyridines, methods for the synthesis of imidazo[1,2]diazines have been rare. Davies's group¹⁷ reported in 2014 the synthesis of imidazo[1,2-*a*]pyridine and imidazo[1,2]diazine structures (Scheme 3.6) through Au-catalyzed cycloaddition of nucleophilic 1,3-*N,N* dipoles 3.15 with electron rich alkynes.

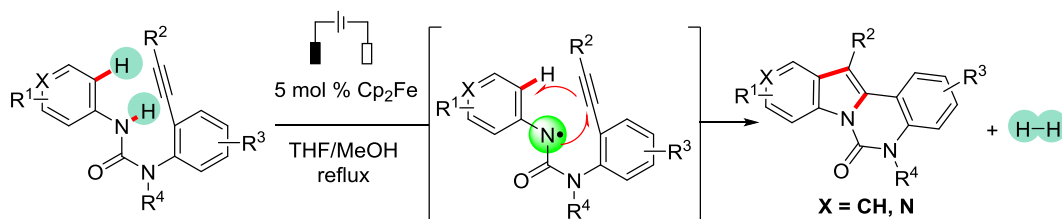


Scheme 3.6

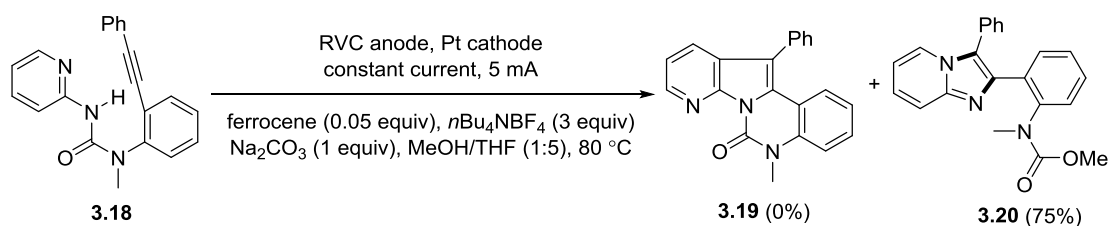
Despite the above-mentioned progress in the synthesis of imidazo-fused N-heteroaromatics, many methods suffer from one or more of the following drawbacks such as limited scope, requiring harsh reactions conditions and transition metal-reagents, and employment of dangerous or expensive chemical oxidants. Therefore, the development of a general and efficient method for the synthesis of imidazo-fused heteroaromatics is urgently needed but remains to be challenging.

3.2 Research Plan

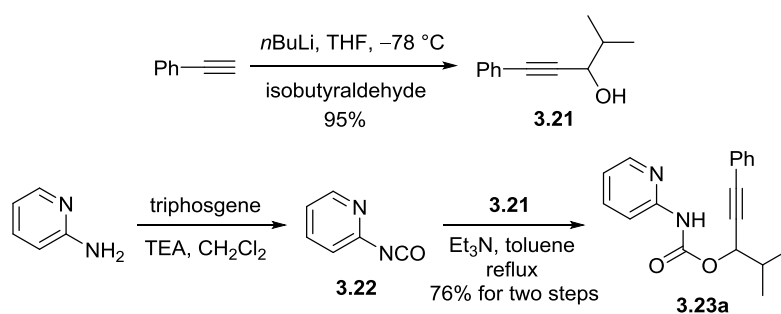
Xu's group has previously reported an electrochemical synthesis of (aza)indoles through ferrocene-catalyzed oxidative intramolecular alkyne annulation (Scheme 3.7).¹⁸



In the course of studying the substrate scope, Zhong-Wei Hou, a M.S. student from the Xu group, found that the oxidative cyclization of 2-aminopyridine derived urea **3.18** afforded no azaindole **3.19**. Instead, imidazo[1,2-*a*]pyridine **3.20** was isolated in 75% yield (Scheme 3.8). It seems that the second cyclization occurred exclusive on the pyridyl nitrogen atom. Radical-mediated homolytic aromatic C–H substitution of N-heteroaromatics has been extensively studied. However, an efficient reaction of carbon radicals with the nitrogen-atom of N-heteroaromatics remained elusive.

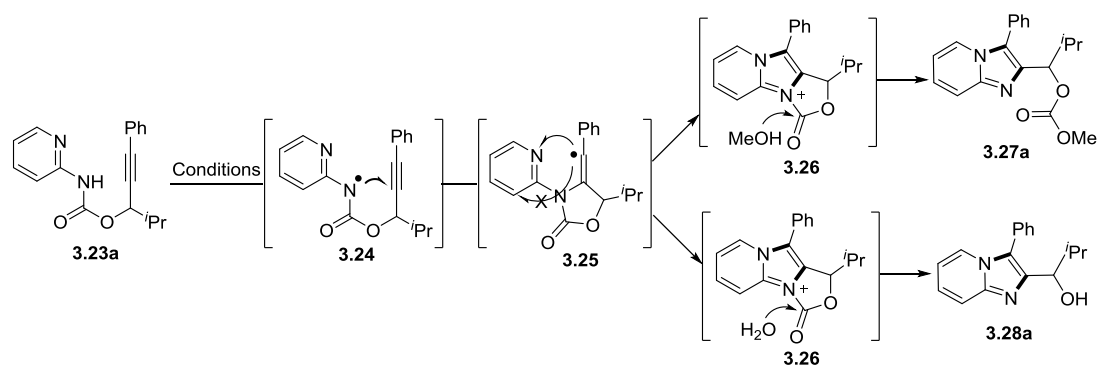


Inspired by this discovery, we wanted to develop a general electrochemical alkyne annulation reaction for the synthesis of imidazo[1,2-*a*]pyridines and related N-heteroatomics. Therefore, we synthesized carbamate-derived substrate **3.23a** from easily available propargyl alcohol **3.21** (Scheme 3.9).



Scheme 3.9

We envisioned that upon oxidative N–H cleavage, a nitrogen-centered radical **3.24** would be formed (Scheme 3.10). *5-exo-dig* cyclization of **3.24** would lead to vinyl radical **3.25**. Selective cyclization of **3.25** onto the nitrogen atom of the pyridine ring followed by electron loss would afford cation **3.26**. Depending on the solvent system, this reactive cation could be converted to carbonate **3.27a** in methanol or free alcohol **3.28a** in water. In the latter case, the carbamate carbonyl group in the starting material served as a traceless linker to control the reactivity as well as the regioselectivity of the annulation reaction.



Scheme 3.10

3.3 Results and Discussion

3.3.1 Optimization of reaction conditions

3.3.1.1 Optimization of reaction conditions employing Ferrocene as the catalyst

The reaction condition employed for the indole synthesis were selected as the starting point for reaction optimization. Hence, the electrolysis of **3.23a** was carried out in relaxing MeOH/THF (1:5) employing ferrocene (5 mol %) as the catalyst, 3 equiv $n\text{Bu}_4\text{NBF}_4$ as the electrolyte, 1 equiv Na_2CO_3 as the base, and a constant current of 7.5 mA. The electrolysis was carried out in a three-necked round bottomed flask using a reticulated vitreous carbon (RVC) anode and a platinum plate cathode (Figure 3.3). Reaction parameters such as base, solvent and electrolyte were screened and the results were summarized in table 3.1. Among various bases studied, Na_2CO_3 was found to be optimal in promoting the cyclization reaction. In terms of solvent, the use of a mixture of MeOH/THF (1:5) or MeOH/MeCN (1:9) seemed to be critical for reaction efficiency. The use of pure methanol as solvent resulted in dramatic reduction in product formation. The identity of the electrolyte did not affect the reaction much as the use of electrolytes as Et_4NBF_4 , $n\text{Bu}_4\text{NPF}_4$, or Et_4NPF_6 led to the formation of **3.27a** in 66–71% yields (entries 12–14).

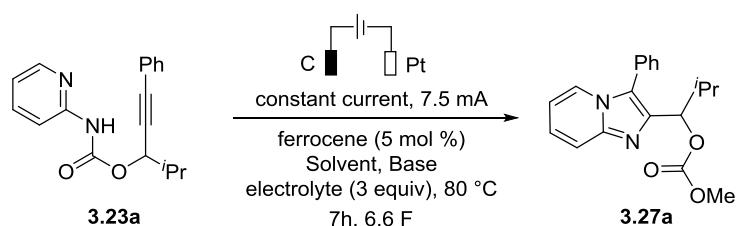


Electrolysis Setup

Electrodes

Figure 3.3

Table 3.1 Optimization of reaction conditions which ferrocene as catalyst



Entry	Base (equiv)	Solent (mL)	Electrolyte	Yield ^a (%)
1	Na ₂ CO ₃ (1.0)	MeOH/THF (1/5)	Bu ₄ NBF ₄	78
2	Na ₂ CO ₃ (0.5)	MeOH/THF (1/5)	Bu ₄ NBF ₄	56
3	NaHCO ₃ (1.0)	MeOH/THF (1/5)	Bu ₄ NBF ₄	43
4	KH ₂ PO ₄ (1.0)	MeOH/THF (1/5)	Bu ₄ NBF ₄	32
5	K ₂ CO ₃ (1.0)	MeOH/THF (1/5)	Bu ₄ NBF ₄	48
6	Na ₂ CO ₃ (1.0)	MeOH	Bu ₄ NBF ₄	46
7	Na ₂ CO ₃ (1.0)	MeOH/THF (1/1)	Bu ₄ NBF ₄	56
8	Na ₂ CO ₃ (1.0)	MeOH/MeCN (1/19)	Bu ₄ NBF ₄	43
9	Na ₂ CO ₃ (1.0)	MeOH/MeCN (1/9)	Bu ₄ NBF ₄	75
10	Na ₂ CO ₃ (1.0)	MeOH/MeCN (1/5)	Bu ₄ NBF ₄	71
11	Na ₂ CO ₃ (1.0)	MeOH/MTBE ^b (1/1)	<i>n</i> Bu ₄ NBF ₄	trace
12	Na ₂ CO ₃ (1.0)	MeOH/THF (1/5)	Et ₄ NBF ₄	71
13	Na ₂ CO ₃ (1.0)	MeOH/THF (1/5)	<i>n</i> Bu ₄ NPF ₆	68
14	Na ₂ CO ₃ (1.0)	MeOH/THF (1/5)	Et ₄ NPF ₆	66

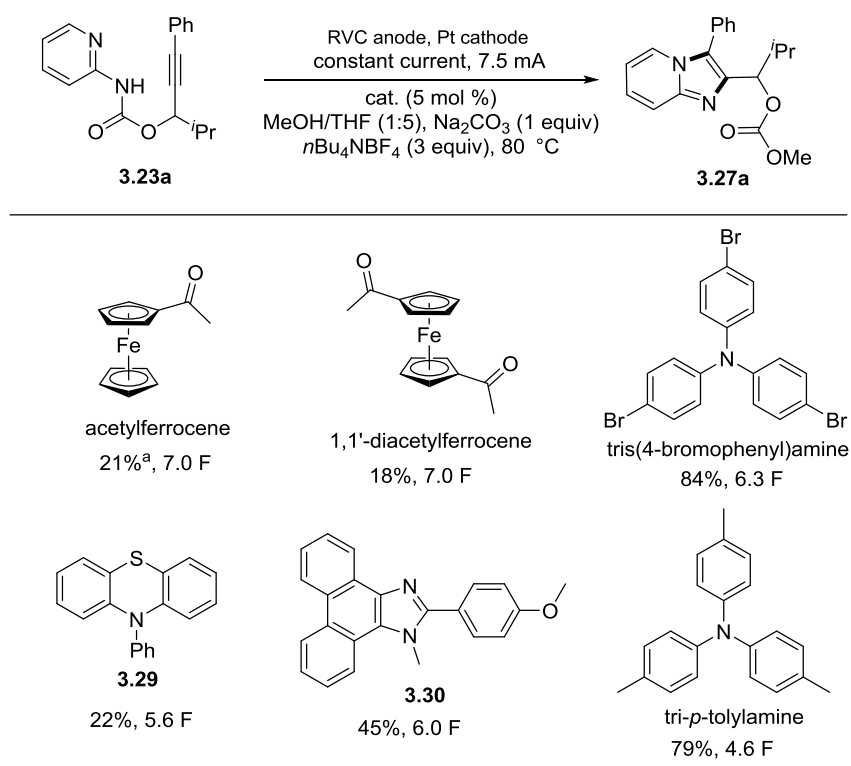
a: Determined by ¹H NMR analysis of the crude reaction mixture. b: MTBE = methyl *tert*-butyl ether

After the preliminary screening of reaction conditions employing ferrocene as redox catalyst (Table 3.1), a good yield of 78% was obtained for the formation of **3.27a**. However, 6 F of current was required to drive the reaction to completion (2 F was needed theoretically). To increase the current efficiency, we started tested other redox catalysts with a focus on organic compounds.

3.3.1.2 Screening of redox catalysts

We first tested electron-deficient ferrocene derivatives and some organic compounds as redox catalyst. When acetylferrocene and 1,1'-diacetylferrocene were found to be rather inefficient probably due to the low stability of their corresponding ferrocenium cation under the reaction conditions. Phenothiazine compound **3.29** and benzimidazole **3.30** were also not suitable in promoting the cyclization. Gladly, the use of tris(4-bromophenyl)amine and tri-*p*-tolylamine resulted in goods yields around 80%.

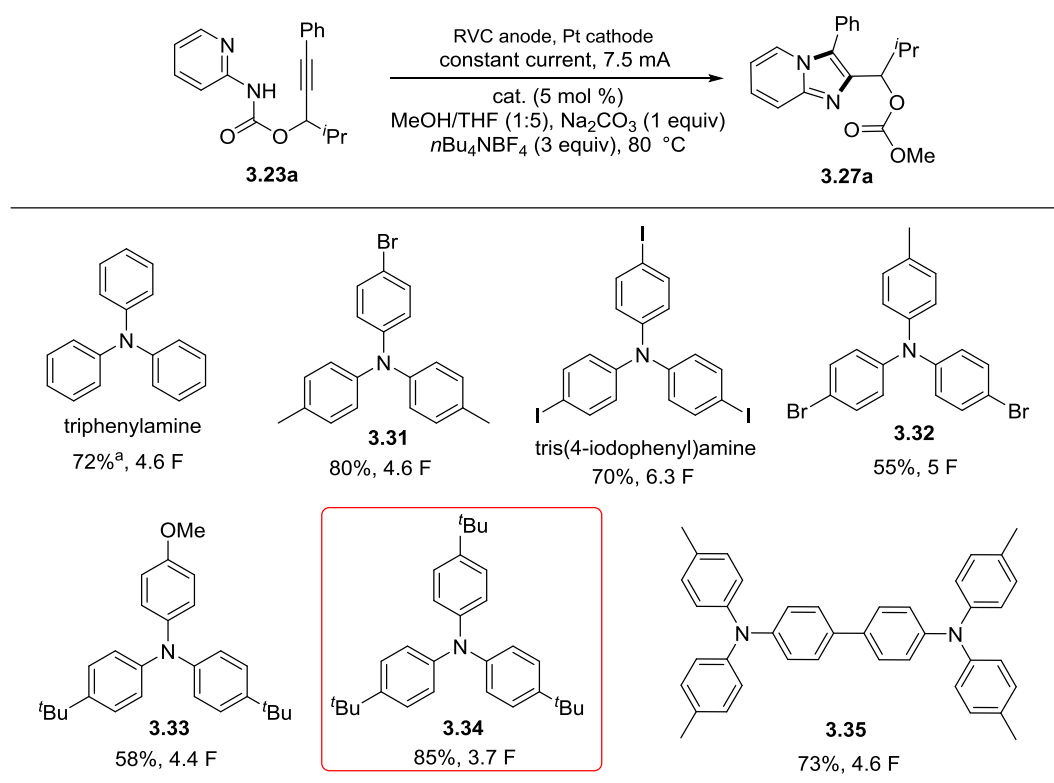
Table 3.2 screening of catalyst



a: Determined by ¹H NMR analysis of the crude reaction mixture.

Encouraged by these results, a variety of triarylamine with different redox properties were investigated leading to the identification of tris(4-(*tert*-butyl)phenyl)amine **3.34** as an optimal catalyst. Under these conditions, the product **3.27a** was formed in 85% NMR yield with after the consumption of of 3.7 F of current.

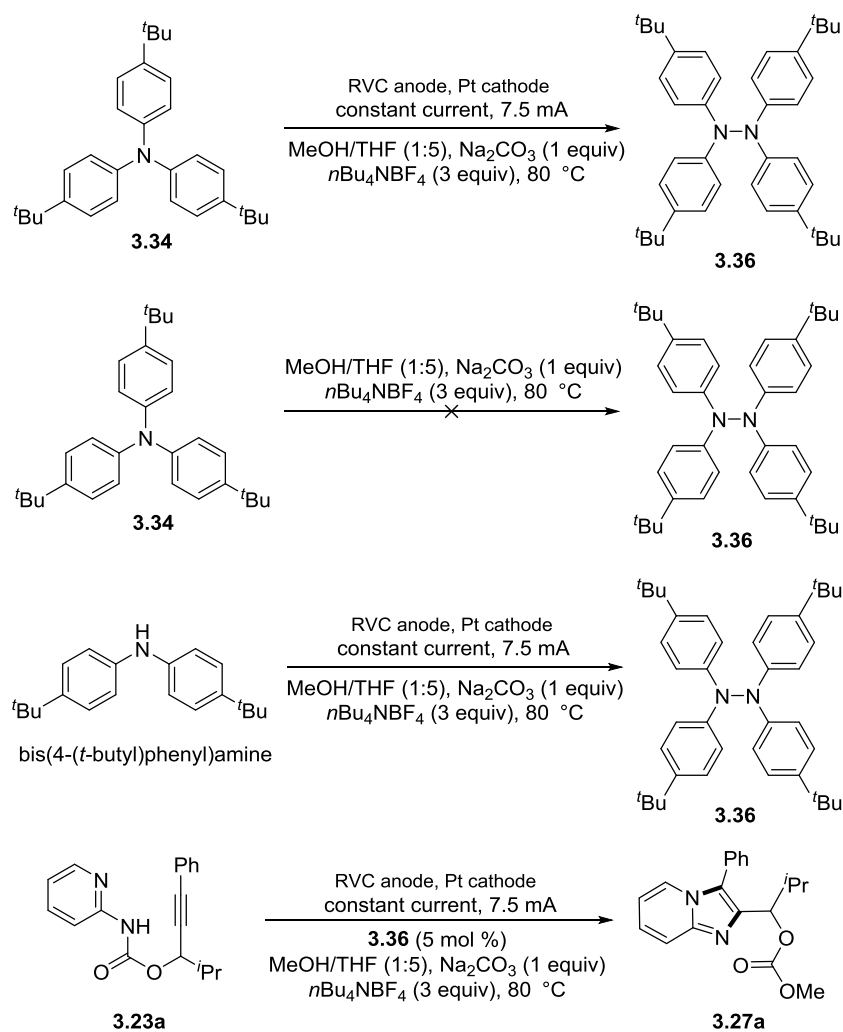
Table 3.3



a: Determined by ¹H NMR analysis of the crude reaction mixture.

Triaryl amines with para-substituents are generally stable after one electron oxidation. Surprisingly, during the electrolysis tris(4-(*tert*-butyl)phenyl)amine **3.34** transformed into another compound. It was assumed that the actual redox catalyst was not the original tris(4-(*tert*-butyl)phenyl)amine **3.34**, but its degradation product.

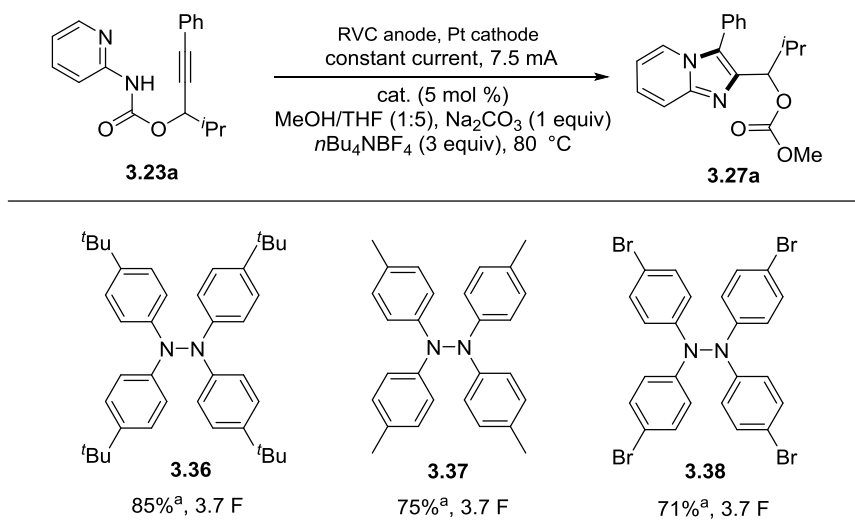
Several experiments were carried out to figure out the actual redox catalyst for the electrolysis. When tris(4-(*tert*-butyl)phenyl)amine was electrolyzed in the absence of the carbamate substrate, 1,1,2,2-tetrakis(4-(*tert*-butyl)phenyl)hydrazine **3.36** was formed. No **3.36** was observed without electric current. In addition, the electrolysis of bis(4-(*tert*-butyl)phenyl)amine also led to the formation of **3.36**. When tetraarylhydrazine **3.36** was used as the redox catalyst for the electrolysis of **3.23a**, the desired product **3.27a** was formed in 85% yield (3.7 F). These results suggested that triarylamine **3.34** was converted hydrazine **3.36** during the electrolysis and the latter served as the redox catalyst for the formation of **3.27a**.



Scheme 3.11

A survey of literature showed that tetraarylhazirines has not been used redox catalyst in organic synthesis.¹⁹ Tetrakis(4-aryl)hydrazine compounds bearing methyl or bromo substituents were found to be less efficient than the *tert*-butyl substituted **3.36** (Table 3.4).

Table 3.4

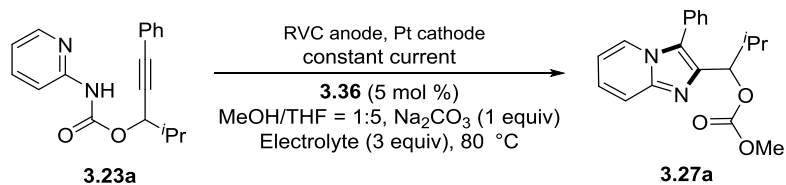


a: Determined by ¹H NMR analysis of the crude reaction mixture.

3.3.1.3 Screening of electrolyte

Different tetraalkylammonium salts were screened as the electrolyte using the model reaction of **3.23a** in the hope to further boost the reaction efficiency.

Table 3.5 screening of electrolyte



Entry	Electrolyte (equiv)	Current (mA)	Electricity (F)	Time (h)	Yield ^a %
1	Et ₄ NOTs (3.0)	10	4.4	3.5	64
2	<i>n</i> Bu ₄ NPF ₆ (3.0)	10	4.4	3.5	76
3	Et ₄ NPF ₆ (3.0)	10	4.4	3.5	78
4	Et ₄ NBF ₄ (3.0)	<10	-	-	-
5 ^b	Et ₄ NBF ₄ (3.0)	7.5	3.0	3.2	87
6 ^b	Et ₄ NBF ₄ (1.0)	7.5	3.0	3.2	89
7 ^b	Et ₄ NBF ₄ (0.5)	<7.5	-	-	-

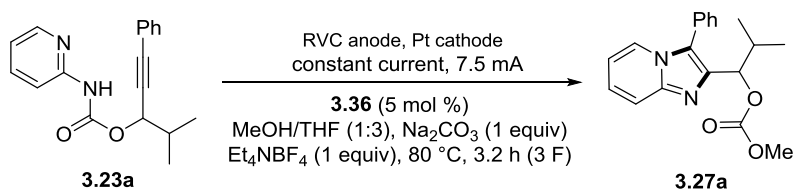
a: Determined by ¹H NMR analysis of the crude reaction mixture. b: MeOH/THF = 1.5 mL/7.5 mL adjust to MeOH/THF = 2.5 mL/7.5 mL

Among the electrolytes studied, Et₄NBF₄ was found to be optimal leading to good yield of **3.27a** with increased current efficiency (3 F). The solvent system was changed to MeOH/THF (1:3) to increase the conductivity. Under these conditions, the electrolyte can be lowered to 1 equiv without affecting reaction efficiency. Further decrease the amount of electrolyte to 0.5 equiv led to low conductivity.

3.3.1.4 Control experiment

Control experiments showed that electricity (entry 2), redox catalyst (entry 3), the basic additive Na₂CO₃ (entry 4) and heating (entry 5) were all critical for the success of the electrochemical cyclization reaction. Importantly, the electrolysis was not very sensitive to oxygen as running the reaction under air also resulted in the formation of the desired **3.27a** in 76% yield (entry 6).

Table 3.6 Control experiment



Entry	Conditions	Yield ^a %
1	MeOH/THF (1:3), 3.36 (5 mol %), Na ₂ CO ₃ (1 equiv), Et ₄ NBF ₄ (1 equiv), 80 °C, 7.5 mA	89
2	entry 1 but no electricity	0
3	entry 1 but no cat.	8
4	entry 1 but no Na ₂ CO ₃	24
5	entry 1 but reaction at RT	trace
6	entry 1 but reaction under air	76

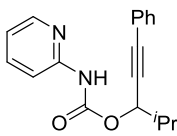
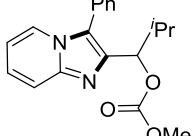
a: Determined by ¹H NMR analysis of the crude reaction mixture.

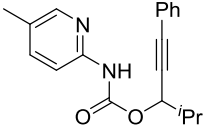
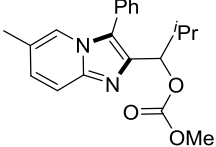
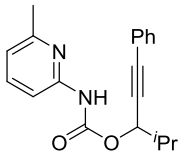
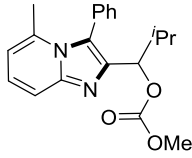
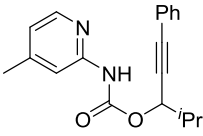
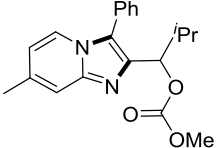
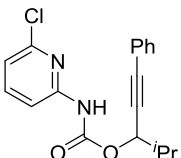
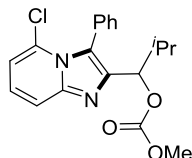
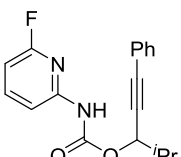
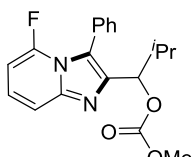
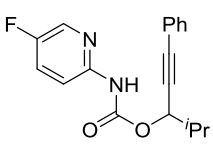
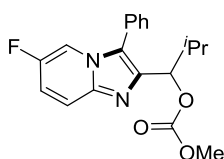
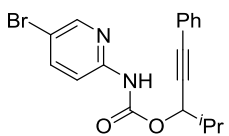
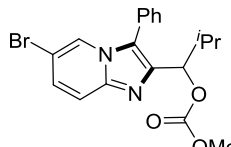
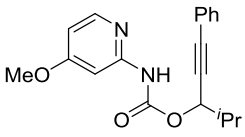
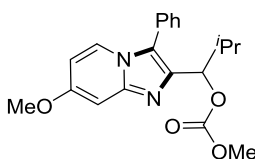
3.3.2 The scope of carbamate substrates

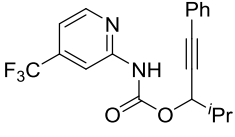
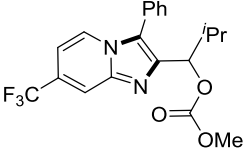
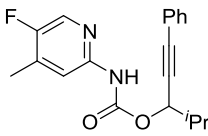
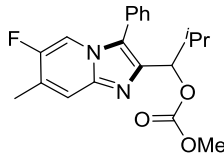
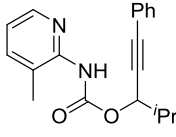
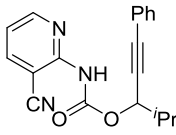
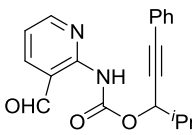
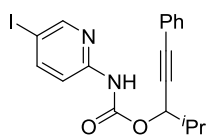
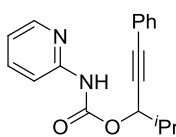
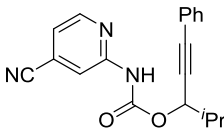
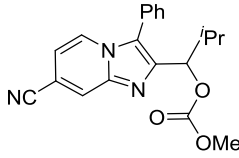
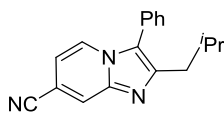
After the optimum conditions was established, we explored the scope of carbamate-derived substrates.

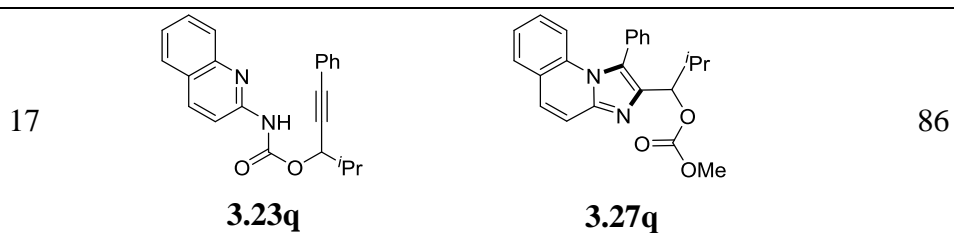
As shown in table 3.7, substitution of the pyridyl ring at position 4, 5 and 6 using substituents with diverse electronic properties were tolerated (3.27a–3.27k). Substitution at position 3 with a methyl or cyano group resulted in no reaction and recover of most of the starting material (3.23l and 3.23m). An aldehyde group at this position led to substrate decomposition and no formation of desired cyclization product (3.23n). Substrate bearing an iodo group at position 5 did not cyclize but afforded dehalogenated carbamate 3.23a. It seemed that cathodic reduction of C–I bond of the substrate competed well with the reduction of methanol solvent. Interestingly, introduction of a highly electron-withdrawing cyano group at position 4 resulted in the formation of the expected product 3.27p in 26% yield along with 3.39 in 65% yield. The carbonate moiety of 3.27p was removed to give 3.39 during the reaction. Further experimentation was required to clarify the mechanism for this transformation. Finally, a 2-aminoquinoline-derived substrate also cyclized smoothly to give 3.27q in 86% yield.

Table 3.7

Entry	Substrates	Product	Yield (%) ^a
1	 3.23a	 3.27a	87

2	 <p>3.23b</p>	 <p>3.27b</p>	75
3	 <p>3.23c</p>	 <p>3.27c</p>	82
4	 <p>3.23d</p>	 <p>3.27d</p>	79
5	 <p>3.23e</p>	 <p>3.27e</p>	80
6	 <p>3.23f</p>	 <p>3.27f</p>	44
7	 <p>3.23g</p>	 <p>3.27g</p>	80
8	 <p>3.23h</p>	 <p>3.27h</p>	86
9	 <p>3.23i</p>	 <p>3.27i</p>	76

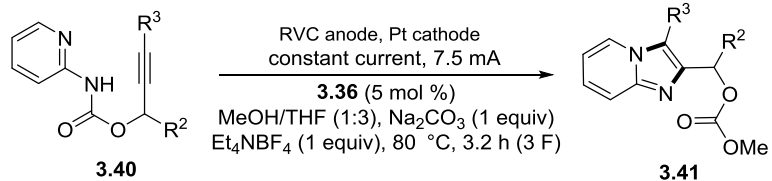
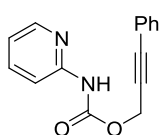
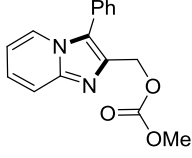
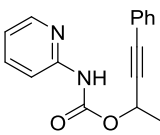
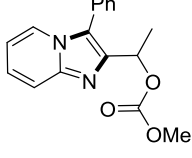
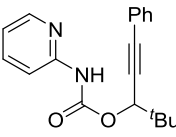
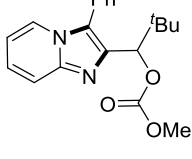
10	 <p>3.23j</p>	 <p>3.27j</p>	87 ^b
11	 <p>3.23k</p>	 <p>3.27k</p>	72
12	 <p>3.23l</p>	N.D.	-
13	 <p>3.23m</p>	N.D.	-
14	 <p>3.23n</p>	N.D.	-
15	 <p>3.23o</p>	 <p>3.23a</p>	53
16	 <p>3.23p</p>	 <p>3.27p</p>	65
		 <p>3.39</p>	26

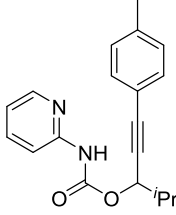
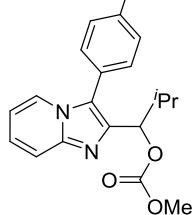
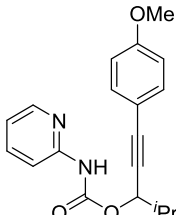
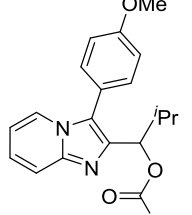
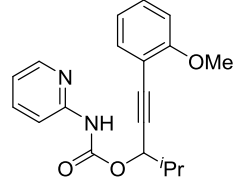
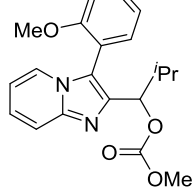
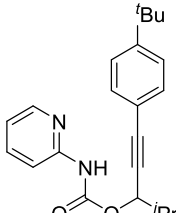
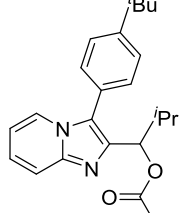
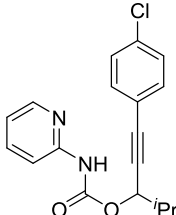
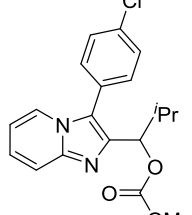
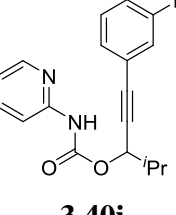
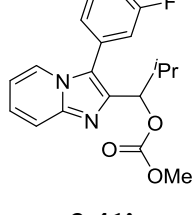


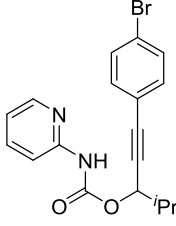
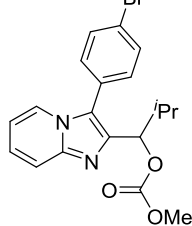
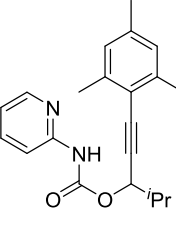
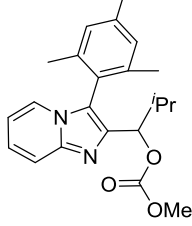
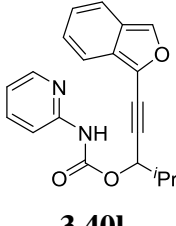
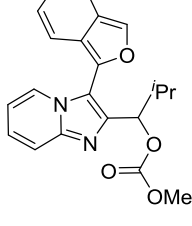
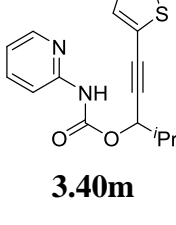
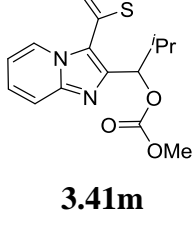
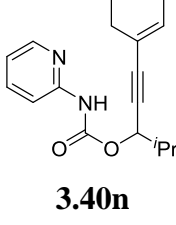
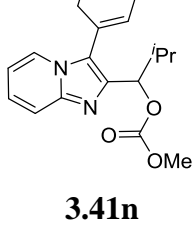
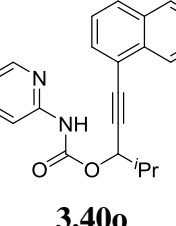
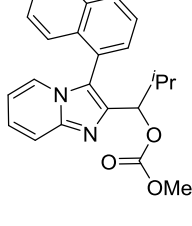
a: Isolated yield of **3.27**. b: The reaction time was 3.5 h (3.3 F)

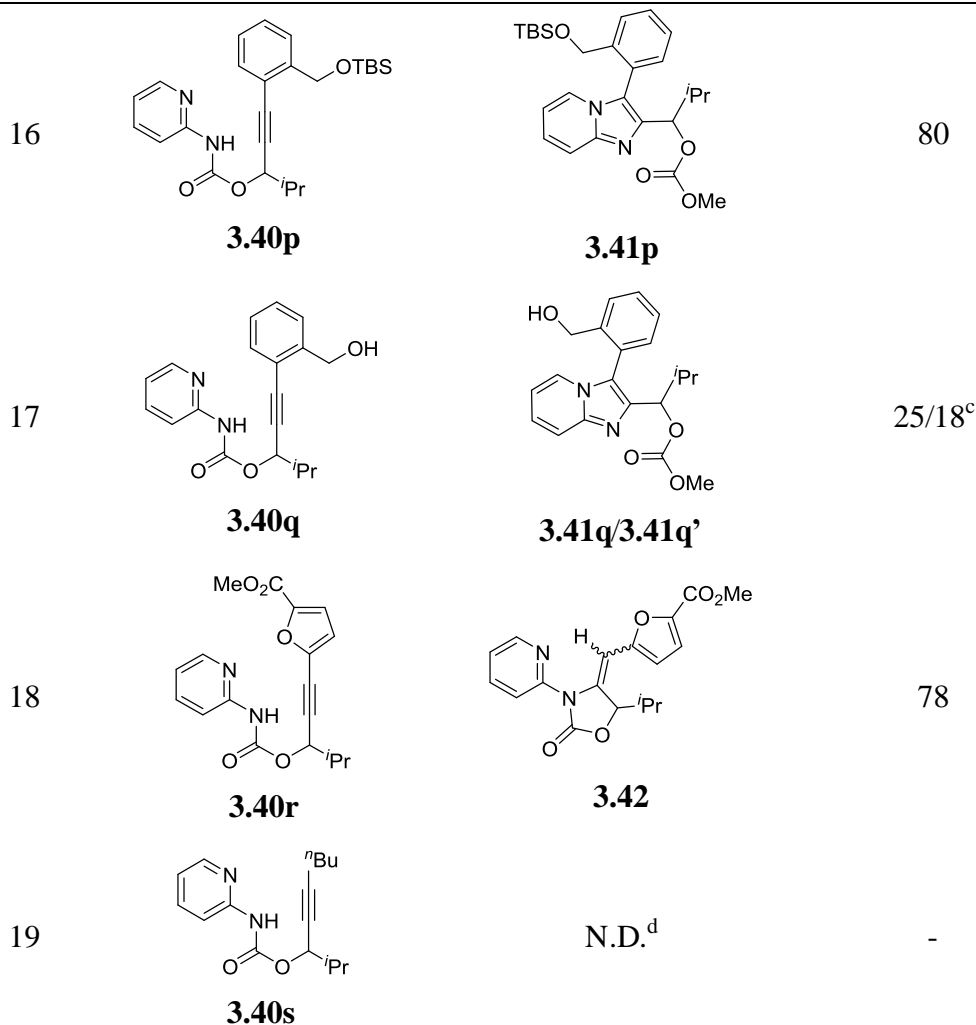
The scope of the alkyne was then investigated (Table **3.8**). First, the R² group at the propargylic position was not limited to isopropyl, as a hydrogen atom, a methyl and a *tert*-butyl group were all accommodated well (**3.41a–3.41c**, 50–92%) with better yields for more bulky groups. Capping the alkyne using phenyl groups with different electronic and steric properties, including multiple substituted aryl group, did not affect much of the reaction efficiency. Other groups such as a benzofuran, thiophene, cyclohexenyl or naphthalene were also tolerated (**3.41d–3.41q**, 44–86%).

Table **3.8**

Entry	Substrates	Product	Yield (%) ^a
	 <p>3.40 → 3.41</p>		
1	 <p>3.40a</p>	 <p>3.41a</p>	50
2	 <p>3.40b</p>	 <p>3.41b</p>	77
3	 <p>3.40c</p>	 <p>3.41c</p>	92

4	 <p>3.40d</p>	 <p>3.41d</p>	82
5	 <p>3.40e</p>	 <p>3.41e</p>	83
6	 <p>3.40f</p>	 <p>3.41f</p>	84
7	 <p>3.40g</p>	 <p>3.41g</p>	79
8	 <p>3.40h</p>	 <p>3.41h</p>	61
9	 <p>3.40i</p>	 <p>3.41i</p>	44

10	 <p>3.40j</p>	 <p>3.41j</p>	68
11	 <p>3.40k</p>	 <p>3.41k</p>	83
12	 <p>3.40l</p>	 <p>3.41l</p>	78
13	 <p>3.40m</p>	 <p>3.41m</p>	86
14	 <p>3.40n</p>	 <p>3.41n</p>	74
15	 <p>3.40o</p>	 <p>3.41o</p>	83



a: Isolated yield of **3.41**. b: The reaction time was 3.5 h (3.3 F). c: Two separated diastereoisomers. d: Substrate decomposition

Products **3.41f** and **3.41o–3.41q** were obtained as mixture stereoisomers. These compounds all contain both central chirality and axial chirality. The latter was because of the restricted rotation of the biaryl C–C bond. Alkynes terminated with electron-deficient aromatic ring or alkyl groups were not viable substrates. For example, substrate **3.40r** bearing a ester-substituted furan ring afforded monocyclized **3.42** as a result of base-promoted alkyne hydroamination. The failure of alkyl-terminated substrates was probably the high tendency of the intermediate vinyl radical toward H-abstraction.

To further extend the scope of substrate, diazine-derived substrates were designed and synthesized.

It can be seen from table **3.9** that all variation of the imidazo[1,2]diazine compounds can be synthesized using this electrocatalytic method. In the case of imidazopyrimidine, a chlorosubstituted product could also be obtained in moderate yield (**3.44d**, 41%). In addition, this electrochemical method was applicable for the synthesis of benzo[*d*]imidazo[2,1-*b*]thiazole (**3.44f**, 78%).

Limitation of the current electrochemical method on the scope of N-heteroaromatic ring includes benzimidazole (**3.43g**), isoxazole (**3.43h**), and pyrazole (**3.43i**). No reaction took place when these substrates were electrolyzed.

Table **3.9**

Entry	Substrates	Product	Yield (%) ^a
1	 3.43a	 3.44a	74
2	 3.43b	 3.44b	74
3	 3.43c	 3.44c	80 ^b
4	 3.43d	 3.44d	72 ^b

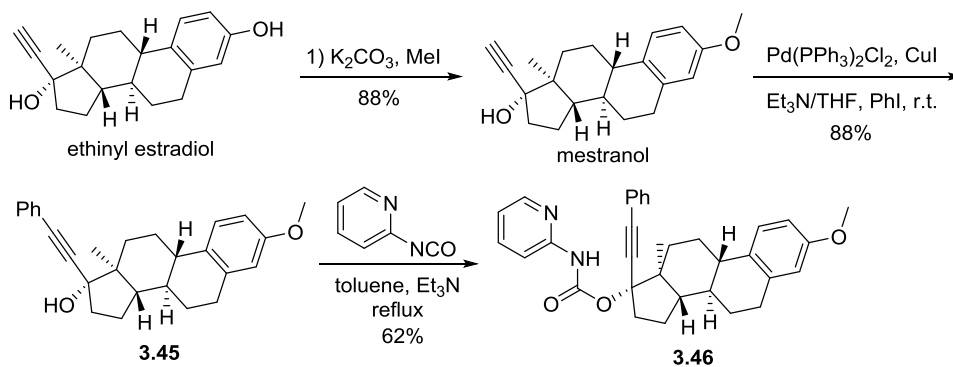
5	<p>3.43e</p>	<p>3.44e</p>	41
6	<p>3.43f</p>	<p>3.44f</p>	78 ^c
7	<p>3.43g</p>	N.D.	-
8	<p>3.43h</p>	N.D. ^d	-
9	<p>3.43i</p>	N.D.	-

a: Isolated yield of **3.44**. b: The reaction time was 3.5 h (3.3 F). c: The reaction time was 4.5 h (4.0 F). d: Recovered substrates.

3.3.3 Late-stage modification of ethinyl estradiol and estrone

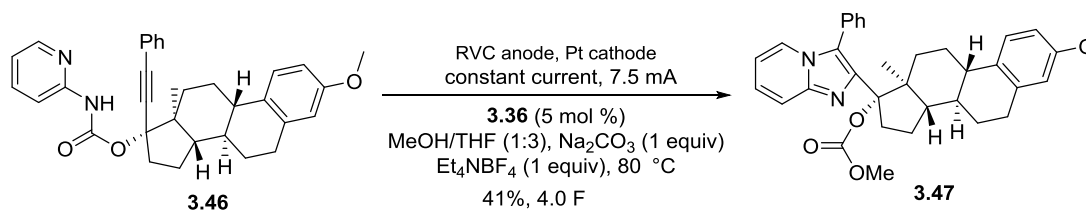
Late-stage modification of drug molecules ethinyl estradiol²⁰ and estrone were conducted to further showcase the robustness of the electrochemical synthesis.

Ethinyl estradiol was methylated to give mestranol²¹ which was transformed to the desired substrate **3.46** for electrolysis through Sonogashira coupling reaction with iodobenzene followed by carbamate formation (Scheme **3.12**).



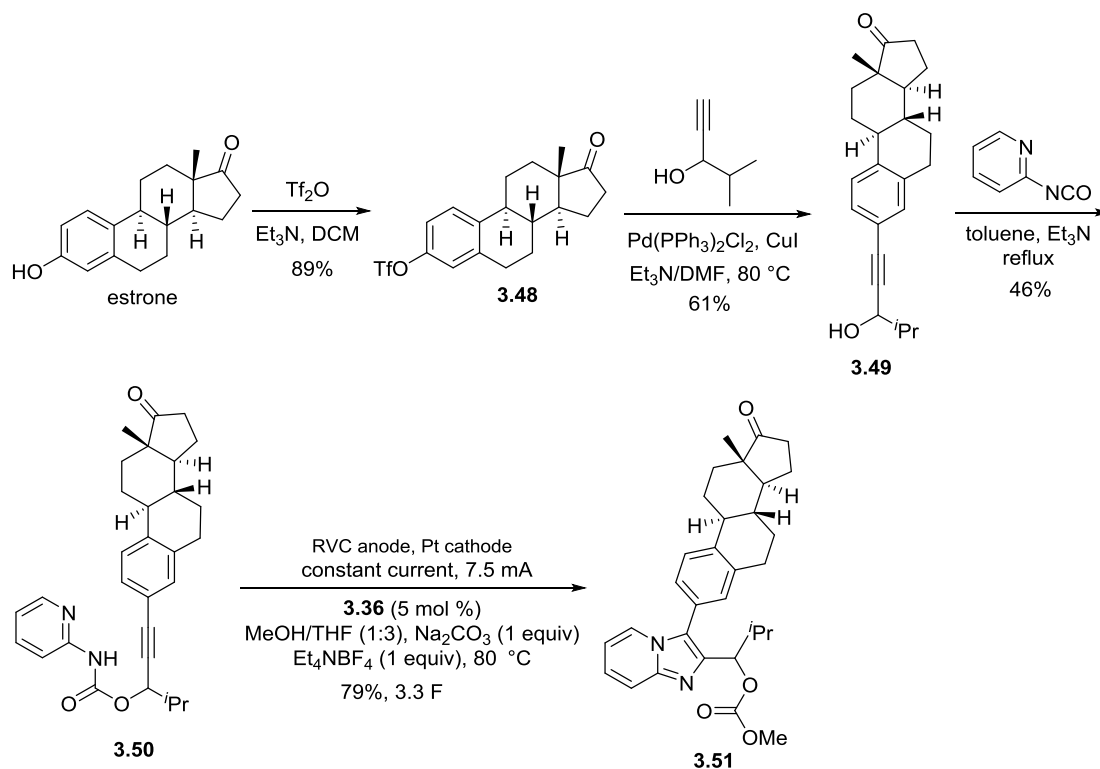
Scheme 3.12

The electrolysis of **3.46** under standard conditions afforded the desired product **3.47** was obtained in 41% yield after 4.5 h (4 F) (Scheme 3.13). The methoxy group substituted electron-rich arene survived in electrochemical conditions.



Scheme 3.13

Estrone was converted to the carbamate **3.50** through trifluoromethyl sulfonylation, Sonogashira coupling and carbamate formation. Electrochemical cyclization of **3.50** proceeded smoothly to afford the desired **3.51** in 79% yield. These results highlights the potential of the electrochemical method for the synthesis of complex structures (Scheme 3.14).

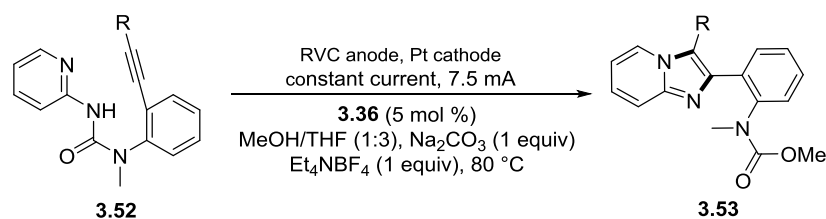


Scheme 3.14

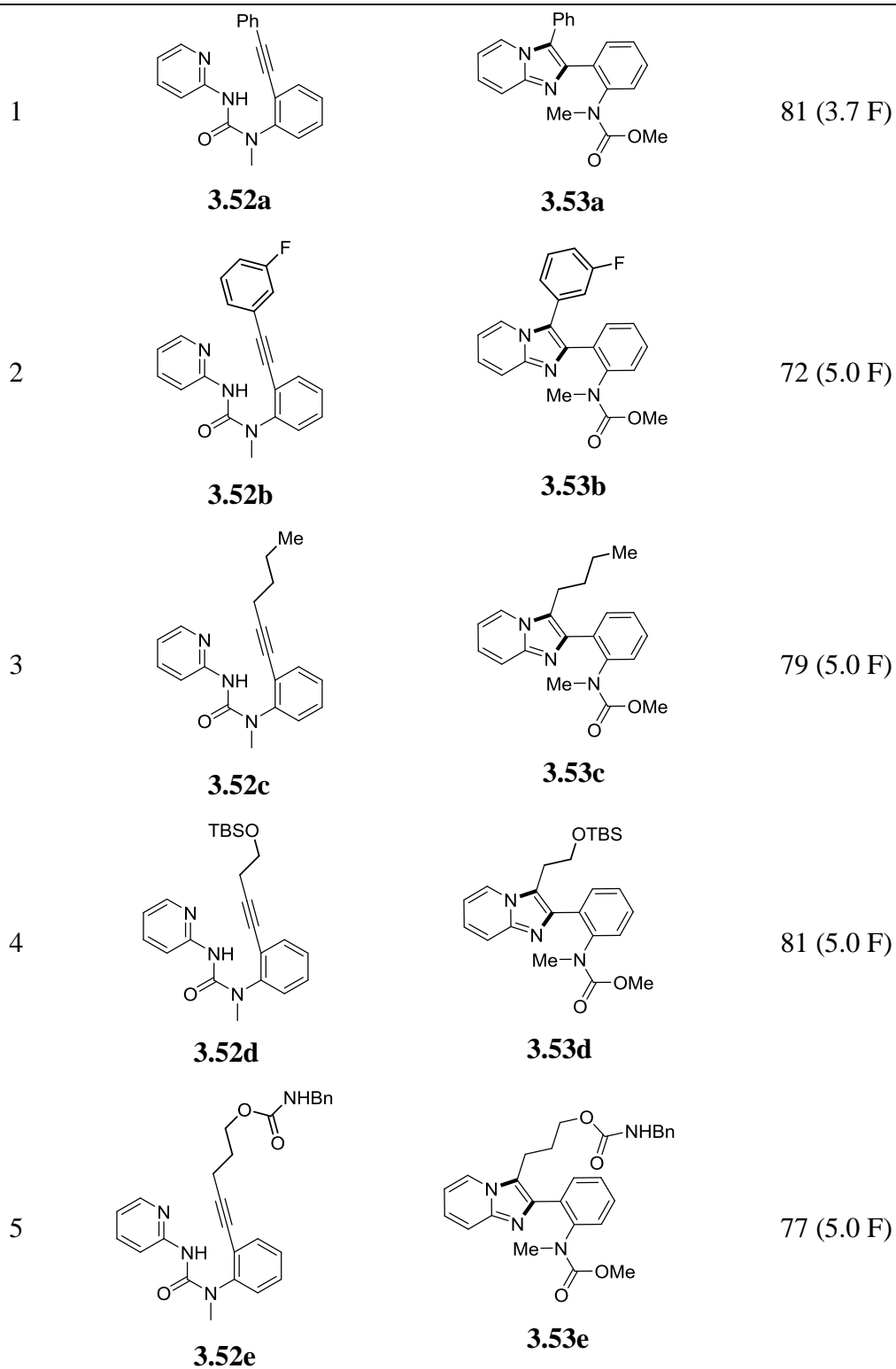
3.3.4 The scope of urea-type substrates

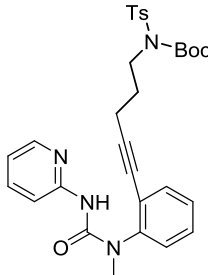
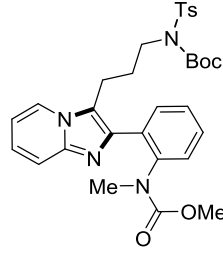
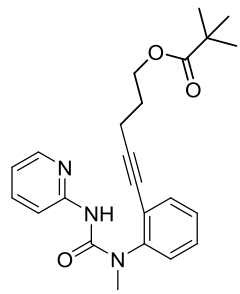
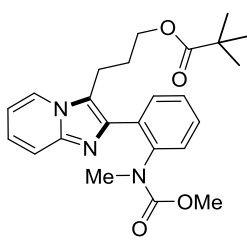
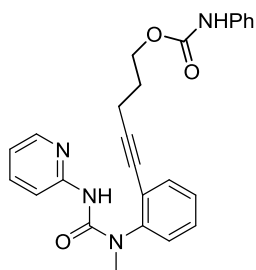
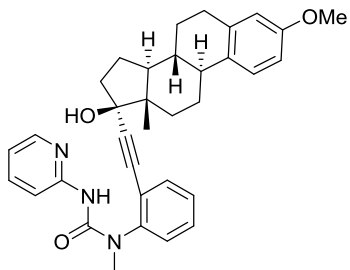
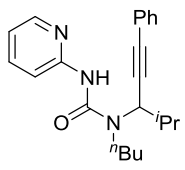
Intermolecular alkyne annulation reactions usually suffer from regioselectivity issues when similar substituted alkynes were employed. However, our method that employs a temporary linker to render the reaction intramolecular is regiospecific. To demonstrate the advantages of such a strategy, urea-type substrates were synthesized. From these substrates, 2,3-bisubstituted imidazo[1,2-*a*]pyridine could be accessed regiospecifically.

Table 3.10 The scope of urea-type substrates



Entry	Substrates	Product	Yield (%) ^a
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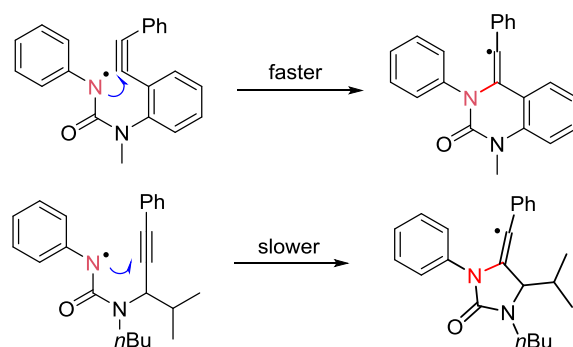


6	 <p>3.52f</p>	 <p>3.53f</p>	48 (8.0 F)
7	 <p>3.52g</p>	 <p>3.53g</p>	76 (7.0 F)
8	 <p>3.52h</p>	N.D. ^b	-
9	 <p>3.52i</p>	N.D. ^c	-
10	 <p>3.52j</p>	N.D. ^b	-

a: Isolated yield of **3.53**. b: Substrate decomposition. c: Complex product.

Interestingly, unlike the cabamate substrates, the urea substrates bearing alkyl groups at the alkyne termini also cyclized smoothly to give the desired products albeit with

reduced current efficiency. Previous studies from the Xu group demonstrated that the intermediate vinyl radical annulated to a six-membered ring cyclizes faster than that fused to a five-membered ring (Scheme 3.15).^{18c}



Scheme 3.15

Note that **3.53g** containing an ester group could be obtained without undergoing alcoholysis. However, substrate **3.52h** bearing a redox active N–H bond underwent decomposition during the electrolysis without affording any desired product. Ethinyl estradiol-derived substrate **3.52i** also failed. Finally, propargylamine derived substrate **3.52j** was not suitable for the cyclization reaction probably because of the difficulty associated with the radical cyclization onto the pyridine ring.

3.4 Reaction in aqueous solution

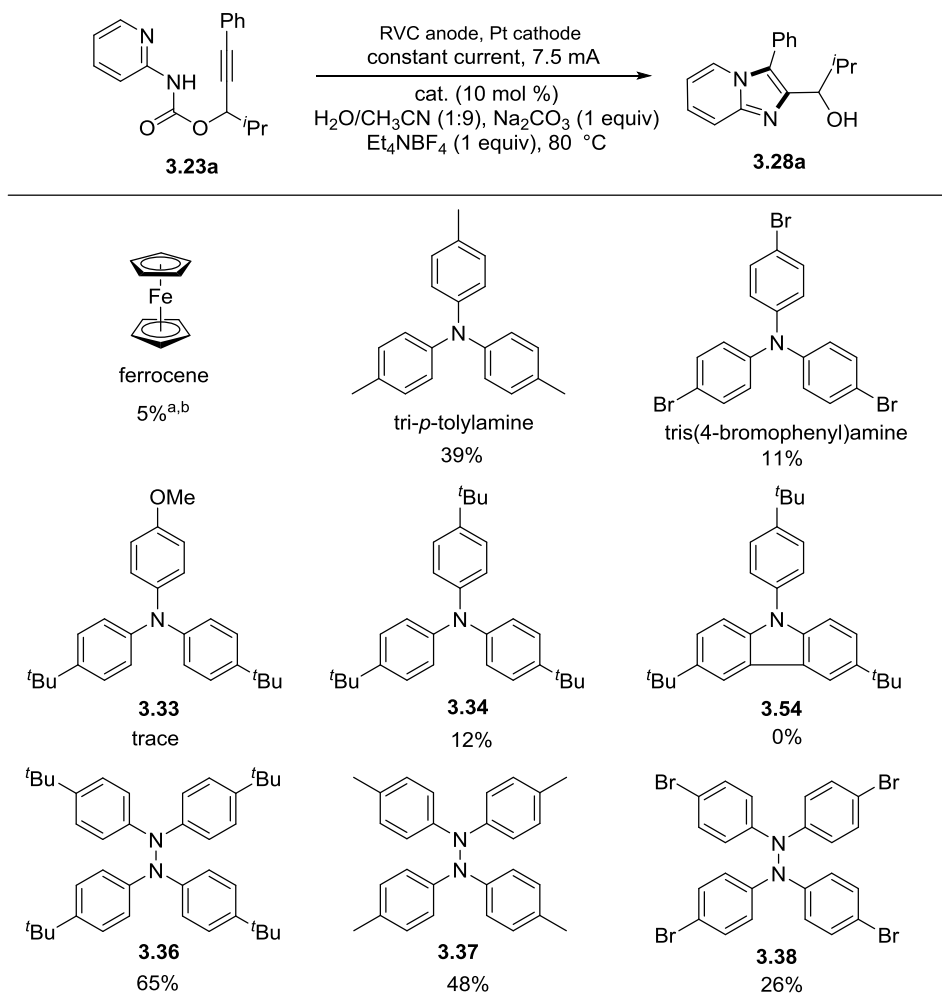
We next investigated the cyclization reaction in aqueous solution to obtain a free alcohol as the product.

3.4.1 Optimization of reaction conditions

3.4.1.1 Screening of redox catalyst

Carbamate **3.23a** were chosen as the model substrate and electrolyzed in a mixture of H₂O and MeCN (1:9).

Table 3.11 Screening of catalysts



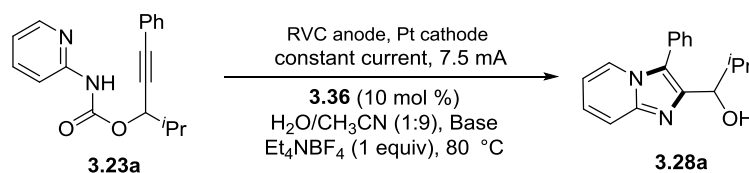
a: Determined by ¹H NMR analysis of the crude reaction mixture. b: All the reaction time were 3.2 h (3.0 F).

Several redox catalysts were tested including ferrocene, triarylaminines, carbazoles, and tetraarylhydrazines. These experiments led to the identification of 1,1,2,2-tetrakis(4-(*tert*-butyl)phenyl)hydrazine **3.36** as the optimum redox catalyst.

3.4.1.2 Screening of bases

Inorganic bases such as NaOH, K₃PO₄, KH₂PO₄, Na₂CO₃, KHCO₃, Na₂HPO₄ and NaHCO₃ were investigated as additives for the electrolysis of **3.23a** using **3.36** as the redox catalyst. These efforts led to the identification of 1 equiv of NaHCO₃ and KHCO₃ as the optimal basic additives. Increasing the amount of NaHCO₃ to 2 equiv further boosted the yield to 91%. Further increase to 2.5 equiv led to similar results. Hence, 2 equiv of NaHCO₃ was used for further reaction optimization.

Table 3.12 Screening of types and equivalents of bases



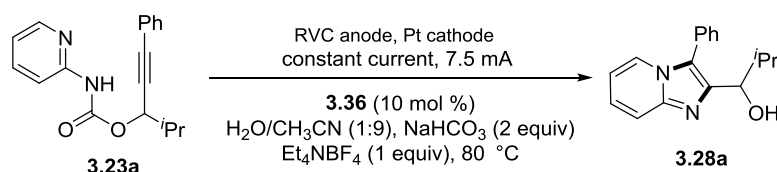
Entry	Base (equiv)	Yield ^a (%)
1	NaOH (0.3)	11%
2	K ₃ PO ₄ (1.0)	26%
3	KH ₂ PO ₄ (1.0)	10%
4	Na ₂ CO ₃ (1.0)	64%
5	KHCO ₃ (1.0)	84%
6	Na ₂ HPO ₄ (1.0)	81%
7	NaHCO ₃ (1.0)	86%
8	NaHCO ₃ (0.5)	84%
9	NaHCO ₃ (2.0)	91%
10	NaHCO ₃ (2.5)	90%

a: Determined by ¹H NMR analysis of the crude reaction mixture.

4.1.3 Screen of solvent and current

The initial water content in the mixture solvent seemed to be optimum as either increase (entry 1) or decrease (entry 2) its concentration resulted in lower product formation. Reduce the current to 5 mA or increase it to 10 or 15 mA also led to slight reduction in reaction efficiency (entries 3–5).

Table 3.13 Screen of solvent and current



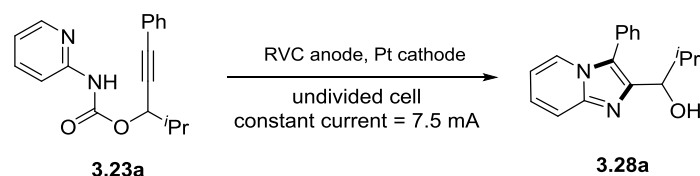
Entry	Current (mA)	Solvent (mL)	Electricity (F mol ⁻¹)	Time (h)	Yield (%)
1	7.5	H ₂ O/CH ₃ CN (1/4)	3.5	3.75	80
2	7.5	H ₂ O/CH ₃ CN (1/19)	3.5	3.75	84
3	5.0	H ₂ O/CH ₃ CN (1/9)	3.5	5.60	84
4	10	H ₂ O/CH ₃ CN (1/9)	3.5	2.80	86
5	15	H ₂ O/CH ₃ CN (1/9)	3.5	1.90	82

a: Determined by ¹H NMR analysis of the crude reaction mixture.

3.4.1.4 Control experiment

The use a RVC anode and a Pt cathode is important for reaction efficiency as the change to a Pt plate cathode or RVC cathode all resulted in dramatic reduction in product formation. Conducting the electrolysis under air led to the formation of **3.28a** in 75% yield suggesting that stringent removal of oxygen from the reaction system is not necessary. Reducing to the reaction temperature to RT or 60 °C resulted in significant yield loss. Reducing the loadings of the catalyst to 0.05 equiv or the electrolytes to 0.5 or 0.2 equiv afforded lower but acceptable yields (71–85%). Finally, the redox catalyst and the electric current were critical for success (entries 11 and 12).

Table 3.14 Control experiment



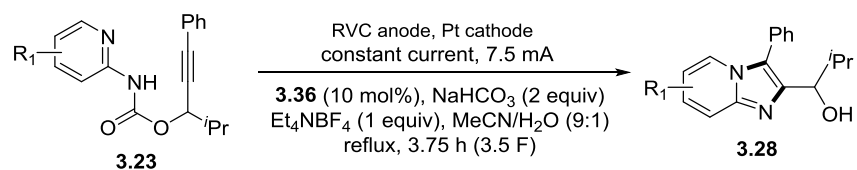
Entry	Conditions	Yield ^a (%)
1	H ₂ O/MeCN (1:9), 3.36 (10 mol%), NaHCO ₃ (2 equiv), Et ₄ NBF ₄ (1 equiv), 80 °C	91 (89 ^b)
2	entry 1 but Pt plate (1 cm x 1 cm) as anode	15
3	entry 1 but RVC (1 cm x 1 cm x 1.2 cm) as cathode	46
4	entry 1 but reaction under air	75
5	entry 1 but reaction under room temperature	30
6	entry 1 but reaction under 60 °C	46
7	entry 1 but use 0.05 equiv catalyst	71
8	entry 1 but use 0.15 equiv catalyst	89
9	entry 1 but use 0.5 equiv electrolyte	85
10	entry 1 but use 0.2 equiv electrolyte	71
11	entry 1 but no catalyst	9
12	entry 1 but no current	0

a: Determined by ¹H NMR analysis of the crude reaction mixture. b: isolated yield.

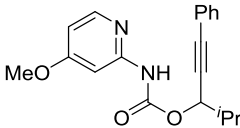
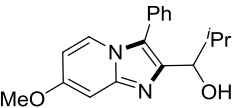
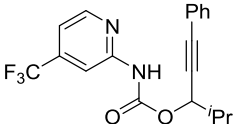
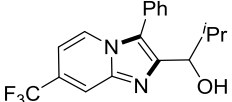
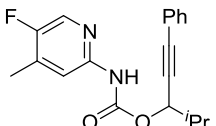
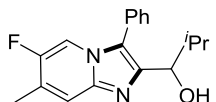
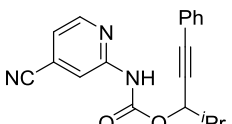
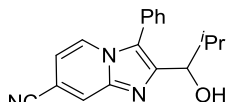
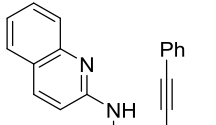
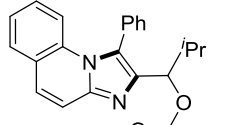
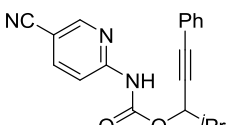
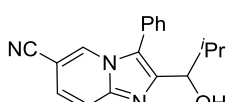
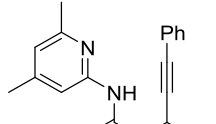
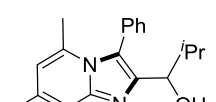
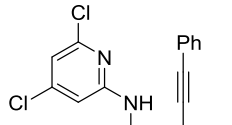
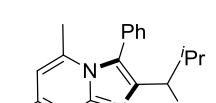
3.4.2 The scope of substrates

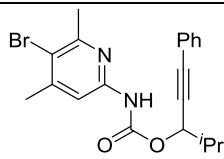
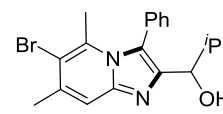
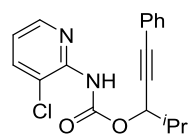
After the optimum electrolytic conditions were established, we next explored the substrate scope. Similar to the reaction in methanol, substrates bearing diverse substituents on various positions of the pyridyl ring were tolerated except position 3. As an example, no reaction occurred when the substrate **3.23v** bearing a chloro group at position 3 was subjected the electrochemical oxidation. Interestingly, **3.28p** bearing a cyano group could be obtained in 85% yield without formation of **3.39** (see section 3.3). Note that densely functionalized products could be obtained in good yields (**3.28k**, **3.28q**, **3.28s–3.28u**, 56%–89%).

Table 3.15



Entry	Substrates	Product	Yield (%) ^a
1	<p style="text-align: center;">3.23a</p>	<p style="text-align: center;">3.28a</p>	89
2	<p style="text-align: center;">3.23b</p>	<p style="text-align: center;">3.28b</p>	81
3	<p style="text-align: center;">3.23c</p>	<p style="text-align: center;">3.28c</p>	88
4	<p style="text-align: center;">3.23d</p>	<p style="text-align: center;">3.28d</p>	83
5	<p style="text-align: center;">3.23e</p>	<p style="text-align: center;">3.28e</p>	83
6	<p style="text-align: center;">3.23g</p>	<p style="text-align: center;">3.28g</p>	86
7	<p style="text-align: center;">3.23h</p>	<p style="text-align: center;">3.28h</p>	74

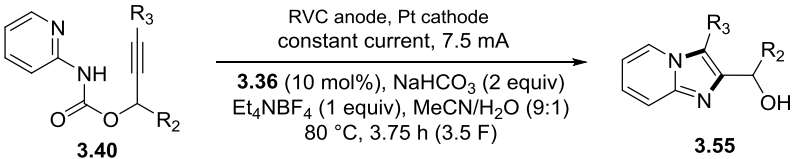
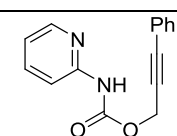
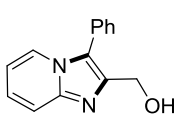
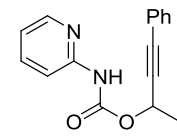
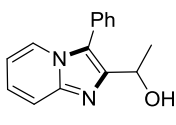
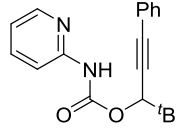
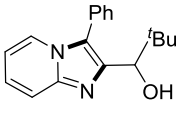
8	 <p>3.23i</p>	 <p>3.28i</p>	73
9	 <p>3.23j</p>	 <p>3.28j</p>	78
10	 <p>3.23k</p>	 <p>3.28k</p>	82
11	 <p>3.23p</p>	 <p>3.28p</p>	85
12	 <p>3.23q</p>	 <p>3.28q</p>	89
13	 <p>3.23r</p>	 <p>3.28r</p>	79
14	 <p>3.23s</p>	 <p>3.28s</p>	72
15	 <p>3.23t</p>	 <p>3.28t</p>	60

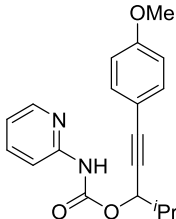
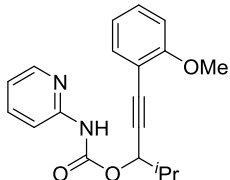
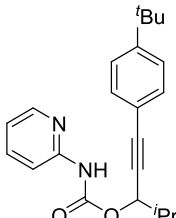
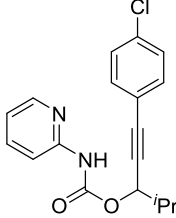
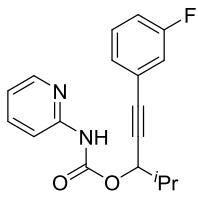
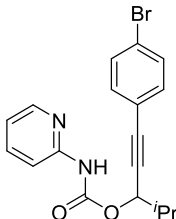
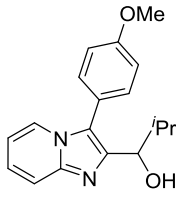
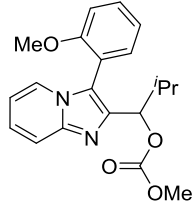
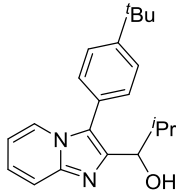
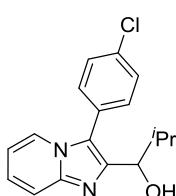
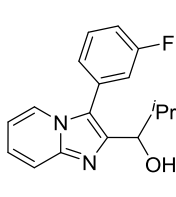
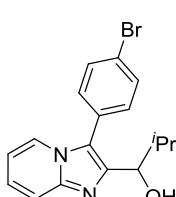
16	 3.23u	 3.28u	56
17	 3.23v	N.D. ^b	-

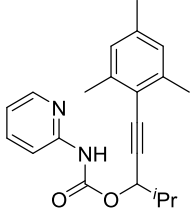
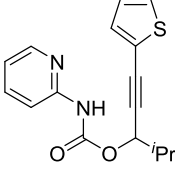
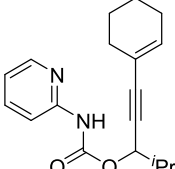
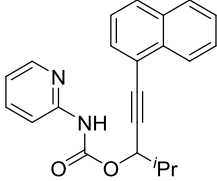
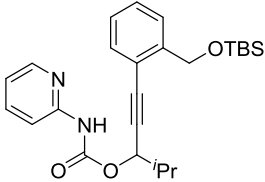
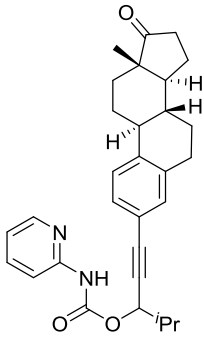
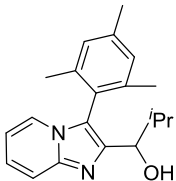
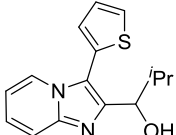
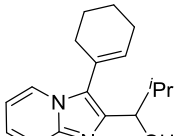
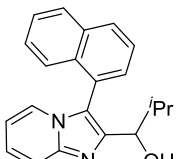
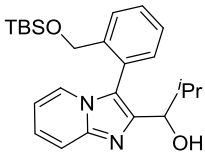
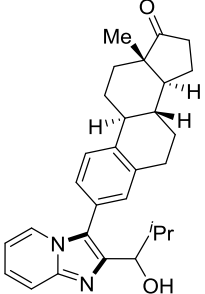
a: Isolated yield of **3.28**. b No reaction.

The scope of the alkyne was also similar to that of the reactions in methanol (Table **3.16**). The trimethylsilyl-terminated alkyne substrate **3.40t** decomposed during the electrolysis and did not afford any of the desired product.

Table **3.16**

			
Entry	Substrates	Product	Yield (%) ^a
1	 3.40a	 3.55a	56
2	 3.40b	 3.55b	73
3	 3.40c	 3.55c	94

4	 <p>3.40e</p>	79
5	 <p>3.40f</p>	84
6	 <p>3.40g</p>	81
7	 <p>3.40h</p>	75
8	 <p>3.40i</p>	53
9	 <p>3.40j</p>	79
	 <p>3.55e</p>	
	 <p>3.55f</p>	
	 <p>3.55g</p>	
	 <p>3.55h</p>	
	 <p>3.55i</p>	
	 <p>3.55j</p>	

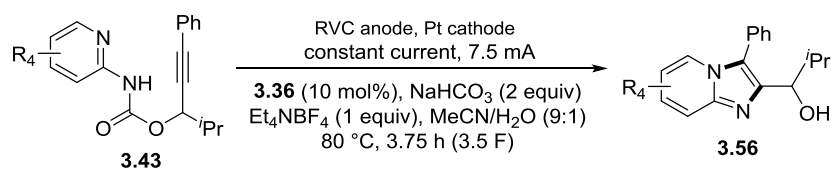
10	 <p>3.40k</p>	79
11	 <p>3.40m</p>	89
12	 <p>3.40n</p>	77
15	 <p>3.40o</p>	90
16	 <p>3.40p</p>	74
17	 <p>3.49</p>	71
	 <p>3.55k</p>	
	 <p>3.55m</p>	
	 <p>3.55n</p>	
	 <p>3.55o</p>	
	 <p>3.55p</p>	
	 <p>3.55q</p>	

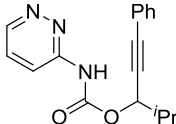
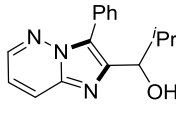
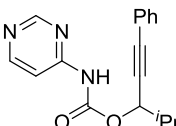
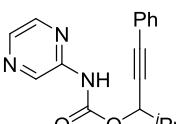
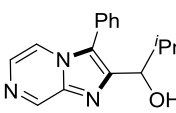
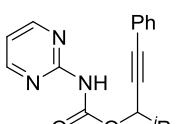
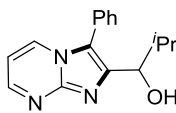


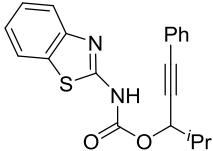
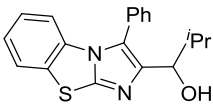
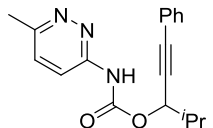
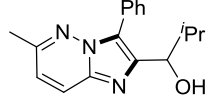
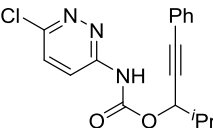
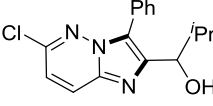
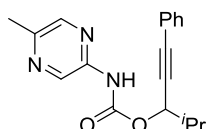
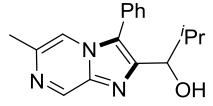
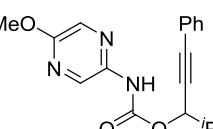
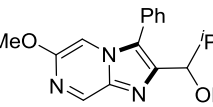
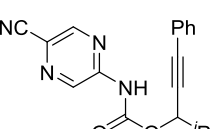
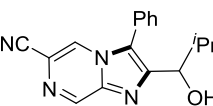
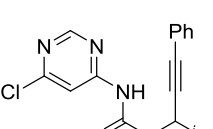
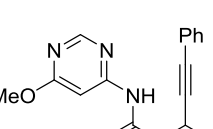
a: Isolated yield of **3.55**. b: Substrated decomposition.

Once again, various diazine-derived substrates were employed for the formation of imidazo[1,2]diazine compounds. Unlike the reaction in methanol that tolerated various diazine combinations, the reaction in aqueous solution was not compatible with 4-aminopyrimidine-derived substrates. For example, no reaction occurred for substrates **3.43b**, **3.43o** and **3.43p**.

Table 3.17

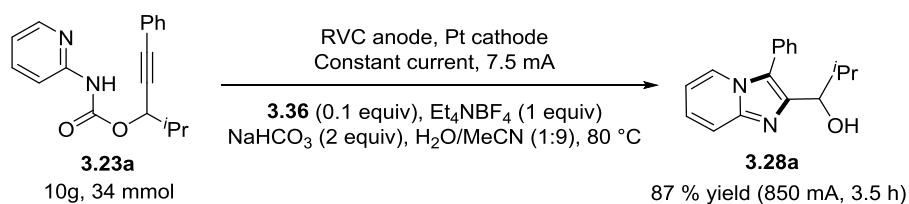


Entry	Substrates	Product	Yield (%) ^a
1	 3.43a	 3.56a	80
2	 3.43b	N.D. ^b	-
3	 3.43c	 3.56c	76
4	 3.43d	 3.56d	42 ^c

5	 <p>3.43f</p>	 <p>3.56f</p>	52
6	 <p>3.43j</p>	 <p>3.56j</p>	80
7	 <p>3.43k</p>	 <p>3.56k</p>	51
8	 <p>3.43l</p>	 <p>3.56l</p>	82
9	 <p>3.43m</p>	 <p>3.56m</p>	65
10	 <p>3.43n</p>	 <p>3.56n</p>	40
11	 <p>3.43o</p>	N.D. ^b	-
12	 <p>3.43p</p>	N.D. ^b	-

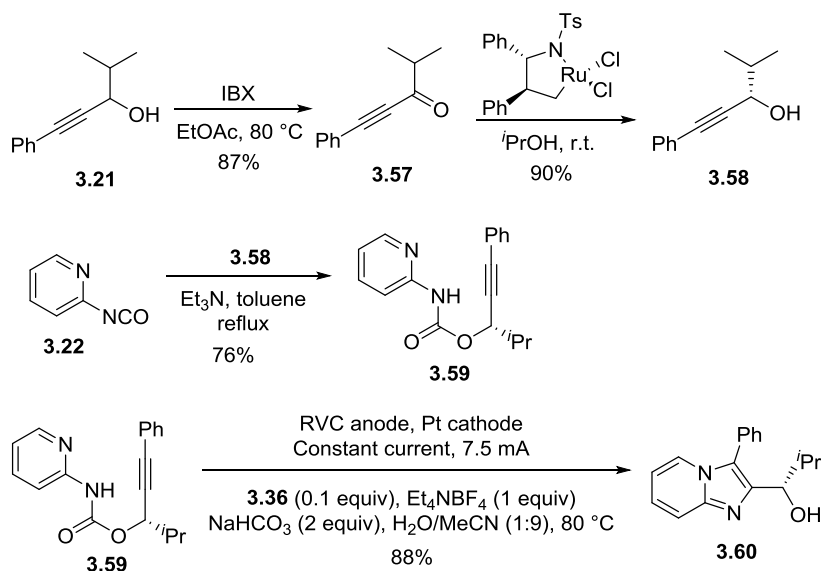
a: Isolated yield of **3.56**. b: No reaction. c: 0.5 equiv of NaHCO₃ was used.

For further explore the practical utility of this electrochemical method, we carried out deca-gram electrolysis of **3.23a**. To finish the large-scale reaction within few hours, a higher current of 850 mA was used. A larger anode was used to keep the current density of the large scale reaction the same as that of the small scale reaction. Under these conditions, the electrolysis completed in 3.5 h (3.2 F) to afford the desired **3.28a** in 87% yield.



Scheme 3.16

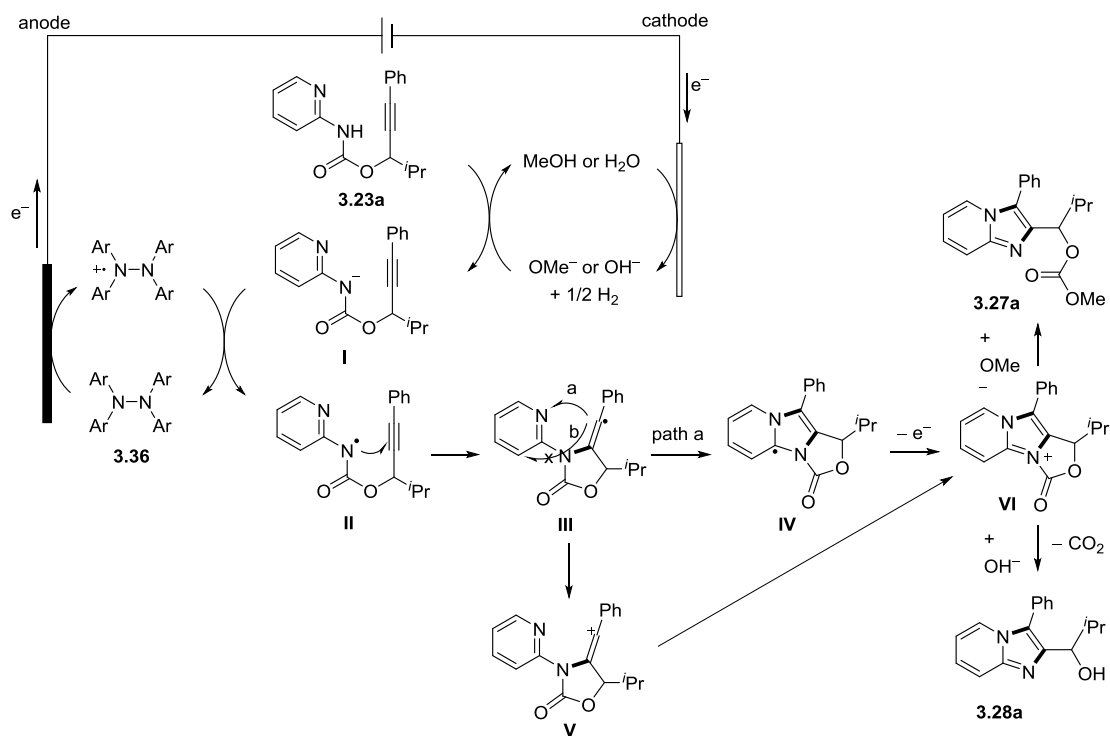
One of the advantages of the electrochemical method is that a chiral center was introduced to the final product. Enantio-enriched cabamate substrate **3.59** was prepared for the asymmetric synthesis of **3.60**. The chiral center of **3.59** was established easily from Noyori hydrogenation. Under standard electrolysis conditions, the desired **3.60** was obtained in 88% yield without erosion of enantiomeric ratio (The er of substrate is 99.6%, the er of product is 97.4%, see experiment section).



Scheme 3.17

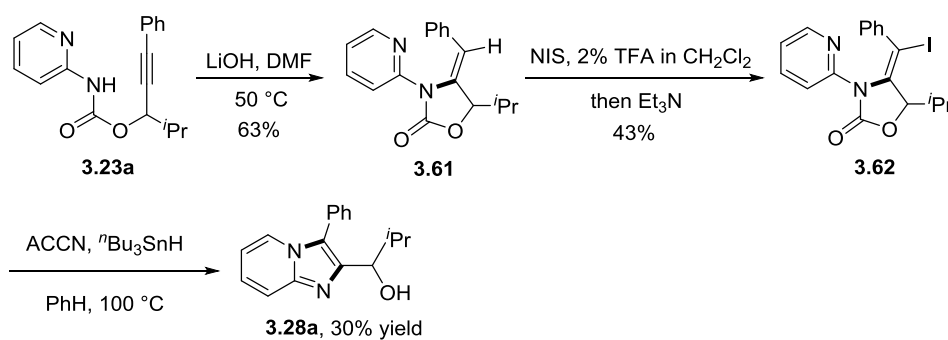
4.2 Discussion on the reaction mechanism

A possible mechanism of this electrolytic reaction was proposed using **3.23a** as a substrate (Scheme 3.18). Upon passing of current through the cell, the redox catalyst loses one electron to the anode to afford its radical cation. In the meanwhile, the protic solvent such as methanol or water gets reduced to produce molecular hydrogen and a base (MeO⁻ or OH⁻). The electrochemically generated base deprotonates the substrate **3.23a** to afford the nitrogen anion **I**. Electron-transfer then occurs between the radical cation **3.36** and the anion **I** to afford nitrogen radical **II** and regenerate the redox catalyst. The radical **II** undergoes 5-exo-dig cyclization to afford vinyl radical **III**. This carbon radical then reacts regioselectively with the pyridyl nitrogen atom leading to the radical **IV** (path a). One electron oxidation of **VI** followed by methanolysis or hydrolysis affords the final product **3.27a** or **3.28a**. An alternative pathway for the transformation of **III** to **VI** is through oxidation to give vinyl cation **V** followed by nucleophilic trapping by the pyridyl nitrogen (path b).



Scheme 3.18

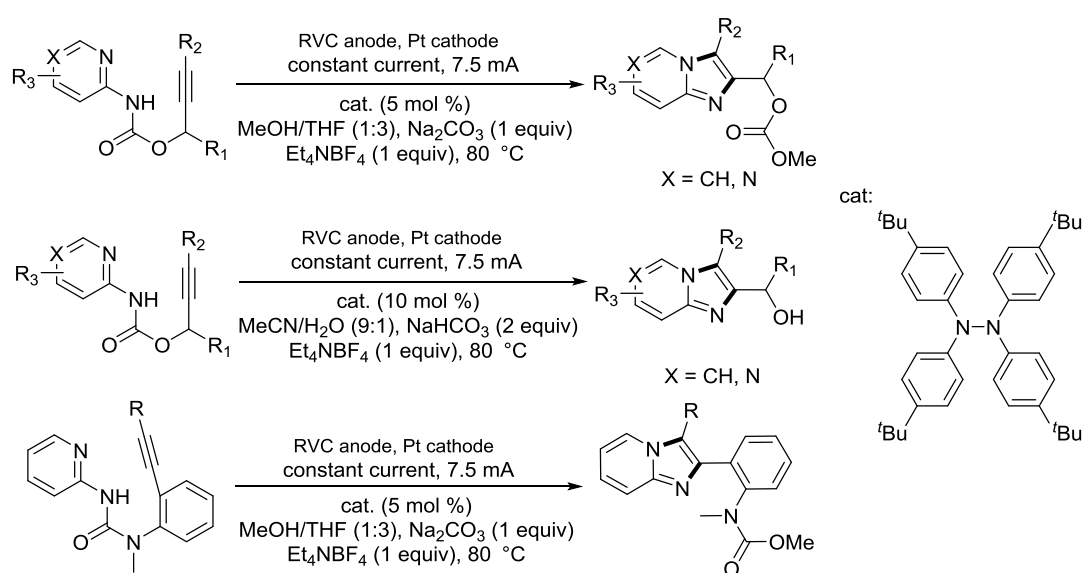
To confirm that the electrosynthetic process involves an azaphilic vinyl radical addition, vinyl iodide compound **3.62** was synthesized from **3.23a** through base-promoted hydroamidation and C–H iodination (Scheme 3.19). Vinyl iodide **3.62**²² was then treated with 1,1'-azobis(cyanocyclohexane) (ACCN) and *n*Bu₃SnH to induce radical cyclization. Under these conditions, cyclized compound **3.28a** was obtained in 30% yield. These results suggested that formation of **3.28a** through vinyl radical cyclization onto the pyridyl nitrogen is possible. Based on these studies, we believe that the formation of **VI** proceeded most likely through radical cyclization (path a).



Scheme 3.19

3.5 Conclusion

An organocatalyzed electrochemical synthesis of several important imidazo-fused N-heteroaromatic structures has been developed through intramolecular oxidative alkyne annulation. The substrates were easily available in a modular fashion. The electrolysis reaction is broad in scope, tolerates many common functional groups, proceeds under mild conditions without the need for any transition-metal catalyst or reagent or chemical oxidant. The alkyne annulation reaction is efficient and regioselective because of the use of a traceless tether.



Scheme 3.28

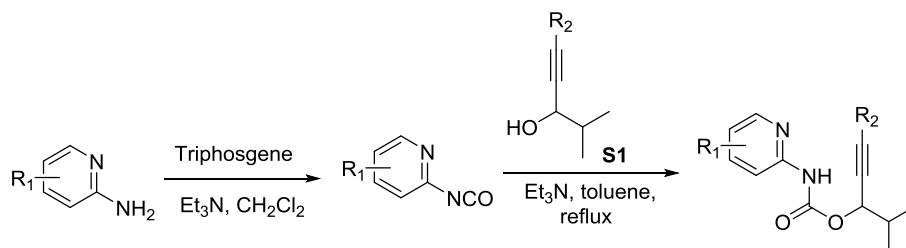
3.6 Experimental Section

General Information

Anhydrous dichloromethane and tetrahydrofuran were obtained by distillation under argon from calcium hydride and sodium/benzophenone, respectively. Flash column chromatography was performed with silica gel (230–400 mesh). NMR spectra were recorded on Bruker AV-400 and Bruker AV-500 instruments. Data were reported as chemical shifts in ppm relative to TMS (0.00 ppm) for ^1H and CDCl_3 (77.2 ppm) for ^{13}C . The abbreviations used for explaining the multiplicities were as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High resolution mass spectra (ESI HRMS) were recorded on a Micromass QTOF2 Quadruple/Time-of-Flight Tandem mass spectrometer by the instrumentation center of Department of Chemistry, Xiamen University. Cyclic voltammograms were obtained on a CHI 760E potentiostat. Infrared spectra (IR) were recorded on a Nicolet AVATER FTIR330 spectrometer. The electrodes used for the preparative electrolysis were the same as those previously reported.

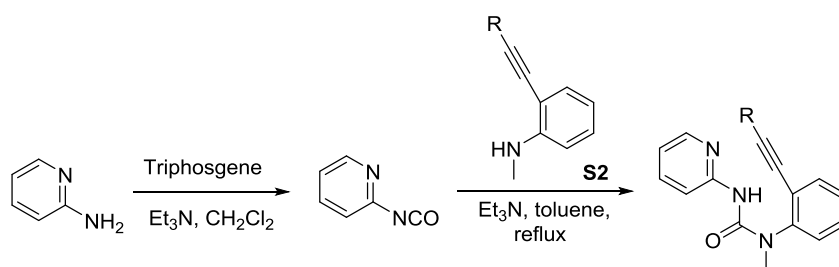
Silica gel (300-400 mesh) was used for flash column chromatography, eluting (unless otherwise stated) with ethyl-acetate/ petroleum ether (PE) (60-90 °C) mixture. THF was distilled over sodium benzophenoneketyl under N_2 . Dichloromethane was distilled over calcium hydride under N_2 .

General procedure A for the synthesis of carbamate substrates:



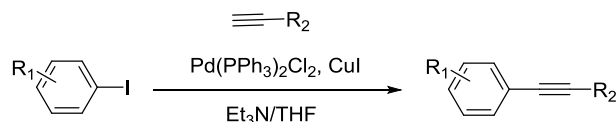
To a solution of triphosgene (2.0 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (8 mL) was added dropwise the aminoarene (4.0 mmol, 2.0 equiv) at 0 °C followed by Et_3N (4.0 mmol, 2.0 equiv). The mixture was stirred at r.t. for 6 h. The solvent was then removed under reduced pressure. The residue was dissolved in toluene (6.0 mL). The papargyl alcohol (2.0 mmol, 1.0 equiv) and Et_3N (4.0 mmol, 2.0 equiv) were added. The resulting mixture was heated to reflux and maintained at this temperature for 36 h. The solvent was evaporated under reduced pressure and the residue was chromatographed through silica gel eluting with ethyl acetate/hexanes to give the product.

General procedure B for the synthesis of urea substrates:



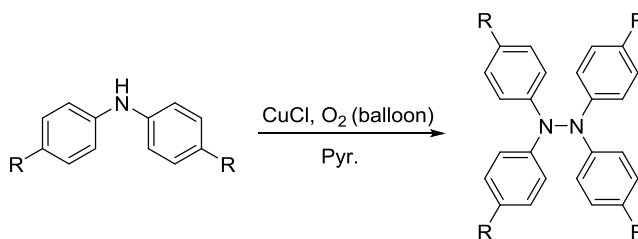
To a solution of triphosgene (2.0 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (8 mL) was added dropwise 2-aminopyridine (4.0 mmol, 2.0 equiv) at 0 °C followed by Et_3N (4.0 mmol, 2.0 equiv). The mixture was stirred at r.t. for 6 h. The solvent was then removed under reduced pressure. The residue was dissolved in toluene (6.0 mL). The alkyne (2.0 mmol, 1.0 equiv) and Et_3N (4.0 mmol, 2.0 equiv) were added. The resulting mixture was heated to reflux and maintained at this temperature for 36 h. The solvent was evaporated under reduced pressure and the residue was chromatographed through silica gel eluting with ethyl acetate/hexanes to give the desired product.

General procedure C for Sonogashira cross-coupling reaction:



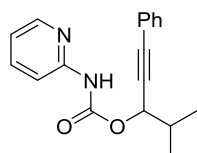
The Compound **S** (5.0 mmol, 1.0 equiv), CuI (5 mol%), and PdCl₂(PPh₃)₂ (2 mol%) were dissolved in Et₃N/THF (1:1, 25 mL) under a nitrogen atmosphere. The terminal alkyne (7.5 mmol, 1.5 equiv) was added. The resulting mixture was stirred at r.t. until the complete consumption of the starting material (monitored by TLC) and filtered through a pad of celite. The filtrate was concentrated under reduced pressure and the residue was chromatographed through silica gel eluting with ethyl acetate/hexanes to give the product.

General procedure D for the synthesis of tetraarylhydrazines



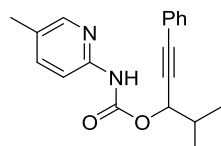
CuCl (1.98 g, 0.02 mol) and pyridine (50 mL) were added in a glass flask immersed in a water bath under argon atmosphere with vigorous stirring, and then the atmosphere was replaced with oxygen. After the oxygen ceased, diarylamine (0.01 mol) in pyridine (10 mL) was added slowly with further absorption of oxygen. Pyridine was distilled off under reduce pressure after the reaction, and the residue was extracted with ether to give the crude product. The crude product was chromatographed on a silicon gel column with CH₂Cl₂-petroleum ether (1:3) to give tetraarylhydrazines.

4-Methyl-1-phenylpent-1-yn-3-yl pyridin-2-ylcarbamate (**3.23a**)



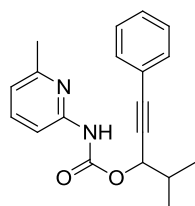
The title compound was prepared starting from 2-aminopyridine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 76%; White solid; ^1H NMR (500 MHz, CDCl_3) δ 9.37 (s, 1H), 8.47–8.32 (m, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.69 (ddd, J = 8.8, 7.3, 1.9 Hz, 1H), 7.51–7.42 (m, 2H), 7.37–7.27 (m, 3H), 7.04–6.90 (m, 1H), 5.54 (d, J = 5.7 Hz, 1H), 2.25–2.11 (m, 1H), 1.13 (d, J = 6.7 Hz, 3H), 1.10 (d, J = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 153.1, 152.6, 147.9, 138.8, 132.0, 128.7, 128.4, 122.6, 118.7, 112.9, 86.5, 85.4, 70.8, 33.0, 18.6, 17.8; IR (neat, cm^{-1}): 3184, 2966, 1735, 1589, 1440, 1219, 1060; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 317.1260, obsd 317.1262; chiral HPLC conditions: Chiralpak AD-H (*n*-hexane/ ethanol, 70:30), flow rate = 1.0 mL/min, R_t = 6.5 and 8.5 min, respectively. The enantiomeric excess was determined to be 1%.

4-Methyl-1-phenylpent-1-yn-3-yl (5-methylpyridin-2-yl)carbamate (3.23b)



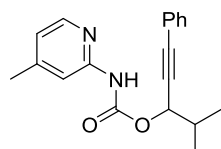
The title compound was prepared starting from 5-methylpyridin-2-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 62%; White solid; ^1H NMR (500 MHz, CDCl_3) δ 9.47 (s, 1H), 8.24 (s, 1H), 7.95 (d, J = 8.5 Hz, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.49–7.41 (m, 2H), 7.35–7.25 (m, 3H), 5.55 (d, J = 5.5 Hz, 1H), 2.24 (s, 3H), 2.23–2.15 (m, 1H), 1.13 (d, J = 6.7 Hz, 3H), 1.11 (d, J = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 152.9, 150.0, 147.5, 139.5, 132.1, 128.7, 128.4, 128.1, 122.6, 112.4, 86.4, 85.5, 70.7, 33.1, 18.5, 17.8 (2C); IR (neat, cm^{-1}): 3406, 2960, 1667, 1596, 1492, 1260, 1026; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 331.1417, obsd 331.1418.

4-Methyl-1-phenylpent-1-yn-3-yl (6-methylpyridin-2-yl)carbamate (3.23c)



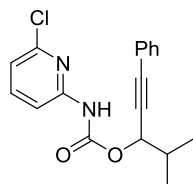
The title compound was prepared starting from 6-methylpyridin-2-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 76%; Yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 8.67 (s, 1H), 7.82 (d, $J = 8.2$ Hz, 1H), 7.60–7.53 (m, 1H), 7.48–7.40 (m, 2H), 7.34–7.24 (m, 3H), 6.83 (d, $J = 7.4$ Hz, 1H), 5.49 (d, $J = 5.6$ Hz, 1H), 2.48 (s, 3H), 2.15–2.05 (m, 1H), 1.04 (d, $J = 6.3$ Hz, 3H), 1.03 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 157.1, 152.7, 151.0, 138.8, 132.0, 128.7, 128.4, 122.6, 118.6, 109.5, 86.3, 85.4, 70.7, 33.0, 24.1, 18.4, 17.8; IR (neat, cm^{-1}): 3196, 2965, 1737, 1583, 1461, 1211, 1080; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 331.1417, obsd 331.1421.

4-Methyl-1-phenylpent-1-yn-3-yl (4-methylpyridin-2-yl)carbamate (3.23d)



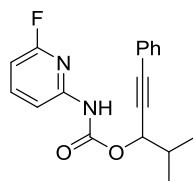
The title compound was prepared starting from 4-methylpyridin-2-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 81%; White solid; ^1H NMR (500 MHz, CDCl_3) δ 10.35 (s, 1H), 8.35 (d, $J = 5.1$ Hz, 1H), 7.93 (s, 1H), 7.50–7.43 (m, 2H), 7.34–7.28 (m, 3H), 6.78 (dd, $J = 5.1, 1.4$ Hz, 1H), 5.55 (d, $J = 5.6$ Hz, 1H), 2.35 (s, 3H), 2.25–2.15 (m, 1H), 1.13 (d, $J = 6.7$ Hz, 3H), 1.10 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 153.1, 152.5, 150.1, 147.5, 132.0, 128.7, 128.4, 122.6, 120.0, 113.3, 86.4, 85.5, 70.7, 33.0, 21.6, 18.6, 17.8; IR (neat, cm^{-1}): 3180, 2965, 1733, 1582, 1427, 1218, 1066, 756; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}^+$): 309.1598, obsd 309.1599.

4-Methyl-1-phenylpent-1-yn-3-yl (6-chloropyridin-2-yl)carbamate (3.23e)



The title compound was prepared starting from 6-chloropyridin-2-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 80%; Yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.83 (d, $J = 8.0$ Hz, 1H), 7.71 (s, 1H), 7.52 (t, $J = 8.0$ Hz, 1H), 7.38–7.30 (m, 2H), 7.25–7.14 (m, 3H), 6.92–6.85 (m, 1H), 5.39 (d, $J = 5.6$ Hz, 1H), 2.11–1.99 (m, 1H), 1.00 (d, $J = 6.7$ Hz, 3H), 0.98 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 152.2, 151.5, 149.1, 140.9, 132.0, 128.7, 128.3, 122.3, 118.9, 110.6, 86.5, 85.0, 71.1, 32.9, 18.3, 17.7; IR (neat, cm^{-1}): 3426, 2966, 1739, 1589, 1574, 1440, 1395, 1210, 1064; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{17}\text{ClN}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 351.0871, obsd 351.0873.

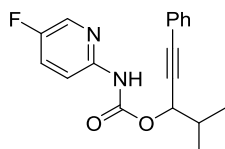
4-Methyl-1-phenylpent-1-yn-3-yl (6-fluoropyridin-2-yl)carbamate (3.23f)



The title compound was prepared starting from 5-fluoropyridin-2-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 70%; Light yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.87 (m, 1H), 7.81–7.72 (m, 1H), 7.60 (s, 1H), 7.49–7.42 (m, 2H), 7.36–7.28 (m, 3H), 6.60 (dd, $J = 7.9, 2.4$ Hz, 1H), 5.49 (d, $J = 5.6$ Hz, 1H), 2.22–2.09 (m, 1H), 1.11 (d, $J = 6.7$ Hz, 3H), 1.09 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 162.2 (d, $J_{\text{C-F}} = 240.6$ Hz), 152.3, 150.0 (d, $J_{\text{C-F}} = 14.6$ Hz), 143.3 (d, $J_{\text{C-F}} = 7.8$ Hz), 132.1, 128.8, 128.4, 122.4, 108.9 (d, $J_{\text{C-F}} = 4.2$ Hz), 103.5 (d, $J_{\text{C-F}} = 34.9$ Hz), 86.6, 85.0, 71.2, 33.0, 18.4, 17.8; ^{19}F NMR (471 MHz, CDCl_3) δ -69.0 (d, $J = 8.1$ Hz); IR (neat, cm^{-1}): 3186, 2916, 1726, 1641, 1585,

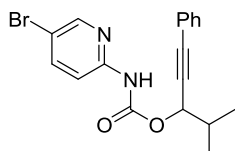
1414, 1132, 1077, 755; HRMS (ESI, m/z) calcd for $C_{18}H_{17}FN_2O_2Na$ ($M+Na^+$): 335.1166, obsd 335.1167.

4-Methyl-1-phenylpent-1-yn-3-yl (5-fluoropyridin-2-yl)carbamate (3.23g)



The title compound was prepared starting from 5-fluoropyridin-2-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 74%; White solid; 1H NMR (500 MHz, $CDCl_3$) δ 9.62 (d, $J = 10.0$ Hz, 1H), 8.26 (d, $J = 2.9$ Hz, 1H), 8.01 (dd, $J = 10.0, 2.9$ Hz, 1H), 7.42–7.34 (m, 3H), 7.28–7.16 (m, 3H), 5.48 (d, $J = 5.6$ Hz, 1H), 2.18–2.07 (m, 1H), 1.06 (d, $J = 6.7$ Hz, 3H), 1.03 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.1 (d, $J_{C-F} = 249.0$ Hz), 152.9, 148.7 (d, $J_{C-F} = 2.2$ Hz), 135.4 (d, $J_{C-F} = 26.2$ Hz), 132.1, 128.8, 128.4, 125.9 (d, $J_{C-F} = 19.6$ Hz), 122.4, 113.6 (d, $J_{C-F} = 4.2$ Hz), 86.8, 85.1, 71.0, 33.1, 18.6, 17.7; ^{19}F NMR (471 MHz, $CDCl_3$) δ -134.3; IR (neat, cm^{-1}): 3435, 2960, 1737, 1602, 1548, 1478, 1396, 1219, 1053; HRMS (ESI, m/z) calcd for $C_{18}H_{17}FN_2O_2Na$ ($M+Na^+$): 335.1166, obsd 335.1168.

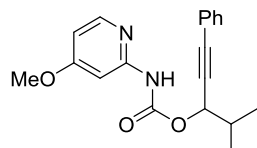
4-Methyl-1-phenylpent-1-yn-3-yl (5-bromopyridin-2-yl)carbamate (3.23h)



The title compound was prepared starting from 5-bromopyridin-2-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 78%; White solid; 1H NMR (500 MHz, $CDCl_3$) δ 9.88 (s, 1H), 8.53 (d, $J = 2.4$ Hz, 1H), 8.03 (d, $J = 9.0$ Hz, 1H), 7.80 (dd, $J = 9.0, 2.4$ Hz, 1H), 7.51–7.44 (m, 2H), 7.36–7.27 (m, 3H), 5.57 (d, $J = 5.6$ Hz, 1H), 2.27–2.14 (m, 1H), 1.15 (d, $J = 6.7$ Hz, 3H), 1.12 (d,

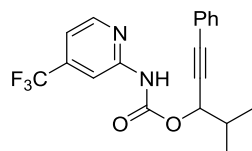
$J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 152.7, 151.1, 148.8, 141.2, 132.2, 128.8, 128.4, 122.5, 114.1, 113.7, 86.8, 85.0, 71.1, 33.1, 18.6, 17.8; IR (neat, cm^{-1}): 3185, 2921, 1738, 1727, 1552, 1377, 1196, 1045; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{17}\text{BrN}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 395.0366, obsd 395.0367.

4-Methyl-1-phenylpent-1-yn-3-yl (4-methoxypyridin-2-yl)carbamate (3.23i)



The title compound was prepared starting from 4-methoxypyridin-2-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 87%; Colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 10.6 (s, 1H), 8.30 (d, $J = 5.9$ Hz, 1H), 7.69 (s, 1H), 7.49–7.43 (m, 2H), 7.36–7.27 (m, 3H), 6.51 (dd, $J = 5.9, 2.4$ Hz, 1H), 5.55 (d, $J = 5.6$ Hz, 1H), 3.87 (s, 3H), 2.26–2.14 (m, 1H), 1.13 (d, $J = 6.7$ Hz, 3H), 1.10 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.8, 154.4, 153.2, 148.7, 132.0, 128.7, 128.4, 122.6, 107.0, 97.1, 86.5, 85.4, 70.8, 55.4, 33.0, 18.6, 17.8; IR (neat, cm^{-1}): 3436, 2921, 1731, 1585, 1541, 1223, 1048; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 347.1366, obsd 347.1368.

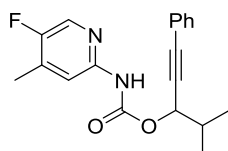
4-Methyl-1-phenylpent-1-yn-3-yl (4-(trifluoromethyl)pyridin-2-yl)carbamate (3.23j)



The title compound was prepared starting from 4-(trifluoromethyl)pyridin-2-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 74%; White solid; ^1H NMR (500 MHz, CDCl_3) δ 10.15 (s, 1H), 8.64 (d, $J = 5.3$ Hz, 1H), 8.40 (s, 1H), 7.50–7.44 (m, 2H), 7.38–7.28 (m, 3H), 7.17 (dd, $J = 5.3, 1.5$ Hz,

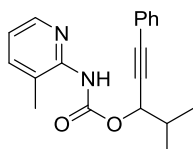
1H), 5.59 (d, $J = 5.6$ Hz, 1H), 2.28–2.18 (m, 1H), 1.15 (d, $J = 6.7$ Hz, 3H), 1.12 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 153.4, 152.8, 149.1, 141.0 (q, $J_{\text{C-F}} = 33.9$ Hz), 132.0, 129.0, 128.5, 122.8 (q, $J_{\text{C-F}} = 273.8$ Hz), 122.3, 114.5 (q, $J_{\text{C-F}} = 3.1$ Hz), 109.1 (q, $J_{\text{C-F}} = 3.7$ Hz), 87.0, 84.9, 71.5, 33.0, 18.6, 17.7; ^{19}F NMR (471 MHz, CDCl_3) δ -64.9; IR (neat, cm^{-1}): 3197, 2966, 2922, 1741, 1590, 1484, 1336, 1214, 1141, 756; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 385.1134, obsd 385.1138.

4-Methyl-1-phenylpent-1-yn-3-yl (5-fluoro-4-methylpyridin-2-yl)carbamate (3.23k).



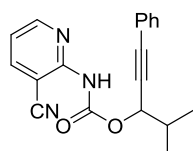
The title compound was prepared starting from 5-fluoro-4-methylpyridin-2-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 54%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 9.02 (s, 1H), 8.15 (s, 1H), 7.93 (d, $J = 5.6$ Hz, 1H), 7.50–7.44 (m, 2H), 7.36–7.27 (m, 3H), 5.52 (d, $J = 5.6$ Hz, 1H), 2.32 (s, 3H), 2.23–2.15 (m, 1H), 1.13 (d, $J = 6.7$ Hz, 3H), 1.10 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.5 (d, $J_{\text{C-F}} = 246.9$ Hz), 153.0, 148.3 (d, $J_{\text{C-F}} = 2.9$ Hz), 137.1 (d, $J_{\text{C-F}} = 15.8$ Hz), 134.5 (d, $J_{\text{C-F}} = 27.5$ Hz), 132.1, 128.7, 128.4, 122.5, 114.8, 86.7, 85.2, 70.9, 33.1, 18.6, 17.7, 15.0 (d, $J_{\text{C-F}} = 2.9$ Hz); ^{19}F NMR (471 MHz, CDCl_3) δ -139.8; IR (neat, cm^{-1}): 3203, 2968, 1736, 1548, 1406, 1223, 756; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{19}\text{FN}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 349.1323, obsd 349.1324.

4-Methyl-1-phenylpent-1-yn-3-yl (3-methylpyridin-2-yl)carbamate (3.23l).



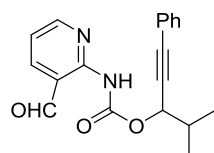
The title compound was prepared starting from 3-methylpyridin-2-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 78%; Yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 8.31 (d, $J = 3.9$ Hz, 1H), 7.98 (s, 1H), 7.53 (d, $J = 7.4$ Hz, 1H), 7.48–7.41 (m, 2H), 7.35–7.27 (m, 3H), 7.10–7.03 (m, 1H), 5.50 (d, $J = 5.6$ Hz, 1H), 2.32 (s, 3H), 2.20–2.09 (m, 1H), 1.10 (d, $J = 6.6$ Hz, 3H), 1.07 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 153.0, 149.5, 146.0, 140.1, 132.0, 128.6, 128.4, 127.4, 122.6, 121.3, 86.3, 85.5, 70.9, 33.0, 18.5, 18.2, 17.7; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 331.1417, obsd 331.1417.

4-Methyl-1-phenylpent-1-yn-3-yl (3-cyanopyridin-2-yl)carbamate (3.23m)



The title compound was prepared starting from 2-aminonicotinonitrile and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 38%; Yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 8.70–8.37 (m, 2H), 8.06–7.96 (m, 1H), 7.55–7.41 (m, 2H), 7.38–7.28 (m, 3H), 7.21–7.14 (m, 1H), 5.60 (d, $J = 5.4$ Hz, 1H), 2.29–2.15 (m, 1H), 1.14 (d, $J = 6.8$ Hz, 3H), 1.11 (d, $J = 6.8$ Hz, 3H); HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 342.1213, obsd 342.1210.

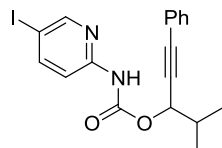
4-Methyl-1-phenylpent-1-yn-3-yl (3-formylpyridin-2-yl)carbamate (3.23n)



The title compound was prepared starting from 2-aminonicotinaldehyde and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 52%; Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 10.44 (s, 1H), 9.93 (s, 1H), 8.66 (dd, $J = 4.9, 2.0$ Hz, 1H), 8.06–8.00 (m, 1H), 7.48–7.42 (m, 2H), 7.33–7.27 (m, 3H), 7.17

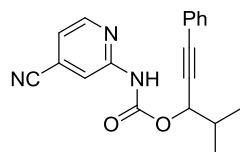
(dd, $J = 7.6, 4.9$ Hz, 1H), 5.56 (d, $J = 5.7$ Hz, 1H), 2.25–2.14 (m, 1H), 1.15 (d, $J = 6.8$ Hz, 3H), 1.12 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 193.1, 154.4, 152.0, 150.8, 143.9, 132.0, 128.6, 128.3, 122.5, 118.3, 117.1, 86.4, 85.2, 71.0, 32.9, 18.4, 17.8.

4-Methyl-1-phenylpent-1-yn-3-yl (5-iodopyridin-2-yl)carbamate (3.23o)



The title compound was prepared starting from 5-iodopyridin-2-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 78%; White solid; ^1H NMR (500 MHz, CDCl_3) δ 9.59 (s, 1H), 8.63 (d, $J = 2.0$ Hz, 1H), 7.99–7.88 (m, 2H), 7.52–7.43 (m, 2H), 7.35–7.27 (m, 3H), 5.55 (d, $J = 5.6$ Hz, 1H), 2.25–2.15 (m, 1H), 1.15 (d, $J = 6.7$ Hz, 3H), 1.12 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 153.8, 152.7, 151.5, 146.6, 132.2, 128.8, 128.4, 122.5, 114.8, 86.8, 85.1, 84.4, 71.1, 33.1, 18.6, 17.9; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{17}\text{IN}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 443.0227, obsd 443.0227.

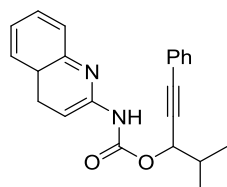
4-Methyl-1-phenylpent-1-yn-3-yl (4-cyanopyridin-2-yl)carbamate (3.23p).



The title compound was prepared starting from 2-aminoisonicotinonitrile and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 75%; White solid; ^1H NMR (500 MHz, CDCl_3) δ 9.83 (s, 1H), 8.60 (d, $J = 8.6$ Hz, 1H), 8.40 (s, 1H), 7.50–7.41 (m, 2H), 7.40–7.29 (m, 3H), 7.19–7.11 (m, 1H), 5.58 (d, $J = 5.6$ Hz, 1H), 2.30–2.15 (m, 1H), 1.14 (d, $J = 6.7$ Hz, 3H), 1.13 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 153.1, 152.5, 149.1, 132.0, 129.0, 128.6, 122.9, 122.2,

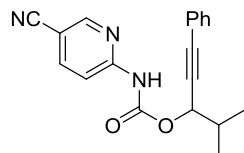
120.2, 116.6, 115.0, 87.1, 84.7, 71.7, 33.0, 18.6, 17.7; IR (neat, cm^{-1}): 3451, 2967, 2238, 1738, 1635, 1574, 1426, 1255, 1055; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 342.1213, obsd 342.1217.

4-Methyl-1-phenylpent-1-yn-3-yl isoquinolin-3-ylcarbamate (3.23q)



The title compound was prepared starting from isoquinolin-3-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 72%; Colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 8.68 (s, 1H), 8.28 (d, $J = 8.9$ Hz, 1H), 8.16 (d, $J = 8.9$ Hz, 1H), 7.88 (d, $J = 8.1$ Hz, 1H), 7.75 (d, $J = 8.1$ Hz, 1H), 7.66–7.58 (m, 1H), 7.49–7.36 (m, 3H), 7.35–7.26 (m, 3H), 5.51 (d, $J = 5.5$ Hz, 1H), 2.15–2.02 (m, 1H), 1.03 (d, $J = 2.6$ Hz, 3H), 1.02 (d, $J = 2.6$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 153.0, 151.2, 146.8, 138.8, 132.1, 130.1, 128.7, 128.4, 127.6 (2C), 126.0, 125.1, 122.5, 113.2, 86.5, 85.3, 71.0, 33.0, 18.4, 17.8; IR (neat, cm^{-1}): 3426, 2964, 2924, 1736, 1605, 1504, 1428, 1329, 1215, 1066; HRMS (ESI, m/z) calcd for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 367.1417, obsd 367.1421.

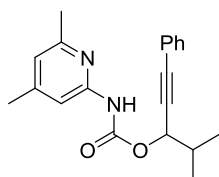
4-Methyl-1-phenylpent-1-yn-3-yl (5-cyanopyridin-2-yl)carbamate (3.23r).



The title compound was prepared starting from 6-aminonicotinonitrile and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 81%; Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 9.68 (s, 1H), 8.72 (d, $J = 2.0$ Hz, 1H), 8.23 (d, $J = 8.8$ Hz, 1H), 7.95 (dd, $J = 8.8, 2.0$ Hz, 1H), 7.52–7.45 (m, 2H), 7.37–7.27 (m, 3H), 5.58 (d, $J = 5.6$ Hz, 1H), 2.28–2.16 (m, 1H), 1.16 (d, $J = 6.7$ Hz, 3H), 1.12 (d,

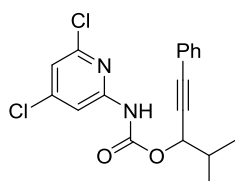
$J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 154.8, 152.2, 151.8, 141.9, 132.2, 129.0, 128.5, 122.1, 116.8, 112.6, 104.3, 87.2, 84.4, 71.8, 33.1, 18.5, 17.8; IR (neat, cm^{-1}): 3219, 2968, 2230, 1742, 1598, 1533, 1388, 1214, 1051; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 342.1213, obsd 342.1215.

4-Methyl-1-phenylpent-1-yn-3-yl (4,6-dimethylpyridin-2-yl)carbamate (3.23s)



The title compound was prepared starting from 4,6-dimethylpyridin-2-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 63%; Yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.80 (s, 1H), 7.64 (s, 1H), 7.48–7.42 (m, 2H), 7.35–7.27 (m, 3H), 6.68 (s, 1H), 5.47 (d, $J = 5.5$ Hz, 1H), 2.40 (s, 3H), 2.30 (s, 3H), 2.18–2.08 (m, 1H), 1.09 (d, $J = 6.7$ Hz, 3H), 1.07 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 156.6, 152.7, 150.9, 150.2, 132.1, 128.7, 128.4, 122.6, 119.8, 110.1, 86.3, 85.4, 70.7, 33.0, 23.9, 21.4, 18.4, 17.8; IR (neat, cm^{-1}): 3204, 2965, 2928, 1735, 1578, 1442, 1212, 1094; HRMS (ESI, m/z) calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 345.1573, obsd 345.1576.

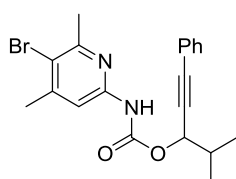
4-Methyl-1-phenylpent-1-yn-3-yl (4,6-dichloropyridin-2-yl)carbamate (3.23t)



The title compound was prepared starting from 4,6-dichloropyridin-2-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 43%; Yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 8.00 (s, 1H), 7.50 (s, 1H), 7.48–7.43 (m, 2H), 7.37–7.27 (m, 3H), 7.04 (s, 1H), 5.46 (d, $J = 5.5$ Hz, 1H), 2.21–2.09 (m, 1H),

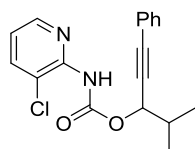
1.11 (d, $J = 6.7$ Hz, 3H), 1.09 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 152.0, 151.9, 149.9, 147.7, 132.1, 128.9, 128.4, 122.3, 119.2, 111.0, 86.9, 84.7, 71.6, 33.0, 18.4, 17.8; IR (neat, cm^{-1}): 3400, 2965, 1743, 1562, 1519, 1417, 1329, 1206, 1161, 1065; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 385.0481, obsd 385.0486.

4-Methyl-1-phenylpent-1-yn-3-yl (5-bromo-4,6-dimethylpyridin-2-yl)carbamate (3.23u).



The title compound was prepared starting from 5-bromo-4,6-dimethylpyridin-2-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 76%; Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.75 (s, 2H), 7.49–7.42 (m, 2H), 7.35–7.27 (m, 3H), 5.46 (d, $J = 5.5$ Hz, 1H), 2.57 (s, 3H), 2.40 (s, 3H), 2.18–2.09 (m, 1H), 1.08 (d, $J = 6.7$ Hz, 3H), 1.07 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.7, 152.5, 149.9, 149.2, 132.1, 128.7, 128.4, 122.5, 117.8, 111.9, 86.5, 85.2, 70.9, 33.0, 25.3, 23.9, 18.4, 17.8; IR (neat, cm^{-1}): 3430, 2965, 2928, 1736, 1597, 1400, 1213, 1097, 1028; HRMS (ESI, m/z) calcd for $\text{C}_{20}\text{H}_{21}\text{BrN}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 423.0679, 425.0658; obsd 423.0681, 425.0661.

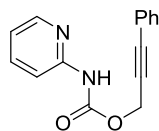
4-Methyl-1-phenylpent-1-yn-3-yl (3-chloropyridin-2-yl)carbamate (3.23v)



The title compound was prepared starting from 3-chloropyridin-2-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 74%; Yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 8.40 (dd, $J = 4.8, 1.5$ Hz, 1H), 7.69 (dd, $J =$

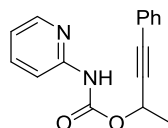
7.9, 1.5 Hz, 1H), 7.52–7.44 (m, 3H), 7.34–7.30 (m, 2H), 7.02 (dd, $J = 7.9, 4.8$ Hz, 1H), 5.59 (d, $J = 5.6$ Hz, 1H), 2.27–2.14 (m, $J = 6.7$ Hz, 1H), 1.14 (d, $J = 6.7$ Hz, 3H), 1.11 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 151.0, 147.6, 147.0, 137.9, 132.1, 128.8, 128.4, 122.5, 120.2, 120.1, 86.6, 85.1, 71.2, 33.0, 18.5, 17.8; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{17}\text{ClN}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 351.0871, obsd 351.0871.

3-Phenylprop-2-yn-1-yl pyridin-2-ylcarbamate (3.40a).



The title compound was prepared starting from 2-aminopyridine and 3-phenylprop-2-yn-1-ol by following the General Procedure A. Yield = 58%; White solid; ^1H NMR (500 MHz, CDCl_3) δ 10.58 (s, 1H), 8.53 (dd, $J = 5.0$ Hz, 1H), 8.07 (d, $J = 8.5$ Hz, 1H), 7.73–7.66 (m, 1H), 7.48 (dd, $J = 7.3, 2.1$ Hz, 2H), 7.37–7.29 (m, 3H), 6.95 (dd, $J = 7.3, 5.0$ Hz, 1H), 5.06 (s, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 153.1, 152.4, 148.0, 138.8, 132.0, 129.0, 128.5, 122.3, 118.9, 112.7, 87.0, 83.2, 53.9; IR (neat, cm^{-1}): 3189, 2920, 1732, 1652, 1540, 1140, 756; HRMS (ESI, m/z) calcd for $\text{C}_{15}\text{H}_{13}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}^+$): 253.0972, obsd 253.0974.

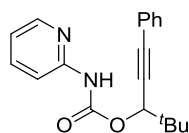
4-Phenylbut-3-yn-2-yl pyridin-2-ylcarbamate (3.40b)



The title compound was prepared starting from 2-aminopyridine and 4-phenylbut-3-yn-2-ol by following the General Procedure A. Yield = 47%; White solid; ^1H NMR (500 MHz, CDCl_3) δ 10.17 (s, 1H), 8.50 (dd, $J = 5.0, 1.8$ Hz, 1H), 8.07 (d, $J = 8.4$ Hz, 1H), 7.73–7.66 (m, 1H), 7.49–7.43 (m, 2H), 7.34–7.29 (m, 3H), 6.96 (dd, $J = 7.2, 5.0$ Hz, 1H), 5.81–5.73 (m, 1H), 1.70 (s, 3H); ^{13}C NMR (126 MHz,

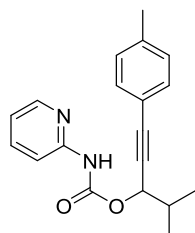
CDCl_3) δ 152.8, 152.5, 148.0, 138.7, 132.0, 128.8, 128.5, 122.4, 118.8, 112.8, 87.6, 85.2, 62.2, 22.1; IR (neat, cm^{-1}): 3185, 1735, 1589, 1440, 1221, 1085, 756; HRMS (ESI, m/z) calcd for $\text{C}_{16}\text{H}_{15}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}^+$): 267.1128, obsd 267.1129.

4,4-Dimethyl-1-phenylpent-1-yn-3-yl pyridin-2-ylcarbamate (3.40c).



The title compound was prepared starting from 2-aminopyridine and 4,4-dimethyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 71%; White solid; ^1H NMR (500 MHz, CDCl_3) δ 9.72 (d, $J = 5.4$ Hz, 1H), 8.46 (dd, $J = 5.4, 1.7$ Hz, 1H), 8.08 (d, $J = 8.5$ Hz, 1H), 7.74–7.66 (m, 1H), 7.48–7.43 (m, 2H), 7.35–7.26 (m, 3H), 7.01–6.94 (m, 1H), 5.48 (s, 1H), 1.12 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 153.1, 152.4, 148.0, 138.7, 132.0, 128.7, 128.4, 122.6, 118.8, 112.9, 86.3, 85.7, 73.6, 36.0, 25.9. IR (neat, cm^{-1}): 3185, 2968, 1736, 1588, 1440, 1307, 1217, 1061; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 331.1417, obsd 331.1419.

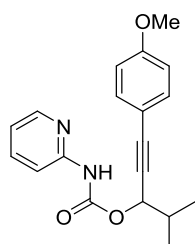
4-Methyl-1-(p-tolyl)pent-1-yn-3-yl pyridin-2-ylcarbamate (3.40d)



The title compound was prepared starting from 2-aminopyridine and 1-(4-methylphenyl)-4-methylpent-1-yn-3-ol by following the General Procedure A. Yield = 53%; Light yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 10.19 (s, 1H), 8.45–8.39 (m, 1H), 8.00 (d, $J = 8.4$ Hz, 1H), 7.64–7.58 (m, 1H), 7.30–7.24 (m, 2H), 7.03 (d, $J = 7.8$ Hz, 2H), 6.89–6.84 (m, 1H), 5.48 (d, $J = 5.6$ Hz, 1H), 2.26 (s, 3H),

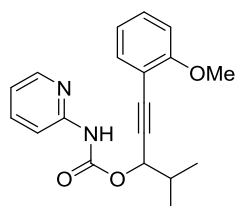
2.15–2.07 (m, 1H), 1.04 (d, $J = 6.7$ Hz, 3H), 1.01 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 153.1, 152.6, 148.0, 138.9, 138.7, 131.9, 129.2, 119.5, 118.7, 112.8, 86.7, 84.7, 70.9, 33.1, 21.6, 18.6, 17.8; IR (neat, cm^{-1}): 3186, 2923, 1731, 1588, 1436, 1218, 159, 778; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 331.1417, obsd 331.1419.

1-(4-Methoxyphenyl)-4-methylpent-1-yn-3-yl pyridin-2-ylcarbamate (3.40e)



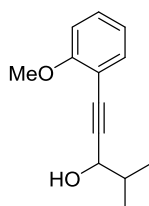
The title compound was prepared starting from 2-aminopyridine and 1-(4-methoxyphenyl)-4-methylpent-1-yn-3-ol by following the General Procedure A. Yield = 80%; White solid; ^1H NMR (500 MHz, CDCl_3) δ 9.87 (s, 1H), 8.49–8.44 (m, 1H), 8.06 (d, $J = 8.4$ Hz, 1H), 7.72–7.66 (m, 1H), 7.43–7.36 (m, 2H), 6.99–6.94 (m, 1H), 6.86–6.80 (m, 2H), 5.54 (d, $J = 5.6$ Hz, 1H), 3.80 (s, 3H), 2.23–2.14 (m, 1H), 1.12 (d, $J = 6.7$ Hz, 3H), 1.09 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 159.9, 153.0, 152.4, 148.0, 138.7, 133.5, 118.8, 114.7, 114.0, 112.8, 86.5, 84.0, 71.0, 55.5, 33.1, 18.6, 17.8; IR (neat, cm^{-1}): 3184, 2964, 1731, 1588, 1440, 1250, 1219, 1035, 832; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 347.1366, obsd 347.1368.

1-(2-Methoxyphenyl)-4-methylpent-1-yn-3-yl pyridin-2-ylcarbamate (3.40f)



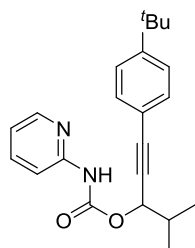
The title compound was prepared starting from 2-aminopyridine and 1-(2-methoxyphenyl)-4-methylpent-1-yn-3-ol by following the General Procedure A. Yield = 66%; Yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 10.05 (s, 1H), 8.51 (dd, $J = 5.0, 1.8$ Hz, 1H), 8.07 (d, $J = 8.4$ Hz, 1H), 7.72–7.65 (m, 1H), 7.42 (dd, $J = 7.6, 1.8$ Hz, 1H), 7.32–7.27 (m, 1H), 6.96–6.84 (m, 3H), 5.63 (d, $J = 5.4$ Hz, 1H), 3.84 (s, 3H), 2.27–2.18 (m, 1H), 1.14 (d, $J = 6.7$ Hz, 3H), 1.12 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 160.5, 153.0, 152.5, 148.1, 138.6, 133.9, 130.2, 120.5, 118.7, 112.7, 111.9, 110.8, 89.4, 82.9, 71.0, 55.9, 33.1, 18.6, 17.6; IR (neat, cm^{-1}): 3182, 2964, 1731, 1588, 1439, 1259, 1219, 1048, 752; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 347.1366, obsd 347.1367.

1-(2-Methoxyphenyl)-4-methylpent-1-yn-3-ol (3.40f')



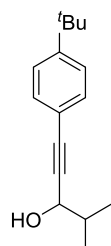
The title compound was prepared starting from 1-iodo-2-methoxybenzene and 4-methylpent-1-yn-3-ol by following the General Procedure C. Yield = 66%; Yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.39 (dd, $J = 7.6, 1.8$ Hz, 1H), 7.31–7.26 (m, 1H), 6.91–6.85 (m, 2H), 4.44 (t, $J = 5.6$ Hz, 1H), 3.86 (s, 3H), 2.20 (d, $J = 5.7$ Hz, 1H), 2.03–1.95 (m, 1H), 1.09 (d, $J = 6.7$ Hz, 3H), 1.07 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 160.3, 133.8, 129.9, 120.6, 112.1, 110.8, 93.4, 81.9, 68.7, 55.9, 34.9, 18.4, 17.7; IR (neat, cm^{-1}): 3406, 2960, 1492, 1463, 1260, 1116, 1026, 752; HRMS (ESI, m/z) calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 227.1043, obsd 227.1047.

1-(4-(*tert*-Butyl)phenyl)-4-methylpent-1-yn-3-yl pyridin-2-ylcarbamate (3.40g)



The title compound was prepared starting from 2-aminopyridine and 1-(4-(*tert*-butyl)phenyl)-4-methylpent-1-yn-3-ol by following the General Procedure A. Yield = 83%; White solid; ^1H NMR (500 MHz, CDCl_3) δ 9.35 (s, 1H), 8.42 (d, J = 4.9 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.74–7.66 (m, 1H), 7.44–7.36 (m, 2H), 7.35–7.30 (m, 2H), 7.02–6.94 (m, 1H), 5.54 (d, J = 5.6 Hz, 1H), 2.25–2.10 (m, 1H), 1.30 (s, 9H), 1.12 (d, J = 6.7 Hz, 3H), 1.09 (d, J = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 152.9, 152.2, 152.0, 148.0, 138.6, 131.8, 125.4, 119.5, 118.9, 112.7, 86.7, 84.7, 70.9, 35.0, 33.1, 31.3, 18.6, 17.8; IR (neat, cm^{-1}): 3215, 2964, 1734, 1589, 1440, 1308, 1219, 1060; HRMS (ESI, m/z) calcd for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 373.1886, obsd 373.1889.

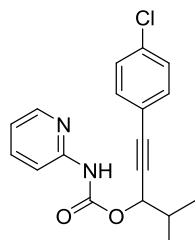
1-(4-(*tert*-Butyl)phenyl)-4-methylpent-1-yn-3-ol (3.40g')



The title compound was prepared starting from 1-(*tert*-butyl)-4-iodobenzene and 4-methylpent-1-yn-3-ol by following the General Procedure C. Yield = 84%; Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.40–7.35 (m, 2H), 7.34–7.30 (m, 2H), 4.39 (t, J = 4.6 Hz, 1H), 2.07–1.88 (m, 2H), 1.30 (s, 9H), 1.07 (d, J = 6.8 Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 151.8, 131.6, 125.4, 119.9, 88.4, 85.9, 68.6, 34.9, 31.3, 18.4, 17.7; IR (neat, cm^{-1}): 3376, 2962, 2905, 2871, 1504, 1465,

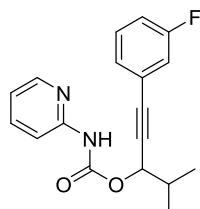
1364, 1268, 1026, 834; HRMS (ESI, m/z) calcd for $C_{16}H_{22}ONa$ ($M+Na^+$): 253.1563, obsd 253.1560.

1-(4-Chlorophenyl)-4-methylpent-1-yn-3-yl pyridin-2-ylcarbamate (3.40h)



The title compound was prepared starting from 2-aminopyridine and 1-(4-chlorophenyl)-4-methylpent-1-yn-3-ol by following the General Procedure A. Yield = 68%; Light yellow oil; 1H NMR (500 MHz, $CDCl_3$) δ 10.56 (s, 1H), 8.50 (dd, $J = 5.1, 1.8$ Hz, 1H), 8.09 (d, $J = 8.5$ Hz, 1H), 7.73–7.66 (m, 1H), 7.40–7.36 (m, 2H), 7.30–7.26 (m, 2H), 6.96 (dd, $J = 7.2, 5.1$ Hz, 1H), 5.55 (d, $J = 5.6$ Hz, 1H), 2.26–2.15 (m, $J = 6.7$ Hz, 1H), 1.13 (d, $J = 6.7$ Hz, 3H), 1.10 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.0, 152.6, 147.8, 138.8, 134.8, 133.2, 128.8, 121.0, 118.7, 112.9, 86.5, 85.3, 70.6, 33.0, 18.6, 17.8; IR (neat, cm^{-1}): 3184, 1732, 1589, 1439, 1220, 1043, 777; HRMS (ESI, m/z) calcd for $C_{18}H_{17}ClN_2O_2Na$ ($M+Na^+$): 351.0871, obsd 351.0872.

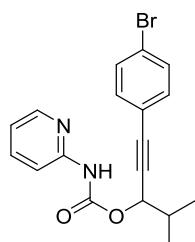
1-(3-Fluorophenyl)-4-methylpent-1-yn-3-yl pyridin-2-ylcarbamate (3.40i)



The title compound was prepared starting from 2-aminopyridine and 1-(3-fluorophenyl)-4-methylpent-1-yn-3-ol by following the General Procedure A. Yield = 49%; Light yellow oil; 1H NMR (500 MHz, $CDCl_3$) δ 10.22 (s, 1H), 8.48 (d, $J = 5.0$ Hz, 1H), 8.08 (d, $J = 8.5$ Hz, 1H), 7.75–7.67 (m, 1H), 7.28–7.22 (m, 2H),

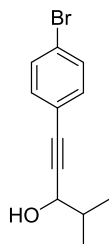
7.19–7.11 (m, 1H), 7.07–7.00 (m, 1H), 6.97 (dd, $J = 7.3, 5.0$ Hz, 1H), 5.55 (d, $J = 5.7$ Hz, 1H), 2.27–2.15 (m, 1H), 1.13 (d, $J = 6.7$ Hz, 3H), 1.10 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 162.4 (d, $J_{\text{C-F}} = 246.7$ Hz), 153.0, 152.5, 147.9, 138.8, 130.0 (d, $J_{\text{C-F}} = 8.6$ Hz), 127.9 (d, $J_{\text{C-F}} = 3.0$ Hz), 124.4 (d, $J_{\text{C-F}} = 9.5$ Hz), 118.82 (d, $J_{\text{C-F}} = 22.8$ Hz), 118.79, 116.1 (d, $J_{\text{C-F}} = 21.1$ Hz), 112.9, 86.5, 85.2 (d, $J_{\text{C-F}} = 3.5$ Hz), 70.6, 33.0, 18.6, 17.8; ^{19}F NMR (471 MHz, CDCl_3) δ -112.9; IR (neat, cm^{-1}): 3185, 2959, 1728, 1581, 1438, 1260, 1227, 1076, 769; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{17}\text{FN}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 335.1166, obsd 335.1167.

1-(4-Bromophenyl)-4-methylpent-1-yn-3-yl pyridin-2-ylcarbamate (3.40j)



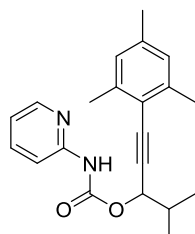
The title compound was prepared starting from 2-aminopyridine and 1-(4-bromophenyl)-4-methylpent-1-yn-3-ol by following the General Procedure A. Yield = 78%; Yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 9.28 (s, 1H), 8.42–8.36 (m, 1H), 8.04 (d, $J = 8.4$ Hz, 1H), 7.74–7.65 (m, 1H), 7.48–7.40 (m, 2H), 7.34–7.28 (m, 1H), 7.00–6.93 (m, 1H), 5.51 (d, $J = 5.6$ Hz, 1H), 2.25–2.10 (m, 1H), 1.12 (d, $J = 6.8$ Hz, 3H), 1.09 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 152.8, 152.2, 148.0, 138.7, 133.5, 131.7, 123.1, 121.5, 119.0, 112.8, 86.7, 85.5, 70.8, 33.0, 18.5, 17.9; IR (neat, cm^{-1}): 3435, 2920, 1732, 1588, 1439, 1218, 1083; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{17}\text{BrN}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 395.0366, 397.0345; obsd 395.0371, 397.0351.

1-(4-Bromophenyl)-4-methylpent-1-yn-3-ol (3.40j')



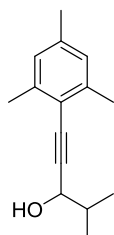
The title compound was prepared starting from 1-bromo-4-iodobenzene and 4-methylpent-1-yn-3-ol by following the General Procedure C. Yield = 85%; Brown oil; ^1H NMR (500 MHz, CDCl_3) δ 7.45–7.41 (m, 2H), 7.31–7.26 (m, 2H), 4.37 (t, J = 5.7 Hz, 1H), 2.11–2.04 (m, 1H), 2.02–1.91 (m, 1H), 1.07 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 133.3, 131.7, 122.7, 121.8, 90.3, 84.7, 68.5, 34.8, 18.3, 17.7; IR (neat, cm^{-1}): 3390, 2961, 2927, 1485, 1393, 1071, 1012, 823; HRMS (ESI, m/z) calcd for $\text{C}_{12}\text{H}_{13}\text{BrONa}$ ($\text{M}+\text{Na}^+$): 275.0042, 277.0022; obsd 275.0046, 277.0025.

1-Mesityl-4-methylpent-1-yn-3-yl pyridin-2-ylcarbamate (3.40k)



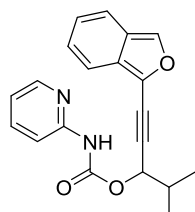
The title compound was prepared starting from 2-aminopyridine and 1-Mesityl-4-methylpent-1-yn-3-ol by following the General Procedure A. Yield = 56%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 10.12 (s, 1H), 8.43–8.38 (m, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.64–7.58 (m, 1H), 6.88–6.83 (m, 1H), 6.77 (s, 2H), 5.59 (d, J = 5.4 Hz, 1H), 2.31 (s, 6H), 2.18 (s, 3H), 2.16–2.10 (m, 1H), 1.07 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 153.1, 152.6, 147.9, 140.6, 138.7, 138.2, 127.7, 119.4, 118.7, 112.8, 92.9, 84.4, 71.2, 33.0, 21.5, 21.2, 18.7, 17.8; IR (neat, cm^{-1}): 3184, 2964, 1732, 1588, 1440, 1307, 1219, 1036, 778; HRMS (ESI, m/z) calcd for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 359.1730, obsd 359.1731.

1-Mesityl-4-methylpent-1-yn-3-ol (3.40k)



The title compound was prepared starting from 2-iodo-1,3,5-trimethylbenzene and 4-methylpent-1-yn-3-ol by following the General Procedure C. Yield = 47%; Light yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 6.84 (s, 2H), 4.51–4.44 (m, 1H), 2.38 (s, 6H), 2.26 (s, 3H), 2.08–2.02 (m, 1H), 2.02–1.95 (m, 1H), 1.09 (d, $J = 6.8$ Hz, 3H), 1.06 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 140.4, 137.9, 127.7, 119.6, 96.7, 83.4, 68.8, 34.9, 21.4, 21.2, 18.5, 17.6; IR (neat, cm^{-1}): 3393, 2960, 1610, 1468, 1378, 1243, 1029, 851; HRMS (ESI, m/z) calcd for $\text{C}_{15}\text{H}_{20}\text{ONa}$ ($\text{M}+\text{Na}^+$): 239.1406, obsd 239.1409.

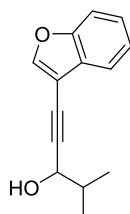
1-(Isobenzofuran-1-yl)-4-methylpent-1-yn-3-yl pyridin-2-ylcarbamate (3.40l)



The title compound was prepared starting from 2-aminopyridine and 1-(isobenzofuran-1-yl)-4-methylpent-1-yn-3-ol by following the General Procedure A. Yield = 42%; Brown oil; ^1H NMR (500 MHz, CDCl_3) δ 10.07 (s, 1H), 8.50–8.45 (m, 1H), 8.08 (d, $J = 8.5$ Hz, 1H), 7.82 (s, 1H), 7.72–7.63 (m, 2H), 7.51–7.45 (m, 1H), 7.36–7.27 (m, 2H), 6.98–6.91 (m, 1H), 5.62 (d, $J = 5.6$ Hz, 1H), 2.30–2.18 (m, 1H), 1.18 (d, $J = 6.8$ Hz, 3H), 1.14 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 154.7, 153.0, 152.5, 148.2, 147.9, 138.7, 127.8, 125.4, 123.6, 120.6, 118.8, 112.9, 111.8, 104.0, 90.3, 76.2, 70.9, 33.0, 18.6, 17.5; IR (neat, cm^{-1}): 3184, 2965, 2928,

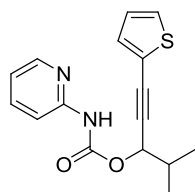
2234, 1732, 1588, 1539, 1440, 1307, 1222, 1107, 1037; HRMS (ESI, m/z) calcd for $C_{20}H_{18}N_2O_3Na$ ($M+Na^+$): 357.1210, obsd 357.1212.

1-(benzofuran-3-yl)-4-methylpent-1-yn-3-ol (3.40l')



The title compound was prepared starting from 1-bromoisobenzofuran and 4-methylpent-1-yn-3-ol by following the General Procedure C. Yield = 36%; Yellow oil; 1H NMR (500 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.68–7.61 (m, 1H), 7.48–7.42 (m, 1H), 7.34–7.24 (m, 2H), 4.47 (d, $J = 5.6$ Hz, 1H), 2.06–1.96 (m, 1H), 1.11 (d, $J = 6.8$ Hz, 3H), 1.07 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.6, 147.7, 127.7, 125.3, 123.4, 120.4, 111.7, 104.1, 93.9, 75.1, 68.5, 34.7, 18.4, 17.7; HRMS (ESI, m/z) calcd for $C_{14}H_{14}O_2Na$ ($M+Na^+$): 237.0886, obsd 237.0886.

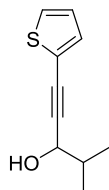
4-Methyl-1-(thiophen-2-yl)pent-1-yn-3-yl pyridin-2-ylcarbamate (3.40m)



The title compound was prepared starting from 2-aminopyridine and 4-Methyl-1-(thiophen-2-yl)pent-1-yn-3-ol by following the General Procedure A. Yield = 83%; White solid; 1H NMR (500 MHz, $CDCl_3$) δ 9.55 (s, 1H), 8.44–8.40 (m, 1H), 8.05 (d, $J = 8.4$ Hz, 1H), 7.74–7.66 (m, 1H), 7.29–7.21 (m, 2H), 7.01–6.94 (m, 2H), 5.55 (d, $J = 5.6$ Hz, 1H), 2.24–2.14 (m, 1H), 1.12 (d, $J = 6.8$ Hz, 3H), 1.09 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.8, 152.2, 148.0, 138.7, 132.8, 127.7, 127.1, 122.4, 118.9, 112.8, 89.4, 79.8, 70.9, 33.0, 18.6, 17.9; IR (neat, cm^{-1}):

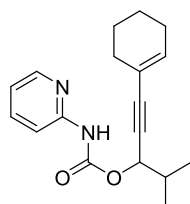
3432, 2919, 1732, 1588, 1439, 1219; HRMS (ESI, m/z) calcd for $C_{16}H_{16}N_2O_2SNa$ ($M+Na^+$): 323.0825, obsd 323.0826.

4-Methyl-1-(thiophen-2-yl)pent-1-yn-3-ol (3.40m')



The title compound was prepared starting from 2-bromothiophene and 4-methylpent-1-yn-3-ol by following the General Procedure C. Yield = 86%; Yellow oil; 1H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, $J = 5.6$ Hz, 1H), 7.19 (dd, $J = 3.6, 1.2$ Hz, 1H), 6.96 (dd, $J = 5.6, 3.6$ Hz, 1H), 4.40 (t, $J = 5.7$ Hz, 1H), 2.05–1.92 (m, 2H), 1.07 (d, $J = 6.8$ Hz, 3H), 1.05 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.3, 127.3, 127.1, 122.8, 93.0, 79.0, 68.7, 34.8, 18.3, 17.8; IR (neat, cm^{-1}): 3375, 2961, 2928, 2872, 1467, 1384, 1190, 1083, 1027, 699; HRMS (ESI, m/z) calcd for $C_{10}H_{12}OSNa$ ($M+Na^+$): 203.0501, obsd 203.0504.

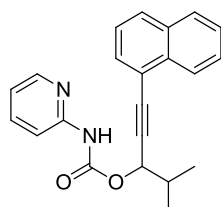
1-(Cyclohex-1-en-1-yl)-4-methylpent-1-yn-3-yl pyridin-2-ylcarbamate (3.40n)



The title compound was prepared starting from 2-aminopyridine and 1-(cyclohex-1-en-1-yl)-4-methylpent-1-yn-3-ol by following the General Procedure A. Yield = 59%; Light yellow oil; 1H NMR (500 MHz, $CDCl_3$) δ 9.55 (s, 1H), 8.42 (d, $J = 5.0$ Hz, 1H), 8.04 (d, $J = 8.4$ Hz, 1H), 7.73–7.66 (m, 1H), 7.01–6.94 (m, 1H), 6.18–6.12 (m, 1H), 5.44 (d, $J = 5.5$ Hz, 1H), 2.15–2.07 (m, 5H), 1.64–1.56 (m, 4H), 1.06 (d, $J = 6.7$ Hz, 3H), 1.04 (d, $J = 6.8$ Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.9, 152.4, 148.0, 138.6, 135.9, 120.2, 118.7, 112.7, 88.4, 82.5, 71.0, 33.0, 29.3,

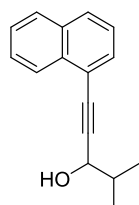
25.8, 22.4, 21.6, 18.6, 17.7; IR (neat, cm^{-1}): 3185, 2930, 1732, 1688, 1540, 1440, 1222, 777; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 321.1573, obsd 321.1574.

4-Methyl-1-(naphthalen-1-yl)pent-1-yn-3-yl pyridin-2-ylcarbamate (3.40o)



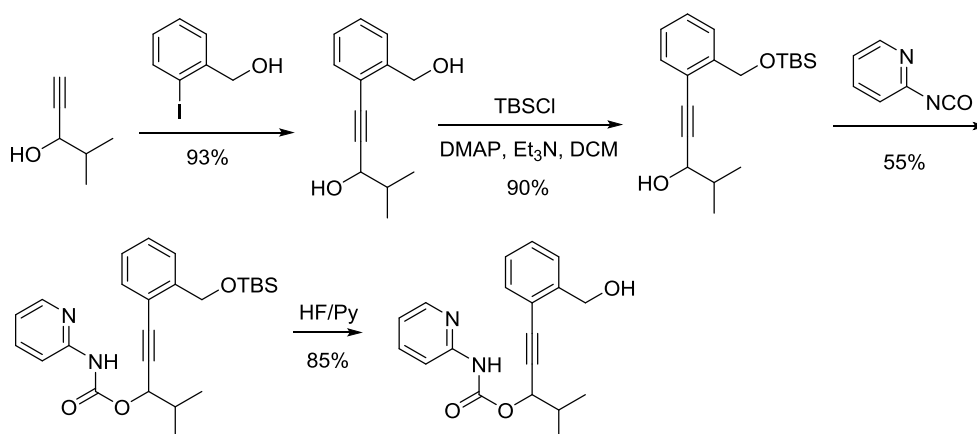
The title compound was prepared starting from 2-aminopyridine and 4-methyl-1-(naphthalen-1-yl)pent-1-yn-3-ol by following the General Procedure A. Yield = 76%; Yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 9.92–9.60 (s, 1H), 8.52–8.44 (m, 1H), 8.32 (d, $J = 8.3$ Hz, 1H) 8.13–8.05 (m, 1H), 7.88–7.80 (m, 2H), 7.73–7.64 (m, 2H), 7.58–7.47 (m, 2H), 7.44–7.38 (m, 1H), 6.96–6.90 (m, 1H), 5.71 (d, $J = 4.9$ Hz, 1H), 2.36–2.24 (m, 1H), 1.22 (d, $J = 6.8$ Hz, 3H), 1.18 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 153.0, 152.3, 148.0, 138.7, 133.6, 133.3, 131.1, 129.2, 128.5, 127.1, 126.6, 126.2, 125.3, 120.2, 118.9, 112.8, 90.3, 84.7, 71.1, 33.2, 18.7, 18.0; IR (neat, cm^{-1}): 3186, 2965, 1731, 1588, 1440, 1307, 1220, 1060; HRMS (ESI, m/z) calcd for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 367.1417, obsd 367.1421.

4-Methyl-1-(naphthalen-1-yl)pent-1-yn-3-ol (3.40o').

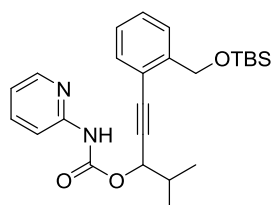


The title compound was prepared starting from 1-iodonaphthalene and 4-methylpent-1-yn-3-ol by following the General Procedure C. Yield = 86%; Colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 8.31 (d, $J = 8.3$ Hz, 1H), 7.86–7.78 (m,

2H), 7.67 (d, $J = 7.2$ Hz, 1H), 7.59–7.54 (m, 1H), 7.54–7.46 (m, 1H), 7.42–7.37 (m, 1H), 4.55 (t, $J = 5.6$ Hz, 1H), 2.13–2.01 (m, 2H), 1.16 (d, $J = 6.8$ Hz, 3H), 1.13 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 133.5, 133.3, 130.8, 129.0, 128.4, 127.0, 126.6, 126.2, 125.3, 120.6, 94.1, 83.9, 68.8, 35.0, 18.5, 17.9; IR (neat, cm^{-1}): 3390, 2961, 2871, 1586, 1462, 1395, 1083, 1027, 799, 772; HRMS (ESI, m/z) calcd for $\text{C}_{16}\text{H}_{16}\text{ONa}$ ($\text{M}+\text{Na}^+$): 247.1093, obsd 247.1091.



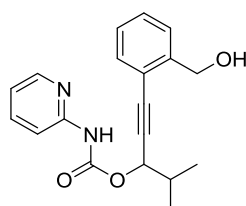
1-(2-(((*tert*-Butyldimethylsilyl)oxy)methyl)phenyl)-4-methylpent-1-yn-3-yl pyridin-2-ylcarbamate (3.40p)



The title compound was prepared starting from 2-aminopyridine and 1-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)-4-methylpent-1-yn-3-ol by following the General Procedure A. Yield = 55%; Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 10.08–10.02 (m, 1H), 8.52–8.46 (m, 1H), 8.11 (d, $J = 8.4$ Hz, 1H), 7.73 (m, 1H), 7.59 (d, $J = 7.8$ Hz, 1H), 7.45 (d, $J = 7.5$ Hz, 1H), 7.41–7.36 (m, 1H), 7.22 (t, $J = 7.5$ Hz, 1H), 7.01–6.95 (m, 1H), 5.62 (d, $J = 5.6$ Hz, 1H), 4.94 (d, $J = 2.6$ Hz, 2H), 2.29–2.20 (m, 1H), 1.18 (d, $J = 6.7$ Hz, 3H), 1.15 (d, $J = 6.7$ Hz, 3H), 0.96 (s, 9H), 0.11 (d, $J = 2.6$ Hz, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 152.9, 152.5, 147.9,

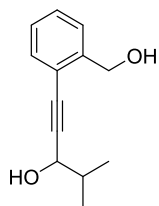
143.7, 138.7, 132.1, 129.0, 126.5, 125.7, 119.1, 118.8, 112.9, 90.3, 83.9, 70.9, 63.4, 32.9, 26.1, 18.7, 18.6, 17.8, -5.2; IR (neat, cm^{-1}): 3188, 2057, 1734, 1589, 1440, 1219, 1079, 838, 777; HRMS (ESI, m/z) calcd for $\text{C}_{25}\text{H}_{34}\text{N}_2\text{O}_3\text{SiNa}$ ($\text{M}+\text{Na}^+$): 461.2231, obsd 461.2236.

1-(2-(Hydroxymethyl)phenyl)-4-methylpent-1-yn-3-yl pyridin-2-ylcarbamate (3.40q)



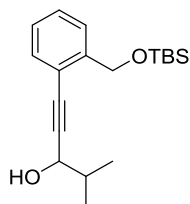
Compound **3.40p** (876 mg, 2 mmol, 1.0 equiv) was dissolved in THF (10 mL) and treated with pyridine hydrofluoride (0.9 mL, 10 mmol, 5.0 equiv). The reaction was stirred at rt for 2 h. The reaction mixture was quenched with NH_4Cl and extracted with EtOAc (15 mL x 3). The combined organic phases are washed with brine and dried over Na_2SO_4 . The filtrate was concentrated under reduced pressure. The residue was chromatographed through silica gel eluting with ethyl acetate/hexanes to give the product as a white solid (551 mg, 85% yield). ^1H NMR (500 MHz, CDCl_3) δ 9.99–9.92 (m, 1H), 8.41 (dd, $J = 5.0, 1.8$ Hz, 1H), 8.05 (d, $J = 8.4$ Hz, 1H), 7.73–7.66 (m, 1H), 7.47–7.40 (m, 2H), 7.33 (t, $J = 7.5$ Hz, 1H), 7.23 (t, $J = 7.5$ Hz, 1H), 6.98 (dd, $J = 7.2, 5.0$ Hz, 1H), 5.48 (d, $J = 5.7$ Hz, 1H), 4.85–4.75 (m, 2H), 2.86–2.75 (m, 1H), 2.24–2.16 (m, 1H), 1.14 (d, $J = 6.8$ Hz, 3H), 1.11 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 153.2, 152.3, 147.8, 143.4, 138.8, 132.6, 129.2, 127.6, 127.5, 120.7, 118.9, 113.0, 90.3, 84.3, 71.2, 64.0, 32.7, 18.6, 17.9; IR (neat, cm^{-1}): 3432, 2957, 1734, 1589, 1440, 1307, 1219, 1079, 838, 777; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 347.1366, obsd 347.1369.

1-(2-(Hydroxymethyl)phenyl)-4-methylpent-1-yn-3-ol (3.30q')



The title compound was prepared starting from (2-iodophenyl)methanol and 4-methylpent-1-yn-3-ol by following the General Procedure C. Yield = 93%; Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.40 (dd, $J = 7.5, 1.3$ Hz, 1H), 7.38–7.35 (m, 1H), 7.30–7.26 (m, 1H), 7.21 (td, $J = 7.5, 1.3$ Hz, 1H), 4.78–4.71 (m, 2H), 4.36 (d, $J = 5.6$ Hz, 1H), 3.65 (s, 1H), 3.38 (s, 1H), 1.99–1.89 (m, 1H), 1.05 (d, $J = 6.7$ Hz, 3H), 1.02 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 142.4, 132.5, 128.7, 127.9, 127.6, 121.6, 94.0, 83.1, 68.3, 63.8, 34.7, 18.5, 17.7; IR (neat, cm^{-1}): 3428, 2960, 1652, 1465, 1383, 1262, 1053, 759; HRMS (ESI, m/z) calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 227.1043, obsd 227.1045.

1-(2-(((*tert*-Butyldimethylsilyloxy)methyl)phenyl)-4-methylpent-1-yn-3-ol
(3.30p')

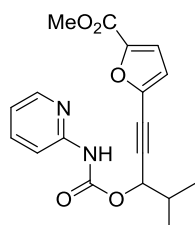


To a solution of compound **3.30q'** (3.27 g, 16 mmol, 1.0 equiv), TBSCl (2.68 g, 17.6 mmol, 1.1 equiv) and DMAP (97.6 mg, 0.8 mmol, 0.05 equiv) in CH_2Cl_2 (30 mL) was added triethylamine (2.5 mL, 1.78 g, 17.6 mmol, 1.1 equiv) at rt. After being stirred for 12 h, the reaction mixture was washed successively with water, saturated NH_4Cl and brine. The organic solution was dried over anhydrous Na_2SO_4 and filtered, and concentrated under reduced pressure. The residue was chromatographed through silica gel eluting with ethyl acetate/hexanes to give the product as a light yellow oil (4.58 g, 90% yield). Yield = 90%; Light yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.55 (d, $J = 7.6$ Hz, 1H), 7.39 (d, $J = 7.6$ Hz, 1H), 7.36–7.32 (m, 1H), 7.18 (t, $J = 7.6$ Hz, 1H),

4.90 (s, 2H), 4.44 (t, $J = 5.4$ Hz, 1H), 2.26–2.23 (m, 1H), 2.05–1.94 (m, 1H), 1.10 (d, $J = 6.8$ Hz, 3H), 1.07 (d, $J = 6.8$ Hz, 3H), 0.97 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 143.3, 132.0, 128.7, 126.6, 125.8, 119.5, 94.0, 83.1, 68.6, 63.5, 34.8, 26.1, 18.6, 18.4, 17.6, -5.2 ; IR (neat, cm^{-1}): 3436, 2957, 1635, 1471, 1254, 1078, 1028, 838, 756; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{30}\text{O}_2\text{SiNa}$ ($\text{M}+\text{Na}^+$): 341.1907, obsd 341.1911.

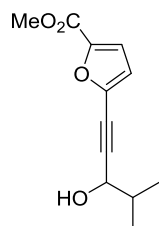
Methyl 5-(4-methyl-3-((pyridin-2-ylcarbamoyl)oxy)pent-1-yn-1-yl)furan-2-

Carboxylate (3.40r)



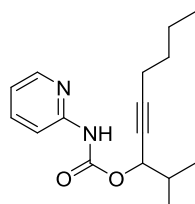
The title compound was prepared starting from 2-aminopyridine and methyl 5-(3-hydroxy-4-methylpent-1-yn-1-yl)furan-2-carboxylate by following the General Procedure A. Yield = 61%; Yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 10.06 (s, 1H), 8.46–8.40 (m, 1H), 8.05 (d, $J = 8.5$ Hz, 1H), 7.76–7.68 (m, 1H), 7.14 (d, $J = 3.6$ Hz, 1H), 7.06–6.99 (m, 1H), 6.67 (d, $J = 3.6$ Hz, 1H), 5.54 (d, $J = 5.8$ Hz, 1H), 3.90 (s, 3H), 2.27–2.14 (m, 1H), 1.12 (d, $J = 6.7$ Hz, 3H), 1.09 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 158.5, 152.7, 152.3, 147.9, 144.7, 139.5, 138.8, 119.0, 118.7, 117.4, 112.9, 91.9, 75.8, 70.3, 52.3, 32.8, 18.5, 17.9.

Methyl 5-(3-hydroxy-4-methylpent-1-yn-1-yl)furan-2-carboxylate (3.40r')



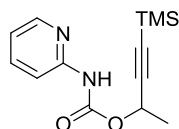
The title compound was prepared starting from methyl 5-bromofuran-2-carboxylate and 4-methylpent-1-yn-3-ol by following the General Procedure C. Yield = 73%; Yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.15 (d, $J = 3.6$ Hz, 1H), 6.62 (d, $J = 3.6$ Hz, 1H), 4.41 (d, $J = 5.7$ Hz, 1H), 3.90 (s, 3H), 2.48 (s, 1H), 2.04–1.94 (m, 1H), 1.07 (d, $J = 6.7$ Hz, 3H), 1.05 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 158.6, 144.4, 139.9, 118.9, 116.7, 95.5, 75.1, 68.3, 52.3, 34.5, 18.2, 17.7; HRMS (ESI, m/z) calcd for $\text{C}_{12}\text{H}_{14}\text{O}_4\text{Na}$ ($\text{M}+\text{Na}^+$): 245.0784, obsd 245.0782.

2-Methylnon-4-yn-3-yl pyridin-2-ylcarbamate (3.40s)



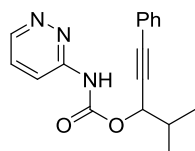
The title compound was prepared starting from 2-aminopyridine and 2-methylnon-4-yn-3-ol by following the General Procedure A. Yield = 65%; White solid; ^1H NMR (500 MHz, CDCl_3) δ 10.01–9.91 (m, 1H), 8.44 (d, $J = 5.1$ Hz, 1H), 8.06 (d, $J = 8.5$ Hz, 1H), 7.74–7.66 (m, 1H), 7.01–6.94 (m, 1H), 5.34–5.28 (m, 1H), 2.25 (td, $J = 7.0, 2.0$ Hz, 2H), 2.11–2.01 (m, 1H), 1.56–1.48 (m, 2H), 1.46–1.38 (m, 2H), 1.04 (d, $J = 6.7$ Hz, 3H), 1.02 (d, $J = 6.7$ Hz, 3H), 0.91 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 153.1, 152.5, 148.0, 138.6, 118.6, 112.8, 87.4, 76.2, 70.8, 33.0, 30.8, 22.1, 18.6 (2C), 17.7, 13.8; IR (neat, cm^{-1}): 3185, 2962, 1732, 1589, 1440, 1308, 1220, 1060, 778; HRMS (ESI, m/z) calcd for $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 297.1573, obsd 297.1577.

4-(Trimethylsilyl)but-3-yn-2-yl pyridin-2-ylcarbamate (3.43t)



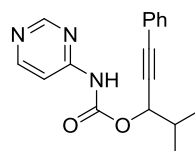
The title compound was prepared starting from 2-aminopyridine and 4-(trimethylsilyl)but-3-yn-2-ol by following the General Procedure A. Yield = 69%; White solid; ^1H NMR (500 MHz, CDCl_3) δ 10.50–9.86 (m, 1H), 8.51–8.44 (m, 1H), 8.05 (d, J = 8.3 Hz, 1H), 7.75–7.67 (m, 1H), 7.03–6.96 (m, 1H), 5.56 (q, J = 6.7 Hz, 1H), 1.59 (s, 3H), 0.19 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 152.7, 152.5, 148.0, 138.7, 118.7, 112.7, 103.7, 90.1, 61.9, 22.1, 0.0; HRMS (ESI, m/z) calcd for $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 285.1030, obsd 285.1029.

4-Methyl-1-phenylpent-1-yn-3-yl pyridazin-3-ylcarbamate (3.43a)



The title compound was prepared starting from pyridazin-3-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 35%; White solid; ^1H NMR (500 MHz, CDCl_3) δ 8.91 (dd, J = 4.7, 1.4 Hz, 1H), 8.29 (d, J = 9.0 Hz, 1H), 7.97 (s, 1H), 7.51–7.42 (m, 3H), 7.37–7.27 (m, 3H), 5.50 (d, J = 5.5 Hz, 1H), 2.25–2.12 (m, 1H), 1.15 (d, J = 6.8 Hz, 3H), 1.12 (d, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.1, 152.5, 148.3, 132.1, 128.9, 128.5, 128.4, 122.3, 117.3, 86.9, 84.8, 71.6, 33.0, 18.4, 17.9; IR (neat, cm^{-1}): 3363, 2958, 2920, 2850, 1732, 1584, 1525, 1444, 1229, 1061; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 318.1213, obsd 318.1216.

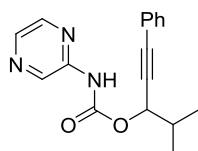
4-Methyl-1-phenylpent-1-yn-3-yl pyrimidin-4-ylcarbamate (3.43b)



The title compound was prepared starting from pyrimidin-4-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 43%;

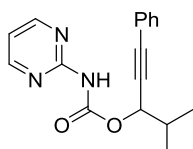
Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 10.11 (s, 1H), 9.02 (s, 1H), 8.64 (d, $J = 5.9$ Hz, 1H), 8.07 (d, $J = 5.9$ Hz, 1H), 7.52–7.43 (m, 2H), 7.35–7.28 (m, 3H), 5.55 (d, $J = 5.8$ Hz, 1H), 2.29–2.15 (m, 1H), 1.15 (d, $J = 6.7$ Hz, 3H), 1.11 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 158.5, 158.3 (2C), 152.4, 132.1, 128.9, 128.5, 122.2, 109.3, 87.1, 84.6, 71.8, 33.0, 18.6, 17.8; IR (neat, cm^{-1}): 3226, 2961, 1755, 1581, 1444, 1206, 1083; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 18.1213, obsd 318.1217.

4-Methyl-1-phenylpent-1-yn-3-yl pyrazin-2-ylcarbamate (3.43c).



The title compound was prepared starting from pyrazin-2-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 38%; White solid; ^1H NMR (500 MHz, CDCl_3) δ 9.44 (s, 1H), 9.36 (s, 1H), 8.38 (d, $J = 2.6$ Hz, 1H), 8.30 (d, $J = 2.6$ Hz, 1H), 7.50–7.44 (m, 2H), 7.38–7.28 (m, 3H), 5.58 (d, $J = 5.6$ Hz, 1H), 2.28–2.16 (m, 1H), 1.15 (d, $J = 6.7$ Hz, 3H), 1.12 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 152.3, 148.7, 141.7, 139.5, 136.3, 132.0, 128.9, 128.5, 122.3, 87.0, 84.8, 71.6, 33.0, 18.6, 17.7; IR (neat, cm^{-1}): 3414, 2910, 1636, 1558, 1418, 1083, 1031; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 318.1213, obsd 318.1216.

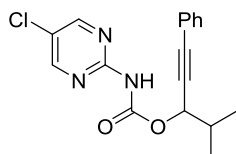
4-Methyl-1-phenylpent-1-yn-3-yl pyrimidin-2-ylcarbamate (3.43d)



The title compound was prepared starting from pyrimidin-2-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 67%;

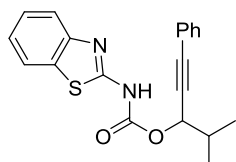
White solid; ^1H NMR (500 MHz, CDCl_3) δ 9.49 (s, 1H), 8.71 (d, $J = 4.9$ Hz, 2H), 7.49–7.41 (m, 2H), 7.37–7.27 (m, 3H), 6.96 (t, $J = 4.9$ Hz, 1H), 5.63 (d, $J = 5.5$ Hz, 1H), 2.28–2.17 (m, 1H), 1.13 (d, $J = 6.7$ Hz, 3H), 1.11 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 158.7, 157.9, 151.0, 132.0, 128.8, 128.5, 122.5, 116.2, 86.7, 85.2, 71.1, 32.9, 18.6, 17.7; IR (neat, cm^{-1}): 3226, 2964, 2920, 1758, 1580, 1443, 1206, 1084; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 318.1213, obsd 318.1216.

4-Methyl-1-phenylpent-1-yn-3-yl (5-chloropyrimidin-2-yl)carbamate (3.43e)



The title compound was prepared starting from 5-chloropyrimidin-2-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 49%; White solid; ^1H NMR (500 MHz, CDCl_3) δ 8.94–8.73 (m, 1H), 8.65–8.58 (m, 2H), 7.49–7.41 (m, 2H), 7.37–7.28 (m, 3H), 5.61 (d, $J = 5.4$ Hz, 1H), 2.26–2.15 (m, 1H), 1.13 (d, $J = 6.7$ Hz, 3H), 1.11 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 157.0, 155.7, 150.7, 132.1, 128.9, 128.4, 125.4, 122.4, 86.9, 84.8, 71.4, 33.0, 18.5, 17.8; IR (neat, cm^{-1}): 3223, 2967, 1740, 1563, 1509, 1491, 1354, 1226, 1133, 1052, 1019; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{16}\text{ClN}_3\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 352.0823, obsd 352.0826.

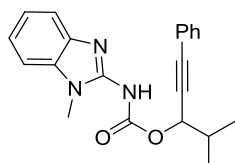
4-Methyl-1-phenylpent-1-yn-3-yl benzo[d]thiazol-2-ylcarbamate (3.43f)



The title compound was prepared starting from benzo[d]thiazol-2-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 62%;

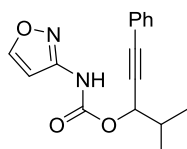
White solid; ^1H NMR (500 MHz, CDCl_3) δ 11.76 (s, 1H), 8.13 (d, $J = 8.1$ Hz, 1H), 7.80 (dd, $J = 7.9, 1.2$ Hz, 1H), 7.51–7.45 (m, 2H), 7.38–7.29 (m, 4H), 7.26–7.23 (m, 1H), 5.71 (d, $J = 5.7$ Hz, 1H), 2.28–2.18 (m, 1H), 1.10 (d, $J = 6.7$ Hz, 3H), 1.08 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 161.8, 153.5, 148.7, 132.1, 131.6, 128.9, 128.5, 126.2, 123.8, 122.4, 121.5, 121.2, 87.4, 84.6, 72.5, 33.1, 18.7, 17.8; IR (neat, cm^{-1}): 3445, 2950, 1634, 1567, 1276, 1236, 1051; HRMS (ESI, m/z) calcd for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_2\text{SNa}$ ($\text{M}+\text{Na}^+$): 373.0981, obsd 373.0974.

4-Methyl-1-phenylpent-1-yn-3-yl (1-methyl-1*H*-benzo[*d*]imidazol-2-yl)carbamate (3.43g)



The title compound was prepared starting from 1-methyl-1*H*-indol-2-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 45%; Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 11.32 (s, 1H), 7.47–7.40 (m, 2H), 7.32–7.13 (m, 7H), 5.46 (d, $J = 6.0$ Hz, 1H), 3.62 (s, 3H), 2.29–2.18 (m, 1H), 1.18 (d, $J = 6.7$ Hz, 3H), 1.12 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 163.5, 154.9, 131.9, 130.6, 128.4, 128.3, 128.2, 123.1, 123.0, 123.0, 110.8, 109.0, 86.8, 85.5, 70.8, 33.0, 28.5, 18.9, 18.1; HRMS (ESI, m/z) calcd for $\text{C}_{21}\text{H}_{21}\text{N}_3\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 370.1526, obsd 370.1525.

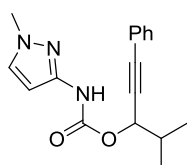
4-Methyl-1-phenylpent-1-yn-3-yl isoxazol-3-ylcarbamate (3.43h)



The title compound was prepared starting from isoxazol-3-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 63%;

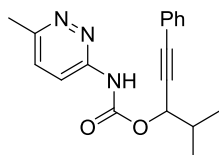
Colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 8.42 (s, 1H), 8.28–8.25 (m, 1H), 7.48–7.43 (m, 2H), 7.34–7.28 (m, 3H), 6.95 (s, 1H), 5.48 (d, $J = 5.6$ Hz, 1H), 2.22–2.12 (m, 1H), 1.14 (d, $J = 6.8$ Hz, 3H), 1.11 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 159.1, 158.0, 152.4, 132.1, 128.8, 128.4, 122.4, 98.6, 86.7, 84.9, 71.7, 33.0, 18.4, 17.8; HRMS (ESI, m/z) calcd for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 307.1053, obsd 307.1053.

4-Methyl-1-phenylpent-1-yn-3-yl (1-methyl-1H-pyrazol-3-yl)carbamate (3.43i)



The title compound was prepared starting from 1-methyl-1H-pyrazol-3-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 43%; Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 9.03 (s, 1H), 7.47–7.40 (m, 2H), 7.34–7.27 (m, 3H), 7.24–7.20 (m, 1H), 6.53 (s, 1H), 5.55 (d, $J = 5.7$ Hz, 1H), 3.86 (s, 3H), 2.20–2.10 (m, 1H), 1.10 (d, $J = 6.8$ Hz, 3H), 1.07 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 153.0, 147.8, 132.0, 131.1, 128.7, 128.4, 122.6, 96.1, 86.3, 85.5, 70.6, 38.9, 33.0, 18.6, 17.7; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 320.1369, obsd 320.1368.

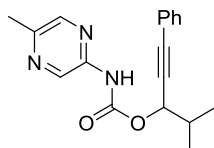
4-Methyl-1-phenylpent-1-yn-3-yl (6-methylpyridazin-3-yl)carbamate (3.43j).



The title compound was prepared starting from 6-methylpyridazin-3-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 76%; White solid; ^1H NMR (500 MHz, CDCl_3) δ 8.27–8.10 (m, 2H), 7.50–7.43 (m, 2H), 7.37–7.27 (m, 4H), 5.48 (d, $J = 5.5$ Hz, 1H), 2.65 (s, 3H), 2.23–2.13 (m, 1H), 1.14 (d,

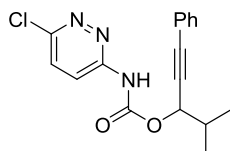
$J = 6.8$ Hz, 3H), 1.11 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 156.6, 153.5, 152.8, 132.1, 129.0, 128.8, 128.4, 122.4, 117.7, 86.7, 85.0, 71.4, 33.0, 21.7, 18.4, 17.8. IR (neat, cm^{-1}): 3430, 2963, 1731, 1531, 1353, 1227, 1118, 1036; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 332.1369, obsd 332.1368.

4-Methyl-1-phenylpent-1-yn-3-yl (5-methylpyrazin-2-yl)carbamate (3.43l).



The title compound was prepared starting from 5-methylpyrazin-2-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 43%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 9.26 (d, $J = 7.2$ Hz, 1H), 8.35 (s, 1H), 8.23–8.15 (m, 1H), 7.49–7.43 (m, 2H), 7.36–7.27 (m, 3H), 5.59–5.53 (m, 1H), 2.49 (d, $J = 4.9$ Hz, 3H), 2.26–2.15 (m, 1H), 1.14 (d, $J = 6.8$ Hz, 3H), 1.12 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 152.4, 148.3, 146.2, 141.0, 134.9, 132.1, 128.9, 128.5, 122.3, 86.9, 84.9, 71.4, 33.0, 20.9, 18.5, 17.7; IR (neat, cm^{-1}): 3217, 2965, 1738, 1567, 1511, 1358, 1228, 1055, 756; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 332.1369, obsd 332.1373.

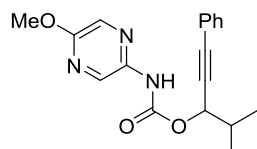
4-Methyl-1-phenylpent-1-yn-3-yl (6-chloropyridazin-3-yl)carbamate (3.43k).



The title compound was prepared starting from 6-chloropyridazin-3-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 37%; Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 8.45–8.29 (m, 2H), 7.53–7.43 (m, 3H), 7.36–7.28 (m, 3H), 5.48 (d, $J = 5.4$ Hz, 1H), 2.24–2.14 (m, 1H), 1.15 (d, $J = 6.7$ Hz, 3H), 1.12 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 154.5, 152.5, 152.1,

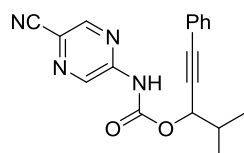
132.1, 130.1, 128.9, 128.5, 122.3, 120.0, 87.0, 84.7, 77.5, 77.2, 76.9, 71.9, 33.0, 18.4, 17.9; IR (neat, cm^{-1}): 3222, 2967, 1740, 1562, 1509, 1445, 1354, 1226, 1133, 1052, 1018; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{16}\text{ClN}_3\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 352.0823, obsd 352.0828.

4-Methyl-1-phenylpent-1-yn-3-yl (5-methoxypyrazin-2-yl)carbamate (3.43m).



The title compound was prepared starting from 5-methoxypyrazin-2-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 42%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 8.83 (s, 1H), 8.21–7.92 (m, 2H), 7.49–7.44 (m, 2H), 7.34–7.29 (m, 3H), 5.53 (d, $J = 5.5$ Hz, 1H), 3.94 (s, 3H), 2.23–2.14 (m, 1H), 1.14 (d, $J = 6.7$ Hz, 3H), 1.11 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 157.3, 152.4, 142.1, 132.1, 131.8, 130.8, 128.8, 128.4, 122.5, 86.7, 85.1, 71.2, 54.1, 33.1, 18.6, 17.8; IR (neat, cm^{-1}): 3224, 2965, 1732, 1530, 1368, 1227, 1028, 756; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 348.1319, obsd 348.1322.

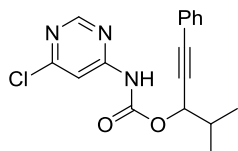
4-Methyl-1-phenylpent-1-yn-3-yl (5-cyanopyrazin-2-yl)carbamate (3.43n).



The title compound was prepared starting from 5-aminopyrazine-2-carbonitrile and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 56%; Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 9.53 (d, $J = 1.5$ Hz, 1H), 8.77 (s, 1H), 8.62 (d, $J = 1.5$ Hz, 1H), 7.50–7.42 (m, 2H), 7.39–7.27 (m, 3H), 5.57 (d, $J = 5.6$ Hz, 1H), 2.27–2.19 (m, 1H), 1.16 (d, $J = 6.7$ Hz, 3H), 1.13 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR

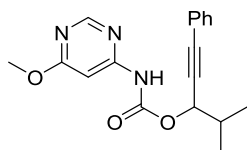
(126 MHz, CDCl_3) δ 151.5, 149.9, 146.3, 136.8, 132.1, 129.1, 128.5, 124.6, 121.9, 115.7, 87.5, 84.0, 72.6, 33.0, 18.5, 17.8; IR (neat, cm^{-1}): 3222, 2969, 2876, 2235, 1747, 1562, 1368, 1221, 1056; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{16}\text{N}_4\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 343.1165, obsd 343.1164.

4-Methyl-1-phenylpent-1-yn-3-yl (6-chloropyrimidin-4-yl)carbamate (3.43o)



The title compound was prepared starting from 6-chloropyrimidin-4-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 61%; White solid; ^1H NMR (500 MHz, CDCl_3) δ 9.72 (s, 1H), 8.77 (s, 1H), 8.13 (s, 1H), 7.50–7.44 (m, 2H), 7.38–7.28 (m, 3H), 5.54 (d, $J = 5.8$ Hz, 1H), 2.25–2.16 (m, 1H), 1.14 (d, $J = 6.7$ Hz, 3H), 1.11 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 162.7, 159.2, 158.2, 152.1, 132.1, 129.0, 128.5, 122.1, 108.9, 87.4, 84.3, 72.2, 33.0, 18.6, 17.9; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{16}\text{ClN}_3\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 352.0823, obsd 352.0823.

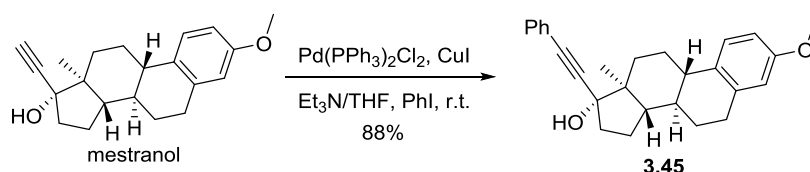
4-Methyl-1-phenylpent-1-yn-3-yl (6-methoxypyrimidin-4-yl)carbamate (3.43p)



The title compound was prepared starting from 6-methoxypyrimidin-4-amine and 4-methyl-1-phenylpent-1-yn-3-ol by following the General Procedure A. Yield = 74%; White solid; ^1H NMR (500 MHz, CDCl_3) δ 10.00 (s, 1H), 8.68–8.63 (m, 1H), 7.53–7.47 (m, 2H), 7.40 (s, 1H), 7.36–7.28 (m, 3H), 5.53 (d, $J = 5.8$ Hz, 1H), 3.98 (s, 3H), 2.27–2.16 (m, 1H), 1.14 (d, $J = 6.7$ Hz, 3H), 1.10 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 171.4, 159.0, 157.9, 152.5, 132.1, 128.8, 128.4, 122.4, 93.6,

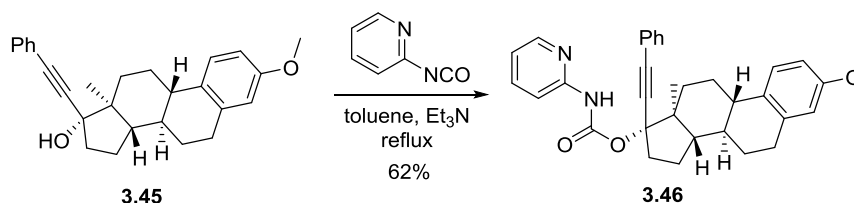
87.0, 84.8, 71.5, 54.3, 33.0, 18.6, 17.8; HRMS (ESI, m/z) calcd for $C_{18}H_{19}N_3O_3Na$ ($M+Na^+$): 348.1319, obsd 348.1316.

(8*R*,9*S*,13*S*,14*S*,17*S*)-3-Methoxy-13-methyl-17-(phenylethynyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-ol (3.45)



The title compound was prepared starting from 2-bromothiophene and 4-methylpent-1-yn-3-ol by following the General Procedure C. Yield = 88%; White solid; 1H NMR (500 MHz, $CDCl_3$) δ 7.50–7.40 (m, 2H), 7.35–7.27 (m, 3H), 7.22 (d, $J = 8.6$ Hz, 1H), 6.71 (dd, $J = 8.6, 2.8$ Hz, 1H), 6.66–6.59 (m, 1H), 3.77 (s, 3H), 2.90–2.80 (m, 2H), 2.47–2.34 (m, 2H), 2.29–2.19 (m, 1H), 2.16–2.05 (m, 1H), 2.05 (s, 1H), 2.03–1.94 (m, 1H), 1.93–1.73 (m, 4H), 1.57–1.31 (m, 4H), 0.93 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.6, 138.1, 132.7, 131.8, 128.5, 128.4, 126.5, 123.1, 114.0, 111.7, 93.0, 86.1, 80.5, 55.4, 49.9, 47.8, 43.8, 39.7, 39.2, 33.3, 30.0, 27.4, 26.7, 23.1, 13.1; HRMS (ESI, m/z) calcd for $C_{27}H_{30}O_2Na$ ($M+Na^+$): 409.2138, obsd 409.2136.

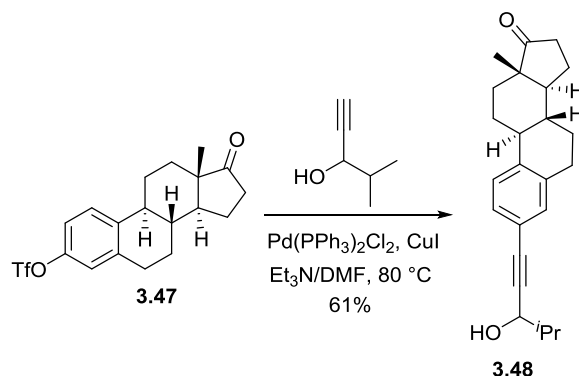
(8*R*,9*S*,13*S*,14*S*,17*S*)-3-Methoxy-13-methyl-17-(phenylethynyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl pyridin-2-ylcarbamate (3.46)



The title compound was prepared starting from 2-aminopyridine and compound 3.45 by following the General Procedure A. Yield = 62%; White solid; 1H NMR (500 MHz,

CDCl₃) δ 8.38 (s, 1H), 8.32–8.27 (m, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.71–7.64 (m, 1H), 7.51–7.45 (m, 2H), 7.32–7.27 (m, 3H), 7.25–7.20 (m, 1H), 6.97 (ddd, J = 7.3, 5.0, 1.0 Hz, 1H), 6.72 (dd, J = 8.6, 2.7 Hz, 1H), 6.63 (d, J = 2.7 Hz, 1H), 3.78 (s, 3H), 2.96–2.80 (m, 3H), 2.45–2.36 (m, 1H), 2.36–2.22 (m, 2H), 2.21–2.11 (m, 1H), 2.00–1.80 (m, 4H), 1.58–1.35 (m, 4H), 0.96 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 157.6, 152.1, 152.1, 147.9, 138.5, 138.1, 132.5, 132.1, 128.5, 128.3, 126.5, 123.0, 118.8, 114.0, 112.8, 111.7, 89.2, 87.2, 86.1, 55.4, 48.9, 48.6, 43.7, 39.4, 38.0, 33.8, 30.0, 27.5, 26.6, 23.6, 13.9; HRMS (ESI, m/z) calcd for C₃₃H₃₄N₂O₃Na (M+Na⁺): 529.2462, obsd 529.2462.

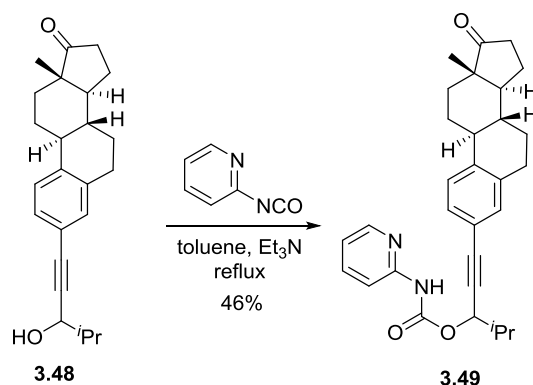
(8R,9S,13S,14S)-3-(3-Hydroxy-4-methylpent-1-yn-1-yl)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[*a*]phenanthren-17-one (3.49).



To a mixture of **3.47** (1.61 g, 4.0 mmol, 1.0 equiv), Pd(PPh₃)₂Cl₂ (0.4 mmol) and CuI (0.4 mmol) in DMF (40 mL) was added Et₃N (2.77 mL, 20.0 mmol, 5.0 equiv), and 4-methylpent-1-yn-3-ol (2.1 mL, 20.0 mmol, 5.0 equiv), then the reaction was stirred at 80 °C for 12 h. Monitored by TLC, when the reaction was completed, the mixture was quenched with water and extracted with EtOAc (50 mL x 3). The combined organic phases are washed with brine and dried over Na₂SO₄. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography to afford product **3.48** as a pale yellow solid (855 mg, 61% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.24–7.20 (m, 2H), 7.18 (s, 1H), 4.41–4.35 (m, 1H), 2.90–2.85 (m, 2H), 2.54–2.47 (m, 1H), 2.42–2.34 (m, 1H), 2.29–2.22 (m, 1H), 2.19–2.11 (m, 1H),

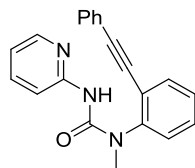
2.08–1.93 (m, 5H), 1.65–1.39 (m, 6H), 1.07 (d, $J = 6.7$ Hz, 3H), 1.05 (d, $J = 6.8$ Hz, 3H), 0.90 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 221.0, 140.4, 136.7, 132.3, 129.2, 125.5, 120.2, 88.5, 85.7, 68.5, 50.6, 48.1, 44.5, 38.1, 36.0, 34.9, 31.7, 29.2, 26.5, 25.7, 21.7, 18.4, 17.7, 14.0; IR (neat, cm^{-1}): 3435, 2928, 1737, 1496, 1468, 1084, 037, 822; HRMS (ESI, m/z) calcd for $\text{C}_{24}\text{H}_{30}\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 373.2138, obsd 373.2138.

4-Methyl-1-((8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl)pent-1-yn-3-yl pyridin-2-ylcarbamate (3.50)



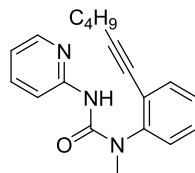
The title compound was prepared starting from compound **3.48** and 2-aminopyridine by following the General Procedure A. Yield = 46%; White solid; ^1H NMR (500 MHz, CDCl_3) δ 9.42–9.34 (m, 1H), 8.45–8.40 (m, 1H), 8.05 (d, $J = 8.4$ Hz, 1H), 7.73–7.67 (m, 1H), 7.26–7.19 (m, 3H), 7.00–6.95 (m, 1H), 5.53 (d, $J = 5.6$ Hz, 1H), 2.91–2.85 (m, 2H), 2.54–2.47 (m, 1H), 2.43–2.37 (m, 1H), 2.32–2.26 (m, 1H), 2.21–2.11 (m, 2H), 2.08–1.95 (m, 3H), 1.65–1.41 (m, 6H), 1.12 (d, $J = 6.8$ Hz, 3H), 1.09 (d, $J = 6.8$ Hz, 3H), 0.91 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 220.9, 152.9, 152.2, 148.0, 140.7, 138.6, 136.7, 132.5, 129.3, 125.5, 119.9, 118.9, 112.7, 86.6, 84.7, 70.9, 50.7, 48.1, 44.6, 38.1, 36.0, 33.1, 31.7, 29.2, 26.5, 25.8, 21.7, 18.6, 17.8, 14.0; IR (neat, cm^{-1}): 3184, 1736, 1588, 1439, 1306, 1218, 1060, 779, 737; HRMS (ESI, m/z) calcd for $\text{C}_{30}\text{H}_{34}\text{N}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 493.2462, obsd 493.2462.

1-Methyl-1-(2-(phenylethynyl)phenyl)-3-(pyridin-2-yl)urea (3.52a)



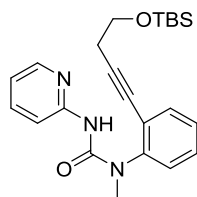
The title compound was prepared starting from 2-aminopyridine and *N*-methyl-2-(phenylethynyl)aniline by following the General Procedure **B**. Yield = 51%; White solid; ^1H NMR (500 MHz, CDCl_3) δ 8.16–8.13 (m, 1H), 8.09–8.06 (m, 1H), 7.66–7.63 (m, 1H), 7.62–7.57 (m, 1H), 7.50–7.44 (m, 2H), 7.43 (dd, $J = 7.0, 2.2$ Hz, 1H), 7.40–7.36 (m, 2H), 7.33–7.29 (m, 3H), 6.91 (s, 1H), 6.87–6.84 (m, 1H), 3.39 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 154.0, 152.7, 147.5, 143.5, 138.2, 133.9, 131.9, 130.3, 129.0, 128.9, 128.8, 128.5, 123.4, 122.7, 118.4, 112.9, 95.4, 85.0, 36.8; IR (neat, cm^{-1}): 3413, 2920, 1681, 1575, 1512, 1431, 1302, 1082, 755; HRMS (ESI, m/z) calcd for $\text{C}_{21}\text{H}_{18}\text{N}_3\text{O}$ ($\text{M}+\text{H}^+$): 328.1444, obsd 328.1445.

1-(2-(Hex-1-yn-1-yl)phenyl)-1-methyl-3-(pyridin-2-yl)urea (3.52c).



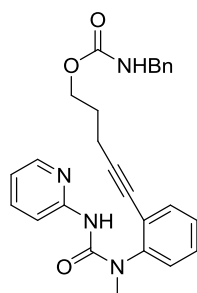
The title compound was prepared starting from 2-aminopyridine and 2-(hex-1-yn-1-yl)-*N*-methylaniline by following the General Procedure **B**. Yield = 76%; Light yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 8.15 (d, $J = 8.5$ Hz, 1H), 8.09 (d, $J = 5.0$ Hz, 1H), 7.66–7.60 (m, 1H), 7.52 (d, $J = 7.2$ Hz, 1H), 7.39–7.29 (m, 3H), 6.88 (dd, $J = 7.2, 5.0$ Hz, 1H), 6.84 (s, 1H), 3.32 (s, 3H), 2.35 (t, $J = 7.2$ Hz, 2H), 1.51–1.45 (m, 2H), 1.40–1.33 (m, 2H), 0.84 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 153.9, 152.8, 147.5, 143.3, 138.1, 134.1, 129.5, 128.8, 128.6, 124.1, 118.3, 112.8, 97.0, 76.3, 36.6, 30.7, 22.0, 19.4, 13.7; IR (neat, cm^{-1}): 3415, 2958, 1685, 1576, 1433, 1304, 1148, 775, 747; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{22}\text{N}_3\text{O}$ ($\text{M}+\text{H}^+$): 308.1757, obsd 308.1757.

1-(2-(4-((*tert*-Butyldimethylsilyl)oxy)but-1-yn-1-yl)phenyl)-1-methyl-3-(pyridin-2-yl)urea (3.52d).



The title compound was prepared starting from 2-aminopyridine and 2-(4-((*tert*-butyldimethylsilyl)oxy)but-1-yn-1-yl)-*N*-methylaniline by following the General Procedure **B**. Yield = 83%; Yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 8.14 (d, $J = 8.5$ Hz, 1H), 8.11–8.05 (m, 1H), 7.66–7.58 (m, 1H), 7.54–7.48 (m, 1H), 7.40–7.28 (m, 3H), 6.90–6.85 (m, 1H), 6.82 (s, 1H), 3.70 (t, $J = 7.3$ Hz, 2H) 3.30 (s, 3H), 2.57 (t, $J = 7.3$ Hz, 2H), 0.86 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 153.9, 152.8, 147.6, 143.5, 138.1, 134.2, 129.8, 128.8, 128.6, 123.8, 118.3, 112.8, 93.6, 77.3, 61.8, 36.6, 26.0, 24.1, 18.4, -5.1 ; IR (neat, cm^{-1}): 3410, 2928, 2816, 1644, 1601, 1575, 1513, 1434, 1305, 1100, 1055, 776, 747; HRMS (ESI, m/z) calcd for $\text{C}_{23}\text{H}_{31}\text{N}_3\text{O}_2\text{SiNa}$ ($\text{M}+\text{Na}^+$): 432.2078, obsd 432.2080.

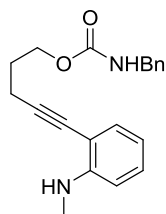
5-(2-(1-Methyl-3-(pyridin-2-yl)ureido)phenyl)pent-4-yn-1-yl benzylcarbamate (3.52e)



The title compound was prepared starting from 2-aminopyridine and 5-(2-(methylamino)phenyl)pent-4-yn-1-yl benzylcarbamate by following the General Procedure **B**. Yield = 53%; Yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 8.11 (d, $J = 8.5$ Hz, 1H), 8.09–8.05 (m, 1H), 7.63–7.56 (m, 1H), 7.52 (dd, $J = 7.6, 1.7$ Hz, 1H),

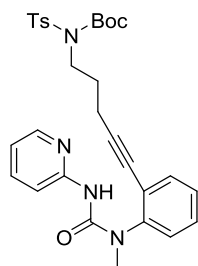
7.41–7.23 (m, 8H), 6.90–6.78 (m, 2H), 5.26 (s, 1H), 4.35 (d, $J = 6.0$ Hz, 2H), 4.14 (t, $J = 6.2$ Hz, 2H), 3.31 (s, 3H), 2.45 (t, $J = 7.0$ Hz, 2H), 1.88–1.81 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 156.7, 154.0, 152.7, 147.6, 143.4, 138.7, 138.2, 134.1, 129.8, 128.8, 128.7, 127.7, 127.6, 123.7, 118.3, 112.8, 95.4, 76.9, 63.7, 45.2, 36.7, 28.1, 16.5; IR (neat, cm^{-1}): 3412, 3328, 3063, 2928, 1682, 1515, 1433, 1339, 1304, 1241, 1145, 775, 754; HRMS (ESI, m/z) calcd for $\text{C}_{26}\text{H}_{26}\text{N}_4\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 465.1897, obsd 465.1901.

5-(2-(Methylamino)phenyl)pent-4-yn-1-yl benzylcarbamate (3.52e')



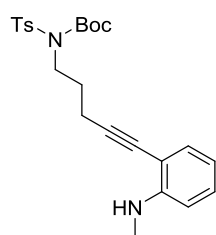
The title compound was prepared starting from 2-iodo-*N*-methylaniline and pent-4-yn-1-yl benzylcarbamate by following the General Procedure C. Yield = 83%; Yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.36–7.29 (m, 2H), 7.29–7.21 (m, 4H), 7.21–7.13 (m, 1H), 6.59 (t, $J = 7.5$ Hz, 1H), 6.55 (d, $J = 8.2$ Hz, 1H), 5.23–4.83 (m, 1H), 4.76–4.60 (m, 1H), 4.35 (d, $J = 6.0$ Hz, 2H), 4.28 (t, $J = 6.2$ Hz, 2H), 2.86 (d, $J = 5.2$ Hz, 3H), 2.56 (t, $J = 7.0$ Hz, 2H), 1.98–1.88 (m, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 156.7, 150.0, 138.6, 132.1, 129.5, 128.8, 127.7, 127.6, 116.2, 109.1, 108.2, 94.5, 78.0, 63.9, 45.3, 30.5, 28.6, 16.7; IR (neat, cm^{-1}): 3411, 2917, 1711, 1512, 1254, 1132, 1082, 746; HRMS (ESI, m/z) calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 345.1573, obsd 345.1571.

***tert*-Butyl (5-(2-(1-methyl-3-(pyridin-2-yl)ureido)phenyl)pent-4-yn-1-yl)(tosyl)-carbamate (3.52f)**



The title compound was prepared starting from 2-aminopyridine and *tert*-butyl (5-(2-(methylamino)phenyl)pent-4-yn-1-yl)(tosyl)carbamate by following the General Procedure **B**. Yield = 41%; Yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 8.15 (d, $J = 8.5$ Hz, 1H), 8.08 (dd, $J = 5.1, 1.7$ Hz, 1H), 7.79 (d, $J = 8.1$ Hz, 2H), 7.64–7.52 (m, 2H), 7.42–7.28 (m, 5H), 6.90–6.84 (m, 2H), 3.90 (t, $J = 6.2$ Hz, 2H), 3.34 (s, 3H), 2.46 (t, $J = 6.2$ Hz, 2H), 2.43 (s, 3H), 2.03–1.95 (m, 2H), 1.31 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 154.0, 152.8, 151.0, 147.5, 144.2, 143.4, 138.2, 137.5, 134.3, 129.7, 129.4, 128.8, 128.6, 128.0, 123.8, 118.3, 112.8, 95.2, 84.4, 46.5, 36.7, 29.2, 28.0, 21.8, 17.3; IR (neat, cm^{-1}): 3415, 2930, 1727, 1684, 1576, 1515, 1433, 1354, 1304, 1156, 1086, 993, 774; HRMS (ESI, m/z) calcd for $\text{C}_{30}\text{H}_{35}\text{N}_4\text{O}_5\text{S}$ ($\text{M}+\text{H}^+$): 563.2323, obsd 563.2327.

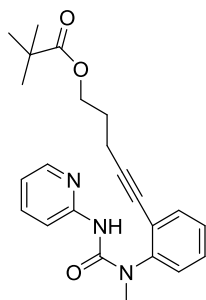
***tert*-Butyl (5-(2-(methylamino)phenyl)pent-4-yn-1-yl)(tosyl)carbamate (3.52f')**



The title compound was prepared starting from 2-iodo-*N*-methylaniline and *tert*-butyl pent-4-yn-1-yl(tosyl)carbamate by following the General Procedure **C**. Yield = 78%; Yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.81–7.76 (m, 2H), 7.30 (d, $J = 8.1$ Hz, 2H), 7.27–7.21 (m, 1H), 7.21–7.13 (m, 1H), 6.62–6.52 (m, 2H), 4.90 (d, $J = 4.0$ Hz, 1H), 4.02 (t, $J = 7.4$ Hz, 2H), 2.87 (d, $J = 4.0$ Hz, 3H), 2.57 (t, $J = 6.8$ Hz, 2H), 2.43 (s, 3H), 2.11–2.03 (m, 2H), 1.34 (s, 9H). ^{13}C NMR (126 MHz, CDCl_3) δ 151.1, 150.2, 144.3,

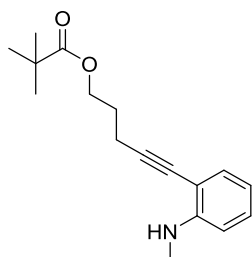
137.5, 132.0, 129.4, 127.9, 115.9, 108.9, 108.0, 94.2, 84.5, 78.2, 46.4, 30.3, 29.4, 28.0, 21.7, 17.3; IR (neat, cm^{-1}): 3413, 2921, 1726, 1599, 1355, 1287, 1156, 1086, 748; HRMS (ESI, m/z) calcd for $\text{C}_{24}\text{H}_{30}\text{N}_2\text{O}_4\text{SNa}$ ($\text{M}+\text{Na}^+$): 465.1818, obsd 465.1817.

5-(2-(1-Methyl-3-(pyridin-2-yl)ureido)phenyl)pent-4-yn-1-yl pivalate (3.52g)



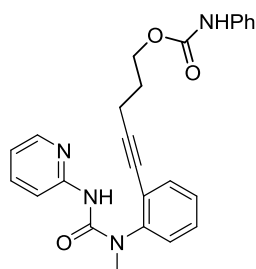
The title compound was prepared starting from 2-aminopyridine and 5-(2-(methylamino)phenyl)pent-4-yn-1-yl pivalate by following the General Procedure B. Yield = 43%; Yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 8.14 (d, $J = 8.5$ Hz, 1H), 8.10 (d, $J = 5.2$ Hz, 1H), 7.63 (ddd, $J = 8.8, 7.4, 1.9$ Hz, 1H), 7.52 (dd, $J = 7.7, 1.6$ Hz, 1H), 7.42–7.30 (m, 3H), 6.89 (dd, $J = 7.4, 4.9$ Hz, 1H), 6.85 (s, 1H), 4.10 (t, $J = 6.2$ Hz, 2H), 3.31 (s, 3H), 2.45 (t, $J = 7.2$ Hz, 2H), 1.89–1.80 (m, 2H), 1.18 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 178.6, 154.0, 152.8, 147.6, 143.4, 138.2, 134.2, 129.9, 128.8, 128.7, 123.7, 118.4, 112.8, 95.2, 77.5, 63.0, 38.9, 36.7, 28.0, 27.4, 16.5; IR (neat, cm^{-1}): 3414, 2920, 1727, 1682, 1575, 1514, 1433, 1304, 1083; HRMS (ESI, m/z) calcd for $\text{C}_{23}\text{H}_{28}\text{N}_3\text{O}_3$ ($\text{M}+\text{H}^+$): 394.2125, obsd 394.2128.

5-(2-(Methylamino)phenyl)pent-4-yn-1-yl pivalate (3.52g')



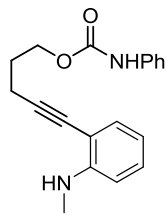
The title compound was prepared starting from 2-iodo-*N*-methylaniline and pent-4-yn-1-yl pivalate by following the General Procedure C. Yield = 79%; Colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 7.24 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.21–7.15 (m, 1H), 6.63–6.53 (m, 2H), 4.66 (s, 1H), 4.24 (t, $J = 6.3$ Hz, 2H), 2.90 (s, 3H), 2.56 (t, $J = 7.0$ Hz, 2H), 2.00–1.90 (m, 2H), 1.22 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 178.7, 150.0, 132.1, 129.5, 116.2, 109.0, 108.0, 94.2, 78.1, 63.0, 39.0, 30.5, 28.2, 27.4, 16.6; IR (neat, cm^{-1}): 3415, 2960, 1727, 1511, 1284, 1157, 747; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 296.1621, obsd 296.1625.

5-(2-(1-Methyl-3-(pyridin-2-yl)ureido)phenyl)pent-4-yn-1-yl phenylcarbamate (3.52h)



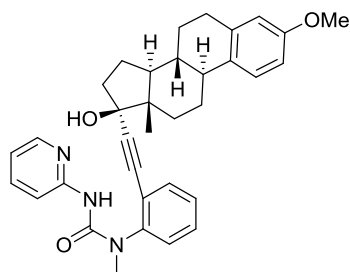
The title compound was prepared starting from 2-aminopyridine and 4-(2-(methylamino)phenyl)but-3-yn-1-yl phenylcarbamate by following the General Procedure B. Yield = 59%; Colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 8.18–8.06 (m, 2H), 7.63–7.54 (m, 1H), 7.51–7.34 (m, 5H), 7.32–7.24 (m, 4H), 7.04 (t, $J = 7.4$ Hz, 1H), 6.92–6.84 (m, 2H), 4.30–4.06 (m, 2H), 3.32 (s, 3H), 2.49 (t, $J = 6.8$ Hz, 2H), 1.91–1.83 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 154.1, 153.7, 152.7, 147.5, 143.3, 138.5, 138.3, 134.0, 129.8, 129.1, 128.7, 128.7, 123.6, 123.2, 118.6, 118.4, 112.9, 95.2, 63.6, 36.7, 27.7, 16.5; IR (neat, cm^{-1}): 3414, 3066, 2928, 1682, 1515, 1433, 1339, 1314, 1241, 1145, 775; HRMS (ESI, m/z) calcd for $\text{C}_{25}\text{H}_{24}\text{N}_4\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 451.1741, obsd 451.1745.

4-(2-(Methylamino)phenyl)but-3-yn-1-yl phenylcarbamate (3.52h')



The title compound was prepared starting from 2-iodo-*N*-methylaniline and pent-4-yn-1-yl pivalate by following the General Procedure C. Yield = 82%; Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.38–7.31 (m, 2H), 7.31–7.23 (m, 3H), 7.21–7.16 (m, 1H), 7.04 (t, $J = 7.3$ Hz, 1H), 6.88 (s, 1H), 6.64–6.55 (m, 2H), 4.71 (s, 1H), 4.35 (t, $J = 6.1$ Hz, 2H), 2.88 (s, 3H), 2.59 (t, $J = 6.8$ Hz, 2H), 2.02–1.94 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 153.7, 150.0, 138.0, 132.1, 129.5, 129.2, 123.5, 118.7, 116.4, 109.2, 108.2, 94.5, 78.1, 64.2, 30.5, 28.4, 16.8.

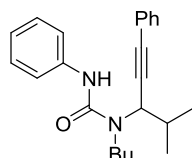
1-(2-(((8*R*,9*S*,13*S*,14*S*,17*S*)-17-Hydroxy-3-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl)ethynyl)phenyl)-1-methyl-3-(pyridin-2-yl)urea (3.52i)



The title compound was prepared starting from 2-aminopyridine and (8*R*,9*S*,13*S*,14*S*,17*S*)-3-methoxy-13-methyl-17-((2-(methylamino)phenyl)ethynyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-ol by following the General Procedure B. Yield = 51%; Yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 8.16 (d, $J = 8.5$ Hz, 1H), 8.09 (dd, $J = 5.0, 1.7$ Hz, 1H), 7.66–7.52 (m, 2H), 7.43–7.32 (m, 3H), 7.18 (d, $J = 8.6$ Hz, 1H), 6.90–6.83 (m, 2H), 6.75–6.70 (m, 1H), 6.65–6.61 (m, 1H), 6.16–6.11 (m, 1H), 3.78 (s, 3H), 3.35 (s, 3H), 2.93–2.79 (m, 2H), 2.36–2.20 (m, 3H), 2.14–2.03 (m, 1H), 1.97–1.86 (m, 2H), 1.64–1.36 (m, 6H), 1.35–1.22 (m,

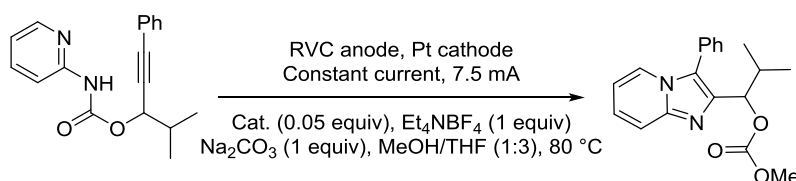
1H), 0.82 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 157.6, 153.7, 152.8, 147.6, 143.0, 138.1, 138.0, 137.7, 137.1, 134.2, 133.0, 130.1, 129.0, 128.8, 126.2, 123.8, 118.3, 114.0, 113.0, 111.6, 91.2, 88.3, 55.6, 55.4, 48.7, 44.4, 37.7, 36.8, 34.6, 32.3, 29.9, 28.0, 26.6, 16.5.

1-Butyl-1-(4-methyl-1-phenylpent-1-yn-3-yl)-3-(pyridin-2-yl)urea (3.52j)



The title compound was prepared starting from 2-aminopyridine and *N*-butyl-4-methyl-1-phenylpent-1-yn-3-amine by following the General Procedure B. Yield = 51%; Light yellow oil; ¹H NMR (500 MHz, CDCl₃) δ 8.22 (dd, *J* = 4.9, Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.69–7.59 (m, 1H), 7.47–7.41 (m, 2H), 7.36–7.27 (m, 4H), 6.94 (dd, *J* = 7.3, 4.9 Hz, 1H), 4.96 (d, *J* = 9.2 Hz, 1H), 3.56–3.46 (m, 1H), 3.41–3.33 (m, 1H), 2.17–2.07 (m, 1H), 1.94–1.84 (m, 1H), 1.83–1.72 (m, 1H), 1.45–1.36 (m, 2H), 1.17 (d, *J* = 6.6 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.97 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 154.2, 152.9, 147.7, 138.2, 131.8, 128.5 (2C), 122.9, 118.6, 113.5, 87.2, 85.6, 55.1, 45.6, 33.1, 31.8, 20.6, 19.9, 19.5, 14.0; IR (neat, cm⁻¹): 3444, 1960, 1667, 1577, 1515, 1432, 1302, 1218, 756; HRMS (ESI, *m/z*) calcd for C₂₃H₂₉N₂O (M+H⁺): 350.2227, obsd 350.2227.

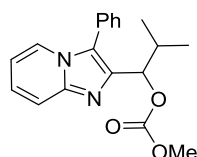
General procedure for the electrolysis (THF/MeOH = 1/3, carbamate-derived substrate)



A 25 mL three-necked round-bottomed flask was charged with catalyst (0.015 mmol), the substrate (0.3 mmol), Et₄NBF₄ (0.3 mmol), and Na₂CO₃ (0.3 mmol). The flask

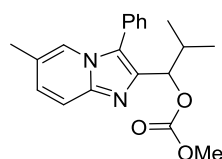
was equipped with a condenser, a reticulated vitreous carbon (100 PPI) anode and a platinum plate (1 cm x 1 cm) cathode and then flushed with argon. THF (7.5 mL) and MeOH (2.5 mL) were added. The electrolysis was carried out at 80 °C (oil bath temperature) using a constant current of 7.5 mA until complete consumption of the substrate (monitored by TLC or ¹H NMR). The reaction mixture was cooled to RT and concentrated under reduced pressure. The residue was chromatographed through silica gel eluting with ethyl acetate/hexanes to give the desired product.

Methyl (2-methyl-1-(3-phenylimidazo[1,2-a]pyridin-2-yl)propyl) carbonate (3.27a)



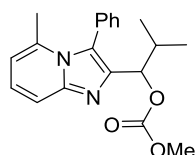
Yield = 87%; Pale yellow oil; ¹H NMR (500 MHz, CDCl₃) δ 7.98–7.91 (m, 1H), 7.64 (dt, *J* = 9.1, 1.1 Hz, 1H), 7.56 (d, *J* = 4.5 Hz, 4H), 7.52–7.45 (m, 1H), 7.22–7.14 (m, 1H), 6.76–6.68 (m, 1H), 5.45 (d, *J* = 8.7 Hz, 1H), 3.68 (s, 3H), 2.53–2.42 (m, 1H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.75 (d, *J* = 6.7 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 155.7, 144.9, 141.2, 130.5, 129.4, 129.0, 128.7, 124.7, 123.6, 123.5, 118.1, 112.4, 79.3, 54.6, 32.8, 18.9 (2C); IR (neat, cm⁻¹): 2960, 2927, 2872, 1745, 1634, 1506, 1442, 1345, 1262, 967, 754, 702; HRMS (ESI, *m/z*) calcd for C₁₉H₂₀N₂O₃Na (M+Na⁺): 347.1366, obsd 347.1368.

Methyl (2-methyl-1-(6-methyl-3-phenylimidazo[1,2-a]pyridin-2-yl)propyl) carbonate (3.27b)



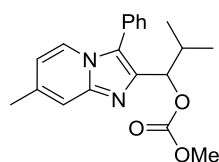
Yield = 75%; Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.71 (s, 1H), 7.59–7.52 (m, 5H), 7.51–7.43 (m, 1H), 7.07–7.00 (m, 1H), 5.42 (d, $J = 8.8$ Hz, 1H), 3.68 (s, 3H), 2.55–2.40 (m, 1H), 2.24 (s, 3H), 1.02 (d, $J = 6.7$ Hz, 3H), 0.74 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.7, 144.0, 140.9, 130.5, 129.3, 128.9, 128.9, 127.9, 123.2, 122.0, 121.1, 117.4, 79.3, 54.6, 32.8, 18.9, 18.9, 18.4; IR (neat, cm^{-1}): 2919, 2927, 2872, 1644, 1490, 1417, 1300, 1083, 969, 766, 704; HRMS (ESI, m/z) calcd for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}^+$): 339.1703, obsd 339.1703.

Methyl (2-methyl-1-(5-methyl-3-phenylimidazo[1,2-*a*]pyridin-2-yl)propyl) carbonate (3.27c)



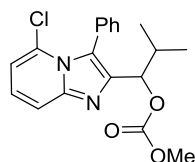
Yield = 82%; Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.68–7.62 (m, 1H), 7.60–7.54 (m, 1H), 7.51–7.44 (m, 2H), 7.44–7.36 (m, 1H), 7.34–7.30 (m, 1H), 7.13–7.05 (m, 1H), 6.44 (dt, $J = 6.8, 1.2$ Hz, 1H), 5.13 (d, $J = 8.9$ Hz, 1H), 3.67 (s, 3H), 2.52–2.38 (m, 1H), 2.04 (s, 3H), 1.00 (d, $J = 6.7$ Hz, 3H), 0.75 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.6, 146.2, 142.0, 136.7, 133.0, 132.8, 131.1, 129.1, 127.8, 127.2, 124.8, 124.4, 116.2, 113.5, 79.0, 54.6, 32.6, 21.6, 19.0, 18.9; IR (neat, cm^{-1}): 2960, 2927, 2872, 1745, 1638, 1516, 1442, 1261, 1082, 966, 770, 704; HRMS (ESI, m/z) calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 361.1523, obsd 361.1522.

Methyl (2-methyl-1-(7-methyl-3-phenylimidazo[1,2-*a*]pyridin-2-yl)propyl) carbonate (3.27d)



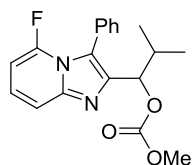
Yield = 78%; Light yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 7.83 (d, $J = 7.0$ Hz, 1H), 7.58–7.51 (m, 4H), 7.49–7.44 (m, 1H), 7.39 (s, 1H), 6.56 (dd, $J = 7.0, 1.6$ Hz, 1H), 5.41 (d, $J = 8.8$ Hz, 1H), 3.68 (s, 3H), 2.52–2.43 (m, 1H), 2.38 (s, 3H), 1.02 (d, $J = 6.7$ Hz, 3H), 0.74 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.8, 145.4, 140.7, 135.7, 130.4, 129.3, 128.8 (2C), 123.0, 122.9, 116.4, 115.0, 79.4, 54.7, 32.8, 21.5, 19.0, 18.9; IR (neat, cm^{-1}): 2958, 1744, 1648, 1506, 1442, 1288, 1261; HRMS (ESI, m/z) calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 361.1523, obsd 361.1523.

1-(5-Chloro-3-phenylimidazo[1,2-*a*]pyridin-2-yl)-2-methylpropyl methyl carbonate (3.27e)



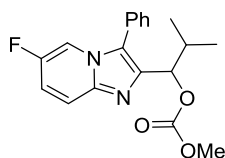
Yield = 76%; Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.68–7.59 (m, 2H), 7.47 (dd, $J = 5.6, 3.4$ Hz, 2H), 7.44–7.36 (m, 1H), 7.32 (d, $J = 7.1$ Hz, 1H), 7.12 (dd, $J = 9.0, 7.2$ Hz, 1H), 6.76 (d, $J = 7.2$ Hz, 1H), 5.18 (d, $J = 8.7$ Hz, 1H), 3.68 (s, 3H), 2.48–2.37 (m, 1H), 1.00 (d, $J = 6.7$ Hz, 3H), 0.76 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.5, 146.6, 143.0, 133.0, 132.4, 130.0, 129.0, 127.7, 127.1 (2C), 124.9, 124.5, 116.8, 114.0, 78.6, 54.6, 32.6, 18.9, 18.8; IR (neat, cm^{-1}): 2960, 2927, 2872, 1746, 1627, 1490, 1442, 1291, 1260, 1083, 969, 766, 704; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{19}\text{ClN}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 381.0976, obsd 381.0977.

1-(5-Fluoro-3-phenylimidazo[1,2-*a*]pyridin-2-yl)-2-methylpropyl methyl carbonate (3.27f)



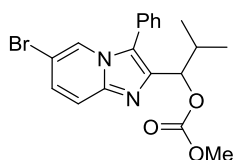
Yield = 44%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 7.76–7.62 (m, 1H), 7.54–7.43 (m, 4H), 7.36 (s, 1H), 7.21–7.14 (m, 1H), 6.39–6.32 (m, 1H), 5.29 (d, $J = 8.8$ Hz, 1H), 3.69 (s, 3H), 2.48–2.37 (m, 1H), 1.00 (d, $J = 6.7$ Hz, 3H), 0.75 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.6, 150.6 (d, $J_{\text{C-F}} = 269.6$ Hz), 146.9 (d, $J_{\text{C-F}} = 3.8$ Hz), 142.3, 131.2, 129.3 (d, $J_{\text{C-F}} = 2.5$ Hz), 128.8, 128.0 (d, $J_{\text{C-F}} = 58.0$ Hz), 125.2 (d, $J_{\text{C-F}} = 6.3$ Hz), 122.0 (d, $J_{\text{C-F}} = 2.5$ Hz), 113.8 (d, $J_{\text{C-F}} = 5.0$ Hz), 93.3 (d, $J_{\text{C-F}} = 16.4$ Hz), 78.6, 54.7, 32.8, 18.8 (2C); ^{19}F NMR (471 MHz, CDCl_3) δ -102.0; IR (neat, cm^{-1}): 2959, 2920, 1745, 1655, 1519, 1442, 1290, 1259; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{19}\text{FN}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 365.1272, obsd 365.1272.

1-(6-Fluoro-3-phenylimidazo[1,2-*a*]pyridin-2-yl)-2-methylpropyl methyl carbonate (3.27g)



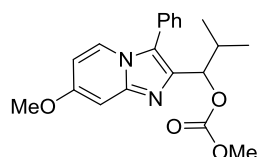
Yield = 81%; Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.87 (dd, $J = 4.4, 2.4$ Hz, 1H), 7.66–7.46 (m, 6H), 7.15–7.07 (m, 1H), 5.43 (d, $J = 8.6$ Hz, 1H), 3.69 (s, 3H), 2.50–2.39 (m, 1H), 1.02 (d, $J = 6.6$ Hz, 3H), 0.75 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.7, 154.4, 152.5, 142.5, 130.2, 129.5, 129.3, 128.1, 124.8 (d, $J_{\text{C-F}} = 2.2$ Hz), 118.6 (d, $J_{\text{C-F}} = 9.1$ Hz), 116.8 (d, $J_{\text{C-F}} = 25.8$ Hz), 110.1 (d, $J_{\text{C-F}} = 41.4$ Hz), 79.1, 54.7, 32.8, 18.8 (2C). ^{19}F NMR (471 MHz, CDCl_3) δ -140.0; IR (neat, cm^{-1}): 2961, 2927, 2872, 1745, 1656, 1535, 1441, 1395, 1261, 1134, 1083, 970, 766, 704; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{19}\text{FN}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 365.1272, obsd 365.1270.

1-(6-Bromo-3-phenylimidazo[1,2-*a*]pyridin-2-yl)-2-methylpropyl methyl carbonate (3.27h)



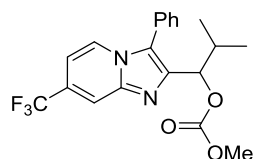
Yield = 88%; Light yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 8.05 (d, $J = 1.7$ Hz, 1H), 7.61–7.50 (m, 6H), 7.24 (dd, $J = 9.5, 1.9$ Hz, 1H), 5.40 (d, $J = 8.7$ Hz, 1H), 3.69 (s, 3H), 2.49–2.38 (m, 1H), 1.01 (d, $J = 6.7$ Hz, 3H), 0.74 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.7, 143.3, 142.1, 130.5, 129.6, 129.4, 128.2, 128.0, 123.9, 123.7, 118.8, 107.3, 79.0, 54.8, 32.9, 18.9 (2C); IR (neat, cm^{-1}): 2958, 1498, 1441, 1284, 1260, 1196, 1132; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{19}\text{BrN}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 425.0471, obsd 425.0473.

1-(7-Methoxy-3-phenylimidazo[1,2-*a*]pyridin-2-yl)-2-methylpropyl methyl carbonate (3.27i)



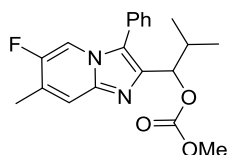
Yield = 76%; Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.77 (d, $J = 7.5$ Hz, 1H), 7.58–7.42 (m, 5H), 6.91 (d, $J = 2.5$ Hz, 1H), 6.45 (dd, $J = 7.5, 2.5$ Hz, 1H), 5.38 (d, $J = 8.8$ Hz, 1H), 3.85 (s, 3H), 3.69 (s, 3H), 2.53–2.42 (m, 1H), 1.02 (d, $J = 6.7$ Hz, 3H), 0.75 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 158.1, 155.7, 146.4, 140.3, 130.4, 129.3, 128.8, 128.7, 124.1, 122.6, 107.5, 95.0, 79.4, 55.6, 54.6, 32.7, 19.0, 18.9; IR (neat, cm^{-1}): 2959, 2927, 2872, 1744, 1650, 1477, 1441, 1288, 1262, 1216, 966, 766, 704; HRMS (ESI, m/z) calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}^+$): 377.1472, obsd 377.1472.

Methyl (2-methyl-1-(3-phenyl-7-(trifluoromethyl)imidazo[1,2-*a*]pyridin-2-yl)propyl) carbonate (3.27j)



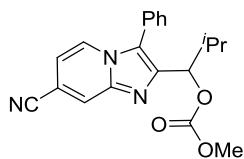
Yield = 90%; Light yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.96 (d, $J = 7.3$ Hz, 1H), 7.89 (s, 1H), 7.54–7.43 (m, 5H), 6.83 (dd, $J = 7.3, 1.7$ Hz, 1H), 5.36 (d, $J = 8.6$ Hz, 1H), 3.62 (s, 3H), 2.42–2.31 (m, 1H), 0.95 (d, $J = 6.7$ Hz, 3H), 0.68 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.7, 143.6, 143.0, 130.4, 129.7, 129.6, 127.8, 126.6 (q, $J_{\text{C-F}} = 34.4$ Hz), 124.9, 124.5, 123.5 (q, $J_{\text{C-F}} = 272.3$ Hz), 116.2 (q, $J_{\text{C-F}} = 5.1$ Hz), 108.4 (q, $J_{\text{C-F}} = 2.9$ Hz), 78.9, 54.8, 32.9, 18.8 (2C); ^{19}F NMR (471 MHz, CDCl_3) δ -63.6; IR (neat, cm^{-1}): 2920, 1747, 1645, 1258, 1196, 1132, 1077; HRMS (ESI, m/z) calcd for $\text{C}_{20}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 415.1240, obsd 415.1240.

1-(6-Fluoro-7-methyl-3-phenylimidazo[1,2-*a*]pyridin-2-yl)-2-methylpropyl methyl carbonate (3.27k)



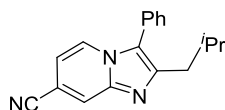
Yield = 72%; Light yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.82 (d, $J = 4.8$ Hz, 1H), 7.59–7.41 (m, 6H), 5.41 (d, $J = 8.8$ Hz, 1H), 3.68 (s, 3H), 2.49–2.37 (m, 1H), 1.01 (d, $J = 6.7$ Hz, 3H), 0.74 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.7, 154.3, 152.4, 142.8, 141.7 (d, $J = 2.1$ Hz), 130.2, 129.5, 129.1, 128.4, 127.6 (d, $J = 21.6$ Hz), 124.1 (2C), 117.5 (d, $J = 5.5$ Hz), 109.6 (d, $J = 43.0$ Hz), 79.2, 60.5, 54.7, 32.8, 18.9, 18.8; IR (neat, cm^{-1}): 2960, 2927, 1745, 1656, 1520, 1441, 1395, 1261, 1134, 1083, 970, 766.

1-(7-Cyano-3-phenylimidazo[1,2-*a*]pyridin-2-yl)-2-methylpropyl methyl carbonate (3.27p)



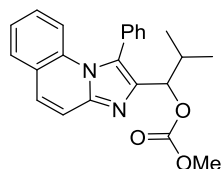
^1H NMR (500 MHz, CDCl_3) δ 8.05 (s, 1H), 8.01 (d, $J = 7.1, 1.0$ Hz, 1H), 7.64–7.51 (m, 5H), 6.88 (dd, $J = 7.2, 1.6$ Hz, 1H), 5.44 (d, $J = 8.4$ Hz, 1H), 3.69 (s, 3H), 2.47–2.35 (m, 1H), 1.02 (d, $J = 6.6$ Hz, 3H), 0.75 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.7, 144.8, 142.7, 130.3, 129.9, 129.8, 127.2, 125.8, 124.4, 124.4, 117.8, 112.7, 107.4, 78.7, 54.9, 32.9, 18.8; IR (neat, cm^{-1}): 2961, 2225, 1633, 1417, 1132, 1082; HRMS (ESI, m/z) calcd for $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 372.1319, obsd 372.1318.

2-Isobutyl-3-phenylimidazo[1,2-*a*]pyridine-7-carbonitrile (3.39)



^1H NMR (500 MHz, CDCl_3) δ 8.06 (d, $J = 7.3$ Hz, 1H), 8.02–7.94 (m, 1H), 7.61–7.56 (m, 1H), 7.56–7.51 (m, 1H), 7.45–7.39 (m, 2H), 6.86 (dd, $J = 7.2, 1.6$ Hz, 1H), 2.68 (d, $J = 7.2$ Hz, 2H), 2.26–2.11 (m, 1H), 0.89 (d, $J = 6.7$ Hz, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 148.5, 142.4, 130.0, 129.7, 129.4, 128.2, 124.8, 123.8, 123.3, 118.2, 112.3, 106.3, 37.0, 29.2, 22.7; IR (neat, cm^{-1}): 2960, 2224, 1631, 1420, 1130, 1081; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{18}\text{N}_3$ ($\text{M}+\text{H}^+$): 276.1495, obsd 276.1494.

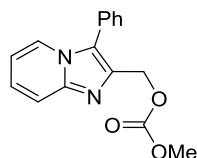
Methyl (2-methyl-1-(1-phenylimidazo[1,2-*a*]quinolin-2-yl)propyl) carbonate (3.27q)



Yield = 86%; Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.76–7.69 (m, 2H), 7.65–7.51 (m, 4H), 7.48 (d, $J = 9.1$ Hz, 1H), 7.38 (d, $J = 7.5$ Hz, 1H), 7.34–7.26 (m, 1H), 7.23–7.13 (m, 2H), 5.21 (d, $J = 6.1$ Hz, 1H), 3.68 (s, 3H), 2.54–2.42 (m, 1H), 1.03 (d, $J = 6.7$ Hz, 3H), 0.77 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ

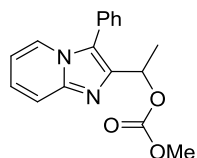
155.5, 144.1, 141.0, 134.1, 131.6, 131.5, 131.3, 129.4, 129.3, 129.1, 128.8, 127.9, 126.7 (2C), 124.6, 124.4, 117.7, 116.8, 78.8, 54.5, 32.6, 19.0 (2C); IR (neat, cm^{-1}): 2960, 2927, 2872, 1745, 1621, 1444, 1261, 1132, 1083, 967, 806, 762, 704; HRMS (ESI, m/z) calcd for $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 397.1523, obsd 397.1522.

Methyl ((3-phenylimidazo[1,2-*a*]pyridin-2-yl)methyl) carbonate (3.41a)



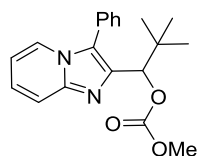
Yield = 50%; Light yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 8.10 (d, $J = 6.8$ Hz, 1H), 7.66 (d, $J = 9.1$ Hz, 1H), 7.58–7.48 (m, 5H), 7.25–7.20 (m, 1H), 6.78 (t, $J = 6.8$ Hz, 1H), 5.31 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.8, 145.1, 137.8, 129.9, 129.5, 129.1, 128.1, 125.3, 124.7, 123.8, 118.3, 112.9, 63.4, 55.0; IR (neat, cm^{-1}): 2021, 1731, 1587, 1542, 1439, 1307, 1224, 1065; HRMS (ESI, m/z) calcd for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 305.0897, obsd 305.0897.

Methyl (1-(3-phenylimidazo[1,2-*a*]pyridin-2-yl)ethyl) carbonate (3.41b)



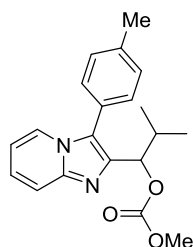
Yield = 76%; Light yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 8.03–7.97 (m, 1H), 7.70–7.63 (m, 1H), 7.58–7.46 (m, 5H), 7.23–7.16 (m, 1H), 6.78–6.71 (m, 1H), 5.92 (q, $J = 6.6$ Hz, 1H), 3.69 (s, 3H), 1.73 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.3, 144.9, 142.4, 130.2, 129.5, 129.1, 128.4, 125.0, 123.7, 122.4, 118.2, 112.6, 70.6, 54.7, 20.8; IR (neat, cm^{-1}): 2956, 2925, 1738, 1588, 1440, 1268, 1221, 1086, 757; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 319.1053, obsd 319.1053.

2,2-Dimethyl-1-(3-phenylimidazo[1,2-*a*]pyridin-2-yl)propyl methyl carbonate
(3.41c)



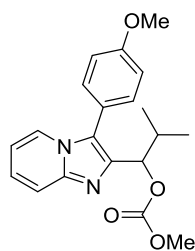
Yield = 92%; White solid; ^1H NMR (500 MHz, CDCl_3) δ 7.97–7.91 (m, 1H), 7.70–7.53 (m, 5H), 7.47 (dt, $J = 8.6, 4.3$ Hz, 1H), 7.20–7.12 (m, 1H), 6.71 (td, $J = 6.8, 2.3$ Hz, 1H), 5.52 (s, 1H), 3.73 (s, 3H), 0.94 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 156.0, 144.5, 140.2, 130.5, 129.5, 129.1, 128.9, 124.4, 123.7, 123.4, 118.1, 112.3, 80.9, 54.6, 36.3, 26.3; IR (neat, cm^{-1}): 2957, 2868, 1744, 1635, 1506, 1442, 1345, 1268, 963, 752, 703; HRMS (ESI, m/z) calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 361.1523, obsd 361.1524.

Methyl (2-methyl-1-(3-(*p*-tolyl)imidazo[1,2-*a*]pyridin-2-yl)propyl) carbonate
(3.41d)



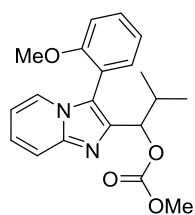
Yield = 83%; Light yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.96–7.90 (m, 1H), 7.66–7.60 (m, 1H), 7.43 (d, $J = 7.8$ Hz, 2H), 7.36 (d, $J = 7.8$ Hz, 2H), 7.20–7.13 (m, 1H), 6.74–6.68 (m, 1H), 5.43 (d, $J = 8.8$ Hz, 1H), 3.69 (s, 3H), 2.52–2.43 (m, 4H), 1.03 (d, $J = 6.7$ Hz, 3H), 0.75 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.8, 144.9, 141.0, 139.0, 130.4, 130.1, 125.6, 124.6, 123.7, 123.6, 118.1, 112.3, 79.3, 54.7, 32.8, 21.6, 19.0; IR (neat, cm^{-1}): 2958, 1744, 1505, 1441, 1343, 1289, 1260; HRMS (ESI, m/z) calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 361.1523, obsd 361.1523.

1-(3-(4-Methoxyphenyl)imidazo[1,2-*a*]pyridin-2-yl)-2-methylpropyl methyl carbonate (3.41e)



Yield = 83%; Light yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.90 (dd, $J = 7.0, 1.2$ Hz, 1H), 7.63 (dd, $J = 9.1, 1.2$ Hz, 1H), 7.47 (d, $J = 8.2$ Hz, 2H), 7.20–7.15 (m, 1H), 7.11–7.05 (m, 2H), 6.75–6.68 (m, 1H), 5.40 (d, $J = 8.8$ Hz, 1H), 3.89 (s, 3H), 3.69 (s, 3H), 2.53–2.40 (m, 1H), 1.03 (d, $J = 6.7$ Hz, 3H), 0.75 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 160.1, 155.8, 144.8, 141.0, 131.9, 124.6, 123.7, 123.4, 120.6, 118.1, 114.8, 112.3, 79.4, 55.5, 54.7, 32.8, 19.0 (2C); IR (neat, cm^{-1}): 2957, 2921, 1744, 1634, 1505, 1441, 1289, 1260; HRMS (ESI, m/z) calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}^+$): 377.1472, obsd 377.1471.

1-(3-(2-Methoxyphenyl)imidazo[1,2-*a*]pyridin-2-yl)-2-methylpropyl methyl carbonate (3.41f)

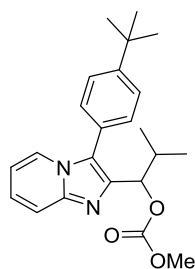


Major isomer: Yield = 57%; Light yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 7.70 (dd, $J = 7.5, 1.7$ Hz, 1H), 7.67–7.63 (m, 1H), 7.59–7.55 (m, 1H), 7.52–7.47 (m, 1H), 7.19–7.14 (m, 2H), 7.06–7.03 (m, 1H), 6.72–6.67 (m, 1H), 5.37 (d, $J = 8.5$ Hz, 1H), 3.72 (s, 6H), 2.57–2.48 (m, 1H), 0.96 (d, $J = 6.7$ Hz, 3H), 0.67 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 158.2, 155.9, 145.1, 141.3, 133.2, 131.0, 125.0, 124.4, 121.4, 120.8, 117.8, 117.1, 111.6, 111.0, 79.4, 55.4, 54.7, 33.1, 18.9, 18.2; IR (neat,

cm^{-1}): 2960, 2922, 1745, 1505, 1440, 1292, 1261, 1022, 754; HRMS (ESI, m/z) calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}^+$): 377.1472, obsd 377.1472.

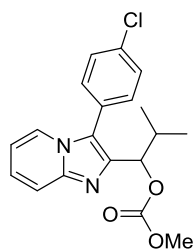
Minor isomer: Yield = 27%; Light yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 7.67–7.63 (m, 1H), 7.61 (dd, $J = 6.8, 1.1$ Hz, 1H), 7.52–7.47 (m, 1H), 7.31–7.28 (m, 1H), 7.19–7.14 (m, 1H), 7.12–7.06 (m, 2H), 6.72–6.67 (m, 1H), 5.47 (d, $J = 8.9$ Hz, 1H), 3.73 (s, 3H), 3.63 (s, 3H), 2.57–2.48 (m, 1H), 1.04 (d, $J = 6.6$ Hz, 3H), 0.87 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 158.3, 155.5, 144.8, 141.6, 133.1 (2 C), 124.8, 124.5, 120.9 (2 C), 117.9, 117.3, 111.8, 111.5, 79.5, 55.6, 54.5, 32.2, 19.4, 18.9; IR (neat, cm^{-1}): 2960, 2922, 1745, 1505, 1440, 1292, 1261, 1022, 754; HRMS (ESI, m/z) calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}^+$): 377.1472, obsd 377.1472.

1-(3-(4-(*tert*-Butyl)phenyl)imidazo[1,2-*a*]pyridin-2-yl)-2-methylpropyl methyl carbonate (3.41g)



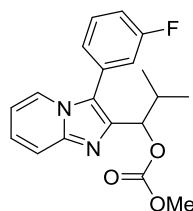
Yield = 79%; Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.96 (d, $J = 7.0$ Hz, 1H), 7.63 (d, $J = 9.1$ Hz, 1H), 7.56 (d, $J = 8.1$ Hz, 2H), 7.47 (d, $J = 8.0$ Hz, 2H), 7.20–7.12 (m, 1H), 6.74–6.67 (m, 1H), 5.46 (d, $J = 8.6$ Hz, 1H), 3.68 (s, 3H), 2.54 – 2.43 (m, 1H), 1.40 (s, 9H), 1.03 (d, $J = 6.7$ Hz, 3H), 0.76 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.8, 152.0, 144.9, 141.0, 130.1, 126.3, 125.5, 124.6, 123.8, 123.6, 118.1, 112.2, 79.4, 54.7, 35.0, 32.9, 31.5, 19.0, 18.9; IR (neat, cm^{-1}): 2965, 2930, 2873, 1711, 1601, 1496, 1438, 1308, 1260, 770, 700; HRMS (ESI, m/z) calcd for $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 403.1992, obsd 403.1994.

1-(3-(4-Chlorophenyl)imidazo[1,2-*a*]pyridin-2-yl)-2-methylpropyl methyl carbonate (3.41h)



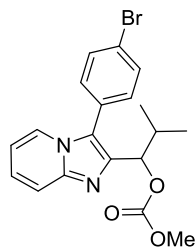
Yield = 62%; Light yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.93–7.88 (m, 1H), 7.67–7.64 (m, 1H), 7.55–7.49 (m, 4H), 7.23–7.18 (m, 1H), 6.76 (t, $J = 6.8$ Hz, 1H), 5.37 (d, $J = 8.8$ Hz, 1H), 3.69 (s, 3H), 2.50–2.43 (m, 1H), 1.03 (d, $J = 6.6$ Hz, 3H), 0.73 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.8, 145.1, 141.5, 135.2, 131.9, 129.8, 127.1, 125.0, 123.4, 122.3, 118.3, 112.7, 79.2, 54.8, 32.8, 19.0, 18.9; IR (neat, cm^{-1}): 2957, 2922, 1743, 1504, 1440, 1290, 1261, 1089; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{19}\text{ClN}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 381.0976, obsd 381.0976.

1-(3-(3-Fluorophenyl)imidazo[1,2-*a*]pyridin-2-yl)-2-methylpropyl methyl carbonate (3.41i)



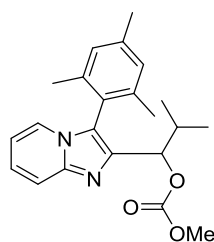
Yield = 43%; Light yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 8.00–7.94 (m, 1H), 7.69–7.62 (m, 1H), 7.57–7.50 (m, 1H), 7.41–7.36 (m, 1H), 7.35–7.30 (m, 1H), 7.23–7.16 (m, 2H), 6.76 (t, $J = 6.8, 1.2$ Hz, 1H), 5.43 (d, $J = 8.8$ Hz, 1H), 3.70 (s, 3H), 2.53–2.43 (m, 1H), 1.04 (d, $J = 6.7$ Hz, 3H), 0.75 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 163.2 (d, $J_{\text{C-F}} = 248.3$ Hz), 155.7, 145.1, 141.6, 131.1 (d, $J_{\text{C-F}} = 8.5$ Hz), 130.8 (d, $J_{\text{C-F}} = 8.3$ Hz), 126.2 (d, $J_{\text{C-F}} = 2.8$ Hz), 125.0, 123.5, 122.2 (d, $J_{\text{C-F}} = 1.9$ Hz), 118.2, 117.3 (d, $J_{\text{C-F}} = 21.9$ Hz), 116.0 (d, $J_{\text{C-F}} = 21.0$ Hz), 112.7, 79.1, 54.7, 32.8, 18.9 (2C); ^{19}F NMR (471 MHz, CDCl_3) δ -111.3; IR (neat, cm^{-1}): 2958, 2925, 1744, 1583, 1292, 261, 790; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{19}\text{FN}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 365.1272, obsd 365.1272.

1-(3-(4-Bromophenyl)imidazo[1,2-*a*]pyridin-2-yl)-2-methylpropyl methyl carbonate (3.41j)



Yield = 68%; Pale yellow oil; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.91 (d, $J = 6.9$ Hz, 1H), 7.72–7.62 (m, 3H), 7.45 (d, $J = 8.1$ Hz, 2H), 7.24–7.17 (m, 1H), 6.79–6.70 (m, 1H), 5.38 (d, $J = 8.7$ Hz, 1H), 3.69 (s, 3H), 2.54–2.40 (m, 1H), 1.03 (d, $J = 6.7$ Hz, 3H), 0.74 (d, $J = 6.7$ Hz, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 155.8, 145.1, 141.5, 132.7, 132.1, 127.6, 125.0, 123.4, 123.4, 122.3, 118.2, 112.7, 79.2, 54.7, 32.8, 18.9, 18.9; IR (neat, cm^{-1}): 2959, 2927, 2872, 1745, 1633, 1581, 1440, 1343, 1261, 1083, 966, 745; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{19}\text{BrN}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 425.0471, 427.0452; obsd 425.0472, 427.0451.

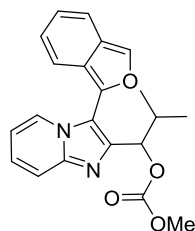
1-(3-(Mesitylimidazo[1,2-*a*]pyridin-2-yl)-2-methylpropyl methyl carbonate (3.41k)



Yield = 82%; Pale yellow solid; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.66 (d, $J = 9.1$ Hz, 1H), 7.39 (d, $J = 6.7$ Hz, 1H), 7.20–7.15 (m, 1H), 7.02 (d, $J = 11.2$ Hz, 2H), 6.73–6.65 (m, 1H), 5.53 (d, $J = 7.1$ Hz, 1H), 3.62 (s, 3H), 2.64–2.51 (m, $J = 6.7$ Hz, 1H), 2.37 (s, 3H), 1.93 (s, 3H), 1.88 (s, 3H), 0.99 (d, $J = 6.7$ Hz, 3H), 0.92 (d, $J = 6.7$ Hz, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 155.9, 144.8, 141.7, 140.0, 139.5, 139.5, 128.8, 128.6, 124.3, 123.9, 123.3, 121.2, 118.0, 112.3, 79.3, 54.6, 32.3, 21.4, 19.8, 19.7, 19.4, 17.9;

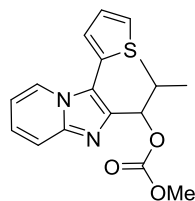
IR (neat, cm^{-1}): 2960, 1746, 1505, 1441, 1342, 1263, 948, 756; HRMS (ESI, m/z) calcd for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 389.1836, obsd 389.1835.

1-(3-(Isobenzofuran-1-yl)imidazo[1,2-*a*]pyridin-2-yl)-2-methylpropyl methyl carbonate (3.41l)



Yield = 78%; Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 8.19 (s, 1H), 7.80 (d, J = 6.9 Hz, 1H), 7.70 (d, 1H), 7.65 (d, J = 8.3 Hz, 1H), 7.44–7.36 (m, 1H), 7.29–7.15 (m, 3H), 6.75 (t, J = 6.8 Hz, 1H), 5.60–5.30 (m, 1H), 3.65 (s, 3H), 1.03 (d, J = 6.6 Hz, 3H), 0.85–0.50 (m, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.8, 146.1, 145.8, 126.7, 125.2, 125.1, 124.6, 123.5, 120.5, 120.3, 118.3, 112.5, 112.4, 79.5, 54.7, 32.5, 19.0, 18.7; IR (neat, cm^{-1}): 2960, 2923, 2872, 1745, 1634, 1504, 1452, 1346, 1266, 1084, 971, 750; HRMS (ESI, m/z) calcd for $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}^+$): 387.1315, obsd 387.1315.

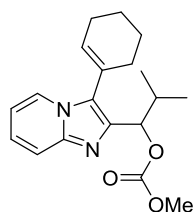
Methyl (2-methyl-1-(3-(thiophen-2-yl)imidazo[1,2-*a*]pyridin-2-yl)propyl) carbonate (3.41m)



Yield = 89%; Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 8.07 (d, J = 6.8 Hz, 1H), 7.64 (d, J = 9.1 Hz, 1H), 7.60–7.55 (m, 1H), 7.35–7.31 (m, 1H), 7.26–7.16 (m, 2H), 6.92–6.75 (m, 1H), 5.50 (d, J = 8.7 Hz, 1H), 3.69 (s, 3H), 2.55–2.43 (m, 1H), 1.06 (d, J = 6.8 Hz, 3H), 0.81 (d, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.7, 145.5,

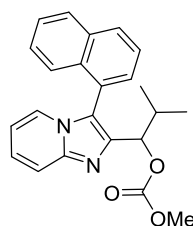
143.3, 130.2, 128.5, 128.3, 128.0, 125.3, 124.1, 118.1, 116.4, 112.7, 79.0, 54.7, 32.7, 19.0, 18.9; IR (neat, cm^{-1}): 2959, 2927, 2872, 1745, 1635, 1504, 1441, 1348, 1260, 1083, 969, 754; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_3\text{SNa}$ ($\text{M}+\text{Na}^+$): 353.0930, obsd 353.0933.

1-(3-(Cyclohex-1-en-1-yl)imidazo[1,2-*a*]pyridin-2-yl)-2-methylpropyl methyl carbonate (3.41n)



Yield = 75%; Light yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.87 (dt, $J = 6.8, 1.2$ Hz, 1H), 7.57 (dt, $J = 9.2, 1.2$ Hz, 1H), 7.15–7.09 (m, 1H), 6.74 (td, $J = 6.8, 1.2$ Hz, 1H), 6.06–5.99 (m, 1H), 5.48 (d, $J = 8.9$ Hz, 1H), 3.71 (s, 3H), 2.59–2.49 (m, 1H), 2.39–2.32 (m, 1H), 2.31–2.28 (m, 2H), 2.21–2.14 (m, 1H), 1.88–1.76 (m, 4H), 1.10 (d, $J = 6.7$ Hz, 3H), 0.82 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.8, 144.4, 139.7, 134.2, 126.3, 125.9, 124.1 (2C), 118.0, 112.0, 79.3, 54.6, 32.5, 28.4, 25.9, 22.9, 22.1, 19.2, 19.0; IR (neat, cm^{-1}): 2926, 1745, 1505, 1441, 1346, 1260; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 351.1679, obsd 351.1679.

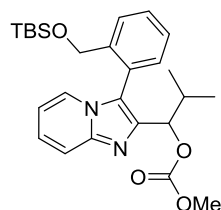
Methyl (2-methyl-1-(3-(naphthalen-1-yl)imidazo[1,2-*a*]pyridin-2-yl)propyl) carbonate (3.41o)



A mixture of stereoisomers were obtained in a ratio of 1.1:1. Yield = 83%; Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 8.06–8.00 (m, 1H), 8.00–7.94 (m, 1H),

7.89–7.86 (m, 0.48H), 7.76–7.59 (m, 2H), 7.55–7.49 (m, 1.52H), 7.41–7.32 (m, 2H), 7.30–7.26 (m, 0.48H), 7.23–7.17 (m, 1H), 7.11 (d, $J = 8.4$ Hz, 0.48H), 6.65 – 6.59 (m, 1H), 5.50–5.41 (m, 1H), 3.58 (s, 1.44 H), 3.51 (s, 1.56H), 2.53–2.40 (m, 1H), 1.01–0.88 (m, 4.56H), 0.69 (d, $J = 6.9$ Hz, 1.44H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.7, 155.3, 145.1, 144.8, 142.7, 142.5, 134.0, 133.9, 132.6, 132.3, 130.8, 130.5, 130.2, 130.1, 129.0, 128.7, 127.0, 127.0, 126.5, 126.3, 126.2, 125.9, 125.6, 125.5, 125.5, 125.0, 124.8, 124.7, 124.3, 124.2, 121.6, 121.5, 118.0, 118.0, 112.3, 112.3, 79.5, 79.5, 54.5, 54.5, 32.8, 32.3, 19.4, 18.8, 18.7, 18.6; IR (neat, cm^{-1}): 2960, 2927, 2872, 1746, 1634, 1504, 1441, 1289, 1262, 969, 780, 754; HRMS (ESI, m/z) calcd for $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 397.1523, obsd 397.1521.

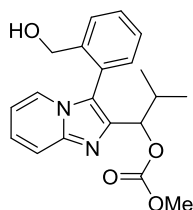
1-(3-(2-(((*tert*-Butyldimethylsilyloxy)methyl)phenyl)imidazo[1,2-*a*]pyridin-2-yl)-2-methylpropyl methyl carbonate (3.41p)



A mixture of stereoisomers were obtained in a ratio of 1.1:1. Yield = 80%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 7.72–7.68 (m, 1.9H), 7.65 (dt, $J = 3.7$, 1.1 Hz, 0.9H), 7.63 (dt, $J = 3.7$, 1.1 Hz, 1H), 7.56–7.47 (m, 4.8H), 7.43 (td, $J = 7.4$, 1.4 Hz, 0.9H), 7.38 (td, $J = 7.5$, 1.4 Hz, 1H), 7.20–7.15 (m, 2.8H), 6.70–6.65 (m, 1.9H), 5.39 (d, $J = 8.0$ Hz, 0.9H), 5.30 (d, $J = 8.3$ Hz, 1H), 4.55 (d, $J = 13.4$ Hz, 1H), 4.35 (d, $J = 13.3$ Hz, 0.9H), 4.26 (d, $J = 2.4$ Hz, 1H), 4.23 (d, $J = 2.3$ Hz, 0.9H), 3.64 (s, 2.7H), 3.59 (s, 3H), 2.58–2.51 (m, 0.9H), 2.50–2.42 (m, 1H), 1.01 (d, $J = 6.7$ Hz, 3H), 0.98 (d, $J = 6.7$ Hz, 2.7H), 0.86 (d, $J = 6.8$ Hz, 3H), 0.82 (s, 8H), 0.81 (s, 9H), 0.79 (d, $J = 6.8$ Hz, 2.7H), -0.07 – -0.10 (m, 5.7H), -0.12 (s, 2.7H), -0.15 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.6 (2C), 144.9 (2C), 142.9, 142.2, 141.6 (2C), 132.4, 132.3, 130.1 (2C), 127.9, 127.8, 127.6, 127.4, 125.7, 125.5, 124.7 (2C), 124.3, 124.2, 121.8, 121.7, 117.9 (2C), 112.3, 112.2, 79.4, 79.1, 62.9, 62.5, 54.7, 54.6, 32.6, 32.5,

26.0 (2C), 19.4, 19.0, 18.7, 18.5, 18.4 (2C), -5.4 (3C), -5.5; IR (neat, cm^{-1}): 2956, 2027, 1747, 1635, 1441, 1262, 1081, 1023, 839; HRMS (ESI, m/z) calcd for $\text{C}_{26}\text{H}_{36}\text{N}_2\text{O}_4\text{SiNa}$ ($\text{M}+\text{Na}^+$): 491.2337, obsd 491.2336.

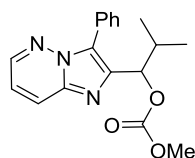
1-(3-(2-(Hydroxymethyl)phenyl)imidazo[1,2-*a*]pyridin-2-yl)-2-methylpropyl methyl carbonate (3.41q)



Major isomer: Yield = 25%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 7.79 (d, $J = 7.8$ Hz, 1H), 7.67–7.55 (m, 2H), 7.50–7.43 (m, 2H), 7.23–7.17 (m, 2H), 6.75–6.69 (m, 1H), 5.12 (d, $J = 9.0$ Hz, 1H), 4.37–4.29 (m, 1H), 4.09 (dd, $J = 12.5, 3.1$ Hz, 1H), 3.61 (s, 3H), 3.20 (dd, $J = 10.1, 3.5$ Hz, 1H), 2.66–2.58 (m, 1H), 1.10 (d, $J = 6.7$ Hz, 3H), 0.90 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 156.2, 145.0, 143.0, 141.3, 132.6, 130.6, 130.4, 128.3, 126.2, 125.0, 123.7, 122.8, 118.1, 112.8, 79.3, 62.2, 54.9, 32.4, 19.6, 19.1; IR (neat, cm^{-1}): 3438, 1636, 1505, 1440, 1260, 1081, 630; HRMS (ESI, m/z) calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}^+$): 377.1472, obsd 367. 377.1474.

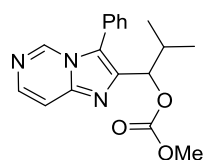
Minor isomer: Yield = 18%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 7.75 (d, $J = 7.7$ Hz, 1H), 7.67–7.55 (m, 2H), 7.50–7.43 (m, 3H), 7.23–7.17 (m, 1H), 6.75–6.69 (m, 1H), 5.53 (d, $J = 6.9$ Hz, 1H), 4.37–4.29 (m, 1H), 4.23 (d, $J = 12.9$ Hz, 1H), 3.57 (s, 3H), 2.54–2.48 (m, 1H), 1.93 (s, 1H), 0.98 (d, $J = 6.7$ Hz, 3H), 0.86 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.8, 144.8, 142.1, 141.7, 132.7, 130.3, 128.7, 128.4, 126.3, 124.9, 123.8, 121.1, 117.8, 112.5, 80.3, 62.2, 54.9, 32.5, 19.0, 18.0; IR (neat, cm^{-1}): 3438, 1636, 1505, 1440, 1260, 1081, 630; HRMS (ESI, m/z) calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}^+$): 377.1472, obsd 367. 377.1476.

Methyl (2-methyl-1-(3-phenylimidazo[1,2-*b*]pyridazin-2-yl)propyl) carbonate (3.44a)



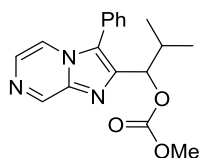
Yield = 74%; Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 8.32–8.26 (m, 1H), 7.99 (dd, $J = 9.2, 1.7$ Hz, 1H), 7.75–7.69 (m, 2H), 7.58–7.53 (m, 2H), 7.50–7.45 (m, 1H), 7.06 (dd, $J = 9.2, 4.3$ Hz, 1H), 5.60 (d, $J = 8.6$ Hz, 1H), 3.71 (s, 3H), 2.50–2.41 (m, 1H), 1.05 (d, $J = 6.7$ Hz, 3H), 0.76 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.8, 143.1, 141.8, 138.7, 130.3, 129.0, 128.9, 127.9, 127.3, 126.0, 117.2, 79.1, 54.8, 33.0, 18.9, 18.9; IR (neat, cm^{-1}): 2962, 2927, 2872, 1745, 1619, 1489, 1442, 1288, 1261, 1165, 966, 792, 698; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 348.1319, obsd 348.1317.

Methyl (2-methyl-1-(3-phenylimidazo[1,2-*c*]pyrimidin-2-yl)propyl) carbonate (3.44b)



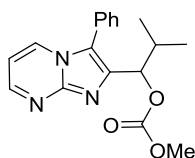
Yield = 74%; Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 8.83 (s, 1H), 7.98–7.90 (m, 1H), 7.63–7.50 (m, 6H), 5.44 (d, $J = 8.5$ Hz, 1H), 3.69 (s, 3H), 2.51–2.40 (m, 1H), 1.03 (d, $J = 6.8$ Hz, 3H), 0.76 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.7, 144.3, 142.5, 139.5, 137.9, 130.4, 129.7, 129.6, 127.1, 122.1, 112.7, 78.7, 54.8, 32.8, 18.8; IR (neat, cm^{-1}): 2959, 2927, 2872, 1746, 1650, 1494, 1444, 1385, 1261, 1083, 969, 766, 704; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 348.1319, obsd 348.1319.

Methyl (2-methyl-1-(3-phenylimidazo[1,2-a]pyrazin-2-yl)propyl) carbonate (3.44c)



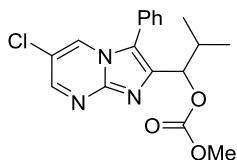
Yield = 80%; Light yellow oil; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.13 (s, 1H), 7.94–7.88 (m, 1H), 7.83 (d, $J = 4.7$ Hz, 1H), 7.62–7.52 (m, 5H), 5.50 (d, $J = 8.4$ Hz, 1H), 3.70 (s, 3H), 2.49–2.38 (m, 1H), 1.03 (d, $J = 6.7$ Hz, 3H), 0.76 (d, $J = 6.7$ Hz, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 155.7, 144.4, 143.7, 140.1, 130.1, 129.8, 129.7, 129.7, 127.2, 124.7, 116.5, 78.7, 54.8, 33.0, 18.8 (2C); IR (neat, cm^{-1}): 2920, 1745, 1659, 1631, 1441, 1286, 1260; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 348.1319, obsd 348.1320.

Methyl (2-methyl-1-(3-phenylimidazo[1,2-a]pyrimidin-2-yl)propyl) carbonate (3.44d)



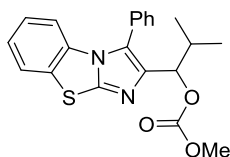
Yield = 72%; Pale yellow oil; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.56 (dd, $J = 4.0, 2.0$ Hz, 1H), 8.26 (dd, $J = 6.9, 2.0$ Hz, 1H), 7.61–7.50 (m, 5H), 6.83 (dd, $J = 6.9, 4.0$ Hz, 1H), 5.47 (d, $J = 8.5$ Hz, 1H), 3.67 (s, 3H), 2.61–2.49 (m, 1H), 1.04 (d, $J = 6.7$ Hz, 3H), 0.78 (d, $J = 6.7$ Hz, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 155.7, 150.3, 147.9, 142.7, 131.2, 130.4, 129.6, 129.5, 127.5, 122.0, 108.9, 108.3, 79.1, 54.7, 32.6, 18.9, 18.8; IR (neat, cm^{-1}): 2960, 2927, 2872, 1745, 1618, 1499, 1442, 1287, 1261, 1083, 969, 766, 704; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 348.1319, obsd 348.1315.

1-(6-Chloro-3-phenylimidazo[1,2-a]pyrimidin-2-yl)-2-methylpropyl methyl carbonate (3.44e)



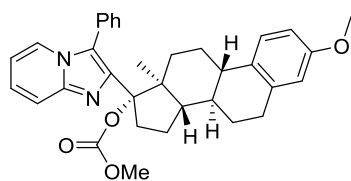
Yield = 41%; Pale yellow solid; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.48 (d, $J = 2.6$ Hz, 1H), 8.23 (d, $J = 2.6$ Hz, 1H), 7.61–7.57 (m, 2H), 7.56–7.51 (m, 3H), 5.44 (d, $J = 8.3$ Hz, 1H), 3.67 (s, 3H), 2.57–2.49 (m, 1H), 1.03 (d, $J = 6.8$ Hz, 3H), 0.78 (d, $J = 6.8$ Hz, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 155.6, 149.3, 146.2, 144.2, 130.3, 129.9, 129.8, 128.5, 127.0, 122.4, 118.4, 78.9, 54.8, 32.7, 18.9, 18.8; IR (neat, cm^{-1}): 2920, 1745, 1469, 1261, 1083, 1031; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{18}\text{ClN}_3\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$): 382.0929, obsd 382.0934.

Methyl (2-methyl-1-(3-phenylbenzo[d]imidazo[2,1-b]thiazol-2-yl)propyl) carbonate (3.44f)



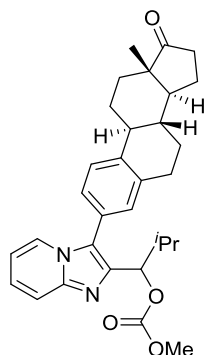
Yield = 78%; Pale yellow oil; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.74 (d, $J = 7.5$ Hz, 1H), 7.65 (dd, $J = 8.0, 1.1$ Hz, 1H), 7.63–7.49 (m, 3H), 7.46–7.40 (m, 1H), 7.26–7.20 (m, 1H), 7.14 (td, $J = 7.8, 7.3, 1.2$ Hz, 1H), 6.94–6.87 (m, 1H), 5.20 (d, $J = 8.9$ Hz, 1H), 3.70 (s, 3H), 2.50–2.36 (m, 1H), 1.01 (d, $J = 6.7$ Hz, 3H), 0.81 (d, $J = 6.7$ Hz, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 155.6, 147.5, 142.0, 133.0, 131.2, 131.1, 130.7, 129.5, 129.3, 128.8, 128.7, 127.2, 125.8, 124.7, 124.3, 113.7, 79.0, 54.7, 32.5, 19.0 (2C); IR (neat, cm^{-1}): 2960, 2927, 2872, 1745, 1615, 1485, 1305, 1260, 1083, 969, 766, 704; HRMS (ESI, m/z) calcd for $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_3\text{SNa}$ ($\text{M}+\text{Na}^+$): 403.1087, obsd 403.1086.

(8R,9S,13S,14S,17S)-3-Methoxy-13-methyl-17-(3-phenylimidazo[1,2-a]pyridin-2-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl methyl carbonate (3.46)



Yield = 41%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 7.64–7.60 (m, 1H), 7.58–7.28 (m, 6H), 7.17–7.06 (m, 2H), 6.69–6.57 (m, 3H), 3.75 (s, 3H), 3.48 (s, 3H), 3.18–3.02 (m, 1H), 2.90–2.76 (m, 2H), 2.24–2.11 (m, 2H), 2.03–1.96 (m, 1H), 1.92–1.82 (m, 2H), 1.52–1.24 (m, 5H), 1.05 (s, 3H), 1.02–0.94 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 157.5, 154.8, 144.4, 143.4, 138.1, 132.8, 130.3, 129.2, 129.0, 126.4, 124.1, 123.6, 121.7, 117.7, 113.9, 112.0, 111.6, 93.3, 55.3, 54.2, 49.5, 47.1, 43.5, 39.3, 36.3, 34.4, 30.1, 27.5, 26.6, 24.1, 15.3.

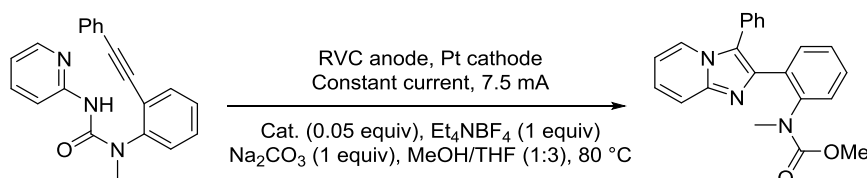
Methyl (2-methyl-1-(3-((8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl)imidazo[1,2-*a*]pyridin-2-yl)propyl) carbonate (3.50)



Yield = 71%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 8.03 (dd, $J = 6.9, 1.3$ Hz, 1H), 7.61 (d, $J = 9.0$ Hz, 1H), 7.44 (d, $J = 8.0$ Hz, 1H), 7.25–7.16 (m, 3H), 6.73 (td, $J = 6.9, 1.3$ Hz, 1H), 4.45 (d, $J = 8.0$ Hz, 1H), 3.04–2.95 (m, 2H), 2.57–2.47 (m, 2H), 2.42–2.37 (m, 1H), 2.25–1.99 (m, 6H), 1.72–1.51 (m, 6H), 1.04 (d, $J = 6.7$, Hz, 3H), 0.97 (s, 3H), 0.77 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 220.9, 145.5, 144.6, 140.6, 137.7, 130.7 (2C), 127.6 (2C), 126.4, 126.2 (2C), 124.7, 123.8, 122.0, 117.7, 112.3, 73.2, 50.7, 48.2, 44.7 (2C), 38.2 (2C), 36.0, 35.0, 31.8, 29.6 (2C),

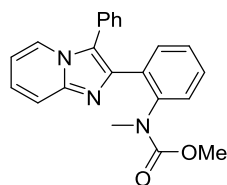
26.6, 25.8 (2C), 21.8, 19.7 (2C), 18.7, 14.1; IR (neat, cm^{-1}): 2924, 1740, 1635, 1440, 1261, 1083, 755; ESI HRMS m/z ($\text{M}+\text{H}$)⁺ calcd 501.2748, obsd 501.2750.

General procedure for the electrolysis (THF/MeOH = 1/3, urea-derived substrates)



A 25 mL three-necked round-bottomed flask was charged with catalyst (0.015 mmol), the substrate (0.3 mmol), Et_4NBF_4 (0.3 mmol), and Na_2CO_3 (0.3 mmol). The flask was equipped with a condenser, a reticulated vitreous carbon (100 PPI) anode and a platinum plate (1 cm x 1 cm) cathode and then flushed with argon. THF (7.5 mL) and MeOH (2.5 mL) were added. The electrolysis was carried out at 80 °C (oil bath temperature) using a constant current of 7.5 mA until complete consumption of the substrate (monitored by TLC or ^1H NMR). The reaction mixture was cooled to RT and concentrated under reduced pressure. The residue was chromatographed through silica gel eluting with ethyl acetate/hexanes to give the desired product.

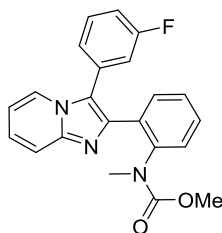
Methyl methyl(2-(3-phenylimidazo[1,2-*a*]pyridin-2-yl)phenyl)carbamate (3.53a).



Yield = 81%; White solid; ^1H NMR (500 MHz, CDCl_3) δ 8.21 (d, J = 6.9 Hz, 1H), 7.66 (d, J = 9.0 Hz, 1H), 7.56 (dd, J = 7.5, 1.8 Hz, 1H), 7.42 (t, J = 7.5 Hz, 2H), 7.38–7.31 (m, 4H), 7.29 (dd, J = 7.5, 1.4 Hz, 1H), 7.21 (dd, J = 8.8, 6.9 Hz, 1H), 7.15–7.10 (m, 1H), 6.78 (t, J = 6.8 Hz, 1H), 3.19 (s, 3H), 2.75 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.8, 145.1, 141.7, 141.5, 132.5, 132.4, 129.7, 129.3, 129.2, 128.9,

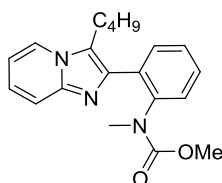
128.3, 127.6, 127.0, 124.7, 123.3, 122.2, 118.0, 112.6, 52.5, 37.5; IR (neat, cm^{-1}): 2921, 1704, 1450, 1356, 1124, 1083, 762; HRMS (ESI, m/z) calcd for $\text{C}_{22}\text{H}_{20}\text{N}_3\text{O}_2$ ($\text{M}+\text{H}^+$): 358.1550, obsd 358.1551.

Methyl (2-(3-(3-fluorophenyl)imidazo[1,2-*a*]pyridin-2-yl)phenyl)(methyl)-carbamate (3.53b).



Yield = 72%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 8.22 (d, $J = 6.9$ Hz, 1H), 7.67 (d, $J = 9.1$ Hz, 1H), 7.54–7.47 (m, 1H), 7.43–7.33 (m, 2H), 7.31–7.27 (m, 1H), 7.25–7.21 (m, 1H), 7.19–7.12 (m, 2H), 7.11–6.96 (m, 2H), 6.82 (t, $J = 6.8$ Hz, 1H), 3.46 (s, 0.54H), 3.25 (s, 2.46H), 2.94 (s, 0.54H), 2.84 (s, 2.46H); ^{13}C NMR (126 MHz, CDCl_3) δ 163.2 (d, $J_{\text{C-F}} = 247.4$ Hz), 155.9, 145.3, 142.1, 141.7, 132.3, 132.2, 131.3 (d, $J_{\text{C-F}} = 8.2$ Hz), 130.8 (d, $J_{\text{C-F}} = 8.5$ Hz), 129.1, 127.8, 127.1, 125.1 (d, $J_{\text{C-F}} = 2.9$ Hz), 125.0, 123.2, 120.9, 118.2, 116.5 (d, $J_{\text{C-F}} = 22.1$ Hz), 115.3 (d, $J_{\text{C-F}} = 21.1$ Hz), 112.9, 52.5, 37.8; ^{19}F NMR (471 MHz, CDCl_3) δ -111.5, -111.8; IR (neat, cm^{-1}): 1699, 1634, 1446, 1355, 1159, 755; HRMS (ESI, m/z) calcd for $\text{C}_{22}\text{H}_{18}\text{FN}_3\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 398.1275, obsd 398.1272.

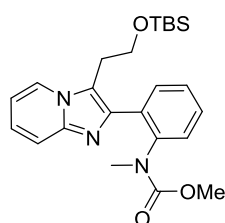
Methyl (2-(3-butylimidazo[1,2-*a*]pyridin-2-yl)phenyl)(methyl)carbamate (3.53c).



Yield = 79%; Yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.94 (d, $J = 7.0$ Hz, 1H), 7.58 (d, $J = 9.0$ Hz, 1H), 7.50–7.44 (m, 1H), 7.42–7.34 (m, 2H), 7.27 (d, $J = 8.0$ Hz,

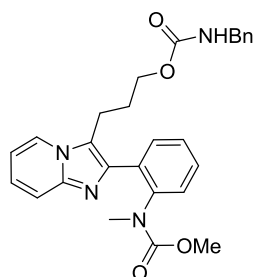
1H), 7.18–7.12 (m, 1H), 6.83 (t, $J = 6.8$ Hz, 1H), 3.55 (s, 3H), 3.00 (s, 3H), 2.82 (t, $J = 7.9$ Hz, 2H), 1.58–1.49 (m, 2H), 1.35–1.27 (m, 2H), 0.87 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 156.5, 144.5, 142.2, 140.6, 133.2, 132.2, 129.0, 128.4, 127.2, 123.5, 123.3, 121.9, 118.1, 112.1, 52.8, 38.4, 29.5, 23.0, 22.8, 13.9; IR (neat, cm^{-1}): 2921, 1708, 1502, 1451, 1360, 1082, 1026; HRMS (ESI, m/z) calcd for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 360.1682, obsd 360.1683.

Methyl (2-(3-(2-((*tert*-butyldimethylsilyloxy)ethyl)imidazo[1,2-*a*]pyridin-2-yl)-phenyl)(methyl)carbamate (3.53d).



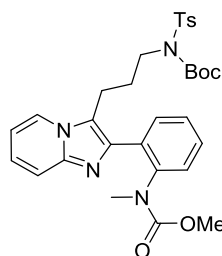
Yield = 81%; Brown oil; ^1H NMR (500 MHz, CDCl_3) δ 8.39–8.18 (m, 1H), 7.56 (d, $J = 9.0$ Hz, 1H), 7.50–7.26 (m, 4H), 7.16 (ddd, $J = 9.1, 6.7, 1.3$ Hz, 1H), 6.79 (t, $J = 6.8$ Hz, 1H), 3.84–3.75 (m, 2H), 3.67–3.50 (m, 3H), 3.10–2.94 (m, 5H), 0.80 (s, 9H), -0.10 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 156.4, 144.6, 142.2, 141.4, 133.1, 132.2, 129.1, 128.5, 127.2, 124.6, 123.8, 119.9, 117.7, 111.8, 62.9, 52.8, 38.4, 26.9, 26.0, 18.4, -5.4; IR (neat, cm^{-1}): 3411, 1633, 1305, 1083, 1064, 765; HRMS (ESI, m/z) calcd for $\text{C}_{24}\text{H}_{34}\text{N}_3\text{O}_3\text{Si}$ ($\text{M}+\text{H}^+$): 440.2364, obsd 440.2360.

Methyl (2-(3-(3-((benzylcarbamoyloxy)propyl)imidazo[1,2-*a*]pyridin-2-yl)-phenyl)(methyl)carbamate (3.53e)



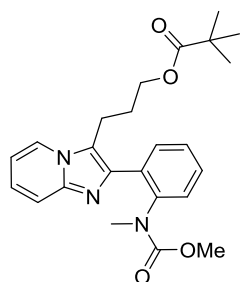
Yield = 77%; Yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 8.00–7.70 (m, 1H), 7.65–7.42 (m, 2H), 7.41–7.20 (m, 8H), 7.19–7.12 (m, 1H), 6.86–6.73 (m, 1H), 5.52 (s, 0.28 H), 4.99 (s, 0.76 H), 4.41–4.20 (m, 2H), 4.14–3.88 (m, 2H), 3.65 (s, 0.84H), 3.59 (s, 2.16H), 3.05–2.76 (m, 5H), 1.93–1.78 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 156.4, 144.6, 142.1, 141.0, 138.5, 132.9, 132.1, 129.1, 128.8, 128.7, 128.4, 127.6, 127.3, 127.1, 123.7, 123.1, 120.5, 118.0, 112.3, 64.0, 52.8, 45.1, 38.4, 26.8, 19.6; IR (neat, cm^{-1}): 3409, 2933, 1713, 1454, 1300, 1260, 1083; HRMS (ESI, m/z) calcd for $\text{C}_{27}\text{H}_{29}\text{N}_4\text{O}_4$ ($\text{M}+\text{H}^+$): 473.2183, obsd 473.2185.

Methyl (2-(3-(3-((*N*-(*tert*-butoxycarbonyl)-4-methylphenyl)sulfonamido)propyl)-imidazo[1,2-*a*]pyridin-2-yl)phenyl)(methyl)carbamate (3.53f).



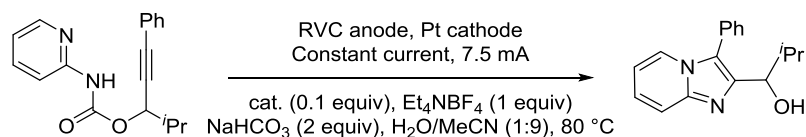
Yield = 48%; yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.93 (d, $J = 6.9$ Hz, 1H), 7.64 (d, $J = 7.9$ Hz, 2H), 7.51 (d, $J = 9.0$ Hz, 1H), 7.42–7.27 (m, 3H), 7.24–7.17 (m, 3H), 7.12–7.06 (m, 1H), 6.78 (t, $J = 6.8$ Hz, 1H), 3.85–3.69 (m, 2H), 3.46 (s, 3H), 3.04–2.78 (m, 5H), 2.35 (s, 3H), 2.00–1.89 (m, 2H), 1.20 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 156.4, 151.0, 144.6, 144.4, 142.3, 141.0, 137.3, 133.1, 132.0, 129.4, 129.2, 128.5, 127.9, 127.3, 123.7, 123.3, 120.4, 118.0, 112.4, 84.5, 52.9, 46.7, 38.5, 27.9, 27.9, 21.7, 20.5. IR (neat, cm^{-1}): 3369, 2945, 2929, 1709, 1597, 1454, 1356, 1286, 1156, 1086, 992, 767, 736; HRMS (ESI, m/z) calcd for $\text{C}_{31}\text{H}_{37}\text{N}_4\text{O}_6\text{S}$ ($\text{M}+\text{H}^+$): 593.2428, obsd 593.2431.

3-(2-(2-((Methoxycarbonyl)(methyl)amino)phenyl)imidazo[1,2-*a*]pyridin-3-yl)propyl pivalate (3.53g).



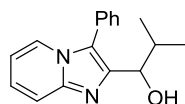
Yield = 76%; Yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.87 (d, $J = 7.0$ Hz, 1H), 7.52 (d, $J = 9.0$ Hz, 1H), 7.43–7.17 (m, 4H), 7.15–7.07 (m, 1H), 6.78 (t, $J = 6.7$ Hz, 1H), 3.96 (t, $J = 6.1$ Hz, 2H), 3.60–3.43 (m, 3H), 3.00–2.80 (m, 5H), 1.88–1.76 (m, 2H), 1.05 (s, 9H). ^{13}C NMR (126 MHz, CDCl_3) δ 178.5, 156.4, 144.6, 142.2, 141.1, 133.0, 132.0, 129.2, 128.5, 127.4, 123.7, 123.0, 120.4, 118.2, 112.4, 63.4, 52.8, 38.8, 38.5, 27.3, 26.6, 19.8; IR (neat, cm^{-1}): 3360, 2959, 2933, 1710, 1453, 1363, 1283, 1158, 765; HRMS (ESI, m/z) calcd for $\text{C}_{24}\text{H}_{30}\text{N}_3\text{O}_4$ ($\text{M}+\text{H}^+$): 424.2231, obsd 424.2229.

General Procedure for the Electrolysis ($\text{MeCN}/\text{H}_2\text{O} = 9/1$, carbamate-derived substrates)



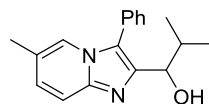
A 25 mL three-necked round-bottomed flask was charged with catalyst (0.03 mmol), the substrate (0.3 mmol), Et_4NBF_4 (0.3 mmol), and NaHCO_3 (0.6 mmol). The flask was equipped with a condenser, a reticulated vitreous carbon (100 PPI) anode and a platinum plate (1 cm x 1 cm) cathode and then flushed with argon. Acetonitrile (9 mL) and water (1 mL) were added. The electrolysis was carried out at 80 °C (oil bath temperature) using a constant current of 7.5 mA until complete consumption of the substrate (monitored by TLC or ^1H NMR). The reaction mixture was cooled to RT and concentrated under reduced pressure. The residue was chromatographed through silica gel eluting with ethyl acetate/hexanes to give the desired product.

2-Methyl-1-(3-phenylimidazo[1,2-*a*]pyridin-2-yl)propan-1-ol (3.28a)



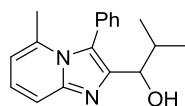
Yield = 87%; White solid; ^1H NMR (500 MHz, CDCl_3) δ 8.02 (d, $J = 7.0$ Hz, 1H), 7.62 (d, $J = 9.1$ Hz, 1H), 7.57–7.51 (m, 2H), 7.51–7.42 (m, 3H), 7.22–7.13 (m, 1H), 6.73 (t, $J = 7.0$ Hz, 1H), 4.43 (d, $J = 8.0$ Hz, 1H), 3.25 (s, 1H), 2.23–2.10 (m, 1H), 1.04 (d, $J = 6.6$ Hz, 3H), 0.74 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 145.8, 144.7, 130.3, 129.4, 128.9, 128.8, 124.8, 123.6, 122.0, 117.7, 112.4, 73.2, 34.9, 19.6, 18.8; IR (neat, cm^{-1}): 3366, 2955, 2866, 1635, 1504, 1345, 1046, 1017; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{ONa}$ ($\text{M}+\text{Na}^+$): 289.1311, obsd 289.1307; chiral HPLC conditions: Chiralpak AD-H+G (*n*-hexane/ ethanol, 70:30), flow rate = 1.0 mL/min, R_t = 6.2 and 7.1 min, respectively. The enantiomeric excess was determined to be 1%.

2-Methyl-1-(6-methyl-3-phenylimidazo[1,2-*a*]pyridin-2-yl)propan-1-ol (3.28b)



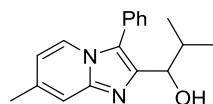
Yield = 81%; White solid; ^1H NMR (500 MHz, CDCl_3) δ 7.79 (s, 1H), 7.58–7.49 (m, 3H), 7.49–7.43 (m, 3H), 7.04 (dd, $J = 9.2, 1.8$ Hz, 1H), 4.42 (d, $J = 7.9$ Hz, 1H), 2.75 (s, 1H), 2.26 (s, 3H), 2.24–2.14 (m, 1H), 1.02 (d, $J = 6.7$ Hz, 3H), 0.74 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 145.6, 143.8, 130.3, 129.4, 129.2, 128.7, 127.9, 122.0, 121.7, 121.2, 117.0, 73.2, 35.0, 19.6, 18.7, 18.5; IR (neat, cm^{-1}): 3405, 2955, 1536, 1444, 1083, 1046; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{ONa}$ ($\text{M}+\text{Na}^+$): 303.1468, obsd 303.1463.

2-Methyl-1-(5-methyl-3-phenylimidazo[1,2-*a*]pyridin-2-yl)propan-1-ol (3.28c).



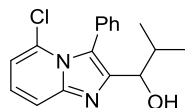
Yield = 88%; Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.61–7.33 (m, 6H), 7.09 (dd, $J = 9.1, 6.8$ Hz, 1H), 6.45 (d, $J = 6.8$ Hz, 1H), 4.12 (d, $J = 7.9$ Hz, 1H), 2.65 (s, 1H), 2.20–2.10 (m, 1H), 2.07 (s, 3H), 0.99 (d, $J = 6.8$ Hz, 3H), 0.73 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 146.8, 146.0, 136.7, 132.9, 132.5, 131.6, 129.0, 127.6, 127.5, 124.7, 122.6, 115.8, 113.4, 73.0, 34.9, 21.7, 19.7, 18.6; IR (neat, cm^{-1}): 3419, 2958, 2923, 1636, 1515, 1456, 1249, 1082; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{ONa}$ ($\text{M}+\text{Na}^+$): 303.1468, obsd 303.1462.

2-Methyl-1-(7-methyl-3-phenylimidazo[1,2-*a*]pyridin-2-yl)propan-1-ol (3.28d)



Yield = 83%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 7.90 (dd, $J = 7.0, 0.8$ Hz, 1H), 7.54–7.49 (m, 2H), 7.48–7.41 (m, 3H), 7.38–7.34 (m, 1H), 6.55 (dd, $J = 7.0, 1.7$ Hz, 1H), 4.40 (d, $J = 8.2$ Hz, 1H), 3.52 (s, 1H), 2.37 (s, 3H), 2.27–2.19 (m, 1H), 1.05 (d, $J = 6.8$ Hz, 3H), 0.72 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 145.4, 145.1, 135.6, 130.2, 129.3, 129.1, 128.6, 122.8, 121.4, 116.0, 114.9, 73.2, 34.9, 21.4, 19.6, 18.9; IR (neat, cm^{-1}): 3304, 2922, 1649, 1604, 1503, 1382, 1132, 1045; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{ONa}$ ($\text{M}+\text{Na}^+$): 303.1468, obsd 303.1469.

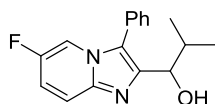
1-(5-Chloro-3-phenylimidazo[1,2-*a*]pyridin-2-yl)-2-methylpropan-1-ol (3.28e).



Yield = 83%; Pale Yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.61 (dd, $J = 9.0, 1.1$ Hz, 1H), 7.49–7.38 (m, 4H), 7.38–7.32 (m, 1H), 7.12 (dd, $J = 9.0, 7.2$ Hz, 1H), 6.77 (dd, $J = 7.2, 1.1$ Hz, 1H), 4.17 (d, $J = 8.0$ Hz, 1H), 3.02 (s, 1H), 2.21–2.09 (m, 1H), 1.00 (d, $J = 6.7$ Hz, 3H), 0.73 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 147.6, 146.5, 132.9, 132.3, 130.4, 128.9, 127.8, 127.4, 127.2, 124.6, 123.4, 116.4, 114.0, 72.8, 34.8,

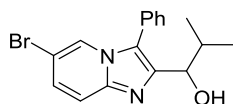
19.6, 18.6; IR (neat, cm^{-1}): 3385, 2956, 1626, 1487, 1152, 1043; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{17}\text{ClN}_2\text{ONa}$ ($\text{M}+\text{Na}^+$): 323.0922, obsd 323.0920.

1-(6-Fluoro-3-phenylimidazo[1,2-*a*]pyridin-2-yl)-2-methylpropan-1-ol (3.28g).



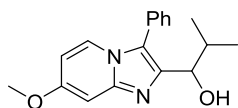
Yield = 86%; Colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 7.94 (ddd, $J = 4.3, 2.4, 0.8$ Hz, 1H), 7.64–7.52 (m, 3H), 7.51–7.44 (m, 3H), 7.15–7.07 (m, 1H), 4.43 (d, $J = 8.0$ Hz, 1H), 3.20 (s, 1H), 2.26–2.15 (m, 1H), 1.03 (d, $J = 6.7$ Hz, 3H), 0.74 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 153.5 (d, $J_{\text{C-F}} = 236.6$ Hz), 147.2 (d, $J_{\text{C-F}} = 2.1$ Hz), 142.4, 130.0, 129.6, 129.2, 128.4, 123.4, 118.2 (d, $J_{\text{C-F}} = 9.0$ Hz), 116.7 (d, $J_{\text{C-F}} = 25.6$ Hz), 110.2 (d, $J_{\text{C-F}} = 41.3$ Hz), 73.2, 34.9, 19.5, 18.7; ^{19}F NMR (471 MHz, CDCl_3) δ -140.1; IR (neat, cm^{-1}): 3375, 2957, 1651, 1534, 1512, 1324, 1225, 1143, 1010; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{17}\text{FN}_2\text{ONa}$ ($\text{M}+\text{Na}^+$): 307.1217, obsd 307.1214.

1-(6-Bromo-3-phenylimidazo[1,2-*a*]pyridin-2-yl)-2-methylpropan-1-ol (3.28h).



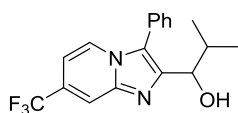
Yield = 74%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 8.11 (d, $J = 1.8$ Hz, 1H), 7.57–7.45 (m, 6H), 7.23 (dd, $J = 9.5, 1.8$ Hz, 1H), 4.40 (d, $J = 8.2$ Hz, 1H), 3.59 (s, 1H), 2.25–2.16 (m, 1H), 1.03 (d, $J = 6.8$ Hz, 3H), 0.72 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 146.7, 143.1, 130.2, 129.6, 129.2, 128.2, 128.1, 123.6, 122.4, 118.3, 107.2, 73.1, 34.8, 19.5, 18.8; IR (neat, cm^{-1}): 3359, 1631, 1468, 1322, 1132, 1082, 1027; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{17}\text{BrN}_2\text{ONa}$ ($\text{M}+\text{Na}^+$): 367.0416, obsd 367.0420.

1-(7-Methoxy-3-phenylimidazo[1,2-*a*]pyridin-2-yl)-2-methylpropan-1-ol (3.28i)



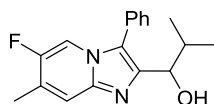
Yield = 73%; Yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 7.90–7.80 (m, 1H), 7.57–7.49 (m, 2H), 7.49–7.40 (m, 3H), 6.91 (s, 1H), 6.48 (d, $J = 7.7$ Hz, 1H), 4.35 (d, $J = 8.2$ Hz, 1H), 4.21–3.78 (m, 1H) 3.86 (s, 3H), 2.28–2.16 (m, 1H), 1.05 (d, $J = 6.6$ Hz, 3H), 0.77–0.64 (m, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 158.5, 146.0, 144.4, 130.2, 129.4, 128.7 (2C), 124.2, 121.1, 107.6, 94.6, 73.1, 55.8, 34.9, 19.6, 19.0. IR (neat, cm^{-1}): 3376, 2957, 2924, 1650, 1478, 1215, 1026; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 319.1417, obsd 319.1413.

2-Methyl-1-(3-phenyl-7-(trifluoromethyl)imidazo[1,2-*a*]pyridin-2-yl)propan-1-ol (3.28j)



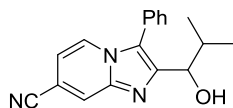
Yield = 78%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 8.10 (d, $J = 7.2$ Hz, 1H), 7.95 (s, 1H), 7.61–7.55 (m, 2H), 7.53–7.46 (m, 3H), 6.91 (dd, $J = 7.3, 1.8$ Hz, 1H), 4.46 ($J = 6.1$ Hz, 1H), 3.39 (s, 1H), 2.26–2.17 (m, 1H), 1.04 (d, $J = 6.8$ Hz, 3H), 0.74 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 148.2, 142.7, 130.2, 129.7, 129.5, 128.0, 126.5 (q, $J_{\text{C-F}} = 34.2$ Hz), 124.5 (q, $J_{\text{C-F}} = 272.0$ Hz), 124.3, 123.5, 115.8 (q, $J_{\text{C-F}} = 4.9$ Hz), 108.3 (q, $J_{\text{C-F}} = 3.0$ Hz), 73.1, 34.9, 19.5, 18.7; ^{19}F NMR (471 MHz, CDCl_3) δ -63.5; IR (neat, cm^{-1}): 3360, 1632, 1469, 1356, 1131, 1083, 1045; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{17}\text{F}_3\text{N}_2\text{ONa}$ ($\text{M}+\text{Na}^+$): 357.1185, obsd 357.1187.

1-(6-Fluoro-7-methyl-3-phenylimidazo[1,2-*a*]pyridin-2-yl)-2-methylpropan-1-ol (3.28k).



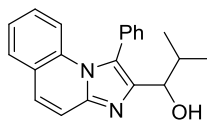
Yield = 82%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 7.89 (d, $J = 4.9$ Hz, 1H), 7.56–7.51 (m, 2H), 7.48–7.43 (m, 3H), 7.39 (dt, $J = 7.2, 1.0$ Hz, 1H), 4.40 (d, $J = 8.2$ Hz, 1H), 3.60 (s, 1H), 2.35 (s, 3H), 2.25–2.18 (m, 1H), 1.04 (d, $J = 6.8$ Hz, 3H), 0.72 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 153.3 (d, $J_{\text{C-F}} = 236.9$ Hz), 146.5 (d, $J_{\text{C-F}} = 2.2$ Hz), 142.6, 130.0, 129.5, 128.9, 128.7, 127.3 (d, $J_{\text{C-F}} = 21.7$ Hz), 122.6 (d, $J_{\text{C-F}} = 1.9$ Hz), 117.1 (d, $J_{\text{C-F}} = 5.4$ Hz), 109.5 (d, $J_{\text{C-F}} = 43.0$ Hz), 73.2, 34.9, 19.6, 18.9, 15.3 (d, $J_{\text{C-F}} = 3.1$ Hz); ^{19}F NMR (471 MHz, CDCl_3) δ -144.1; IR (neat, cm^{-1}): 3412, 2921, 1618, 1466, 1225, 1027; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{19}\text{FN}_2\text{ONa}$ ($\text{M}+\text{Na}^+$): 321.1374, obsd 321.1376.

2-(1-Hydroxy-2-methylpropyl)-3-phenylimidazo[1,2-*a*]pyridine-7-carbonitrile (3.28p).



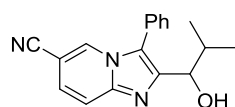
Yield = 85%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 8.08 (d, $J = 7.2$ Hz, 1H), 8.04 (s, 1H), 7.64–7.50 (m, 3H), 7.50–7.44 (m, 2H), 6.90 (d, $J = 7.2$ Hz, 1H), 4.48 (t, $J = 7.4$ Hz, 1H), 3.13 (d, $J = 7.4$ Hz, 1H), 2.25–2.14 (m, 1H), 1.02 (d, $J = 6.6$ Hz, 3H), 0.75 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 149.3, 142.4, 130.1, 129.8, 127.4, 124.4, 124.3, 123.9, 117.8, 112.7, 107.2, 73.1, 35.0, 19.4, 18.5; IR (neat, cm^{-1}): 3454, 2225, 2065, 1635, 1349, 1231, 1013; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{17}\text{N}_3\text{ONa}$ ($\text{M}+\text{Na}^+$): 314.1264, obsd 314.1257.

2-Methyl-1-(3-phenylimidazo[1,2-*b*]isoquinolin-2-yl)propan-1-ol (3.28q)



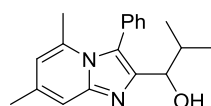
Yield = 89%; Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.76–7.71 (m, 1H), 7.60–7.47 (m, 6H), 7.45–7.40 (m, 1H), 7.35–7.29 (m, 1H), 7.28–7.25 (m, 1H), 7.22–7.16 (m, 1H), 4.18 (d, $J = 8.1$ Hz, 1H), 2.92 (s, 1H), 2.26–2.15 (m, 1H), 1.04 (d, $J = 6.8$ Hz, 3H), 0.76 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 145.7, 143.9, 134.2, 131.7, 131.6, 131.3, 129.4, 129.3, 129.2, 129.0, 128.0, 126.7, 125.0, 124.6, 124.4, 117.5, 116.8, 72.9, 34.9, 19.7, 18.8; IR (neat, cm^{-1}): 3406, 2955, 1621, 1537, 1445, 1383, 1042; HRMS (ESI, m/z) calcd for $\text{C}_{21}\text{H}_{20}\text{N}_2\text{ONa}$ ($\text{M}+\text{Na}^+$): 339.1468, obsd 339.1464.

2-(1-Hydroxy-2-methylpropyl)-3-phenylimidazo[1,2-*a*]pyridine-6-carbonitrile (3.28r).



Yield = 79%; White solid; ^1H NMR (500 MHz, CDCl_3) δ 8.42 (s, 1H), 7.71 (d, $J = 9.4$ Hz, 1H), 7.63–7.57 (m, 2H), 7.57–7.51 (m, 1H), 7.49–7.43 (m, 2H), 7.32–7.28 (m, 1H), 4.44 (d, $J = 7.9$ Hz, 1H), 3.29 (s, 1H), 2.29–2.15 (m, 1H), 1.04 (d, $J = 6.7$ Hz, 3H), 0.74 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 148.1, 143.8, 130.2, 130.0, 129.9 (2C), 127.2, 124.5, 123.3, 118.7, 116.8, 98.8, 73.0, 34.9, 19.5, 18.6; IR (neat, cm^{-1}): 3417, 2917, 1633, 1417, 1132, 1082; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{17}\text{N}_3\text{ONa}$ ($\text{M}+\text{Na}^+$): 314.1264, obsd 314.1262.

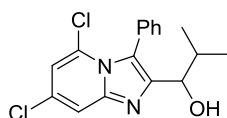
1-(5,7-Dimethyl-3-phenylimidazo[1,2-*a*]pyridin-2-yl)-2-methylpropan-1-ol (3.28s)



Yield = 72%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 7.47–7.31 (m, 5H), 7.28 (s, 1H), 6.29 (s, 1H), 4.08 (d, $J = 8.1$ Hz, 1H), 3.29 (s, 1H), 2.33 (s, 3H), 2.21–2.09 (m, 1H), 2.02 (s, 3H), 1.00 (d, $J = 6.8$ Hz, 3H), 0.71 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 146.4 (2C), 135.7, 135.4, 132.9, 132.5, 131.7, 128.8,

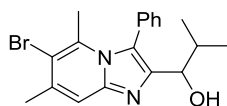
127.9, 127.5, 122.0, 116.0, 114.2, 73.0, 34.8, 21.5, 21.1, 19.7, 18.8; IR (neat, cm^{-1}): 3399, 2957, 2920, 2866, 1650, 1513, 1443, 1260, 1043; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{ONa}$ ($\text{M}+\text{Na}^+$): 317.1624, obsd 317.1618.

1-(5,7-Dichloro-3-phenylimidazo[1,2-*a*]pyridin-2-yl)-2-methylpropan-1-ol (3.28t)



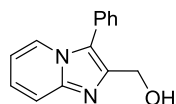
Yield = 60%; Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.62 (d, $J = 2.0$ Hz, 1H), 7.49–7.38 (m, 4H), 7.35–7.31 (m, 1H), 6.79 (d, $J = 2.0$ Hz, 1H), 4.14 (d, $J = 8.0$ Hz, 1H), 3.09 (s, 1H), 2.19–2.06 (m, 1H), 1.00 (d, $J = 6.6$ Hz, 3H), 0.72 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 148.5, 145.8, 132.9, 132.2, 130.6, 129.8, 129.2, 127.9, 127.7, 127.6, 123.7, 115.3, 115.0, 72.7, 34.8, 19.5, 18.6; IR (neat, cm^{-1}): 3381, 2957, 2925, 2869, 1619, 1491, 1232, 1147, 1045, 832; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{16}\text{Cl}_2\text{N}_2\text{ONa}$ ($\text{M}+\text{Na}^+$): 357.0532, obsd 357.0533.

1-(6-Bromo-5,7-dimethyl-3-phenylimidazo[1,2-*a*]pyridin-2-yl)-2-methylpropan-1-ol (3.28u).



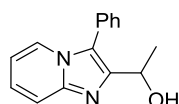
Yield = 56%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 7.51–7.35 (m, 5H), 7.35–7.28 (m, 1H), 4.09 (d, $J = 7.8$ Hz, 1H), 2.75 (s, 1H), 2.47 (s, 3H), 2.28 (s, 3H), 2.16–2.05 (m, 1H), 0.98 (d, $J = 6.7$ Hz, 3H), 0.71 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 147.4, 144.8, 135.8, 134.8, 132.5, 132.1, 131.7, 129.0, 128.3, 127.9, 123.2, 114.9, 114.0, 72.9, 34.9, 24.4, 21.7, 19.6, 18.5; IR (neat, cm^{-1}): 3431, 2957, 1634, 1495, 1435, 1083; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{22}\text{BrN}_2\text{O}$ ($\text{M}+\text{H}^+$): 373.0910, 375.0890; obsd 373.0912, 375.0891.

(3-Phenylimidazo[1,2-*a*]pyridin-2-yl)methanol (3.55a)



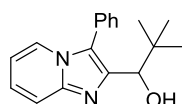
Yield = 56%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 8.16 (dt, $J = 7.0, 1.2$ Hz, 1H), 7.67–7.63 (m, 1H), 7.59–7.52 (m, 4H), 7.48–7.42 (m, 1H), 7.22–7.18 (m, 1H), 6.76 (td, $J = 7.0, 1.2$ Hz, 1H), 5.35 (s, 1H), 4.85 (s, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 144.9, 143.9, 129.8, 129.4, 128.7, 128.6, 125.1, 123.7, 122.5, 117.7, 112.7, 57.2. (Known compound)

1-(3-Phenylimidazo[1,2-*a*]pyridin-2-yl)ethan-1-ol (3.55b)



Yield = 73%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 8.05 (dt, $J = 7.0, 1.2$ Hz, 1H), 7.64 (dt, $J = 9.1, 1.2$ Hz, 1H), 7.56–7.50 (m, 2H), 7.50–7.42 (m, 3H), 7.20–7.14 (m, 1H), 6.73 (td, $J = 6.8, 1.2$ Hz, 1H), 5.04 (q, $J = 6.6$ Hz, 1H), 4.40 (s, 1H), 1.63 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 147.2, 144.7, 130.0, 129.3, 128.7 (2C), 124.8, 123.5, 120.7, 117.7, 112.5, 63.6, 24.2; IR (neat, cm^{-1}): 3439, 2917, 1645, 1079; HRMS (ESI, m/z) calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{ONa}$ ($\text{M}+\text{Na}^+$): 261.0998, obsd 261.1000.

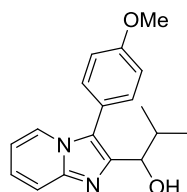
2,2-Dimethyl-1-(3-phenylimidazo[1,2-*a*]pyridin-2-yl)propan-1-ol (3.55c)



Yield = 94%, white solid; ^1H NMR (500 MHz, CDCl_3) δ 7.97 (dt, $J = 6.9, 1.2$ Hz, 1H), 7.63 (dt, $J = 9.0, 1.2$ Hz, 1H), 7.57–7.50 (m, 2H), 7.50–7.42 (m, 3H), 7.22–7.15 (m, 1H), 6.73 (td, $J = 6.8, 1.2$ Hz, 1H), 4.58 (s, 1H), 3.18 (s, 1H), 0.87 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 144.6, 144.2, 130.6, 129.6, 129.4, 128.9, 124.7, 123.5, 122.3,

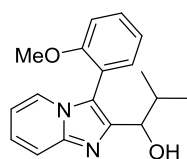
117.6, 112.3, 75.0, 37.3, 26.2; IR (neat, cm^{-1}): 3417, 2951, 1504, 1345, 1077, 1015; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{ONa}$ ($\text{M}+\text{Na}^+$): 303.1468, obsd 303.1470.

1-(3-(4-Methoxyphenyl)imidazo[1,2-*a*]pyridin-2-yl)-2-methylpropan-1-ol (3.55e)



Yield = 63%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 7.96 (dt, $J = 6.9, 1.2$ Hz, 1H), 7.60 (dt, $J = 9.1, 1.2$ Hz, 1H), 7.42–7.35 (m, 2H), 7.20–7.14 (m, 1H), 7.09–7.03 (m, 2H), 6.72 (td, $J = 6.8, 1.2$ Hz, 1H), 4.41 (d, $J = 8.0$ Hz, 1H), 3.89 (s, 3H), 2.85 (s, 1H), 2.25–2.16 (m, 1H), 1.03 (d, $J = 6.7$ Hz, 3H), 0.75 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 160.0, 145.5, 144.5, 131.7, 124.6, 123.9, 121.7, 120.9, 117.6, 114.9, 112.3, 73.3, 55.5, 35.0, 19.6, 18.8; IR (neat, cm^{-1}): 3359, 2920, 1632, 1510, 1468, 1252, 1082, 1024; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 319.1417, obsd 319.1419.

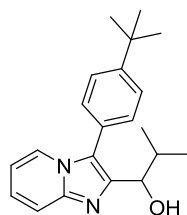
1-(3-(2-Methoxyphenyl)imidazo[1,2-*a*]pyridin-2-yl)-2-methylpropan-1-ol (3.55f)



Major isomer: Yield = 50%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 7.64–7.59 (m, 2H), 7.50–7.46 (m, 1H), 7.42 (dd, $J = 7.4, 1.8$ Hz, 1H), 7.21–7.16 (m, 1H), 7.12–7.08 (m, 1H), 7.08–7.04 (m, 1H), 6.74–6.69 (m, 1H), 4.43 (d, $J = 7.8$ Hz, 1H), 3.75 (s, 3H), 2.88 (s, 1H), 2.13–2.04 (m, 1H), 0.94 (d, $J = 6.7$ Hz, 3H), 0.65 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 158.1, 145.8, 144.7, 133.0, 130.9, 125.1, 124.4, 121.4, 119.3, 117.5, 117.3, 111.6, 111.4, 73.4, 55.6, 35.2, 18.8, 18.6; IR (neat, cm^{-1}): 3412, 2919, 1639, 1464, 1299, 1062, 1026; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 319.1417, obsd 319.1420.

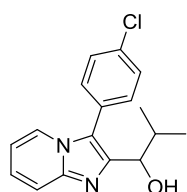
Minor isomer: Yield = 34%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 7.70 (dt, $J = 7.0, 1.2$ Hz, 1H), 7.64–7.59 (m, 1H), 7.50–7.46 (m, 1H), 7.33 (dd, $J = 7.5, 1.8$ Hz, 1H), 7.21–7.16 (m, 1H), 7.12–7.08 (m, 1H), 7.08–7.04 (m, 1H), 6.74–6.69 (m, 1H), 4.36 (d, $J = 7.9$ Hz, 1H), 3.76 (s, 3H), 2.88 (s, 1H), 2.32–2.21 (m, 1H), 1.06 (d, $J = 6.6$ Hz, 3H), 0.84 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 158.0, 146.4, 144.9, 132.8, 130.9, 125.1, 124.5, 121.1, 118.7, 117.6, 117.3, 111.8, 111.6, 73.4, 55.7, 34.4, 19.9, 18.7; IR (neat, cm^{-1}): 3412, 2919, 1639, 1464, 1299, 1062, 1026; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 319.1417, obsd 319.1419.

1-(3-(4-(*tert*-Butyl)phenyl)imidazo[1,2-*a*]pyridin-2-yl)-2-methylpropan-1-ol (3.55g)



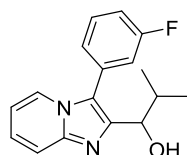
Yield = 81%; white solid; ^1H NMR (500 MHz, CDCl_3) δ 8.09–8.01 (m, 1H), 7.63–7.57 (m, 1H), 7.57–7.51 (m, 2H), 7.43–7.36 (m, 2H), 7.20–7.13 (m, 1H), 6.75–6.68 (m, 1H), 4.44 (d, $J = 7.8$ Hz, 1H), 2.97 (s, 1H), 2.31–2.17 (m, 1H), 1.39 (s, 9H), 1.05 (d, $J = 6.7$ Hz, 3H), 0.76 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 151.9, 145.6, 144.6, 129.9, 126.3, 125.7, 124.6, 123.8, 122.1, 117.6, 112.2, 73.2, 35.0, 31.5, 19.6, 18.8, 18.8; IR (neat, cm^{-1}): 3426, 2961, 2868, 1635, 1505, 1362, 1269, 1014; HRMS (ESI, m/z) calcd for $\text{C}_{21}\text{H}_{26}\text{N}_2\text{ONa}$ ($\text{M}+\text{Na}^+$): 345.1937, obsd 343.1936.

1-(3-(4-Chlorophenyl)imidazo[1,2-*a*]pyridin-2-yl)-2-methylpropan-1-ol (3.55h)



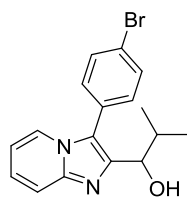
Yield = 75%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 7.98 (dt, $J = 6.9, 1.2$ Hz, 1H), 7.62 (dt, $J = 9.2, 1.2$ Hz, 1H), 7.54–7.49 (m, 2H), 7.46–7.41 (m, 2H), 7.23–7.17 (m, 1H), 6.76 (td, $J = 6.9, 1.2$ Hz, 1H), 4.39 (d, $J = 8.1$ Hz, 1H), 3.11 (s, 1H), 2.25–2.16 (m, 1H), 1.04 (d, $J = 6.7$ Hz, 3H), 0.73 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 146.1, 144.8, 134.9, 131.6, 129.8, 127.4, 125.0, 123.3, 120.7, 117.8, 112.7, 73.3, 34.9, 19.6, 18.8; IR (neat, cm^{-1}): 3300, 2955, 1509, 1467, 1344, 1089, 1024; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{17}\text{ClN}_2\text{ONa}$ ($\text{M}+\text{Na}^+$): 323.0922, obsd 323.0924.

1-(3-(3-Fluorophenyl)imidazo[1,2-*a*]pyridin-2-yl)-2-methylpropan-1-ol (3.55i)



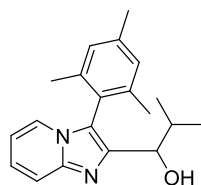
Yield = 53%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 8.03 (dt, $J = 7.0, 1.2$ Hz, 1H), 7.63 (dt, $J = 9.1, 1.2$ Hz, 1H), 7.55–7.48 (m, 1H), 7.30–7.27 (m, 1H), 7.23–7.14 (m, 3H), 6.77 (td, $J = 6.8, 1.2$ Hz, 1H), 4.42 (d, $J = 8.1$ Hz, 1H), 3.35 (s, 1H), 2.27–2.19 (m, 1H), 1.05 (d, $J = 6.7$ Hz, 3H), 0.74 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 163.3 (d, $J_{\text{C-F}} = 247.8$ Hz), 146.2, 144.9, 131.1 (d, $J_{\text{C-F}} = 8.6$ Hz), 131.0 (d, $J_{\text{C-F}} = 8.2$ Hz), 126.0 (d, $J_{\text{C-F}} = 3.0$ Hz), 125.1, 123.4, 120.7 (d, $J_{\text{C-F}} = 2.3$ Hz), 117.8, 117.0 (d, $J_{\text{C-F}} = 21.5$ Hz), 115.9 (d, $J_{\text{C-F}} = 20.9$ Hz), 112.7, 73.2, 34.9, 19.6, 18.8; ^{19}F NMR (471 MHz, CDCl_3) δ -111.4; IR (neat, cm^{-1}): 3394, 2919, 1645, 1469, 1132, 1077; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{17}\text{FN}_2\text{ONa}$ ($\text{M}+\text{Na}^+$): 307.1217, obsd 307.1219.

1-(3-(4-Bromophenyl)imidazo[1,2-*a*]pyridin-2-yl)-2-methylpropan-1-ol (3.55j)



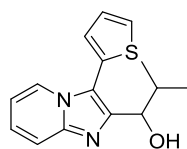
Yield = 79%; Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 7.98 (d, $J = 6.8$ Hz, 1H), 7.73–7.56 (m, 3H), 7.44–7.30 (m, 2H), 7.21 (dd, $J = 9.0, 6.8$ Hz, 1H), 6.77 (t, $J = 6.8$ Hz, 1H), 4.39 (d, $J = 7.9$ Hz, 1H), 2.99 (s, 1H), 2.26–2.13 (m, 1H), 1.04 (d, $J = 6.7$ Hz, 3H), 0.74 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 146.1, 144.9, 132.8, 131.8, 127.9, 125.0, 123.4, 123.1, 120.8, 117.9, 112.7, 73.3, 35.0, 19.6, 18.7; IR (neat, cm^{-1}): 3442, 2955, 1635, 1505, 1071, 1010; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{17}\text{BrN}_2\text{ONa}$ ($\text{M}+\text{Na}^+$): 367.0416, 369.0396; obsd 367.0412, 369.0391.

1-(3-Mesitylimidazo[1,2-*a*]pyridin-2-yl)-2-methylpropan-1-ol (3.55k)



Yield = 79%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 7.65 (dt, $J = 9.0, 1.2$ Hz, 1H), 7.43 (dt, $J = 6.8, 1.2$ Hz, 1H), 7.21–7.16 (m, 1H), 7.03 (d, $J = 9.0$ Hz, 2H), 6.71 (td, $J = 6.8, 1.2$ Hz, 1H), 4.19 (d, $J = 7.3$ Hz, 1H), 3.05 (s, 1H), 2.37 (s, 3H), 2.20–2.11 (m, 1H), 2.03 (s, 3H), 1.92 (s, 3H), 0.99 (d, $J = 6.7$ Hz, 3H), 0.78 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 145.9, 144.8, 139.9, 139.5 (2C), 129.0, 128.7, 124.3, 124.0, 123.5, 119.8, 117.6, 112.3, 73.6, 34.7, 21.4, 20.1, 19.7 (2C), 18.3; IR (neat, cm^{-1}): 3336, 2919, 1635, 1506, 1470, 1132, 1078; HRMS (ESI, m/z) calcd for $\text{C}_{20}\text{H}_{24}\text{N}_2\text{ONa}$ ($\text{M}+\text{Na}^+$): 331.1781, obsd 331.1783.

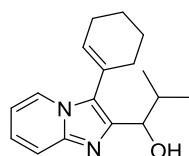
2-Methyl-1-(3-(thiophen-2-yl)imidazo[1,2-*a*]pyridin-2-yl)propan-1-ol (3.55m)



Yield = 89%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 8.12 (d, $J = 6.9$ Hz, 1H), 7.61 (d, $J = 9.1$ Hz, 1H), 7.57–7.50 (m, 1H), 7.26–7.15 (m, 3H), 6.86–6.76 (m, 1H), 4.56 (d, $J = 7.6$ Hz, 1H), 2.99 (s, 1H), 2.25–2.14 (m, 1H), 1.05 (d, $J = 6.8$ Hz,

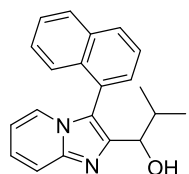
3H), 0.82 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 147.9, 145.2, 129.5, 128.8, 128.1, 128.0, 125.2, 124.1, 117.6, 114.6, 112.7, 73.1, 35.0, 19.6, 18.5; IR (neat, cm^{-1}): 3381, 2955, 1634, 1503, 1350, 1237, 1040; HRMS (ESI, m/z) calcd for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{OSNa}$ ($\text{M}+\text{Na}^+$): 295.0876, obsd 295.0874.

1-(3-(Cyclohex-1-en-1-yl)imidazo[1,2-*a*]pyridin-2-yl)-2-methylpropan-1-ol (3.55n)



Yield = 77%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 7.91 (dt, $J = 6.8$, 1.2 Hz, 1H), 7.53 (dt, $J = 9.0$, 1.2 Hz, 1H), 7.15–7.09 (m, 1H), 6.74 (td, $J = 6.8$, 1.2 Hz, 1H), 6.02–5.96 (m, 1H), 4.43 (d, $J = 7.8$ Hz, 1H), 3.03 (s, 1H), 2.33–2.15 (m, 5H), 1.84–1.72 (m, 4H), 1.08 (d, $J = 6.7$ Hz, 3H), 0.81 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 144.4, 144.1, 133.8, 126.5, 124.1, 124.0, 123.9, 117.5, 111.9, 73.4, 34.9, 28.7, 25.8, 22.9, 22.1, 19.7, 18.7; IR (neat, cm^{-1}): 3336, 2925, 1659, 1503, 1462, 1381; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{ONa}$ ($\text{M}+\text{Na}^+$): 293.1624, obsd 293.1625.

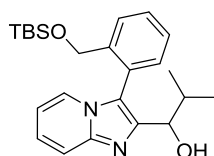
2-Methyl-1-(3-(naphthalen-1-yl)imidazo[1,2-*a*]pyridin-2-yl)propan-1-ol (3.55o)



A mixture of stereoisomers were obtained in a ratio of 3:2. Yield = 90%; Pale yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 8.10–7.91 (m, 2H), 7.75–7.15 (m, 8H), 6.71–6.58 (m, 1H), 4.51–4.20 (m, 1H), 2.90 (s, 1H), 2.23–2.01 (m, 1H), 1.02–0.88 (m, 3H), 0.82–0.57 (m, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 147.1, 146.9, 145.0, 144.8, 134.2, 134.1, 132.6, 132.4, 130.5, 130.3, 130.1, 130.1, 129.1, 128.8, 127.4, 127.2, 126.7,

126.5, 126.2, 126.0, 126.0, 125.7, 125.2, 125.2, 124.8, 124.4, 124.1, 120.4, 119.4, 117.6, 117.6, 112.3, 112.3, 73.5, 73.3, 35.0, 34.8, 19.7, 19.4, 18.5, 18.4. IR (neat, cm^{-1}): 3439, 2956, 1635, 1504, 1032, 1017, 803, 780; HRMS (ESI, m/z) calcd for $\text{C}_{21}\text{H}_{20}\text{N}_2\text{ONa}$ ($\text{M}+\text{Na}^+$): 339.1468, obsd 339.1464.

1-(3-(2-(((*tert*-Butyldimethylsilyloxy)methyl)phenyl)imidazo[1,2-*a*]pyridin-2-yl)-2-methylpropan-1-ol (3.55p)



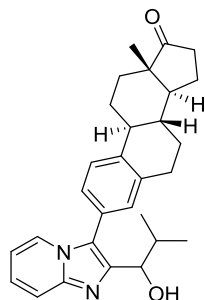
A mixture of stereoisomers were obtained in a ratio of 1:1.

Yield = 37%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 7.69 (dd, $J = 7.8, 1.2$ Hz, 1H), 7.62 (dt, $J = 9.1, 1.2$ Hz, 1H), 7.58 (dt, $J = 6.8, 1.2$ Hz, 1H), 7.53 (td, $J = 7.6, 1.4$ Hz, 1H), 7.41 (td, $J = 7.4, 1.4$ Hz, 1H), 7.23 (dd, $J = 7.4, 1.4$ Hz, 1H), 7.21–7.17 (m, 1H), 6.69 (td, $J = 6.8, 1.2$ Hz, 1H), 4.51 (d, $J = 13.2$ Hz, 1H), 4.38 (d, $J = 13.2$ Hz, 1H), 4.17–4.10 (m, 1H), 2.83 (s, 1H), 2.22–2.14 (m, 1H), 1.00 (d, $J = 6.7$ Hz, 3H), 0.80 (s, 9H), 0.75 (d, $J = 6.7$ Hz, 3H), -0.08 (s, 3H), -0.15 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 146.0, 144.9, 142.5, 132.2, 130.1, 128.5, 127.8, 126.3, 124.7, 124.1, 119.7, 117.5, 112.3, 73.4, 63.0, 34.8, 26.0, 19.6, 18.6, 18.4, -5.3 , -5.4 ; HRMS (ESI, m/z) calcd for $\text{C}_{24}\text{H}_{34}\text{N}_2\text{O}_2\text{SiNa}$ ($\text{M}+\text{Na}^+$): 433.2282, obsd 433.2286.

Yield = 37%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 7.67 (dd, $J = 7.8, 1.2$ Hz, 1H), 7.63 (dt, $J = 9.1, 1.2$ Hz, 1H), 7.55–7.51 (m, 2H), 7.41 (td, $J = 7.4, 1.4$ Hz, 1H), 7.32 (dd, $J = 7.6, 1.4$ Hz, 1H), 7.22–7.17 (m, 1H), 6.70 (td, $J = 6.8, 1.2$ Hz, 1H), 4.41 (d, $J = 6.9$ Hz, 1H), 4.34 (s, 2H), 3.11 (s, 1H), 2.18–2.08 (m, 1H), 0.94 (d, $J = 6.7$ Hz, 3H), 0.84 (s, 9H), 0.78 (d, $J = 6.7$ Hz, 3H), -0.06 (s, 3H), -0.08 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 146.4, 144.6, 141.8, 132.2, 130.1, 128.3, 128.2, 126.5, 124.7, 124.1, 120.1, 117.5, 112.3, 73.6, 62.9, 34.5, 26.0, 19.6, 18.5, 18.0, -5.3 , -5.4 ;

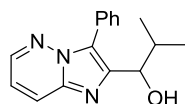
IR (neat, cm^{-1}): 3416, 2922, 1635, 2464, 1299, 1062, 1027; HRMS (ESI, m/z) calcd for $\text{C}_{24}\text{H}_{34}\text{N}_2\text{O}_2\text{SiNa}$ ($\text{M}+\text{Na}^+$): 433.2282, obsd 433.2286.

(8*R*,9*S*,13*S*,14*S*)-3-(2-(1-Hydroxy-2-methylpropyl)imidazo[1,2-*a*]pyridin-3-yl)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (3.55q)



Yield = 71%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 8.03 (dd, $J = 6.9, 1.3$ Hz, 1H), 7.61 (d, $J = 9.0$ Hz, 1H), 7.44 (d, $J = 8.0$ Hz, 1H), 7.25–7.16 (m, 3H), 6.73 (td, $J = 6.9, 1.3$ Hz, 1H), 4.45 (d, $J = 8.0$ Hz, 1H), 3.04–2.95 (m, 2H), 2.57–2.47 (m, 2H), 2.42–2.37 (m, 1H), 2.25–1.99 (m, 6H), 1.72–1.51 (m, 6H), 1.04 (d, $J = 6.7$, Hz, 3H), 0.97 (s, 3H), 0.77 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 220.9, 145.5, 144.6, 140.6, 137.7, 130.7, 127.6, 126.4, 126.2, 124.7, 123.8, 122.0, 117.7, 112.3, 73.2, 50.7, 48.2, 44.7, 38.2, 36.0, 35.0, 31.8, 29.6, 26.6, 25.8 (2C), 21.8, 19.7, 18.7, 14.1; IR (neat, cm^{-1}): 3432, 2926, 1737, 1634, 1505, 1455, 1084, 1041, 755; HRMS (ESI, m/z) calcd for $\text{C}_{29}\text{H}_{35}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}^+$): 443.2693, obsd 443.2692.

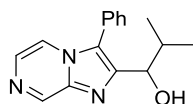
2-Methyl-1-(3-phenylimidazo[1,2-*b*]pyridazin-2-yl)propan-1-ol (3.56a).



Yield = 80%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 8.30 (d, $J = 4.4$ Hz, 1H), 7.97 (d, $J = 9.1$ Hz, 1H), 7.69–7.63 (m, 2H), 7.56–7.42 (m, 3H), 7.06 (dd, $J = 9.1, 4.4$ Hz, 1H), 4.63 (d, $J = 7.7$ Hz, 1H), 3.01 (s, 1H), 2.29–2.21 (m, 1H), 1.04 (d, $J = 6.7$

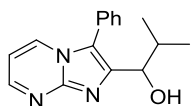
Hz, 3H), 0.77 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 146.3, 143.0, 138.4, 130.1, 128.9, 128.8, 128.1, 125.9, 125.5, 117.1, 73.2, 34.9, 19.6, 18.5; IR (neat, cm^{-1}): 3449, 2920, 1636, 1490, 1033, 757; HRMS (ESI, m/z) calcd for $\text{C}_{16}\text{H}_{17}\text{N}_3\text{ONa}$ ($\text{M}+\text{Na}^+$): 290.1264, obsd 290.1266.

2-Methyl-1-(3-phenylimidazo[1,2-*a*]pyrazin-2-yl)propan-1-ol (3.56c)



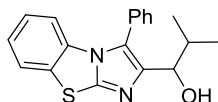
Yield = 76%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 9.09 (d, $J = 1.5$ Hz, 1H), 7.97 (dd, $J = 4.7, 1.5$ Hz, 1H), 7.84 (d, $J = 4.7$ Hz, 1H), 7.60–7.55 (m, 2H), 7.54–7.49 (m, 3H), 4.53 (d, $J = 7.9$ Hz, 1H), 3.59 (s, 1H), 2.28–2.19 (m, 1H), 1.04 (d, $J = 6.7$ Hz, 3H), 0.75 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 148.3, 143.8, 139.8, 129.9, 129.8, 129.7, 129.6, 127.4, 123.5, 116.4, 73.0, 34.9, 19.4, 18.6; IR (neat, cm^{-1}): 3391, 2919, 1492, 1346, 1293, 1024; HRMS (ESI, m/z) calcd for $\text{C}_{16}\text{H}_{17}\text{N}_3\text{ONa}$ ($\text{M}+\text{Na}^+$): 290.1264, obsd 290.1266.

2-Methyl-1-(3-phenylimidazo[1,2-*a*]pyrimidin-2-yl)propan-1-ol (3.56d)



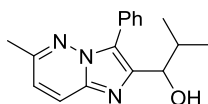
Yield = 42%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 8.55 (dd, $J = 4.0, 2.0$ Hz, 1H), 8.35 (dd, $J = 6.9, 2.0$ Hz, 1H), 7.60–7.53 (m, 2H), 7.53–7.44 (m, 3H), 6.85 (dd, $J = 6.9, 4.0$ Hz, 1H), 4.50 (d, $J = 7.4$ Hz, 1H), 3.03 (s, 1H), 2.27–2.15 (m, 1H), 1.02 (d, $J = 6.7$ Hz, 3H), 0.77 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 149.9, 147.7, 147.5, 131.1, 130.0, 129.7, 129.3, 127.7, 120.2, 108.9, 73.1, 35.0, 19.5, 18.4; IR (neat, cm^{-1}): 3390, 2956, 2923, 1498, 1260, 1083; HRMS (ESI, m/z) calcd for $\text{C}_{16}\text{H}_{17}\text{N}_3\text{ONa}$ ($\text{M}+\text{Na}^+$): 290.1264, obsd 290.1263.

2-Methyl-1-(3-phenylbenzo[d]imidazo[2,1-*b*]thiazol-2-yl)propan-1-ol (3.56f)



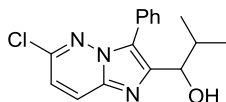
Yield = 52%; Yellow solid; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.66 (d, $J = 8.1$ Hz, 1H), 7.60–7.42 (m, 5H), 7.29–7.24 (m, 1H), 7.19–7.12 (m, 1H), 7.03–6.97 (m, 1H), 4.18 (t, $J = 8.0$ Hz, 1H), 2.55 (d, $J = 8.0$ Hz, 1H), 2.23–2.12 (m, 1H), 1.05 (d, $J = 6.7$ Hz, 3H), 0.79 (d, $J = 6.7$ Hz, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 147.3, 146.8, 133.1, 131.0, 130.6, 129.3, 129.2, 129.0, 128.9, 125.9, 125.5, 124.6, 124.4, 113.6, 73.1, 34.9, 19.6, 19.0; IR (neat, cm^{-1}): 3392, 2955, 2923, 1580, 1483, 1312, 1083, 1026, 747; HRMS (ESI, m/z) calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{OSNa}$ ($\text{M}+\text{Na}^+$): 345.1032, obsd 345.1033.

2-Methyl-1-(6-methyl-3-phenylimidazo[1,2-*b*]pyridazin-2-yl)propan-1-ol (3.56j)



Yield = 80%; Yellow solid; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.83 (d, $J = 9.2$ Hz, 1H), 7.73–7.65 (m, 2H), 7.55–7.48 (m, 2H), 7.46–7.40 (m, 1H), 6.92 (d, $J = 9.2$ Hz, 1H), 4.60 (d, $J = 7.9$ Hz, 1H), 2.93 (s, 1H), 2.53 (s, 3H), 2.30–2.19 (m, 1H), 1.04 (d, $J = 6.8$ Hz, 3H), 0.76 (d, $J = 6.8$ Hz, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 151.9, 145.7, 137.4, 130.1, 128.7, 128.5, 128.4, 125.6, 125.0, 119.2, 73.2, 34.8, 22.0, 19.6, 18.6; IR (neat, cm^{-1}): 3400, 2957, 2922, 1548, 1446, 1303, 1082, 1041, 748; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{19}\text{N}_3\text{ONa}$ ($\text{M}+\text{Na}^+$): 304.1420, obsd 304.1419.

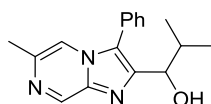
1-(6-Chloro-3-phenylimidazo[1,2-*b*]pyridazin-2-yl)-2-methylpropan-1-ol (3.56k)



Yield = 51%; Pale yellow solid; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.91 (d, $J = 9.3$ Hz, 1H), 7.71–7.61 (m, 2H), 7.57–7.43 (m, 3H), 7.07 (d, $J = 9.3$ Hz, 1H), 4.61 (d, $J = 7.7$ Hz, 1H), 3.07 (s, 1H), 2.28–2.18 (m, 1H), 1.03 (d, $J = 6.7$ Hz, 3H), 0.76 (d, $J = 6.7$ Hz,

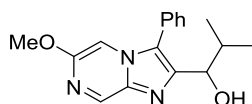
3H); ^{13}C NMR (126 MHz, CDCl_3) δ 147.2, 146.8, 137.0, 130.0, 129.0, 128.9, 127.4, 126.8, 126.5, 119.0, 73.1, 34.7, 19.5, 18.6; IR (neat, cm^{-1}): 3366, 2957, 2924, 2869, 1603, 1520, 1456, 1296, 1098, 1041, 758; HRMS (ESI, m/z) calcd for $\text{C}_{16}\text{H}_{16}\text{ClN}_3\text{ONa}$ ($\text{M}+\text{Na}^+$): 324.0874, obsd 324.0873.

2-Methyl-1-(6-methyl-3-phenylimidazo[1,2-*a*]pyrazin-2-yl)propan-1-ol (3.56l)



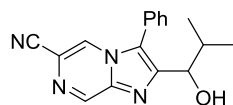
Yield = 82%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 9.02 (d, $J = 1.4$ Hz, 1H), 7.77 (s, 1H), 7.60–7.56 (m, 2H), 7.54–7.47 (m, 3H), 4.51 (d, $J = 7.8$ Hz, 1H), 3.20 (s, 1H), 2.47 (s, 3H), 2.23–2.15 (m, 1H), 1.02 (d, $J = 6.8$ Hz, 3H), 0.74 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 148.2, 142.6, 138.8, 138.7, 130.0, 129.7, 129.5, 127.7, 123.0, 113.3, 73.0, 34.9, 21.1, 19.5, 18.5; IR (neat, cm^{-1}): 3366, 2923, 1621, 1511, 1445, 1322, 1133, 1042, 702; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{19}\text{N}_3\text{ONa}$ ($\text{M}+\text{Na}^+$): 304.1420, obsd 304.1423.

1-(6-Methoxy-3-phenylimidazo[1,2-*a*]pyrazin-2-yl)-2-methylpropan-1-ol (3.56m)



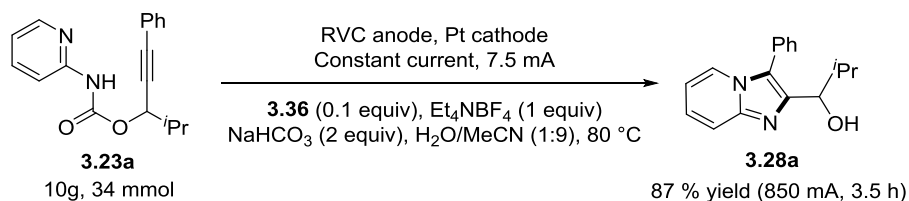
Yield = 65%; Pale yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 8.81 (d, $J = 1.3$ Hz, 1H), 7.58–7.54 (m, 3H), 7.52–7.47 (m, 3H), 4.52 (d, $J = 7.6$ Hz, 1H), 3.93 (s, 3H), 3.24 (s, 1H), 2.21–2.14 (m, 1H), 1.00 (d, $J = 6.7$ Hz, 3H), 0.75 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 153.9, 149.7, 139.9, 138.5, 129.7 (2C), 129.4, 127.8, 123.6, 99.6, 73.1, 55.3, 34.9, 19.5, 18.4; IR (neat, cm^{-1}): 3390, 2924, 1624, 1504, 1464, 1242, 1147, 1027, 762; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 320.1369, obsd 320.1373.

**2-(1-Hydroxy-2-methylpropyl)-3-phenylimidazo[1,2-*a*]pyrazine-6-carbonitrile
(3.56n)**



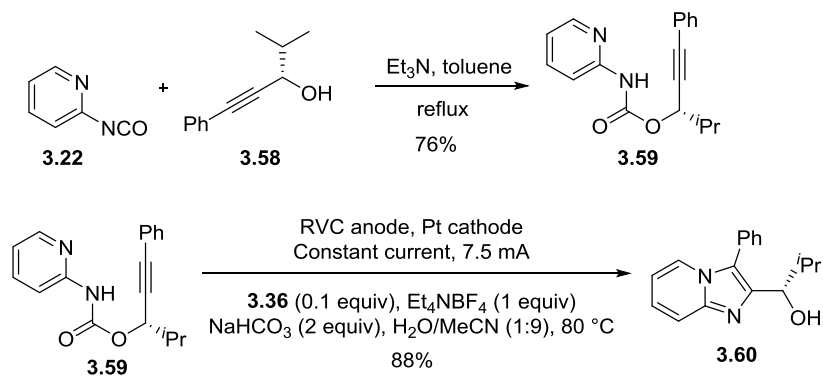
Yield = 40%; Yellow solid; ^1H NMR (500 MHz, CDCl_3) δ 9.09 (s, 1H), 8.42 (s, 1H), 7.67–7.56 (m, 3H), 7.50–7.45 (m, 2H), 4.56 (d, $J = 7.4$ Hz, 1H), 2.71 (s, 1H), 2.25–2.14 (m, 1H), 1.02 (d, $J = 6.7$ Hz, 3H), 0.77 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 150.5, 144.6, 138.7, 130.6, 130.1, 129.9, 125.9, 125.0, 123.8, 116.4, 116.1, 72.9, 34.9, 19.3, 18.3; IR (neat, cm^{-1}): 3426, 2920, 1651, 1538, 1260, 1083, 759; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{16}\text{N}_4\text{ONa}$ ($\text{M}+\text{Na}^+$): 315.1216, obsd 315.1218.

Deca-gram-scale synthesis

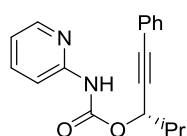


The decagram (34 mmol) scale electrolysis of compound was conducted in a 1 L beaker-type cell using two RVC plates (6.5 cm x 8.5 cm x 1.2 cm) as anode, a Pt plate cathode (5 cm x 5 cm), and a constant current of 850 mA. Added NaHCO_3 (5.7 g, 68 mmol) Et_4NBF_4 (7.4 g, 34 mmol), cat. **3.36** (1.9 g, 3.4 mmol) and $\text{MeCN}/\text{H}_2\text{O}$ (810 mL/ 90 mL) in beaker-type cell. The electrolysis was carried out at 80 °C (oil bath temperature) using a constant current of 850 mA for 3.5 h. The reaction mixture was cooled to RT and concentrated under reduced pressure.

Chiral carbamate substrate

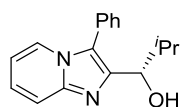


4-Methyl-1-phenylpent-1-yn-3-yl pyridin-2-ylcarbamate (**3.59**)



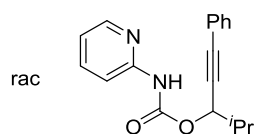
The title compound was prepared starting from 2-aminopyridine and compound **3.58** by following the General Procedure A. Yield = 76%; White solid; ^1H NMR (500 MHz, CDCl_3) δ 9.37 (s, 1H), 8.47–8.32 (m, 1H), 8.05 (d, $J = 8.4$ Hz, 1H), 7.69 (ddd, $J = 8.8, 7.3, 1.9$ Hz, 1H), 7.51–7.42 (m, 2H), 7.37–7.27 (m, 3H), 7.04–6.90 (m, 1H), 5.54 (d, $J = 5.7$ Hz, 1H), 2.25–2.11 (m, 1H), 1.13 (d, $J = 6.7$ Hz, 3H), 1.10 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 153.1, 152.6, 147.9, 138.8, 132.0, 128.7, 128.4, 122.6, 118.7, 112.9, 86.5, 85.4, 70.8, 33.0, 18.6, 17.8; IR (neat, cm^{-1}): 3184, 2966, 1735, 1589, 1440, 1219, 1060; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 317.1260, obsd 317.1262; chiral HPLC conditions: Chiralpak AD-H (*n*-hexane/ethanol, 70:30), flow rate = 1.0 mL/min, $R_t = 8.0$ min, respectively. The enantiomeric excess was determined to be 99%.

2-Methyl-1-(3-phenylimidazo[1,2-a]pyridin-2-yl)propan-1-ol (**3.60**)

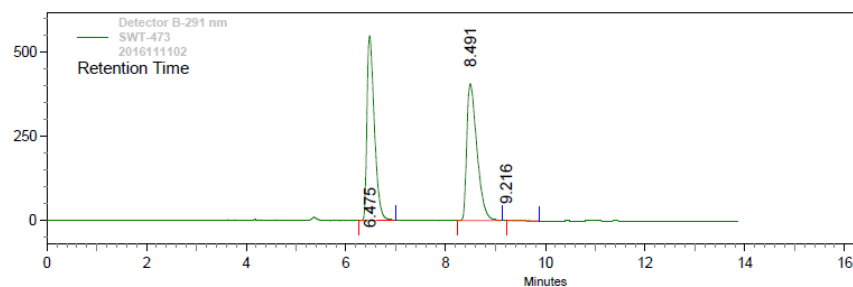


Yield = 87%; White solid; ^1H NMR (500 MHz, CDCl_3) δ 8.02 (d, $J = 7.0$ Hz, 1H), 7.62 (d, $J = 9.1$ Hz, 1H), 7.57–7.51 (m, 2H), 7.51–7.42 (m, 3H), 7.22–7.13 (m, 1H),

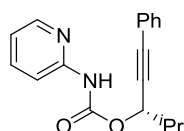
6.73 (t, $J = 7.0$ Hz, 1H), 4.43 (d, $J = 8.0$ Hz, 1H), 3.25 (s, 1H), 2.23–2.10 (m, 1H), 1.04 (d, $J = 6.6$ Hz, 3H), 0.74 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 145.8, 144.7, 130.3, 129.4, 128.9, 128.8, 124.8, 123.6, 122.0, 117.7, 112.4, 73.2, 34.9, 19.6, 18.8; IR (neat, cm^{-1}): 3366, 2955, 2866, 1635, 1504, 1345, 1046, 1017; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{ONa}$ ($\text{M}+\text{Na}^+$): 289.1311, obsd 289.1307; chiral HPLC conditions: Chiralpak AD-H+G (*n*-hexane/ ethanol, 70:30), flow rate = 1.0 mL/min, $R_t = 7.2$ min, respectively. The enantiomeric excess was determined to be 98%.



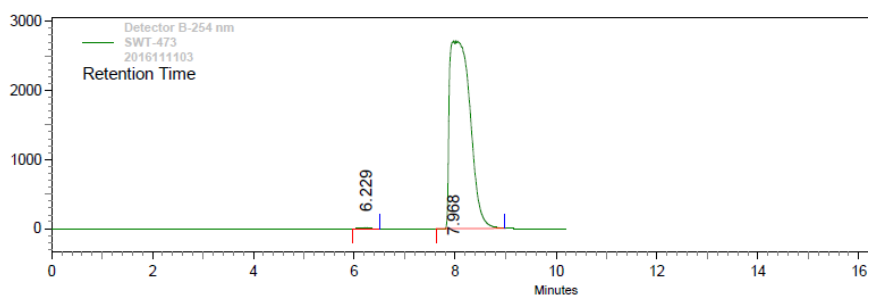
Column: Chiralpak AD -H
 Mobile Phase: Hex/EtOH (70/30, v/v)
 Flow Rate: 1.0mL/min
 CT: 30°C Sample Name: rac MZY-1



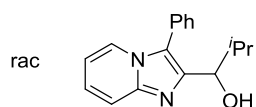
Detector B-291 nm				
Pk #	Retention Time	Area	Area Percent	Resolution
1	6.475	5666521	49.43	0.00
2	8.491	5795724	50.56	6.16
3	9.216	1348	0.01	0.00
Totals		11463593	100.00	



Column: Chiralpak AD-H
 Mobile Phase: Hex/EtOH (70/30, v/v)
 Flow Rate: 1.0 mL/min
 CT: 30°C
 Sample Name: MZY-1

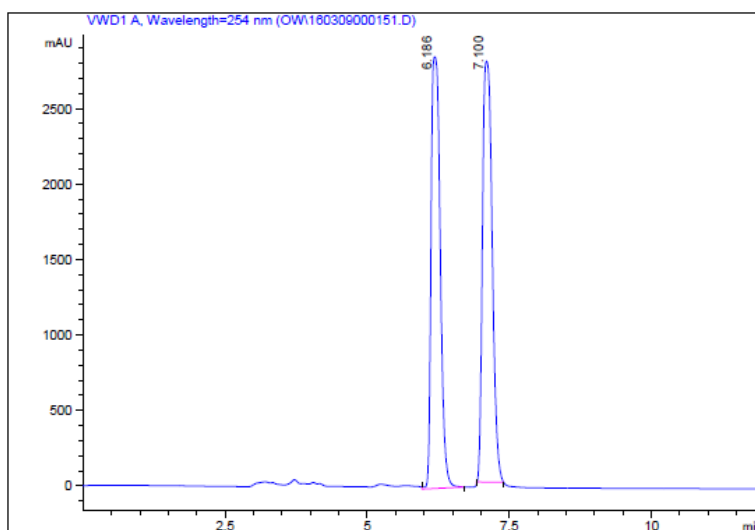


Detector B-254 nm	Pk #	Retention Time	Area	Area Percent	Resolution
	1	6.229	163108	0.21	0.00
	2	7.968	76734844	99.79	0.00
Totals			76897952	100.00	

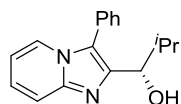


色谱柱: ChiralpakAD-H+G
 流动相: Hex/EtOH=70/30 V/V
 柱温: 30°C
 流速: 1.000 mL/min

Nano pump test method

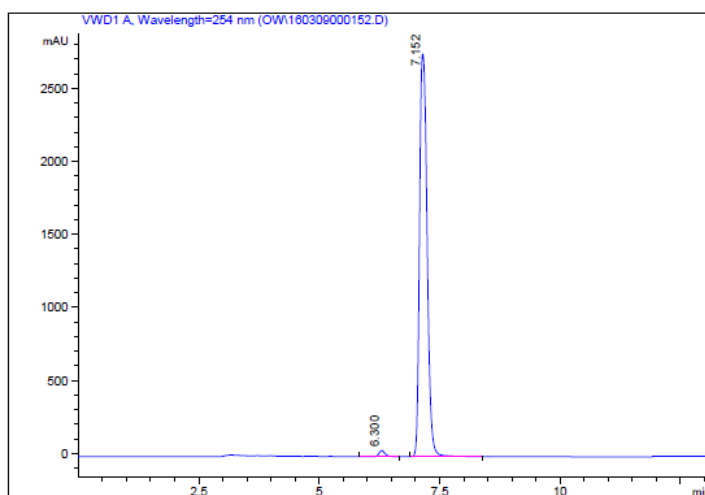


保留时间 [min]	峰高	峰宽 [min]	峰面积	峰面积 %
6.186	2.860e3	0.221	31890.441	49.11
7.100	2.790e3	0.197	33042.262	50.89



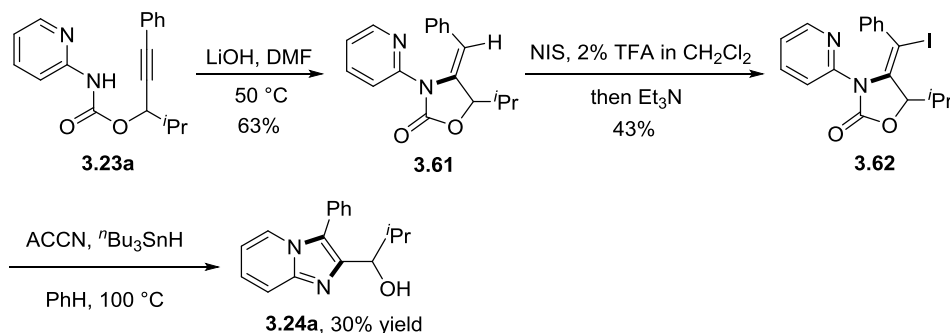
色谱柱: ChiralpakAD-H+G
 流动相: Hex/EtOH=70/30 V/V
 柱温: 30°C
 流速: 1.000 mL/min

Nano pump test method

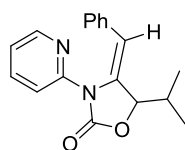


保留时间 [min]	峰高	峰宽 [min]	峰面积	峰面积 %
6.300	42.330	0.140	395.923	1.30
7.152	2.755e3	0.173	30138.311	98.70

Mechanism confirmatory experiment

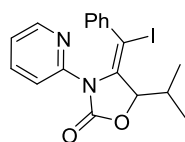


(Z)-4-Benzylidene-5-isopropyl-3-(pyridin-2-yl)oxazolidin-2-one (3.61)



Yield = 86%; Light yellow oil; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.96 (dd, $J = 5.0, 1.8$ Hz, 1H), 7.55 (td, $J = 7.8, 1.8$ Hz, 1H), 7.32–7.28 (m, 1H), 6.96–6.85 (m, 4H), 6.74–6.69 (m, 2H), 5.78 (d, $J = 1.8$ Hz, 1H), 5.16 (dd, $J = 2.9, 1.8$ Hz, 1H), 2.25–2.17 (m, 1H), 1.23 (d, $J = 6.8$ Hz, 3H), 1.12 (d, $J = 6.8$ Hz, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 156.4, 148.4, 148.3, 137.6, 135.2, 134.4, 127.8, 127.5, 125.9, 122.2, 121.4, 102.6, 84.1, 34.3, 18.8, 14.7; IR (neat, cm^{-1}): 2920, 2850, 1776, 1631, 1588, 1470, 1132, 1081; ESI HRMS m/z ($\text{M}+\text{Na}$) $^+$ calcd 317.1260, obsd 317.1260.

(E)-4-(Iodo(phenyl)methylene)-5-isopropyl-3-(pyridin-2-yl)oxazolidin-2-one (3.62)



Yield = 31%; Pale yellow oil; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.90 (dd, $J = 4.9, 1.8$ Hz, 1H), 7.48–7.38 (m, 1H), 7.12 (d, $J = 8.0$ Hz, 1H), 6.98–6.90 (m, 2H), 6.89–6.80 (m, 4H), 5.14 (d, $J = 2.0$ Hz, 1H), 3.03–2.91 (m, 1H), 1.24 (d, $J = 6.9$ Hz, 3H), 1.10 (d, $J = 6.9$ Hz, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 156.3, 148.6, 147.9, 140.5, 137.4,

136.9, 129.1, 127.6, 127.5, 122.1, 121.6, 87.8, 71.2, 31.0, 19.2, 14.2; IR (neat, cm^{-1}):
2920, 2850, 1778, 1633, 1588, 1469, 1368, 1132, 1082; HRMS (ESI, m/z) calcd for
 $\text{C}_{18}\text{H}_{17}\text{IN}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 443.0227, obsd 443.0230.

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Chapter 4 Toward Analogs of the 2-Carboxyl-6-HydroxyOctahydroIndole (CHOI) Unit

Aeruginosins^{1,2} are marine natural products isolated from sponges and cyanobacterial water blooms (blue-green algae). Murakami and co-workers reported the isolation of aeruginosin 298A in 1994.² This allowed the introduction of a new class of marine natural products to the chemistry community. Twenty more compounds structurally and pharmacologically related to aeruginosin 298A have also been isolated over the past decade. These peptidic structures that incorporate the 2-carboxyl-6 α -hydroxy-octahydroindole (CHOI) bicyclic structure hydroxylated in 5 and/ or 6 positions shown potent *in vitro* inhibition of various serine proteases including thrombin and trypsin (Figure 4.1). Since the discovery of their potent anticoagulant action, structure-activity relationship (SAR) studies on aeruginosin family are constantly and intensively pursued. It's found that this kind of SAR was probably due to the highly binding compact between aeruginosin family and the catalytic binding pocket of trypsin, thrombin, and other serine proteases.

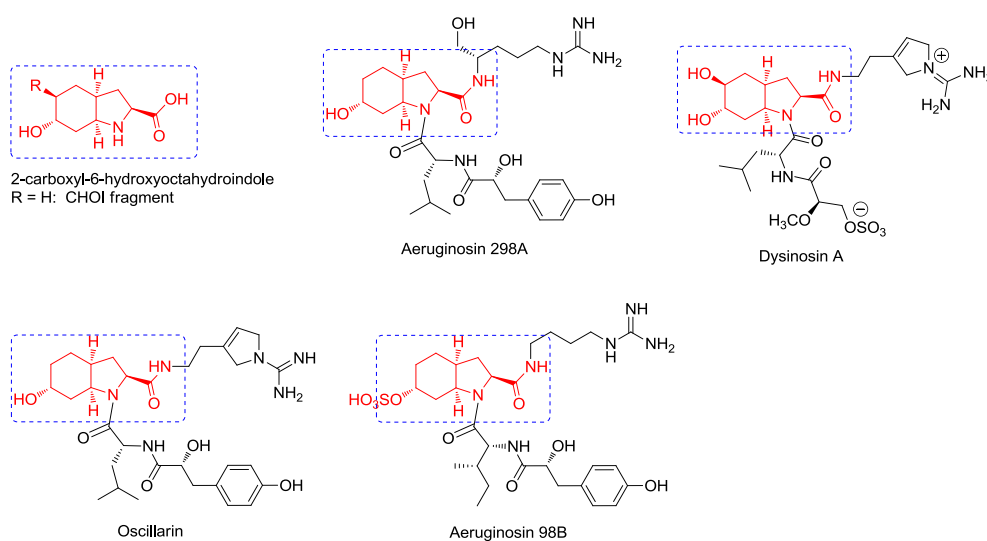


Figure 4.1 CHOI motif and some members of Aeruginosin family.

Aeruginosins are marine natural products that have been iso-

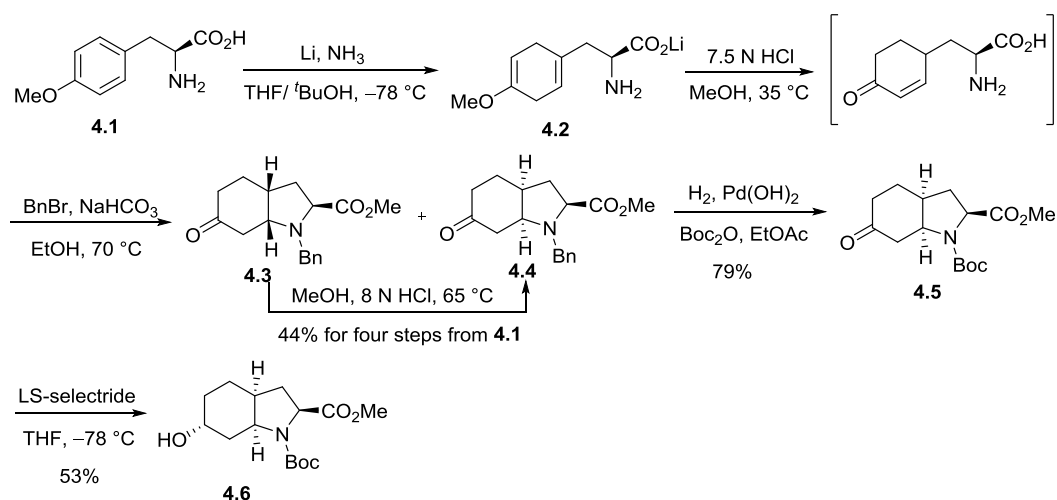
Aeruginosins have been isolated with yields in the range of 0.01–0.05 %. This low availability, combined with their interesting biological activities and novelty structure, stresses the need for an efficient and modular synthetic method to these marine compounds.

4.1 Review of the Reported Synthetic Methods

The members of the Aeruginosin family have garnered considerable attention from synthetic organic chemists because of their structural novelty and biological activity. Different approaches have been reported to construct the bicyclic CHOI core by several research groups.³ Herein, we introduce some of these synthetic routes to Choi motif briefly.

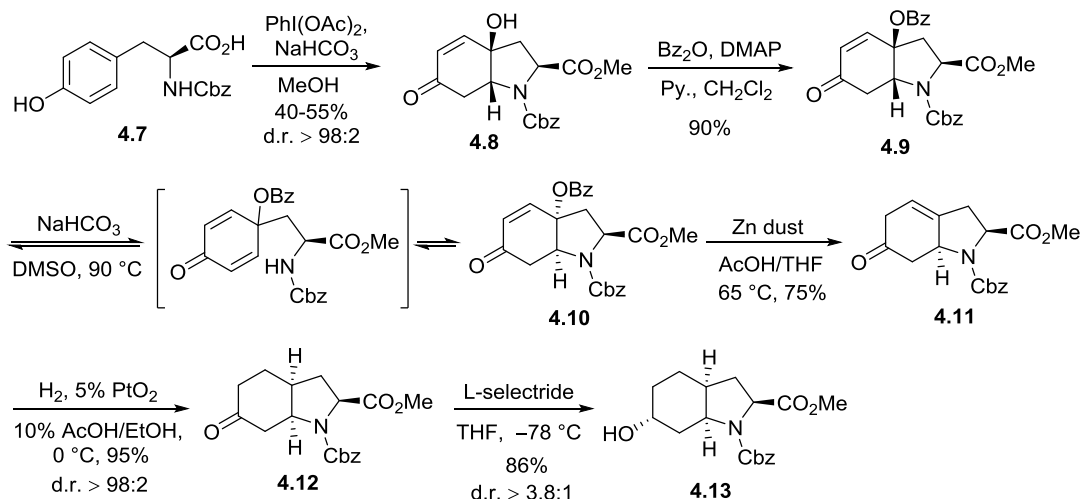
4.1.1 Bonjoch group's synthesis of CHOI core

In 2000, Bonjoch's group^{3b} described an efficient method for the synthesis of (2*S*,3*aS*,6*R*,7*aS*)-6-hydroxyoctahydroindole-2-carboxylic acid (L-CHOI) motif presents in many of the aeruginosins. Furthermore, this method was used in the first total synthesis of aeruginosins 298A.^{3c} First, the Birch reduction of the protected L-tyrosine **4.1**, followed by acidic cleavage of the resulting enol ether and then Michael-type addition of the pendant amine nucleophile led to a mixture of octahydroindol-6-ones, which were directly benzylated to afford a diastereomeric mixture of *exo* and *endo* isomers in a 1.8:1 ratio. Thermodynamic equilibration of this mixture through retro-Michael and Michael addition sequence in the presence of MeOH/aq. 8 N HCl at 65 °C provided the more stable isomer **4.4** (*endo* isomer) in 44% overall yield from **4.1**. To achieve the functionalization and stereochemistry adequate at C-6, after a Bn-to-Boc *N*-protection switch by hydrogenation and Boc protection method, a variety of ketone-reduction conditions were examined for **4.5** to obtain the desired 6*R* stereochemistry of the alcohol. Finally, optimal selectivity in favor of the 6*R* isomer (8:1) was achieved by reduction with LS-selectride and then obtained the protected L-CHOI derivative **4.6**.



Scheme 4.1 Bonjoch's synthesis of the L-CHOI derivative 4.6.

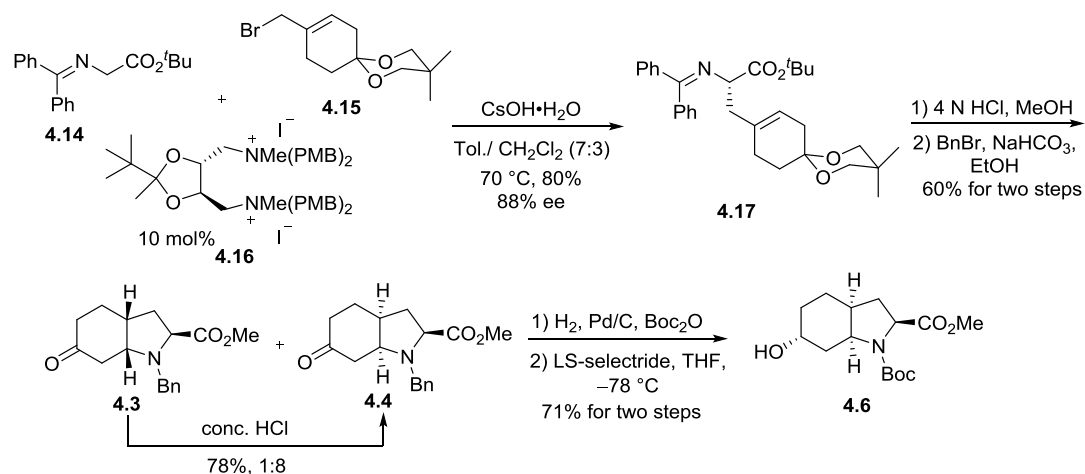
In comparison with the tyrosine-reduction route reported by the Bonjoch's group, Wipf's group^{3a} developed a tyrosine oxidation-rearrangement approach toward the key CHOI bicyclic hydroindole for the total synthesis of aeruginosin 298A. Oxidation of the protected L-tyrosine 4.7 with $\text{PhI}(\text{OAc})_2$ ⁴ followed by exposure to basic methanol solution gave 4.8 with a diastereoselectivity of d.r. > 98:2. After the benzoyl group protection of alcohol formed compound 4.9, the desired stereochemistry at the ring-junction carbons was possible by the thermodynamic equilibration of 4.9 to give the more stable isomer 4.10 through a retro-Michael and then Michael addition sequence in basic DMSO at 90 °C. The resulting 1.6:1 mixture of products was then separated to give 4.10 in 78% yield after recycling of recovered 4.9. Reductive displacement of the benzoate ester using activated Zn dust gave the unsaturated ketone 4.11 and subsequent hydrogenation gave the *cis*-fused azabicyclic ketone 4.12. Reduction of the ketone with L-Selectride afforded a 3.8:1 mixture of the reduction products 4.13 which bear *exo* and *endo* hydroxy groups.



Scheme 4.2 Wipf's synthesis of the L-CHOI derivative **4.13**.

4.1.2 Shibasaki group's synthesis of CHOI core

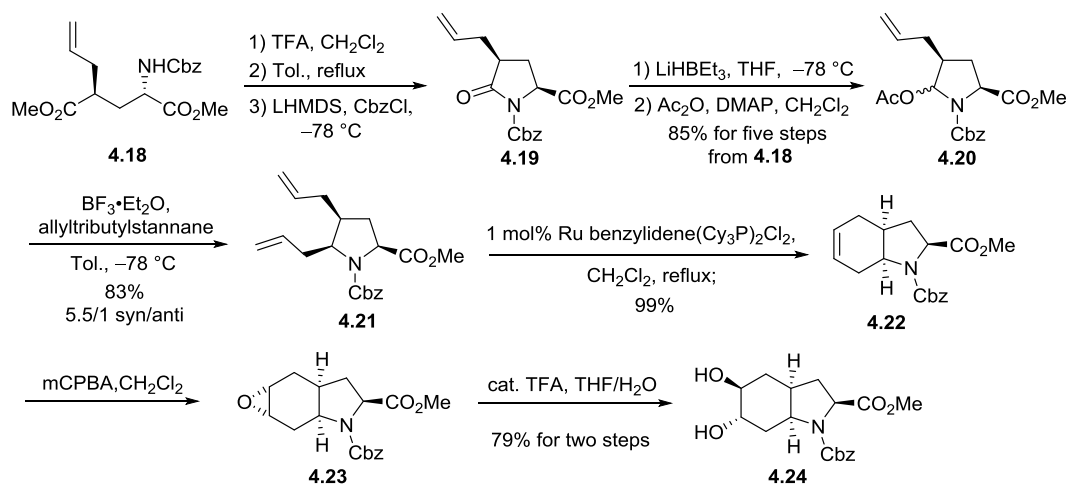
In 2003, Shibasaki's group^{3d} presented a synthesis of the L-CHOI core via application of catalytic asymmetric phase-transfer alkylation reactions⁵ (Scheme 4.3). For the synthesis of the CHOI core of aeruginosin 298A, the enolate of **4.14** was alkylated with the allylic bromide **4.15** in the presence of 10 mol% **4.16** as a catalyst, to give the desired product **4.17** in 80% yield and 88% ee. Treatment of **4.17** with 4 N HCl in methanol promoted in one-pot: deprotection of the benzophenone imine, of the ketal and then transesterification, migration of the C-C double bond, and finally intramolecular Michael-type addition. Subsequent N-benylation afforded the bicyclic ketones **4.3** and **4.4**, which were converted to **4.6** following the same route as Bonjoch's method.



Scheme 4.3 Shibasaki's synthesis of the L-CHOI derivative **4.6**.

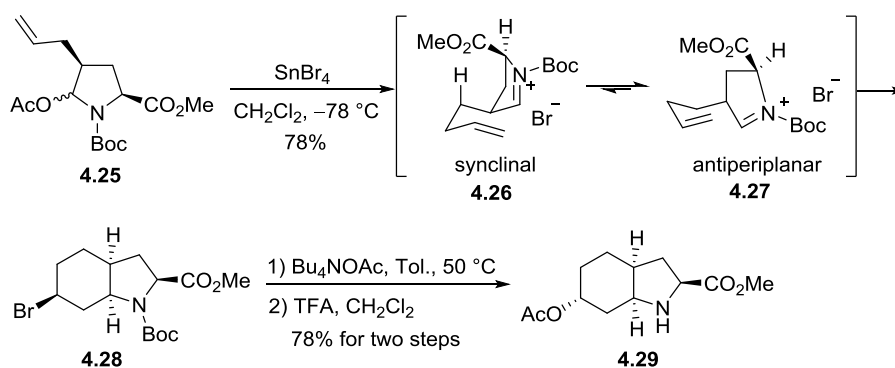
4.1.3 Hanessian group's synthesis of CHOI core

Hanessian's group^{3f} developed a different strategy towards the hydroxy-CHOI motif present in dysinosin A (Scheme 4.4). This method relies on the use of asymmetric alkylation of L-glutamic acid derivatives as the chiral starting material, N-acyl iminium ion alkylation and ring-closing metathesis. In this approach, the (4*S*)-allylglutamate precursor **4.18**, which is readily available from L-glutamic acid via an asymmetric alkylation with allyl bromide,⁶ was first converted into C4-substituted pyroglutamate **4.19**. Reduction of the lactam by treating with LiBHET₃ and O-acetylation of the hemiaminal provided **4.20**. Then, several solvents, Lewis acids and also *N*-protecting groups were investigated in order to achieve the C5-allylation via an N-acyl iminium ion intermediate. They have shown that this step could be achieved by treating the *N*-Cbz-protected derivative **4.20** with allyltributylstannane and BF₃·Et₂O in toluene, which gave the *syn*-diallyl-substituted proline derivative **4.21** in 83% yield and 5.5:1 diastereoselectivity in favor of the desired product. Treatment of **4.21** with Grubbs' first generation catalyst in refluxing CH₂Cl₂ afforded bicyclic alkene **4.22**, which was transformed into the epoxide **4.23** by highly selective epoxidation, probably due to an attack from the more accessible convex face of the bicyclic system. TFA-catalyzed epoxyde opening with aqueous TFA solution furnished stereospecifically the hydroxy-L-CHOI derivative **4.24**.



Scheme 4.4 Hanessian's synthesis of the hydroxy-L-CHOI derivative **4.24**.

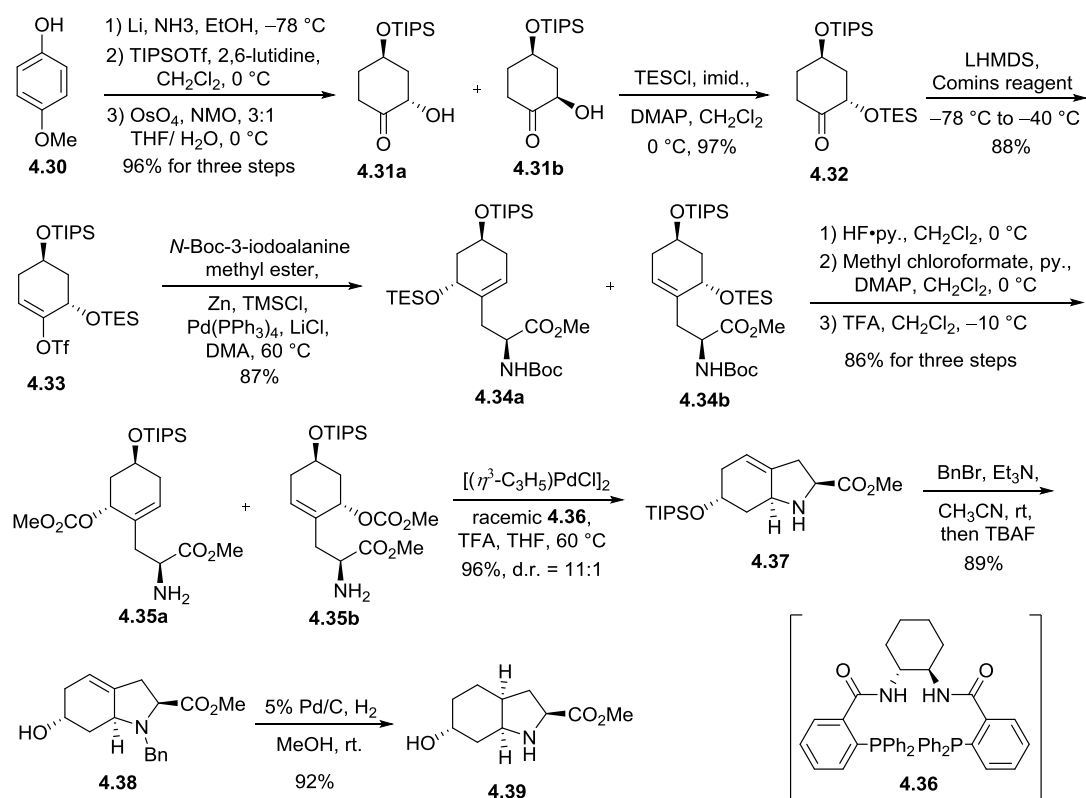
Hanessian's group^{3g} adopted another strategy towards the L-CHOI motif present in oscillarin, based on an azonia-prins halocarbocyclization⁷ as the key reaction (Scheme 4.5). First of all, the O-acetyl hemiaminal derivative **4.25** was synthesized using the same procedure as that described for dysinosin A. Then, treatment of **4.25** with SnBr₄ in CH₂Cl₂ at -78 °C gave the brominated bicyclic product **4.28** as a single isomer. The result was rationalized by an antiperiplanar approach of the alkene tether onto the iminium ion, as in the transition-state model **4.27**. The other isomer is expected to be disfavored due to the less favorable orbital overlap associated with a synclinal approach as well as a possible steric clash between the ester substituent and the axial H-4. Elaboration of **4.28** to L-CHOI derivative **4.29** was achieved by displacement of the bromide by the acetate anion with tetrabutylammonium acetate and removal of the Boc protecting group.



Scheme 4.5 Hanessian's synthesis the L-CHOI derivative **4.29**.

4.1.3 Trost group's synthesis of CHOI core

In 2012, Trost's group^{3j} developed a new strategy to access the CHOI fragment in aeruginosins 98B (Scheme 4.6). The key step was based on a Pd-catalyzed intramolecular asymmetric allylic alkylation (AAA) reaction⁸ of a diastereomeric mixture of allyl carbonates **4.35a** and **4.35b** using the racemic ligand **4.36**. Birch reduction of **4.30** followed by TIPS group protection of the resulting alcohol and OsO₄ dihydroxylation of double bond formed a mixture of compound **4.31a** and **4.31b** which ratio was 2:1. Then, **4.31a** was protected with TES group under standard conditions. The vinyl triflate **4.33** was obtained through reaction between the enolate of ketone **4.32** and Comins reagent. Compound **4.33** could be coupled with alkylzinc reagent to afford **4.34a** and **4.34b** as a 1:1 diastereomeric mixture. Deprotection of TES group with HF-pyridine complex gave the corresponding allylic alcohols, which were then converted into the corresponding allylic carbonates. Subsequently removal of the Boc protecting group under standard conditions gave amino esters **4.35a** and **4.35b**. When a racemic mixture of **4.36** was used as the ligand, the diastereoselectivity of the Pd-catalyzed allylic alkylation, which favored compound **4.37**, jumped to 11:1. Due to the instability of the hexahydroindole derivative **4.37** under TBAF conditions, intermediate **4.37** was first N-benzylated, then treated with TBAF in a one-pot procedure to give alcohol **4.38**. Finally, hydrogenation of **4.38** led to the CHOI fragment **4.39**.

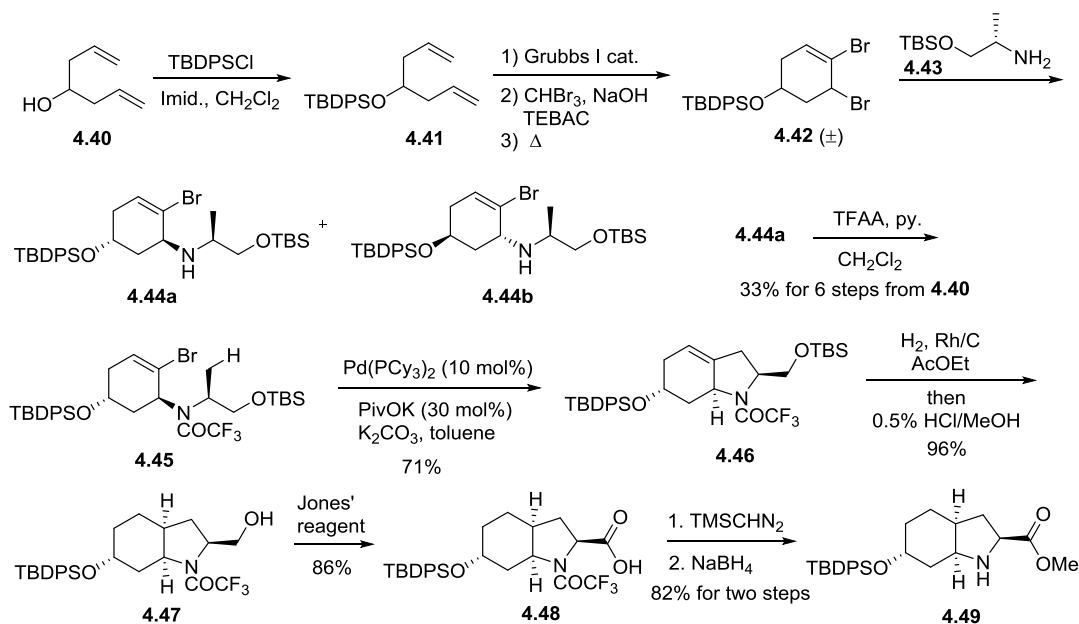


Scheme 4.6 Trost's synthesis of the L-CHOI fragment **4.39**.

4.1.3 Baudoin group's synthesis of CHOI core

More recently, Baudoin's group^{3m} reported a general and scalable access to the aeruginosin family (Scheme 4.7). They developed a Pd catalyzed C(sp³)-H activation strategy to obtain the common CHOI core of the target molecules (Scheme 4.7). The C-H activation precursor **4.45** was prepared from the 1,6-diene **4.40**. TBDPS group protection of the alcohol gave the silyl ether **4.41**. Subsequent treatment of **4.41** with Gubbs I catalyst through olefin metathesis gave protected cyclopent-3-enol. Then dibromocyclopropanation followed by thermal electrocyclic ring-opening^[9] furnished compound **4.42**. The *trans*-selective nucleophilic substitution of the enantiopure amine **4.43** on **4.42** provided a 1:1 mixture of two diastereoisomers **4.44a, b**, which can be separated. The amine group of the desired diastereoisomer **4.44a** was then protected as a trifluoroacetamide **4.45**. Compound **4.45** smoothly afforded bicyclic hydroindole **4.46** via the key Pd-catalyzed intramolecular C(sp³)-H alkenylation of the alkenyl halide.^{3k} Then, the diastereoselective reduction of the trisubstituted alkene **4.46**

by catalytic hydrogenation and the acid-mediated deprotection of the TBS group were performed in a one-pot manner giving alcohol **4.47**. This primary alcohol was then oxidized under Jones' conditions. Finally, the resulting carboxylic acid **4.48** was esterified and the trifluoroacetyl group was removed under reductive conditions to give L-CHOI fragment **4.49**.

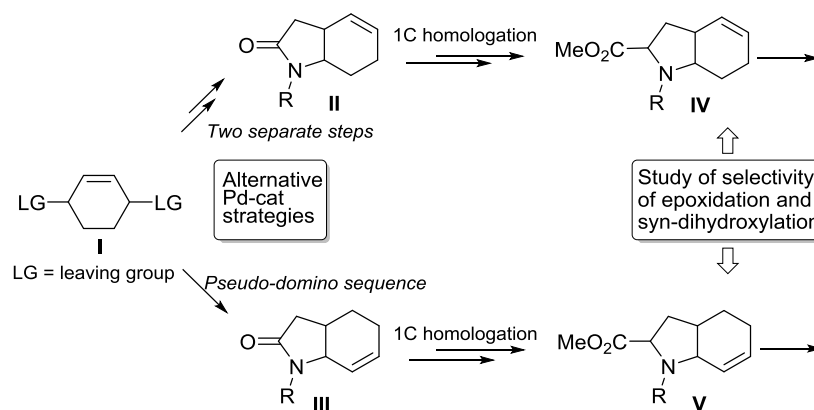


Scheme 4.7 Baudoin's synthesis of the L-CHOI fragment **4.49**.

Although there are many elegant synthetic approaches to the CHOI core and the aeruginosin natural products, further studies are still desirable, especially those focusing on the common bicyclic CHOI fragment and access to analogues of it.

4.2 Research Plan

In light of the synthetic interest associated to the CHOI fragment and analogs of it, and on the basis of the previous experience the laboratory in palladium chemistry,¹⁰ we decided to tackle the synthesis of analogues of the CHOI motif as our ideal targets. The key step of our strategy is based on a double Pd-catalyzed allylation (amination and alkylation) starting from a cyclic bis-allylic substrate **I** (Scheme 4.8). This step can be realized as separated allylations, following an amination / alkylation sequence, or in a domino path, starting from an appropriate bis-nucleophilic malonamide, and leading to an alkylation/ amination domino sequence. Depending on the chronological order of the allylation steps, the targeted bicyclic compounds **II** and **III** incorporate a final unsaturation in different strategic positions. Further functionalizations of the alkene moiety in the resulting bicyclic compound **IV** and **V** allow affording analogs of the targeted structure.



Scheme 4.8 Synthetic strategy toward the CHOI analogs

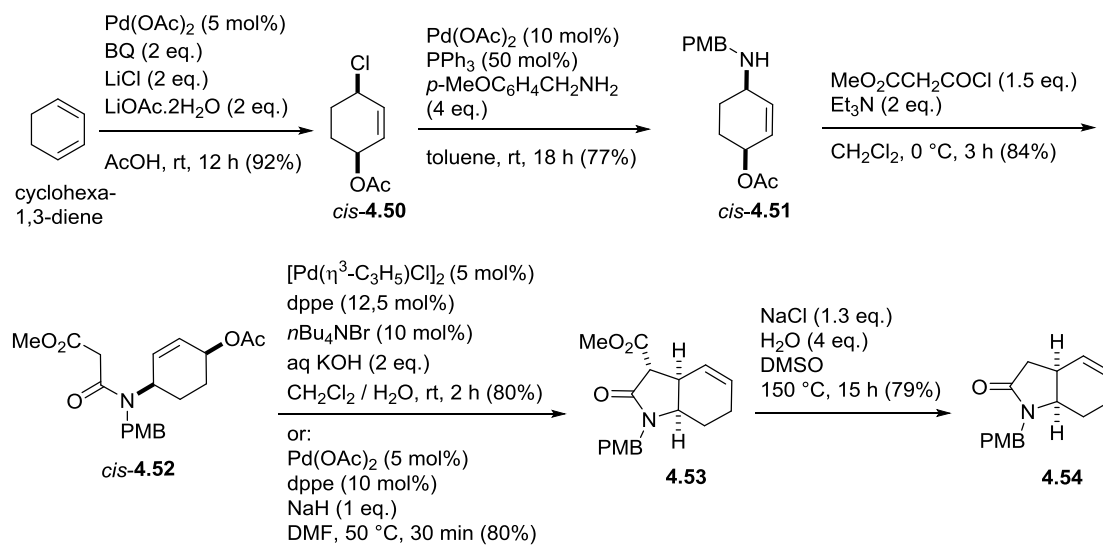
4.3 Results and discussion

4.3.1 First approach: “separated allylations” strategy.

This strategy is based on the construction of the bicyclic tetrahydroindolone structure **4.54** through a five-step sequence starting from the commercial available 1,3-cyclohexadiene (Scheme **4.9**). Two key steps of this synthetic sequence are based on palladium catalysis.

First of all, the diene was converted into the corresponding *cis*-**4.50** in 92% yield according to Bäckvall's protocol.^{11a,b} The mechanism of this *cis*-1,4-acetoxychlorination reaction involves first coordination of the Pd(II) catalyst with the diene followed by the *trans* acetoxypalladation of one of the double bonds to give a (π -allyl)-Pd intermediate. Coordination of *p*-benzoquinone followed by an external *trans* attack by a chloride ion affords the observed product with overall *cis* stereochemistry.^{11c,d}

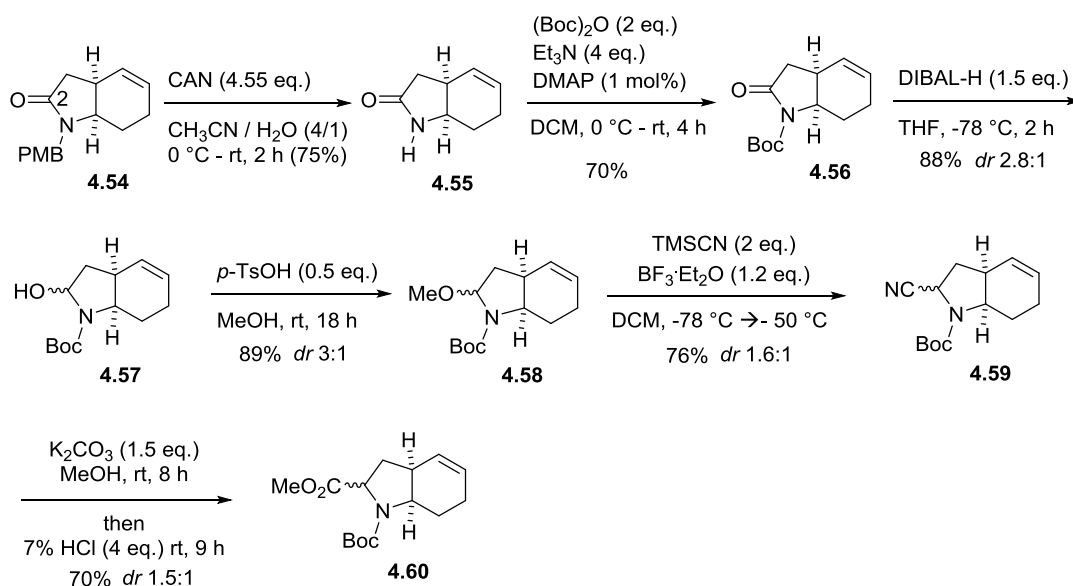
Then, palladium-catalyzed allylation of *p*-methoxybenzylamine with the allylic chloride *cis*-**4.50** afforded *cis*-**4.51** in 77% yield. Following standard amidation of *cis*-**4.51** with methyl 3-chloro-3-oxopropionate gave the 1, 4-disubstituted amide *cis*-**4.52**. Then, a smooth intramolecular allylic alkylation could be carried out via two alternative palladium-catalyzed protocols: a) [NaH/ Pd(OAc)₂/ dppe/ DMF], and b) [KOH/ [Pd(η^3 -C₃H₅)₂]/ dppe/ TBABr/ DCM-H₂O], both leading to bicyclic amide **4.53** in 80% as a single diastereoisomer. Finally, demethoxycarbonylation of **4.53** under Krapcho¹² conditions led to amide **4.54** in 79% yield.



Scheme 4.9 Synthesis of the bicyclic tetrahydroindolone **4.54**.

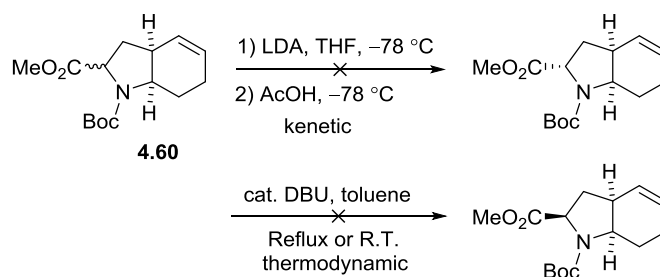
With the key amide **4.54** in hand, we next focused on the introduction of the carboxyl substituent at position 2 of the hexahydroindole bicycle. The key step of this strategy was based on α -aminoether homologation (Scheme 4.10). However, this type of strategy is feasible only when the nitrogen atom of the aminoether function is electron-poor. Therefore, we switched *N*-protection group from PMB to Boc through treatment with CAN followed by Boc protection condition to afford **4.56**. Reduction of **4.56** with Dibal-H led to carbinolamine **4.57** and then furnished the desired α -aminoether **4.58** as a 3:1 diastereomeric mixture through treatment with MeOH in the presence of a catalytic amount of *p*-TsOH. The C1-homologation was achieved through TMSCN addition to **4.58** in the presence of $\text{BF}_3\cdot\text{Et}_2\text{O}$. This homologation has also been tested directly on the carbinolamine **4.57** with TMSCN in the presence of $\text{BF}_3\cdot\text{Et}_2\text{O}$, leading to the desired cyano derivative **4.59** only in low yield (~30%). Finally, several nitrile methanolyses of **4.59** were tested before finding the satisfactory protocol. Indeed, strongly acidic (TMSCl, MeOH, reflux) or strongly basic (10N NaOH, MeOH, reflux) conditions cannot be used, since simultaneous deprotection of the *N*-Boc group or substrate degradation was obtained, respectively. The best results were finally achieved operating under moderately basic conditions (K_2CO_3 , MeOH, rt) followed by the formation of the methyl ester derivative via adding of 7% HCl solution at room temperature. In this way, the desired

2-methoxycarbonylated derivative **4.60** was obtained as an inseparable 1.5:1 diastereoisomeric mixture (Scheme 4.10).



Scheme 4.10 Synthesis of the methoxycarbonylated derivative **4.60**.

In order to obtain a single (or at least prevalent) diastereoisomer of **4.60**, many epimerization methods were tried (Scheme 4.11). However, treatment of ester **4.60** with a stoichiometric amount of LDA or LiNEt_2 followed by kinetic quenching, or treatment with catalytic amount of DBU at room temperature or reflux which was in the aim of achieving the thermodynamic control product, leading only to degradation products, or recovered starting material with unchanged diastereoisomeric ratio.



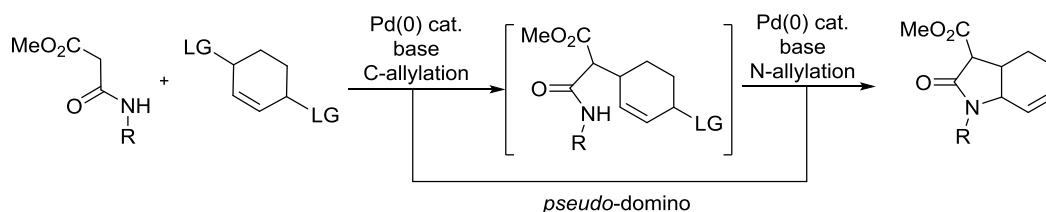
Scheme 4.11 Attempt to obtain a single diastereoisomer of **4.60**.

Furthermore, double bond functionalization (dihydroxylation and epoxidation) of intermediates **4.56**, **4.59** and **4.60** under various conditions showed to be rather non-selective.

At this stage, we considered that an unsaturation at position 4,5 of the hexahydroindole bicycle was likely to be intrinsically unbiased for diastereoselective functionalizations. Therefore, we decided to focus on an alternative way of generating the bicyclic unit so as to obtain the unsaturation at position 6,7. The tactic to obtain such a modification is based on a modified palladium-catalyzed domino sequence.¹³

4.3.2 Second approach: domino sequence.

This second strategy is based on the double Pd-catalyzed allylation of a malonamide as a C/ N double nucleophile on a cyclohexenyl bis-allylic system, according to a C-allylation/ N-allylation *pseudo-domino* sequence,¹⁴ as originally pioneered by Mori¹⁵ (Scheme 12).



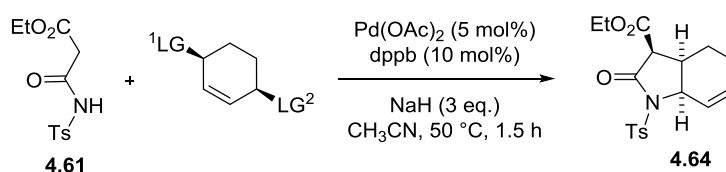
Scheme 4.12 Palladium-catalyzed C-allylation/ N-allylation domino sequence.

First, *N*-tosylmalonamide **4.61**¹⁶ was chosen as the appropriate C/ N double nucleophile to test its reaction with *cis*-OBz cyclohexene *cis*-**4.62** (Table 4.1). In particular, use of NaH (3 equiv) as the base, gave the bicyclic product **60** in 67% yield (entry 1). If we switched the base used from NaH (3.0 equiv) to K₂CO₃ (3.0 equiv) afforded **4.64** in 45% yield, while no product could be obtained without base. This result confirmed that malonamides can be effective C/ N bis-nucleophiles for η^3 -allyl palladium chemistry. Moreover, as the unsaturation in **4.64** was found at position 6,7,

it means that the carbanionic site reacts before the nitrogen atom in the domino sequence.

Other cyclohexenyl *cis* bis-allylic systems were also tested. Diacetate *cis*-**4.63** gave the corresponding bicyclic product **4.64** in 52% yield (entry 2), while the chloroacetate *cis*-**4.50** intermediate smoothly led to 79% yield (entry 3).

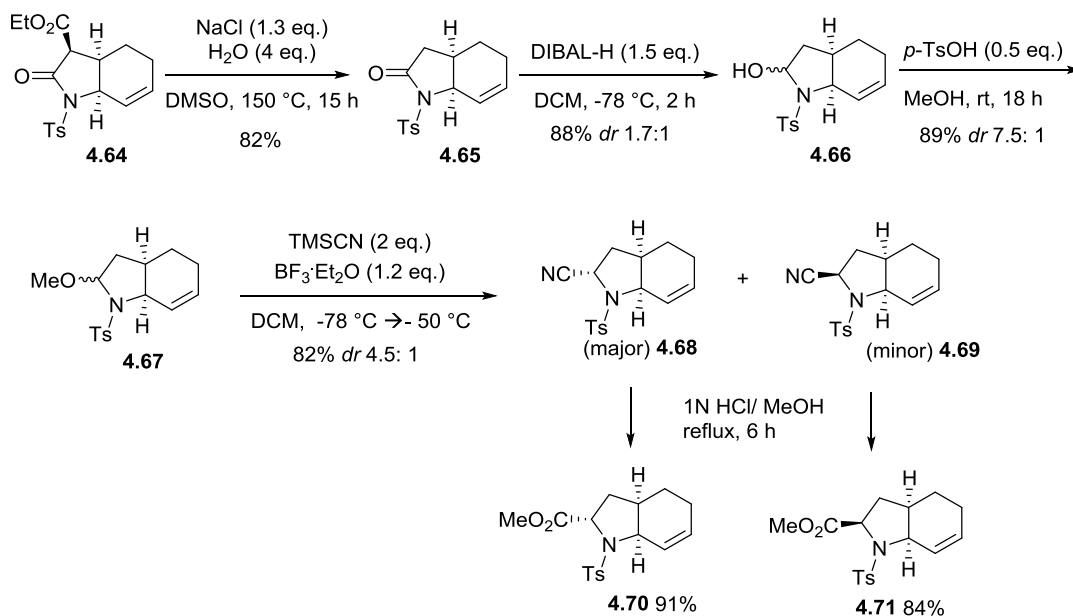
Table 4.1 Palladium-catalyzed bis-allylation of the *cis*-OBz cyclohexene with *N*-tosyl malonamide.



entry	LG ¹	LG ²	cyclohexenyl <i>cis</i> bis-allylic systems	4.64 (yield ^a %)
1	OBz	OBz	4.62	67
2	OAc	OAc	4.63	52
3	Cl	OAc	4.50	79

a: Isolated yield of **4.64**.

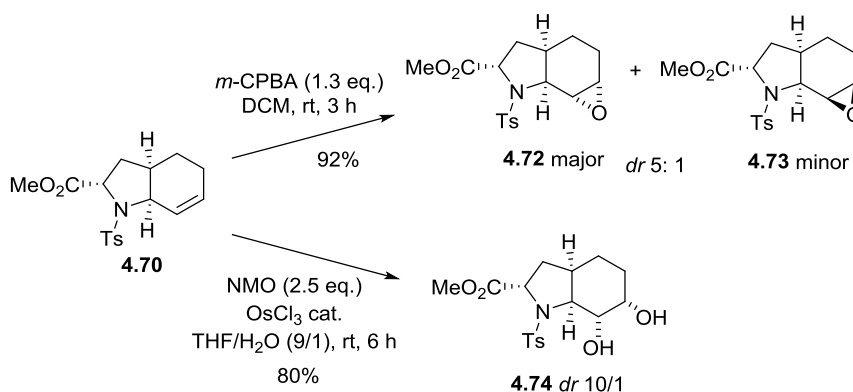
Starting from the 6,7-unsaturated bicyclic structure **4.64**, we applied the same sequence as previously described for the 4,5-unsaturated structure. Demethoxycarbonylation of **4.64** under Krapcho conditions¹² led to amide **4.65** in 82% yield. Then, DIBAL-H reduction of **4.65** led to carbinolamine **4.66** and then treatment with MeOH in the presence of a catalytic amount of *p*-TsOH gave the desired α -aminoether **4.67** as a 1.7:1 diastereomeric mixture. TMSCN addition to **4.67** in the presence of BF₃·Et₂O gave the corresponding nitriles **4.68** and **4.69** in 4.5:1 ratio, easily separated by chromatography column. Finally, separate acidic methanolysis of the two epimeric nitriles gave the two corresponding methyl esters **4.70** and **4.71**. Gratifyingly, all the steps of this synthetic sequence turned out to be high yielding (Scheme 4.13).



Scheme 4.13 Synthesis of the epimeric methoxycarbonylated derivative **4.70** and **4.71**

Then, double bond functionalization (dihydroxylation and epoxidation) of the two separated epimeric bicyclic structures **4.70** and **4.71** were tested.

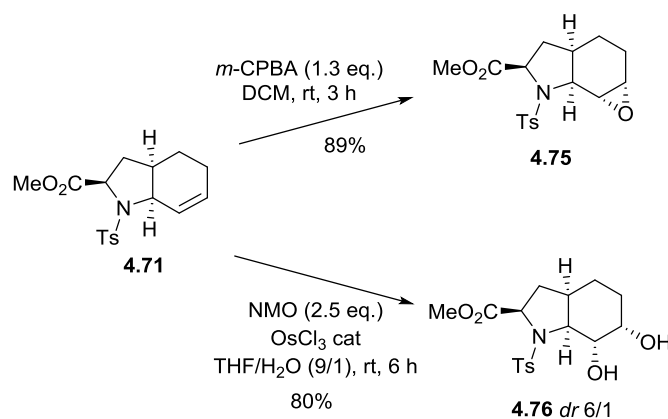
Treatment of the major epimeric ester **4.70** with *m*-CPBA led to a 5:1 ratio of epoxides **4.72** and **4.73** (Scheme 4.14). On the other hand, *syn*-dihydroxylation of **4.70** with cat. OsCl₃ and NMO¹⁷ gave the *syn*-dihydroxylated products **4.74** in good yield and interesting diastereoselectivity (*dr* 10:1).



Scheme 4.14 Double bond functionalization of 2-methoxycarbonyl derivative **4.70**

Under the same epoxidation conditions as above the minor isomer **4.71** reacted in a totally stereoselective way affording the epoxide **4.75** as a single isomer (Scheme

4.15). Finally, *syn*-dihydroxylation of **4.71** with catalytic OsCl₃ and NMO¹⁷ gave the *syn*-dihydroxylated product **4.76** in 80% yield. However, in this case the diastereoselectivity was not as good as the osmylation of the major isomer. The configurations of major diastereoisomers were confidently assigned via ¹H NMR, NOESY and coupling constant analysis.



Scheme **4.15** Double bond functionalization of 2-methoxycarbonyl derivative **4.71**

According to the above results, we can affirm that while an unsaturation at position 4,5 of the hexahydroindole bicycle (such as **4.60**) behaves non-selectively toward the tested electrophilic reagents, unsaturation at position 6,7 (such as substrates **4.70** and **4.71**) is biased to react in a highly diastereoselective way.

A simple substrate conformational analysis (Figure **4.2**) suggests that the large difference in diastereoselectivity existing between substrates **4.60**, **4.60'** and **4.70**, **4.71** is steric in nature and is likely due to the different steric requirements of the substituents linked to the allylic stereogenic center of the cyclohexenyl ring. Indeed, while the stereogenic center of substrates **4.60** or **4.60'** carries only a tiny CH₂ group, the one of substrates **4.70** and **4.71** carries a bulky *N*-Ts moiety. Therefore, approach to the π -system of the alkene from the side opposite to the fused cycle is in this latter case much more favored.

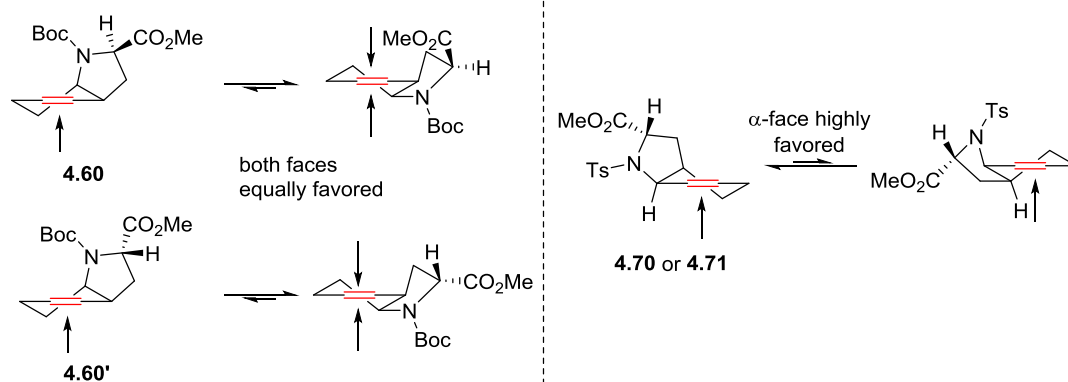


Figure 4.2 Comparison of selectivity of epoxidation and *syn*-dihydroxylation between substrates **4.60**, **4.70** and **4.71** differing in the position of double bond.

4.4 Conclusion

Through the work described in this chapter, we have developed two approaches toward analogs of the CHOI unit. The key steps of the synthetic route were based on Pd-catalyzed C-allylation and Pd-catalyzed N-allylation, which converted a cyclic bis-allylic substrate into a hexahydroindole structure. Noteworthy, the unsaturations of the resulting hexahydroindole structures can be obtained at different positions, depending on the strategy applied. After one-carbon homologation, investigation on the selectivity of the alkene functionalization (epoxidation and *syn*-dihydroxylation) of the isomeric bicyclic intermediates allowed us to conclude that unsaturation at 6,7 is more biased for diastereoselective electrophilic transformations.

4.5 Experimental Section

General Information

Unless special mention, all reactions were carried out under an argon atmosphere, glassware was flame-dried under an argon gas flow prior to use. Diethyl ether, THF, DMF and dichloromethane were dried on a Braun purification system MB SPS-800. Reagents and others solvents were purchased from commercial sources and used as received without further purification. Silica gel (40-63 μm) was used for chromatographic purifications. TLC plates were performed on Merck precoated 60 F₂₅₄ plates and visualized under UV light and spraying with KMnO₄ (5 % in water), vanillin or *p*-anisaldehyde.

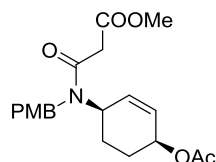
NMR spectra were recorded (Bruker AVANCE 400 or 300 MHz, ¹H, and 100 or 75 MHz, respectively for ¹³C) in CDCl₃ (which also provided the lock signal at $\delta = 7.26$ ppm for ¹H and $\delta = 77.0$ ppm for ¹³C). Chemical shifts are reported in ppm and coupling constants *J* in Hertz.

IR spectra were recorded on a Bruker Tensor 27 apparatus and only the strongest or the structurally most important peaks were listed. High resolution mass spectra (HRMS) were recorded at the Institut de Chimie Moléculaire (FR 2769) of our university (electrospray source).

Synthesis and Characterization of various compounds

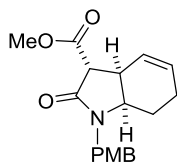
First approach: multi-step synthesis

(±)-Methyl 3-**{(1*S*,4*R*) -[4-(acetyloxy)cyclohex-2-en-1-yl](4-methoxybenzyl) amino}**-3-oxopropanoate (*cis*-4.52)



NEt₃ (0.684 mL, 4.9 mmol, 2 equiv.) and methyl chlorocarbonylacetate (0.394 mL, 3.675 mmol, 1.5 equiv.) were added dropwise to a solution of the allylic amine **cis-4.51**¹⁴ (675 mg, 2.45 mmol, 1 equiv.) in CH₂Cl₂ (30 mL) cooled to 0 °C. After 4 h of stirring at room temperature, the reaction mixture was diluted with diethyl ether (50 mL) and hydrolyzed with water (3 × 20 mL). The collected organic layers were dried over MgSO₄ and the solvents were evaporated under reduced pressure. The crude material was purified by silica gel column chromatography (eluent: cyclohexane/ethyl acetate, 5:5) to afford 773 mg of the desired product **cis-4.52** as a yellow oil (84% yield, rotamers ratio 1.9/1). ¹H NMR (CDCl₃, 400 MHz) δ 7.18 (d, *J* = 8.7 Hz, 2 H, 34%), 7.11 (d, *J* = 8.7 Hz, 2 H, 66%), 6.87 (d, *J* = 8.7 Hz, 2 H, 66%), 6.79 (d, *J* = 8.7 Hz, 2 H, 34%), 5.96–5.86 (m, 1 H), 5.80–5.73 (m, 1 H), 5.27–5.19 (m, 1 H, 66%), 5.14–5.07 (m, 1 H), 4.64 (AB system, *J* = 15.0 Hz, 1 H, 34%), 4.46 (AB system, *J* = 17.8 Hz, 1 H, 66%), 4.39 (AB system, *J* = 17.8 Hz, 1 H, 66%), 4.32 (AB system, *J* = 15.0 Hz, 1 H, 34%), 4.29–4.20 (m, 1 H, 34%), 3.77 (s, 3 H, 66%), 3.75 (s, 3 H, 34%), 3.74 (s, 3 H, 34%), 3.68 (s, 3 H, 66%), 3.57 (s, 2 H, 34%), 3.29 (s, 2 H, 66%), 2.02 (s, 3 H, 34%), 1.98 (s, 3 H, 66%), 1.91–1.60 (m, 4 H); The major isomer: ¹³C NMR (CDCl₃, 100 MHz) δ 170.3, 168.1, 167.4, 158.9, 133.8, 129.3, 128.5, 126.8, 114.3, 65.1, 55.2, 52.2, 51.7, 47.4, 41.5, 26.8, 22.4, 21.1; The minor isomer: ¹³C NMR (CDCl₃, 100 MHz) δ 170.2, 167.9, 166.2, 158.5, 134.0, 130.5, 128.7, 128.4, 113.7, 64.4, 55.8, 55.1, 52.4, 47.4, 41.5, 26.9, 23.6, 21.0; IR (neat, cm⁻¹): 3034, 2996, 2952, 2838, 1728, 1684, 1236, 1171, 1153, 1027, 995; HRMS (ESI, *m/z*) calcd for C₂₀H₂₅NNaO₆ (M+Na⁺): 398.1580, found 398.1574.

(±)-Methyl (3*R*,3*aR*,7*aR*)-1-(4-methoxybenzyl)-2-oxo-2,3,3*a*,6,7,7*a* hexahydro-1*H*-indole-3-carboxylate (**4.53**)

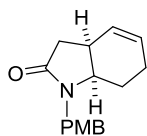


Method A: NaH (55 mg, 60% dispersion in mineral oil, 1.36 mmol, 1 equiv.) was added to a solution of the precursor **cis-4.52** (510 mg, 1.36 mmol, 1 equiv.) in dry DMF (5 mL) cooled to 0 °C, and the mixture was stirred at room temperature for 10 min. In a separate flask, Pd(OAc)₂ (13 mg, 0.068 mmol, 5 mol%) and dppe (54 mg, 0.136 mmol, 10 mol%) were dissolved in dry DMF (2 mL). The resulting enolate was then transferred with a cannula under argon pressure to the preformed palladium(0) complex, and the resulting mixture was stirred at 50 °C for 30 min. After cooling at room temp. and dilution with a saturated aqueous solution of NH₄Cl (10 mL), the product was extracted with diethyl ether (3 × 10 mL). The collected organic layers were dried over MgSO₄ and the solvents were evaporated under reduced pressure. The crude material was purified by silica gel column chromatography (eluent: cyclohexane/ethyl acetate, 6:4) to afford 343 mg of the expected product **4.53** as a yellow oil (80% yield).

Method B: To a solution of tetrabutylammonium bromide (5 mg, 0.0157 mmol, 10 mol%) in dichloromethane (500 μL) were added allylpalladium chloride dimer (3 mg, 0.00785 mmol, 5 mol%) and dppe (7.9 mg, 0.02 mmol, 12.5 mol%). The solution was stirred at room temperature for 5 min. Then, a solution of the precursor **cis-4.52** (59 mg, 0.157 mmol, 1 equiv.) in dichloromethane (1.5 mL), water (1.5 mL) and 50% KOH aqueous solution (0.314 mmol) were successively added. The resulting biphasic system was stirred vigorously at room temperature for 2 h. A saturated aqueous NH₄Cl solution (5 mL) was added and the aqueous phase was extracted with Et₂O (3 × 10 mL). The collected organic layers were washed with brine, dried over MgSO₄ and the solvents were evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent: cyclohexane/ethyl acetate, 6:4) to afford 40 mg of the expected product **4.53** as a yellow oil (80% yield). ¹H NMR (CDCl₃, 400 MHz) δ 7.19 (d, *J* = 8.6 Hz, 2 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 5.86–5.79

(m, 1 H), 5.61–5.54 (m, 1 H), 4.93 (AB system, $J = 15.0$ Hz, 1 H), 3.98 (AB system, $J = 15.0$ Hz, 1 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 3.67–3.61 (m, 1 H), 3.27 (d, $J = 7.7$ Hz, 1 H), 3.16–3.08 (m, 1 H), 2.05–1.75 (m, 3 H), 1.65–1.45 (m, 1 H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 170.1, 169.2, 159.1, 129.2, 128.7, 128.2, 125.7, 114.1, 55.2, 54.4, 54.0, 52.6, 44.0, 36.6, 24.0, 21.4 ppm; IR (neat, cm^{-1}): 3027, 2930, 2839, 1736, 1687, 1611, 1513, 1433, 1418, 1244, 1165, 1031, 999; HRMS (ESI, m/z) calcd for $\text{C}_{18}\text{H}_{21}\text{NNaO}_4$ ($\text{M}+\text{Na}^+$): 338.1368, found 338.1363.

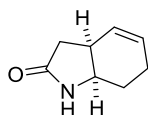
(±)-(3a*S*,7a*R*)-1-(4-Methoxybenzyl)-3,3a,7,7a-tetrahydro-1*H*-indol-2(6*H*)-one
(4.54)



Water (0.167 mL, 9.28 mmol, 4 equiv.) and NaCl (177 mg, 3.02 mmol, 1.3 equiv.) were added in sequence to a solution of the methyl ester derivative **4.53** (731 mg, 2.32 mmol, 1 equiv.) in DMSO (5 mL). The resulting mixture was warmed to 155 °C, and stirred for 15 h. Then, the reaction mixture was cooled down to room temp., water (20 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The collected organic layers were washed with a saturated NaCl aqueous solution (3×10 mL), dried over MgSO_4 and the solvents were evaporated under reduced pressure. The crude oil was purified by silica gel column chromatography (eluent: cyclohexane/ethyl acetate, 1:1) to afford 471 mg of the decarboxylated product **4.54** as a brown oil (79% yield). ^1H NMR (CDCl_3 , 400 MHz) δ 7.20–7.15 (m, 2 H), 6.87–6.82 (m, 2 H), 5.81–5.73 (m, 1 H), 5.59–5.52 (m, 1 H), 4.93 (AB system, $J = 14.8$ Hz, 1 H), 3.93 (AB system, $J = 14.8$ Hz, 1 H), 3.79 (s, 3 H), 3.58–3.50 (m, 1 H), 2.76 (m, 1 H), 2.60 (ABX system, $J = 16.5, 9.0$ Hz, 1 H), 2.22 (ABX system, $J = 16.4, 7.2$ Hz, 1 H), 2.00–1.75 (m, 3 H), 1.65–1.55 (m, 1 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 174.3, 159.0, 129.3, 129.0, 127.6, 127.5, 114.0, 55.2, 43.4, 37.5, 32.1, 23.6, 21.2; IR

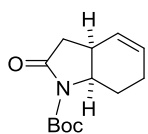
(neat, cm^{-1}): 3023, 2924, 2838, 1681, 1611, 1512, 1433, 1416, 1245, 1175, 1032;
HRMS (ESI, m/z) calcd for $\text{C}_{16}\text{H}_{19}\text{LiNO}_2$ ($\text{M}+\text{Li}^+$): 264.1571, found 264.1566.

(±)-(3a*S*,7a*R*)-3,3a,7,7a-Tetrahydro-1*H*-indol-2(6*H*)-one (4.55)



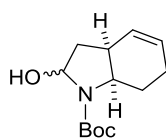
To a solution of the decarboxylated product **4.54** (102 mg, 0.4 mmol, 1 equiv.) in MeCN (16 mL) at 0 °C were added water (4 mL) and slowly ceric ammonium nitrate (CAN) (1g, 1.82 mmol, 4.55 equiv.). The resulting mixture was warmed to room temp. and stirred for 2 h. Then, the reaction mixture was cooled down to 0 °C, water (20 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The collected organic layers were washed with a saturated NaCl aqueous solution (10 mL), dried over MgSO_4 and the solvents were evaporated under reduced pressure. The crude oil was purified by silica gel column chromatography (eluent: cyclohexane/ethyl acetate, 1:9) to afford 41 mg of the desired product **4.55** as a white solid (75% yield). ^1H NMR (CDCl_3 , 400 MHz) δ 6.08 (s, 1 N-H), 5.87–5.76 (m, 1 H), 5.62–5.49 (m, 1 H), 3.90–3.79 (m, 1 H), 2.95 (d, $J = 2.2$ Hz, 1 H), 2.55 (dd, $J = 16.6$, 8.9 Hz, 1 H), 2.10 (dd, $J = 16.5$, 6.0 Hz, 2H), 2.01–1.90 (m, 1 H), 1.83–1.63 (m, 2 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 177.8, 127.6, 127.6, 52.5, 34.2, 26.0, 20.6; IR (neat, cm^{-1}): 3233, 3023, 2923, 1692, 1437, 1392, 1298, 1266, 1092; HRMS (ESI, m/z) calcd for $\text{C}_8\text{H}_{11}\text{NONa}$ ($\text{M}+\text{Na}^+$): 160.0733, found 160.0732.

(±)-(3a*S*,7a*R*)-*tert*-Butyl-2-oxo-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1-carboxylate (4.56)



NEt₃ (0.85 mL, 6.12 mmol, 4.0 equiv.) and a catalytic amount of DMAP (2 mg, 0.015 mmol, 1 mol%) were added to a solution of starting material **4.55** (210 mg, 1.53 mmol, 1 equiv.) in CH₂Cl₂ (15 mL). The resulting mixture was cooled to 0 °C and di-*tert*-butyl dicarbonate (670 mg, 3.07 mmol, 2.0 equiv.) was added in one portion. After 15 min of stirring at 0 °C, the mixture was warmed to room temp. and then stirred for a further 4 h. A saturated aqueous NaHCO₃ solution (2 mL) was then added and the aqueous phase was extracted with diethyl ether (3 × 10 mL). After dried over MgSO₄ and concentration under reduced pressure, the crude oil was purified by silica gel column chromatography (eluent: cyclohexane/ethyl acetate, 1:1) to afford 257 mg of desired product **4.56** as a white solid (70%). ¹H NMR (CDCl₃, 400 MHz) δ 5.86–5.79 (m, 1 H), 5.68–5.62 (m, 1 H), 4.13 (ddd, *J* = 11.5, 7.5, 4.1 Hz, 1 H), 2.88–2.75 (m, 1 H), 2.62 (ABX system, *J* = 17.1, 8.5 Hz, 1 H), 2.32 (ABX system, *J* = 17.1, 11.6 Hz, 1 H), 2.21–1.99 (m, 3 H), 1.53 (s, 9 H), 1.58–1.46 (m, 1 H);. ¹³C NMR (CDCl₃, 100 MHz) δ 173.2, 150.0, 128.2, 126.3, 82.7, 56.9, 38.7, 31.6, 28.0, 24.5, 23.0; IR (neat, cm⁻¹): 2977, 2925, 1784, 1750, 1711, 1330, 1306, 1155; HRMS (ESI, *m/z*) calcd for C₁₃H₁₉NNaO₃ (M+Na⁺): 260.1257, found 260.1248.

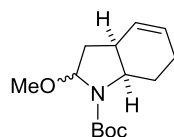
(±)-(3a*S*,7a*R*)-*tert*-Butyl-2-hydroxy-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1-carboxylate (4.57)



To a solution of starting material **4.56** (210 mg, 0.88 mmol, 1 equiv.) in THF (2.15 mL) cooled to -78 °C was added dropwise DIBAL-H (1.31 mL, 1.33 mmol, 1.5 equiv.) (1M in hexane), and the mixture was stirred for 2 h at -78 °C. A saturated aqueous NH₄Cl solution (2 mL), CH₂Cl₂ (10 mL) and a 5% aqueous Na₂CO₃ solution (mL) were successfully added. The resulting mixture was stirred at room temp. for 15 min, and the aqueous phase was extracted with CH₂Cl₂ (3 × 20 mL). After dried over MgSO₄ and concentration under reduced pressure, the crude oil was purified by silica

gel column chromatography (eluent: cyclohexane/ethyl acetate, 4:1) to afford 188 mg of the desired product **4.57** as a white solid (88%, *dr* 2.8/1). ¹H NMR (CDCl₃, 400 MHz) δ 5.83–5.72 (m, 1 H), 5.71–5.63 (m, 1 H), 5.48–5.31 (m, 1 H), 3.84–3.02 (m, 1 H), 3.83–3.68 (m, 1 H, 74%), 3.16–3.06 (s, 1 H, 26%), 2.69–2.54 (m, 1 H), 2.43–2.26 (m, 1 H), 2.13–1.92 (m, 2 H), 1.80–1.59 (m, 2 H), 1.48 (s, 9 H); ¹³C NMR (CDCl₃, 100 MHz) δ 155.3, 128.1, 127.7, 82.6, 80.2, 56.0, 38.0, 36.0, 28.5, 25.6, 23.2; IR (neat, cm⁻¹): 3459, 2974, 2930, 1679, 1399, 1382, 1366, 1167, 1111; HRMS (ESI, *m/z*) calcd for C₁₃H₂₁NNaO₃ (M+Na⁺): 262.1414, found 262.1408.

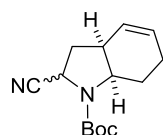
(±)-(3a*S*,7a*R*)-tert-Butyl-2-methoxy-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1-carboxylate (4.58)



A solution of APTS (33 mg, 0.19 mmol, 0.5 equiv.) in CH₃OH (4 mL) was added in a 25 mL flask containing starting material **4.57** (90 mg, 0.38 mmol, 1 equiv.). The mixture was stirred for 18 h at room temperature. Finally, an aqueous Na₂CO₃ solution (10%, 5 mL) was added and the aqueous phase was extracted with CH₂Cl₂ (3 × 20 mL). After dried over MgSO₄ and concentration under reduced pressure, the crude oil was purified by silica gel column chromatography (eluent: cyclohexane/ethyl acetate, 4:1) to afford 86 mg of the desired product **4.58** as a yellow oil (89%, *dr* 3/1). ¹H NMR (CDCl₃, 400 MHz) δ 5.80–5.71 (m, 1 H), 5.70–5.64 (m, 1 H, 75%), 5.62–5.56 (m, 1 H, 25%), 5.23–4.84 (m, 1 H), 4.12–3.72 (m, 1 H), 3.39 (s, 3 H, 25%), 3.32 (s, 3 H, 75%), 2.95–2.78 (m, 1 H, 75%), 2.74–2.64 (m, 1 H, 25%), 2.45–2.16 (m, 1 H), 2.08–1.89 (m, 3 H), 1.83–1.52 (m, 2 H), 1.48 (s, 9 H), 1.20–1.01 (m, 1 H); ¹³C NMR (CDCl₃, 100 MHz) δ 154.7, 153.7, 128.7, 128.1, 127.6, 127.4, 127.3, 127.1, 89.7, 88.7, 88.4, 79.7, 56.4, 56.0, 55.6, 55.4, 37.4, 36.6, 36.1, 35.1, 29.7, 28.4, 24.6, 23.8, 23.7, 23.5; IR (neat, cm⁻¹): 2974, 2930, 1699, 1397,

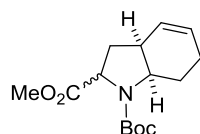
1365, 1168, 1121, 1082; HRMS (ESI, m/z) calcd for $C_{14}H_{23}NNaO_3$ ($M+Na^+$): 276.1570, found 276.1560.

(±)-(3a*S*,7a*R*)-*tert*-Butyl-2-cyano-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1-carboxylate (4.59)



To a solution of the methoxycarbamate **4.58** (60 mg, 0.24 mmol, 1 equiv.) in CH_2Cl_2 (5 mL) cooled to $-78\text{ }^\circ C$ were added $BF_3 \cdot Et_2O$ (48 μL , 0.29 mmol, 1.2 equiv.) and TMSCN (64 μL , 0.48 mmol, 2 equiv.). The resulting solution was stirred at $-78\text{ }^\circ C$ for 10 min. and then the temperature was slowly warmed to $-50\text{ }^\circ C$. Then, a saturated solution of $NaHCO_3$ (10 mL) was finally added and the aqueous phase was extracted with CH_2Cl_2 ($3 \times 15\text{ mL}$). The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude oil was purified by silica gel column chromatography (eluent: cyclohexane/ethyl acetate, 4:1) to afford 45 mg of desired product **11** as a white solid (76%, *dr* 1.6/1). 1H NMR ($CDCl_3$, 400 MHz) δ 5.87–5.78 (m, 1 H), 5.70–5.61 (m, 1 H), 4.52 (d, $J = 7.9\text{ Hz}$, 1 H, 39%), 4.45 (d, $J = 7.9\text{ Hz}$, 1 H, 61%), 3.99–3.90 (m, 1 H, 61%), 3.87–3.76 (m, 1 H, 39%), 3.03–2.84 (m, 1 H), 2.37 (dd, $J = 6.1\text{ Hz}$, 1 H, 61%), 2.34 (d, $J = 6.1\text{ Hz}$, 1 H, 39%), 2.29–2.20 (m, 1 H, 61%), 2.18–2.09 (m, 1 H, 39%), 2.07–1.89 (m, 3 H), 1.51 (s, 9 H, 61%), 1.49 (s, 9 H, 39%), 1.25–1.14 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.5, 152.7, 129.3, 128.9, 125.4, 125.2, 119.2, 119.9, 81.4, 81.0, 55.7, 55.6, 47.1, 46.1, 37.8, 36.8, 35.9, 35.1, 28.3, 25.0, 24.4, 23.5, 23.4; IR (neat, cm^{-1}): 3030, 2976, 2933, 2330, 1699, 1397, 1378, 1367, 1169, 1124; HRMS (ESI, m/z) calcd for $C_{14}H_{20}N_2NaO_2$ ($M+Na^+$): 271.1417, found 271.1410.

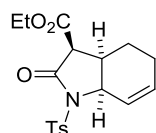
(±)-(3a*S*,7a*R*)-1-*tert*-Butyl-2-methyl-3,3a,7,7a-tetrahydro-1*H*-indole-1,2(2*H*,6*H*)-dicarboxylate (3.60)



To a solution of the cyano compound **3.59** (102 mg, 0.41 mmol, 1 equiv.) in MeOH (5 mL) cooled to 0 °C was added potassium carbonate (80 mg, 0.62 mmol, 1.5 equiv.). The resulting solution was stirred at room temperature for 8 h., then a 7% hydrochloric acid solution (1 ml, 1.64 mmol, 4 equiv.) was added dropwise at 0 °C, and the resulting mixture was stirred at room temperature for 9 h. Then, a saturated solution of NaHCO₃ (120 mL) was finally added and the aqueous phase was extracted with CH₂Cl₂ (3 × 15 mL). After the organic layers were dried over MgSO₄ and concentrated under reduced pressure. The crude oil was purified by silica gel column chromatography (eluent: cyclohexane/ethyl acetate, 4:1) to afford 80 mg of the desired product **12** as a colorless oil (70%, *dr* 1.5/1). ¹H NMR (CDCl₃, 400 MHz) δ 5.81–5.71 (m, 1 H), 5.64–5.54 (m, 1 H), 4.32 (d, *J* = 8.9 Hz, 1 H, 40%), 4.25 (d, *J* = 8.1 Hz, 1 H, 60%), 4.08–3.98 (m, 1 H, 60%), 3.91 (ddd, *J* = 11.8, 7.4, 4.4 Hz, 1 H, 40%), 3.73–3.69 (m, 3 H), 2.85–2.70 (m, 1 H), 2.25–2.16 (m, 2 H, 40%), 2.16–2.05 (m, 2 H, 60%), 2.04–1.86 (m, 3 H), 1.46 (s, 9 H, 40%), 1.39 (s, 9 H, 60%), 1.35–1.26 (m, 1 H); ¹³C NMR (CDCl₃, 100 MHz) δ 173.7, 173.4, 154.4, 153.5, 128.6, 128.2, 126.6, 126.4, 79.8, 79.82, 58.9, 58.4, 56.0, 52.1, 51.9, 37.0, 36.1, 35.4, 34.5, 28.4, 28.3, 25.3, 24.7, 23.6, 23.4; IR (neat, cm⁻¹): 2974, 2953, 2932, 1748, 1695, 1396, 1381, 1365, 1200, 1168, 1122; HRMS (ESI, *m/z*) calcd for C₁₅H₂₃NNaO₄ (M+Na⁺) : 304.1519, found 304.1531.

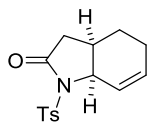
Second approach: domino sequence

(±)-(3aR,7aR)-Ethyl-2-oxo-1-tosyl-2,3,3a,4,5,7a-hexahydro-1H-indole-3-carboxylate (**4.64**)



To a stirred suspension of NaH (480 mg, 60% dispersion in mineral oil, 12 mmol, 3 equiv.) in CH₃CN at 0 °C was added dropwise the solution of starting material (±)-(1*S*,4*R*)-4-chloro-2-cyclohexen-1-yl acetate **cis-4.50**¹¹ (700 mg, 4 mmol, 1 equiv.) and ethyl 3-(4-methylphenylsulfonamido)-3-oxopropanoate¹⁶ (1.7 g, 6 mmol, 1.5 equiv.) in CH₃CN. The solution was stirred at room temperature for 10 min, the solution of Pd(OAc)₂ (45 mg, 0.2 mmol, 5 mol%) and dppb (200 mg, 0.4 mmol, 10 mol%) in CH₃CN at 0 °C was added dropwise. Then, the solution was stirred at 50 °C for 1.5 h. To the reaction mixture was added 5% HCl (50 mL) at 0 °C and the aqueous layer was extracted with AcOEt (3 × 50 mL). The organic layer was washed successively with a solution of saturated NaHCO₃ and brine, dried over Na₂SO₄ and concentrated. The residue was purified by silica gel column chromatography (eluent: cyclohexane/ethyl acetate, 1:1) to afford 1.15 g of the desired product **4.64** as a white solid product (79%). ¹H NMR (CDCl₃, 400 MHz) δ 7.93 (d, *J* = 8.2 Hz, 2 H), 7.32 (d, *J* = 8.2 Hz, 2 H), 6.05–5.98 (m, 1 H), 5.97–5.90 (m, 1 H), 4.89–4.83 (m, 1 H), 4.19 (qd, *J* = 7.1, 4.3 Hz, 2 H), 3.40 (d, *J* = 11.7 Hz, 1 H), 3.08–2.98 (m, 1 H), 2.42 (s, 3 H), 2.11–2.00 (m, 2 H), 1.88–1.71 (m, 2 H), 1.25 (t, *J* = 7.1 Hz, 3 H); ¹³C NMR (CDCl₃, 75 MHz) δ 167.9, 167.4, 145.2, 135.6, 130.9, 129.6, 128.4, 124.9, 61.9, 56.4, 50.7, 35.3, 21.7, 21.6, 19.7, 14.1; IR (neat, cm⁻¹): 3035, 2983, 2927, 2864, 2845, 1749, 1724, 1362, 1333, 1287, 1171, 1146, 1112, 1085, 1026, 668; HRMS (ESI, *m/z*) calcd for C₁₈H₂₁NNaO₅S (M+Na⁺): 386.1033, found 386.1044.

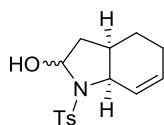
(±)-(3*aR*,7*aS*)-1-Tosyl-3,3*a*,4,5-tetrahydro-1*H*-indol-2(7*aH*)-one (**4.65**)



Water (0.176 mL, 9.28 mmol, 4 equiv.) and NaCl (177 mg, 3.02 mmol, 1.3 equiv.) were added in sequence to a solution of the methyl ester derivative **4.64** (842 mg, 2.32 mmol, 1 equiv.) in DMSO (5 mL). The resulting mixture was warmed to 155 °C for 15 h. Then, the reaction mixture was cooled to room temperature, water (20 mL) was added and the mixture was extracted with CH₂Cl₂ (3 × 15 mL). The collected organic

layers were washed with a saturated NaCl aqueous solution (3 × 10 mL), dried over MgSO₄ and the solvents were evaporated under reduced pressure. The crude oil was purified by silica gel column chromatography (eluent: cyclohexane/ethyl acetate, 1:1) to afford 554 mg of the decarboxylated product **4.65** as a brown oil (82%). ¹H NMR (CDCl₃, 400 MHz) δ 7.99–7.92 (m, 2 H), 7.37–7.30 (m, 2 H), 6.05–5.99 (m, 1 H), 5.97–5.91 (m, 1 H), 4.87–4.76 (m, 1 H), 2.74–2.62 (m, 1 H), 2.41 (s, 3 H), 2.42 (dd, *J* = 16.8, 11.0 Hz, 1 H), 2.29 (dd, *J* = 16.9, 8.3 Hz, 1 H), 2.08–1.99 (m, 2H), 1.85–1.65 (m, 2 H); ¹³C NMR (CDCl₃, 100 MHz) δ 172.9, 144.8, 136.1, 130.8, 129.4, 128.2, 124.9, 58.1, 34.5, 31.1, 22.5, 21.6, 19.8; IR (neat, cm⁻¹): 3070, 3032, 2923, 2860, 1735, 1597, 1356, 1161, 1110, 1090, 951, 677, 660; HRMS (ESI, *m/z*) calcd for C₁₅H₁₇NNaO₃S (M+Na⁺): 314.08217, found 314.0827.

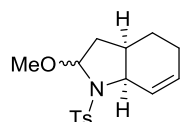
(±)-(3a*R*,7a*S*)-1-Tosyl-2,3,3a,4,5,7a-hexahydro-1*H*-indol-2-ol (4.66)



To a solution of starting material **4.65** (256 mg, 0.88 mmol, 1 equiv.) in CH₂Cl₂ (2.15 mL) cooled to -78 °C was added dropwise DIBAL-H (1.31 mL, 1.33 mmol, 1.5 equiv.) (1M in hexane), and the mixture was stirred for 2 h at -78 °C. A saturated aqueous NH₄Cl solution (2 mL), 10 ml CH₂Cl₂ and 5 ml of a 5 % aqueous Na₂CO₃ solution were added. The resulting mixture was stirred at room temperature for 15 min, and extracted with CH₂Cl₂ (3 × 20 mL). After dried over MgSO₄ and concentration under reduced pressure, the crude oil was purified by silica gel column chromatography (eluent: cyclohexane/ethyl acetate, 4:1) to afford 227 mg of desired product **4.66** as a white solid (88%, *dr* 1.7/1). ¹H NMR (CDCl₃, 400 MHz) δ 7.81–7.71 (m, 2 H), 7.34–7.27 (m, 2 H), 5.82–5.64 (m, 2 H), 5.52–5.48 (m, 1 H, 37%), 5.44–5.38 (m, 1 H, 63%), 4.24 (dt, *J* = 7.1, 2.0 Hz, 1 H, 37%), 3.94–3.88 (m, 1 H, 63%), 3.63 (t, *J* = 2.0 Hz, 1 H, 37%), 3.35 (d, *J* = 2.7 Hz, 1 H, 63%), 2.80–2.67 (m, 1 H, 37%), 2.43 (s, 3 H, 63%), 2.41 (s, 3 H, 37%), 2.09–1.60 (m, 6 H + 1 H 63%); ¹³C NMR (CDCl₃, 100

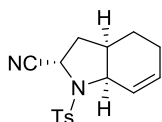
MHz) δ 143.7, 143.3, 138.2, 135.7, 129.8, 129.6, 128.7, 128.6, 127.3, 127.2, 127.1, 125.5, 85.0, 83.3, 57.7, 57.1, 35.4, 35.1, 34.6, 33.8, 22.9, 21.6, 21.5, 20.7, 19.9; IR (neat, cm^{-1}): 3524, 3504, 3066, 2923, 2841, 1336, 1326, 1154, 1106, 1029, 1003; HRMS (ESI, m/z) calcd for $\text{C}_{15}\text{H}_{19}\text{NNaO}_3\text{S}$ ($\text{M}+\text{Na}^+$): 316.0978, found 316.0981.

(\pm)-(3aR,7aS)-2-Methoxy-1-tosyl-2,3,3a,4,5,7a-hexahydro-1H-indole (4.67)

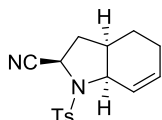


A solution of APTS (33 mg, 0.19 mmol, 0.5 equiv.) in CH_3OH (4 mL) was added in a 25 mL flask contained starting material **4.66** (111 mg, 0.38 mmol, 1 equiv.). The mixture was stirred for 18 h at room temperature. Finally, a saturated aqueous Na_2CO_3 solution (10%, 5 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3×20 mL). After dried over MgSO_4 and concentration under reduced pressure, the crude oil was purified by silica gel column chromatography (eluent: cyclohexane/ethyl acetate, 4:1) to afford 104 mg of the desired product **4.67** as a yellow oil (89%, *dr* 7.5/1). ^1H NMR (CDCl_3 , 400 MHz) δ 7.82–7.71 (m, 2 H), 7.32–7.23 (m, 2 H), 5.98–5.67 (m, 2 H), 5.13 (dd, $J = 5.3, 3.7$ Hz, 1 H, 89%), 5.07 (d, $J = 4.4$ Hz, 1 H, 11%), 3.99 (dt, $J = 6.9, 2.1$ Hz, 1 H, 11%), 3.96–3.87 (m, 1 H, 89%), 3.39 (s, 3 H, 89%), 3.29 (s, 3 H, 11%), 2.41 (s, 3 H, 89%), 2.43 (s, 3 H, 11%), 2.07–1.90 (m, 2 H), 1.88–1.65 (m, 4 H), 1.64–1.53 (m, 1 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 143.4, 142.8, 136.3, 129.6, 129.5, 129.1, 127.9, 127.81, 127.6, 127.3, 127.2, 92.6, 91.6, 58.1, 56.5, 55.5, 55.3, 36.4, 35.8, 33.8, 32.3, 26.8, 24.1, 22.1, 21.9, 21.4, 19.7; IR (neat, cm^{-1}): 3067, 3034, 2990, 2929, 2837, 1598, 1438, 1345, 1156, 1090, 1072, 1027, 951, 676, 600; HRMS (ESI, m/z) calcd for $\text{C}_{16}\text{H}_{21}\text{NNaO}_3\text{S}$ ($\text{M}+\text{Na}^+$): 330.1140, found 330.1134.

(\pm)-(2S,3aR,7aS)-1-Tosyl-2,3,3a,4,5,7a-hexahydro-1H-indole-2-carbonitrile (major product 4.68).



(±)-(2*R*,3*aR*,7*aS*)-1-Tosyl-2,3,3*a*,4,5,7*a*-hexahydro-1*H*-indole-2-carbonitrile
(minor product **4.69**).



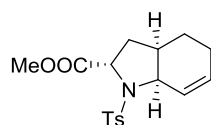
To a solution of the methoxycarbamate **4.67** (74 mg, 0.24 mmol, 1 equiv.) in CH₂Cl₂ (5 mL) cooled to -78 °C were added BF₃·Et₂O (48 μL, 0.29 mmol, 1.2 equiv.) and TMSCN (64 μL, 0.48 mmol, 2 equiv.). The resulting solution was stirred at -78 °C for 10 min and then the temperature was slowly warmed to -50 °C. Then, a saturated solution of NaHCO₃ (10 mL) was finally added and the aqueous phase was extracted with CH₂Cl₂ (3 × 15 mL). The organic layers were dried over MgSO₄ and concentrated under reduced pressure. The crude oil was purified by silica gel column chromatography (eluent: cyclohexane/ethyl acetate, 4:1) to afford 59 mg of the two isomers **4.68** (48 mg) and **4.69** (11 mg) as white solids (82%, *dr* 4.5/1).

Compound **4.68**: ¹H NMR (CDCl₃, 400 MHz) δ 7.86 (d, *J* = 8.3 Hz, 2 H), 7.34 (d, *J* = 8.1 Hz, 2 H), 6.00–5.94 (m, 1 H), 5.81–5.74 (m, 1 H), 4.67 (d, *J* = 7.7 Hz, 1 H), 4.14 (d, *J* = 7.4 Hz, 1 H), 2.70–2.53 (m, 1 H), 2.44 (s, 3 H), 2.26 (td, *J* = 12.6, 7.8 Hz, 1 H), 2.05 (dd, *J* = 12.4, 5.9 Hz, 1 H), 2.02–1.89 (m, 2 H), 1.86–1.68 (m, 2 H); ¹³C NMR (CDCl₃, 100 MHz) δ 144.2, 135.5, 129.7, 128.5, 127.9, 126.2, 117.9, 57.2, 48.4, 36.1, 32.6, 21.8, 21.6, 19.7; IR (neat, cm⁻¹): 3037, 2925, 2844, 2327, 1751, 1598, 1348, 1159, 1131, 1103, 1089, 1059, 1043, 672, 614; HRMS (ESI, *m/z*) calcd for C₁₆H₁₈N₂NaO₂S (M+Na⁺): 325.0981, found 325.0972.

Compound **4.69**: ¹H NMR (CDCl₃, 400 MHz) δ 7.78 (d, *J* = 8.3 Hz, 2 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 5.84–5.75 (m, 1 H), 5.65–5.58 (m, 1 H), 4.50–4.44 (m, 1 H), 4.23 (s, 1

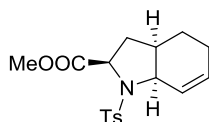
H), 2.44 (s, 3 H), 2.31–2.22 (m, 1 H), 2.21–2.12 (m, 2 H), 2.10–1.91 (m, 2 H), 1.79–1.67 (m, 2 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 144.4, 135.1, 130.0, 129.5, 127.5, 125.6, 119.0, 58.6, 47.5, 36.2, 33.7, 22.2, 21.6, 20.6; IR (neat, cm^{-1}): 3036, 2925, 2844, 2327, 1750, 1597, 1348, 1159, 1130, 1103, 1084, 1058, 1040.

(±)-(2*S*,3*aR*,7*aS*)-Methyl 1-tosyl-2,3,3*a*,4,5,7*a*-hexahydro-1*H*-indole-2-carboxylate (4.70)



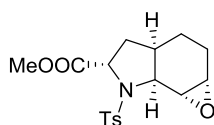
The cyano compound **4.68** (54 mg, 0.179 mmol, 1 equiv.) was dissolved in 2 mL of 1N HCl/MeOH solution. The resulting solution was heated to 75 °C to reflux for 6 h. Then, the temperature was warmed to room temperature. 4 mL of a saturated solution of NaHCO_3 were finally added and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). After the organic phase was dried over MgSO_4 and concentrated under reduced pressure, the crude oil was purified by silica gel column chromatography (eluent: cyclohexane ethyl acetate, 4:1) to afford 52 mg of the desired product **4.70** as a white solid (91%). ^1H NMR (CDCl_3 , 300 MHz) δ 7.79–7.72 (m, 2 H), 7.30–7.24 (m, 2 H), 5.93–5.84 (m, 1 H), 5.74–5.64 (m, 1 H), 4.43 (dd, $J = 9.0, 1.8$ Hz, 1 H), 4.37 (dd, $J = 4.9, 1.8$ Hz, 1 H), 3.70 (s, 3 H), 2.73–2.55 (m, 1 H), 2.45 (s, 3 H), 2.21 (dd, $J = 12.0, 3.0$ Hz, 1 H), 1.95–1.88 (m, 1 H), 1.91–1.64 (m, 3 H), 1.60–1.48 (m, 1 H) ppm. ^{13}C NMR (CDCl_3 , 75 MHz) δ 173.1, 143.1, 137.8, 129.3, 128.6, 127.5, 125.7, 59.8, 57.9, 52.2, 35.0, 32.0, 22.0, 21.5, 20.1; IR (neat, cm^{-1}): 3031, 2952, 2923, 2845, 1759, 1735, 1348, 1160, 1091, 1050; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{21}\text{NNaO}_4\text{S}$ ($\text{M}+\text{Na}^+$): 358.1083, found 358.1069.

(±)-(2*R*,3*aR*,7*aS*)-Methyl 1-tosyl-2,3,3*a*,4,5,7*a*-hexahydro-1*H*-indole-2-carboxylate (4.71)

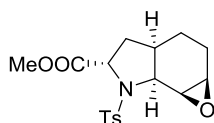


The cyano compound **4.69** (34 mg, 0.11 mmol, 1 equiv.) was dissolved in 1 mL of 1N HCl/MeOH solution. The resulting solution was heated to 75 °C to reflux for 6 h. Then, the temperature was warmed to room temperature. 4 mL of a saturated solution of NaHCO₃ were finally added and the aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL). After the organic phase was dried over MgSO₄ and concentrated under reduced pressure, the crude oil was purified by silica gel column chromatography (eluent: cyclohexane/ethyl acetate, 4:1) to afford 29 mg of the desired product **4.71** as a white solid (84%). ¹H NMR (CDCl₃, 400 MHz) δ 7.80 (d, *J* = 8.3 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 5.71 (d, *J* = 10.1 Hz, 1 H), 5.63 (dd, *J* = 10.3, 2.1 Hz, 1 H), 4.24 (dd, *J* = 8.9, 7.4 Hz, 1 H), 4.19–4.13 (m, 1 H), 3.75 (s, 3 H), 2.43 (s, 3 H), 2.14–1.88 (m, 5 H), 1.74–1.57 (m, 2 H); ¹³C NMR (CDCl₃, 100 MHz) δ 172.7, 143.6, 135.5, 129.7, 127.9, 127.7, 126.9, 60.5, 58.7, 52.4, 36.1, 32.3, 22.1, 21.5, 19.9; IR (neat, cm⁻¹): 3031, 2952, 2923, 2843, 1758, 1733, 1348, 1328, 1158, 1090, 1050.

(±)-(1a*S*,3a*R*,5*S*,6a*S*,6b*R*)-Methyl 6-tosyl octahydro-1a*H*-oxireno[2,3-*g*]indole-5-carboxylate (major product **4.72)**



(±)-(1a*R*,3a*R*,5*S*,6a*S*,6b*S*)-Methyl 6-tosyl octahydro-1a*H*-oxireno[2,3-*g*]indole-5-carboxylate (minor product **4.73)**

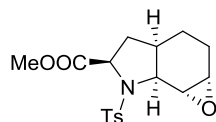


To a solution of alkene **4.70** (20 mg, 0.06 mmol, 1 equiv.) in CH₂Cl₂ (1 mL) was added a solution of 70% *m*-chloroperoxybenzoic acid (14 mg, 0.08 mmol, 1.3 equiv.) in CH₂Cl₂ (0.5 mL). The resulting mixture was stirred at room temperature for 3 h. 4 mL of a saturated solution of NaHCO₃ were finally added and the aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL). After the organic phase was dried over MgSO₄ and concentrated under reduced pressure, the crude oil was purified by silica gel column chromatography (eluent: cyclohexane/ethyl acetate, 4:1) to afford 15 mg of the epoxide **4.72** and 3 mg of the epoxide **4.73** as white solids (92%, *dr* 7.5/1).

Compound **4.72**: ¹H NMR (CDCl₃, 400 MHz) δ 7.81–7.72 (m, 2 H), 7.33–7.28 (m, 2 H), 4.55 (d, *J* = 8.7 Hz, 1 H), 4.01 (d, *J* = 7.9 Hz, 1 H), 3.61 (s, 3 H), 3.43 (dd, *J* = 3.8, 1.1 Hz, 1 H), 3.16–3.12 (m, 1 H), 2.59–2.48 (m, 1 H), 2.43 (s, 3 H), 2.16 (d, *J* = 8.8 Hz, 1 H), 2.01–1.93 (m, 1 H), 1.91–1.77 (m, 1 H), 1.74–1.64 (m, 2 H), 1.34–1.26 (m, 1 H); ¹³C NMR (CDCl₃, 100 MHz) δ 172.3, 143.6, 136.8, 129.4, 127.8, 60.9, 56.0, 52.3, 52.2, 51.9, 33.0, 31.6, 21.5, 18.3, 16.0; IR (neat, cm⁻¹): 2952, 2922, 2860, 1752, 1676, 1340, 1201, 1154, 1097, 1065, 666, 596; HRMS (ESI, *m/z*) calcd for C₁₇H₂₁NNaO₅S (M+Na⁺): 374.1033, found 374.1032.

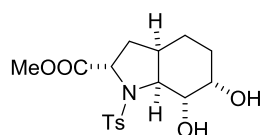
Compound **4.73**: ¹H NMR (CDCl₃, 400 MHz) δ 7.83–7.78 (m, 2 H), 7.32–7.27 (m, 2 H), 4.37–4.30 (m, 2 H), 3.71 (s, 3 H), 3.49 (dd, *J* = 4.2, 2.5 Hz, 1 H), 3.29–3.26 (m, 1 H), 2.71–2.52 (m, 1 H), 2.44–2.39 (s, 3 H), 2.21 (ddd, *J* = 14.2, 10.6, 7.1, 1 H), 1.87–1.76 (m, 3 H), 1.64–1.47 (m, 2 H); ¹³C NMR (CDCl₃, 100 MHz) δ 173.4, 143.4, 137.6, 129.5, 127.3, 60.2, 58.4, 54.4, 52.4, 52.2, 34.1, 33.8, 21.9, 21.6, 19.3; IR (neat, cm⁻¹): 2953, 2921, 2860, 1754, 1679, 1203, 1154, 1099, 1067, 667; HRMS (ESI, *m/z*) calcd for C₁₇H₂₁NNaO₅S (M+Na⁺): 374.1033, found 374.1032.

(±)-(1a*S*,3a*R*,5*R*,6a*S*,6b*R*)-Methyl 6-tosyloctahydro-1a*H*-oxireno[2,3-*g*]indole-5-carboxylate (4.75)



To a solution of alkene **4.71** (15 mg, 0.045 mmol, 1 equiv.) in CH_2Cl_2 (1 mL) was added a solution of 70% *m*-chloroperoxybenzoic acid (12 mg, 0.07 mmol, 1.3 equiv.) in CH_2Cl_2 (0.5 mL). The resulting mixture was stirred at room temperature for 3 h. 4 mL of a saturated solution of NaHCO_3 were finally added and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). After the organic phase was dried over MgSO_4 and concentrated under reduced pressure, the crude oil was purified by silica gel column chromatography (eluent: cyclohexane/ethyl acetate, 1:3) to afford 13 mg of epoxide **4.75** as a white solid (89%). ^1H NMR (CDCl_3 , 400 MHz) δ 7.83–7.77 (m, 2 H), 7.37–7.31 (m, 2 H), 4.15–4.08 (m, 1 H), 3.89 (d, $J = 7.3$ Hz, 1 H), 3.80 (s, 3 H), 3.25–3.20 (m, 2 H), 2.44 (s, 3 H), 2.07–1.78 (m, 5 H), 1.66–1.59 (m, 2 H), 1.33–1.27 (m, 1 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 172.5, 144.1, 134.3, 129.9, 127.8, 61.4, 57.0, 53.4, 52.6, 52.2, 34.2, 32.1, 21.6, 18.4, 16.1; IR (neat, cm^{-1}): 2954, 2924, 2853, 1757, 1598, 1350, 1161, 1093.

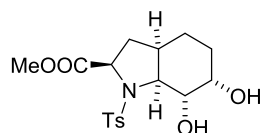
(±)-(2*S*,3*aR*,6*S*,7*R*,7*aS*)-Methyl 6,7-dihydroxy-1-tosyloctahydro-1*H*-indole-2-carboxylate (**4.74**)



To a solution of alkene **4.70** (20 mg, 0.06 mmol, 1 equiv.) in 1 mL of THF/ H_2O (9:1) was added *N*-methyl morpholine-*N*-oxide (15.5 mg, 0.132 mmol, 2.5 equiv.) and a catalytic amount of OsCl_3 . The resulting solution was stirred at room temperature for 6 h. 4 mL of a saturated solution of $\text{Na}_2\text{S}_2\text{O}_3$ were finally added and the aqueous phase was extracted with ethyl acetate (3×10 mL). After the organic phase was dried over MgSO_4 and concentrated under reduced pressure, the crude oil was purified by silica gel column chromatography (eluent: ethyl acetate) to afford 18 mg of product

4.74 as a colorless oil (80% *dr* 10/1). Major isomer: ^1H NMR (CDCl_3 , 400 MHz) δ 7.74 (d, $J = 8.3$ Hz, 2 H), 7.34 (d, $J = 8.0$ Hz, 2 H), 4.14–4.06 (m, 2 H), 3.90 (br s, 1 H), 3.81 (s, 3 H), 3.77 (dd, $J = 8.8$, 2.6 Hz, 1 H), 3.71–3.65 (m, 1 H), 2.65 (br s, 1 H), 2.44 (s, 3 H), 2.13–2.95 (m, 1 H), 1.96–1.74 (m, 4 H), 1.56–1.32 (m, 1H), 1.38–1.31 (m, 1 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 172.6, 144.3, 133.9, 130.1, 127.4, 72.2, 68.3, 64.1, 61.4, 52.8, 37.7, 33.5, 24.1, 21.6, 18.5; IR (neat, cm^{-1}): 3486, 2954, 2924, 2852, 1755, 1598, 1342, 1158, 1098, 666; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{23}\text{NNaO}_6\text{S}$ ($\text{M}+\text{Na}^+$): 392.1138, found 392.1149.

(±)-(2*R*,3*aR*,6*S*,7*R*,7*aS*)-Methyl 6,7-dihydroxy-1-tosyl octahydro-1*H*-indole-2-carboxylate (4.76)



To a solution of alkene **4.71** (10 mg, 0.03 mmol, 1 equiv.) in 1 ml of THF/ H_2O (9:1) was added *N*-methyl morpholine-*N*-oxide (9 mg, 0.12 mmol, 2.5equiv.) and a catalytic amount of OsCl_3 . The resulting solution was stirred at room temperature for 6 h. 4 mL of a saturated solution of $\text{Na}_2\text{S}_2\text{O}_3$ were finally added and the aqueous phase was extracted with ethyl acetate (3×10 mL). After the organic phase was dried over MgSO_4 and concentrated under reduced pressure, the crude oil was purified by silica gel column chromatography (eluent: ethyl acetate) to afford 9 mg of product **4.76** as a colorless oil (80% *dr* 6/1). Major isomer: ^1H NMR (CDCl_3 , 400 MHz) δ 7.74 (d, $J = 8.3$ Hz, 2 H), 7.34 (d, $J = 8.0$ Hz, 2 H), 4.14–4.05 (m, 2 H), 3.89 (br s, 1 H), 3.80 (s, 3 H), 3.77 (dd, $J = 8.8$, 2.6 Hz, 1 H), 3.71–3.62 (m, 1 H), 2.66 (br s, 1 H), 2.44 (s, 3 H), 2.13–2.05 (m, 1 H), 1.95–1.71 (m, 4 H), 1.55–1.45 (m, 1 H), 1.38–1.31 (m, 1 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 172.6, 144.3, 133.95, 130.1, 127.4, 72.2, 68.2, 64.0, 61.4, 52.8, 37.7, 33.5, 24.1, 21.6, 18.5; IR (neat, cm^{-1}): 3462, 2954, 2925, 2893, 2853, 1755, 1598, 1342, 1157, 1097, 665; HRMS (ESI, m/z) calcd for $\text{C}_{17}\text{H}_{23}\text{NNaO}_6\text{S}$ ($\text{M}+\text{Na}^+$): 392.1137, found 392.1149.

Reference

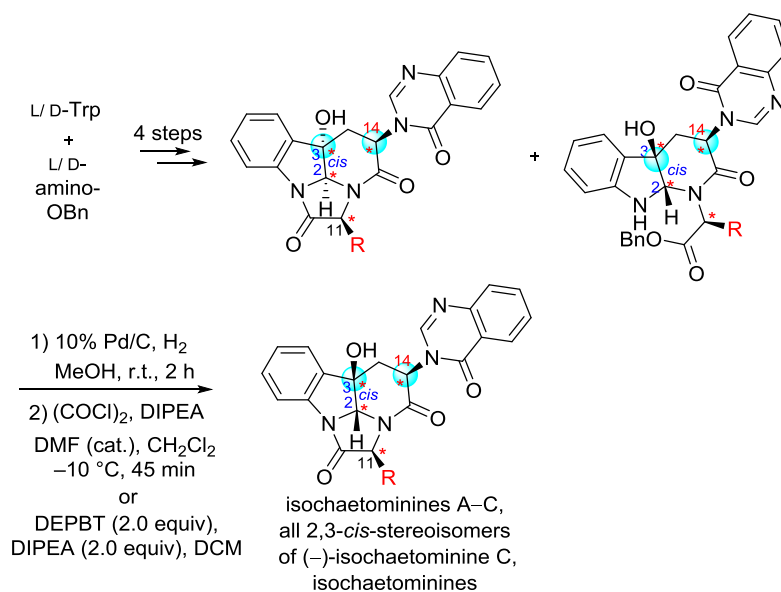
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Chapter 5 Conclusion

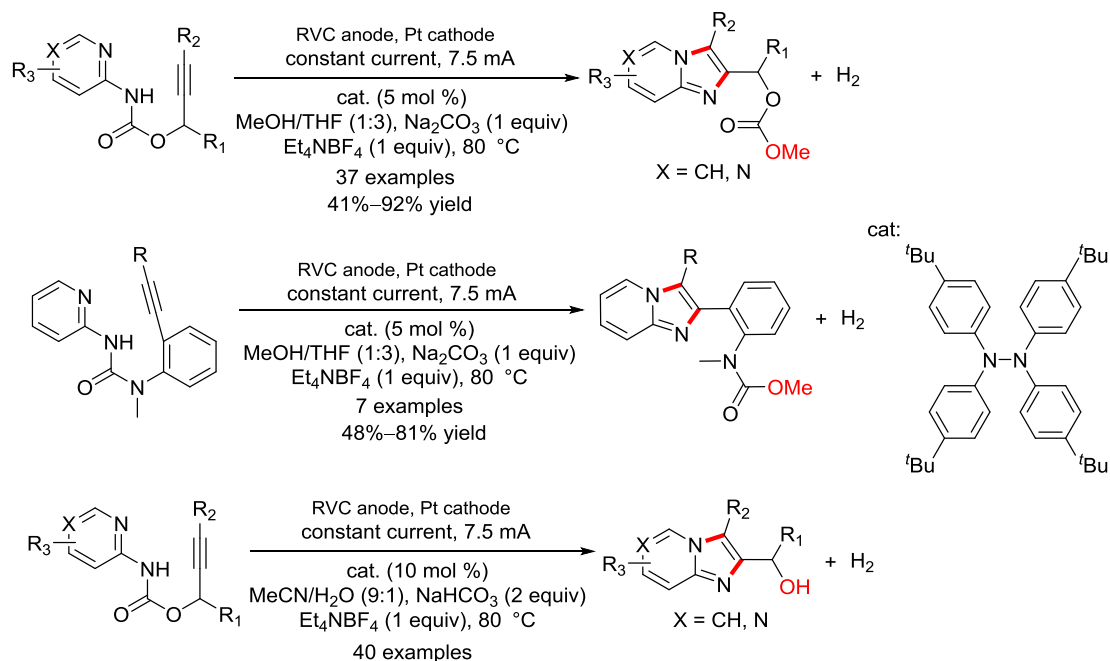
We achieved the following results from this thesis:

1. A highly efficient strategy has been developed for the enantioselective total syntheses of the proposed structures of (-)-pseudofischerine, (-)-aniquinazoline D and (-)-isochaetominine, (-)-isochaetominines A–C, (+)-14-*epi*-isochaetominine C, as well as other four hitherto unknown stereoisomers of isochaetominine C.

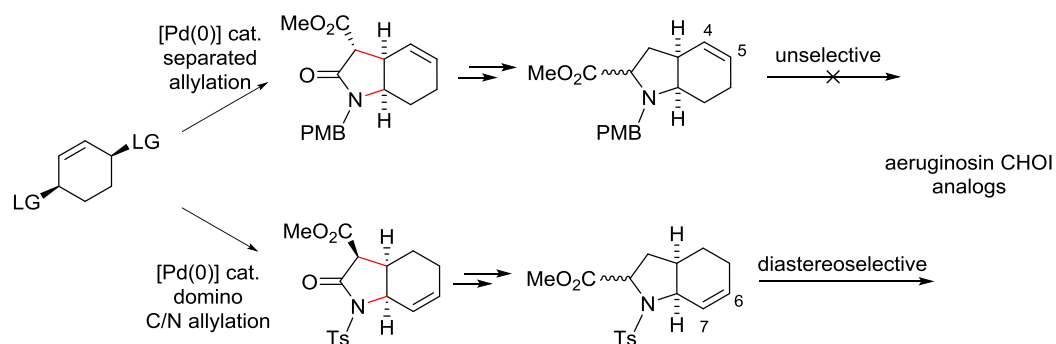


The structures of natural (-)-pseudofischerine, (-)-aniquinazoline D have been revised both to (-)-isochaetominine C and the structure of the natural (-)-isochaetominine have been revised to (-)-11-*epi*-chaetominine based on our synthetic efforts.

2. An organocatalyzed electrochemical synthesis of several important imidazo-fused N-heteroaromatic structures has been developed through intramolecular oxidative alkyne annulation. The substrates were easily available in a modular fashion. The electrolysis reaction is broad in scope, tolerates many common functional groups, proceeds under mild conditions without the need for any transition-metal catalyst or reagent or chemical oxidant. The alkyne annulation reaction is efficient and regiospecific because of the use of a traceless tether.



3. We have developed two approaches toward analogs of the CHOI unit. The key steps of the synthetic route were based on Pd-catalyzed C-allylation and Pd-catalyzed N-allylation, which converted a cyclic bis-allylic substrate into a hexahydroindole structure. Noteworthy, the unsaturations of the resulting hexahydroindole structures can be obtained at different positions, depending on the strategy applied. After one-carbon homologation, epoxidation or *syn*-dihydroxylation of the resulting isomeric bicyclic advanced intermediates allowed to establish that unsaturation at 6,7 is more biased for diastereoselective electrophilic transformations to reach CHOI analogues.



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1. **Mao, Z.-Y.**; Geng, H.; Zhang, T.-T.; Ruan, Y.-P.; Ye, J.-L.; Huang, P.-Q.* Stereodivergent and enantioselective total syntheses of isochaetominines A–C and four pairs of isochaetominine C enantiomers: a six-step approach. *Org. Chem. Front.* **2016**, *3*, 24.
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