Synthetic Studies of Amide-functionalized Helicene-like Molecules

アミド基を持つヘリセン様分子の合成研究

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List of abbreviation

AcOEt	ethyl acetate
aq.	aqueous
*n*Bu	normal butyl
cat.	catalyst
DBU	diazabicycloundecene
DCC	dicyclohexylcarbodiimide
DIPEA	diisopropylethylamine
DPPA	diphenylphosphoryl azide
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine 4-dimethylaminopyridine
DMF	*N*, *N*-dimethylformamide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
ESI	electrospray ionization
FAB	fast-atom ionization
HOBT	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometer
IR	infrared
Me	methyl
min	minute
mp	melting point
ND	not detected
NMR	nuclear magnetic resonance
PTLC	preparative thin-layer chromatography
PMB	*p*-methoxybenzene
PMP	*p*-mehoxyphenyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TS	transition state
UV	ultraviolet

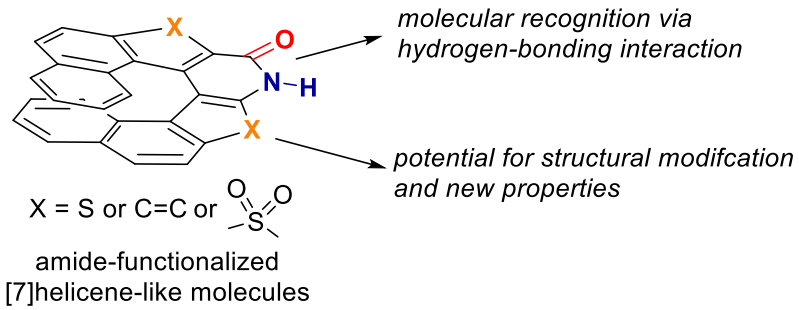
Theoretical Section

Foreword

During the past one hundred and twenty years, helicenes gradually draw more and more attention because of the diversity of helical aromatic structures and various functionalizations,[1] which make helicenes to be unique π-conjugated systems provided with special chemical properties[2] and wide range of applications.[3] Possessing inherent chirality, helicenes are believed to be chiral elements and show particular chiroptical properties with introduction of different functional groups. The ability of self-assembly promotes helicenes to be highlighted in the area of organic materials.[4]

A specific attention has been paid to heterohelicenes and heterohelicene-like molecules, bearing hetero-functional groups as constituent moieties in helical backbones, generally because of their special properties, interesting chemical behaviors and therefore varieties of potential applications as chiral elements in organic materials, chiral catalysts,[5] and bioactive compounds.[6] Since there's a growing demand of these attractive helical molecules, it becomes highly desirable to synthesize hetero-functionalized helicenes or helicene-like molecules with concise synthetic strategies.

Among heterohelicenes and heterohelicene-like molecules, amide-functionalized helicenes and helicene-like molecules, bearing the amide functional group at the periphery of the helical backbones especially draw the author's interests, as shown below, through the synthetic background as described in **Chapter 1**.



Compared with carbohelicenes, the amide group inserted into helix will offer the potential to obtain a variety of functionalized helical structures, and there will be a possibility of adding sulfonyl groups on the helicene outer core which might change the acidity of amide, induce new molecular recognition areas and change other helical properties by the replacement of thiophene ring instead of benzene ring. These amide-functionalized molecules might also show special self-assembly phenomenon with amide groups through intramolecular hydrogen-bonding interaction.

The self-assembling property is a key feature for exhibiting the functions of helicene molecules.[7] Therefore, the amide-functionalized helicene and helicene-like molecules would be promising as functionalized structures which exhibit special properties through molecular assembly. Therefore, the author motivated development of the new and concise synthetic methods towards heterohelicenes and heterohelicene-like molecules.

Chapter 1
Introduction

1.1 General introduction of helicenes and heterohelicenes

Helicenes are a kind of unique π-conjugated and characteristically helical polyaromatic compounds, which mainly consist of *ortho*-fused benzene or other aromatic rings with nonplanar screw-shaped skeletons and show a distinctive helical chirality (**Figure 1-1**).[8,9] Particularly, heterohelicenes are a significant class of helicenes, which are usually represented as helical heteroaromatics and generally considered to be composed of *ortho* (or mostly *ortho*) condensed benzene, pyridine, pyrrole, thiophene, furan and other heterocyclic rings to form a helical backbone. Additionally, they can be fused and functionalized.

Besides the traditional definition of helicene and heterohelicene molecules, there also exist helical structures (**Figure 1-1**), called helicene-like molecules. Helicene-like molecules usually contain at least one saturated atom as a part of the fused rings in the helicene-type core system. In the case of the author's target compounds **1a** and **1b**, since the tautomerism configuration of amide is not definite, whilst pyridin-2(1*H*)-one moiety is not an aromatic ring, the molecules therefore are called [7]helicene-like molecules.

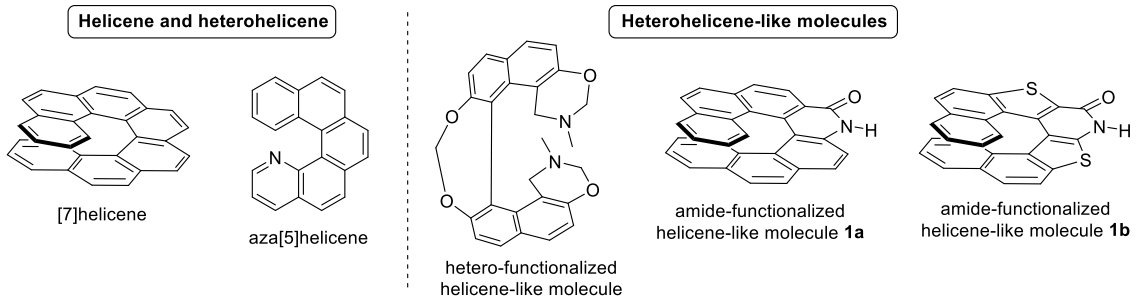


Figure 1-1. Examples of helicene, heterohelicene and helicene-like molecules
(for selected examples see: ref. 8, 9)

The structural features and helicity are described with [6]helicene as example (**Figure 1-2**). The helicene's inner core can be distinguished that the helix experiences steric clashes towards the inner side. On the contrary, the outer skeleton of the helicene is called the helicene's outer core. The benzene rings at the beginning and at the end of the helical arrangement are called the terminal or peripheral rings. This structural organization results in a helical chiral cavity (**Figure 1-2A**).

In general, helicene exists as helically chiral molecule in the case of the terminal aromatic moieties, leading to steric repulsion. The helical structure is assigned the name (*P*)-enantiomer

observed as right-handed helix (clockwise moving from up to down) or (*M*)-enantiomer observed as left-handed helix (anti clockwise moving from up to down) (**Figure 1-2B**).

Due to the *ortho*-fusion mode, each aromatic ring contributes to the total helicity of the structure through an in-plane turn angle (**Figure 1-2C**). The molecule is forced to adopt a helically chiral structure when the sum of the in-plane angles of the rings in helicene core becomes 360° or more, caused by the corresponding steric clashes among the terminal/peripheral rings.

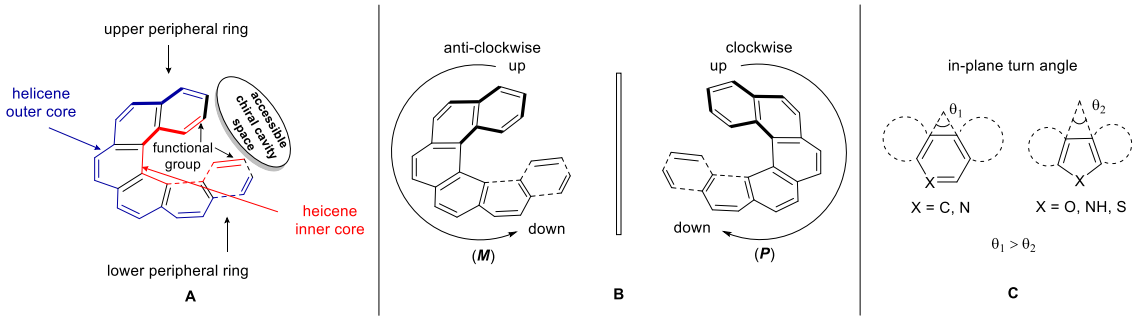


Figure 1-2. (A) Explanation of terms used for helicene structures and chiral cavity; (B) Helicity and enantiomers of [6]helicene; (C) Comparison of the in-plane turn angles (θ) of different rings.

Helicenes show particularly attractive chiroptical properties because of their helical shape, π-electronic conjugation, self-assembly and other features, such as circular dichroism (CD) which gives the structural information about the electronic ground state. Because of inherent chirality and functional groups, heterohelicenes have the potential of a series of promising applications in asymmetric catalysis,[3i,5] enantioselective molecular recognition and chiroptical or electro-optical functional materials.[4] Besides, heterohelicenes, especially thiahelicenes, might show biological activities such as protein inhibitors and interactions with DNA acting as a new scaffold for new drugs.[6] Several examples are displayed in **Figure 1-3**.

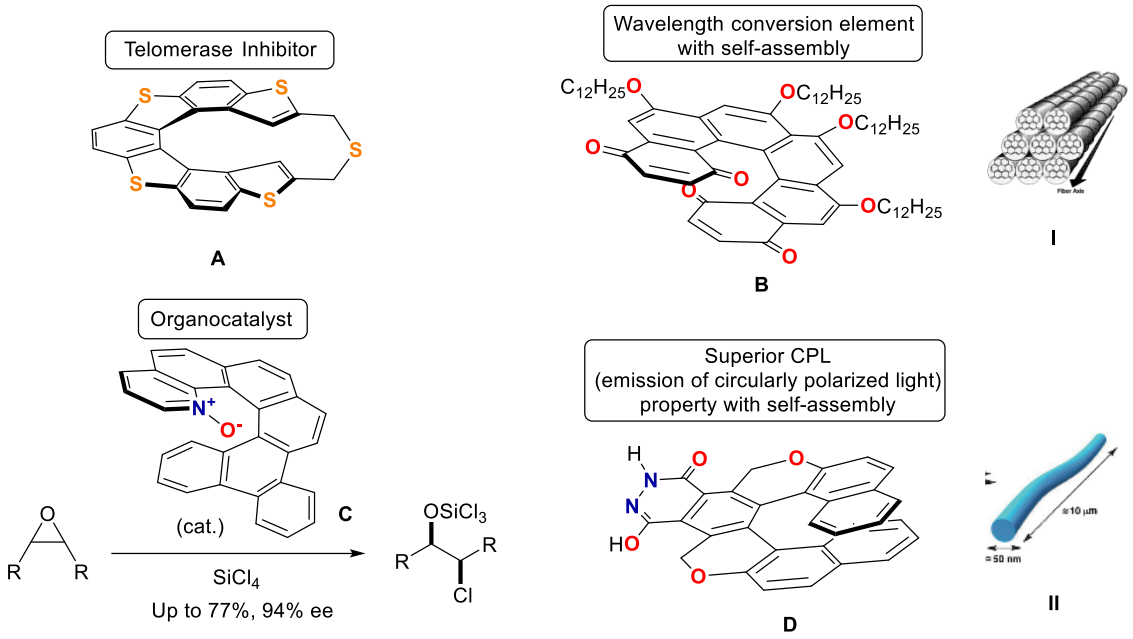


Figure 1-3. Representative applications of helicenes (For **A**, see ref. 6f; Figure I is the schematic representation of column of stacked helicene molecules **B** as observed in solid bulk samples, see ref. 4b; For **C**, see ref. 3i; Figure II is the schematic representation of the formation of fibrous aggregations from the trimeric disk of compound **D** dissolved in toluene, see ref. 4c)

1.2 Examples of synthesis of amide-functionalized helicenes and helicene-like molecules

Since the first helicene was synthesized, there has been 120 years. Till now, more and more new methods of synthesis of helicenes with satisfactory results have been developed. However, the examples of synthesis of amide-functionalized helicenes and helicene-like molecules have been reported in the limited examples as summarized below. Espeically for multiple fused helical structures, one of the challenges in synthesis is to overcome the steric repulsion at terminal part. Compound **1a** is taken as example to show steric clash at peripheral rings (**Figure 1-4**), as well as contributing to the formation of helical shape and unique properties such as high racemization barriers, which will be discussed in detail in **Chapter 4**.

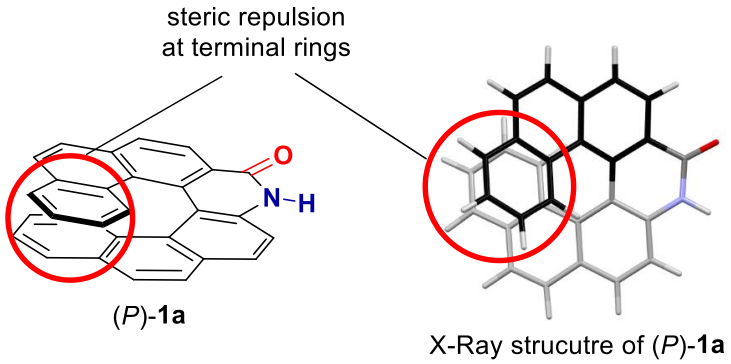
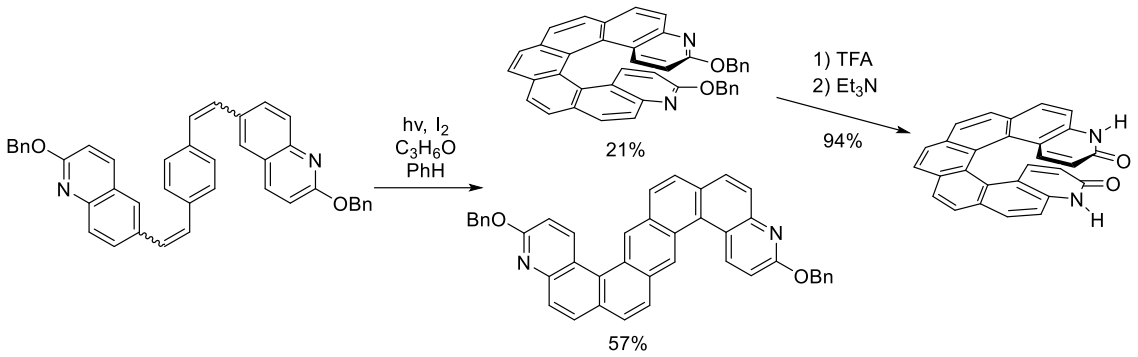


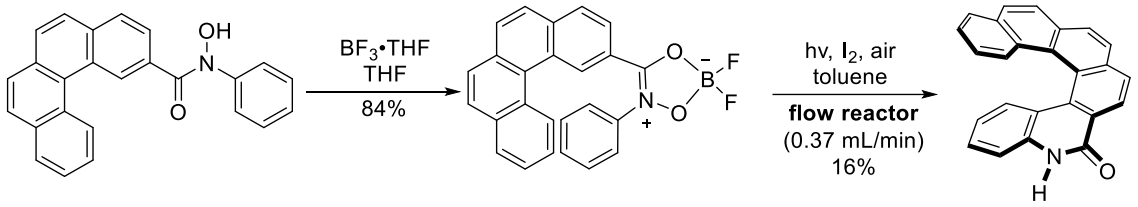
Figure 1-4. One example of steric clash in helical structure

To achieve the cyclization to sterically hindered helical structures in these amide-functionalized molecules, a photo-induced cyclization has been adapted, which is originally applied in carbohelicene synthesis.[1h,1n,1o,1p] In 2000, Branda prepared terminal amide-functionalized [7]helicene, in minor amounts through irradiation of an isomeric mixture with iodine as an oxidizing agent and propylene oxide as an HI scavenger and the following removal of the benzyl groups (**Scheme 1-1**).[7d] However, this method is not readily applicable to gram-scale syntheses because high-dilution conditions and special apparatuses for the photo-irradiation were needed and a undesirable isomer was obtained as the main product.



Scheme 1-1. Synthesis of terminal amide-functionalized [7]helicene-like molecule by Branda

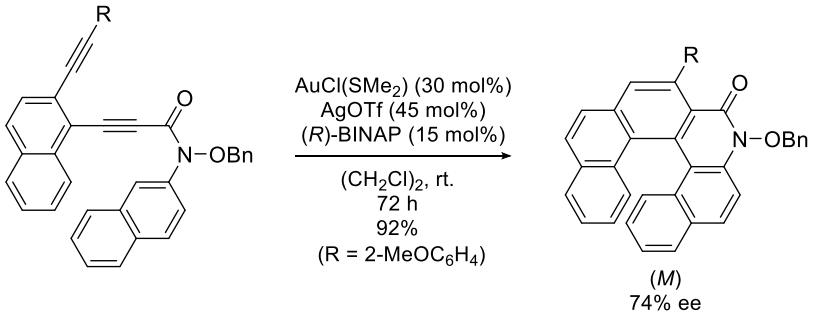
Reported by Suzuki and Murase, a continuous flow strategy was performed to furnish amide-type aza[6]helicene by virtue of the borate structure, in which the phenyl group located in close to the fused cyclic rings. The oxidative photocyclization and easy brokenness of nitrogen-oxygen bond gave the amide-functionalized helicene-like molecule (**Scheme 1-2**).[10] Cumbersome experimental operations, harsh reaction conditions, and low yield make it difficult to obtain the desired product conveniently and efficiently.



Scheme 1-2. Synthesis of amide-type aza[6]helicene by Suzuki and Murase

Transition-metal catalyzed reactions represent another promising pathway for asymmetric synthesis of heterohelicenes and heterohelicene-like molecules,[1s,4c,11] which have been proved to be powerful enough to overcome the terminal steric repulsion, especially in highly fused systems.

A highly efficient method for the enantioselective synthesis of azahelicenes has been achieved through the Au-catalyzed sequential intramolecular hydroarylation of alkynes by Tanaka in 2014. The amide-type [6]helicene was afforded in 92% yield with 74% ee value by Au-catalyzed enantioselective sequential intramolecular hydroarylation from a diyne substrate with two naphthyl groups (**Scheme 1-3**).[11b] Although this method is quite powful, further improvement of the enantioselectivity would be needed.

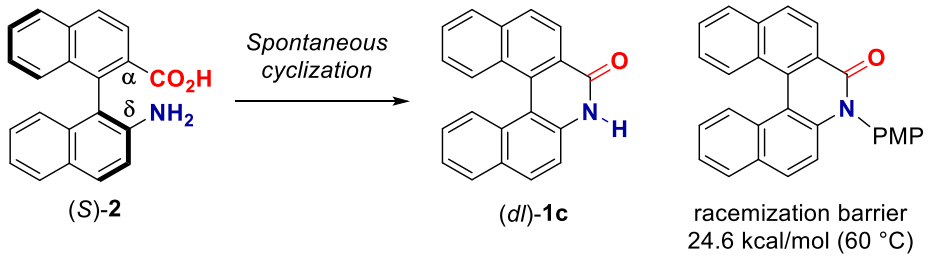


Scheme 1-3. Synthesis of (*M*)-amide-type [6]helicene by Tanaka

With the short review of synthesis of amide-functionalized helicene-like molecules, it has been realized that very limited methods have been developed to achieve the cyclization by overcoming terminal steric effect, especially in highly fused systems. Furthermore, photocyclization methods are hardly applied to the scaled-up preparation of heterohelicenes and heterohelicene-like molecules. Therefore, simple cyzliation conditions that do not use photocyclization are required.

1.3 Background and design of the synthetic strategies to amide-functionalized [7]helicene-like molecules

Previously, a synthetic investigation of axially chiral biary δ-amino acid **2** processing aniline-type amino and carboxy groups at 2,2'-position has been conducted in the author's group (**Scheme 1-4**).[12] In the course of this research, it has been discovered that there exists a spontaneous cyclization of (*S*)-binaphthyl-type δ-amino acid molecule, furnishing an (*dl*)-amide-functionalized [5]helicene-like molecule. In this process, the amide group was incorporated into the fused heterocyclic system as a constituent moiety.[12a] Moreover, the properties of *N*-PMP substituted amide-functionalized [5]helicene-like molecule, for instance, its twisted aromatic system, were also revealed by X-Ray analysis. However, the racemization barrier is too low (24.6 kcal/mol at 60°C) to permit it to exist in a configurationally stable form at ambient temperature.

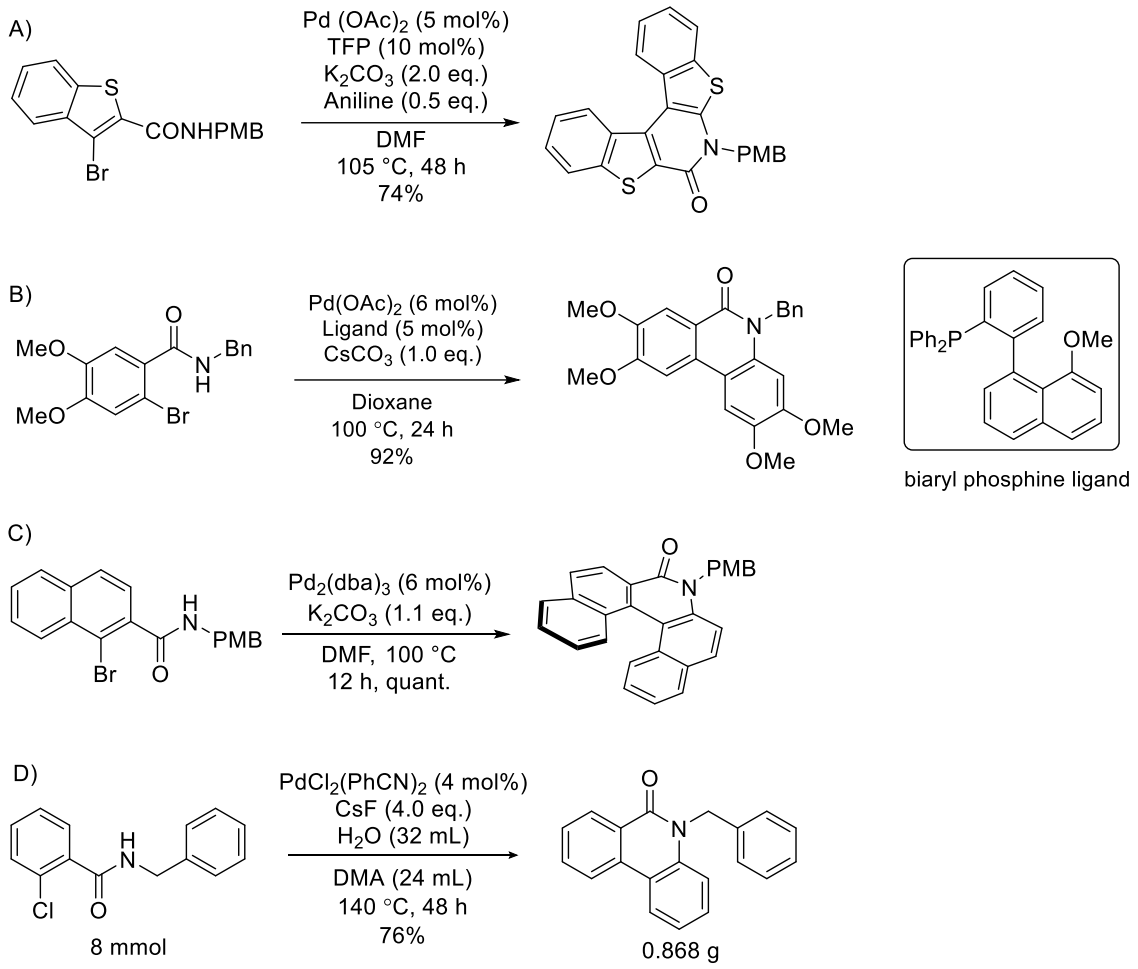


Scheme 1-4. Discovery of spontaneous cyclization process

It's envisioned that if the racemization barrier energy was increased sufficiently, such amide-functionalized molecules could become promising chiral functionalized heterohelicene-like molecules. To the best of my knowledge, there is no precedent for employing an lactamization for a cyclization reaction that yields a heterhelicene-like molecule except for our example.[12a] Therefore, it was intended to prepare amide-functionalized [7]helicene-like molecules, with the expectation that it would exhibit stable helical chirality.

Furthermore, a series of palladium-catalyzed domino reaction of *ortho*-halobenzamide to phenanthridinone derivatives have been conducted by Catellani (**Scheme 1-5A**),[13] our group (**Scheme 1-5B and C**)[12a, 14] and Chen (**Scheme 1-5D**).[15] Early in 2006, Catellani discovered that a catalytic multistep process sequence combining the palladium-catalyzed homocoupling of *ortho*-bromobenzothiophene amide in the presence of $Pd(OAc)_2$/TFP as the catalyst leads to *N*-PMB sulfur-containing fused cyclic compound, that can be recognized as an amide-functionalized [5]helicene-type molecule, under mild conditions (**Scheme 1-5A**). Our group also developed this-type of coupling in the presence of biaryl phosphine ligand (**Scheme 1-5B**).[14] Further investigation in our group found the phosphine-ligand-free conditions (cat. $Pd_2(dba)_3$, K_2CO_3 in

DMF), which led to amide-functionalized [5]helicene-like molecule in excellent yield in a single step (**Scheme 1-5C**).[12a]

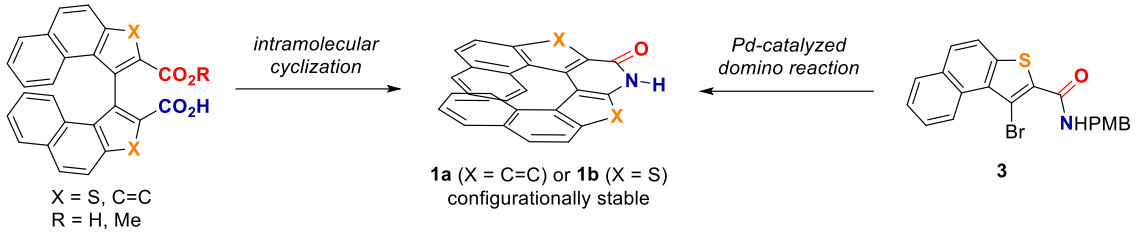


Scheme 1-5. Palladium-catalyzed domino reactions to phenanthridione derivatives

The domino reaction of *ortho*-chlorobenzamides was further investigated by Chen (**Scheme 1-5D**).[15] After optimization of conditions, the catalytic system was established to be $PdCl_2(PhCN)_2$ as catalyst, CsF as base, water as additive at 140 °C in DMA. A broad substrate scope of *N*-substituted 2-chlorobenzamides as well as a scaled-up experiment were exemplified in this protocol.

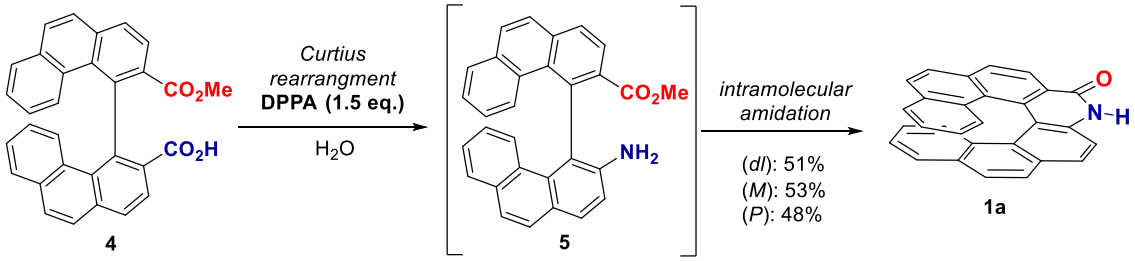
However, to my best knowledge, there is no report for this domino approach applied with the highly fused cyclic system such as naphtho[2,1-*b*]thiophene **3** towards amide-functionalized [7]helicene-like molecules which are also regarded as optically active helical molecules (**Scheme 1-6**). Thus, an strategy for the synthesis of sulfur containing amide-functionalized [7]helicene-like molecule **1a** and **1b** via palladium-catalyzed domino reaction would be worthy to examine.

Taking these backgrounds into account, basically two strategies were proposed to achieve the synthesis, including lactamization and palladium catalyzed domino reaction (**Scheme 1-6**).



Scheme 1-6. Synthetic strategies towards amide-functionalized [7]helicene-like molecules

In **Chapter 2**, the author designed the lactamization as a key to amide-functionalized [7]helicene-like molecules. After being prepared the monomethyl ester of biphenanthryl dicarboxylic acid **4**, helicene-like molecule **1a** was obtained under Curtius reaction conditions with DPPA and subsequent addition of H_2O via the lactamization of the intermediary aniline-type δ-amino acid derivative **5**. This cyclization was readily expanded to the preparation of optically active (*M*)- and (*P*)-helicene-like molecules **1a** from (*R*)- and (*S*)-biphenanthryl monomethyl ester **4**, respectively (**Scheme 1-7**).

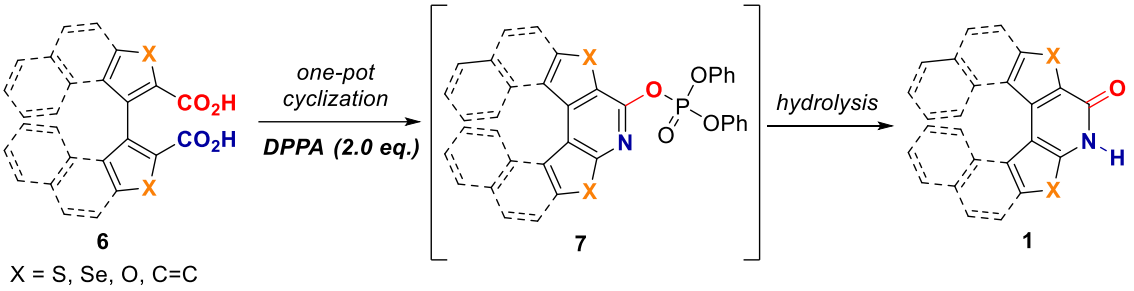


Scheme 1-7. Lactamization strategy

In **Chapter 3**, a novel and efficient direct one-pot cyclization protocol has been developed to furnish phenanthridinones and amide-functionalized [7]helicene-like molecules **1** (**Scheme 1-8**). The author envisioned that direct cyclization from the dicarboxylic acid **6** to helicene-like molecules as well as phenanthridinone derivatives would be possible, if the *in-situ* generated amino group undergoes cyclization with the alternative carboxy group under Curtius reaction conditions. By the survey of the reaction conditions, use of 2 equivalents of DPPA gave the desired product. This reaction conditions can be applicable to the preparation of optically active (*M*)- and (*P*)-amide-functionalized [7]helicene-like molecules including sulfur containing derivatives from the corresponding (*R*)- and (*S*)-biaryl dicarboxylic acids **6**. During the survey of the conditions, the author noticed the phosphate ester derivatives **7** were generated under Curtius

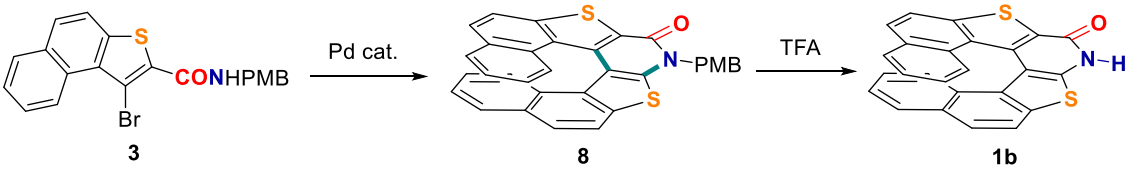
conditions in the case of the substrates including chalcogen atoms and subsequent treatment of the basic conditions gave the corresponding helicene-like molecules.

Furthermore, these conditions were applicable to the biaryl dicarboxylic acid derivatives to furnish phenanthridinone derivatives bearing a variety of substituents.



Scheme 1-8. Direct one-pot cyclization strategy

A palladium-catalyzed domino reaction through C–C and C–N bond formation involving *ipso* substitution is described in **Chapter 4** to obtain a sulfur containing amide-functionalized [7]helicene-like molecule **1b** efficiently. In the strategies described in **Chapter 2** and **Chapter 3**, the key intramolecular amide bond formations were proceeded from the biaryl substrates prepared in prior to the cyclization. Further straightforward way to access amide-functionalized helicene-like molecules would be the domino process through the biaryl formation and the lactamization. The author envisioned that the Pd catalyzed domino process previously developed in our laboratory can be applicable to this strategy. After the survey of the reaction conditions, **8** was obtained from the bromo naphthothiophene amide **3** through subsequent C–C and C–N bond formations (shown in the green bonds). The PMB-protecting group was readily deprotected to give **1b** (**Scheme 1-9**).

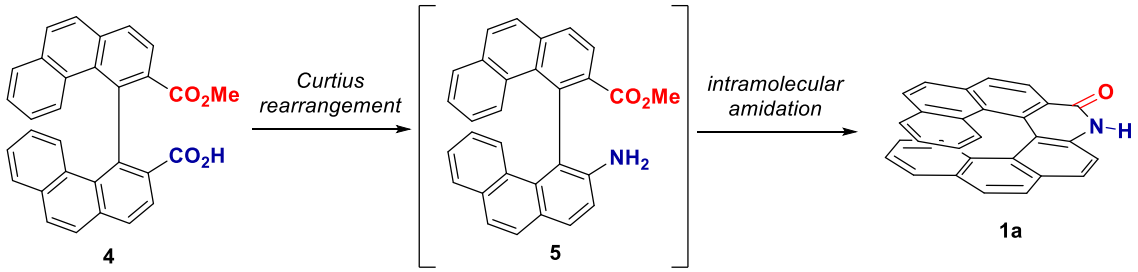


Scheme 1-9. Palladium-catalyzed domino reaction strategy

Details on the three strategies will be described in the following chapters.

Chapter 2
Synthesis of an amide-functionalized [7]helicene-like molecule via lactamization of biphenanthryl monomethyl ester and its structural analysis

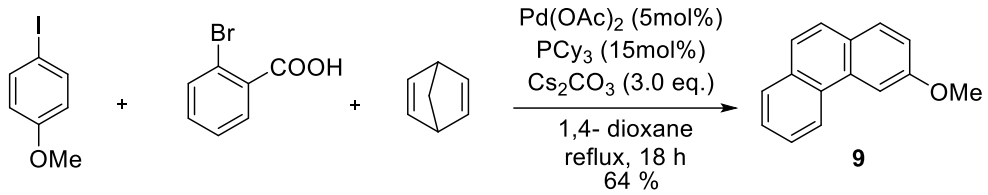
In this Chapter, it was intended to prepare amide-functionalized [7]helicene-like molecule **1a**, through an lactamization of the intermediary axialy chiral δ-amino acids formed by the Curtius rearrangement of biphenanthryl monomethyl ester **4** (**Scheme 2-1**). Furthermore, the author reports the crystal structure of **1a**.



Scheme 2-1. Synthetic strategies of **1a** via lactamization

2.1 Preparation of monomethyl ester for the lactamization

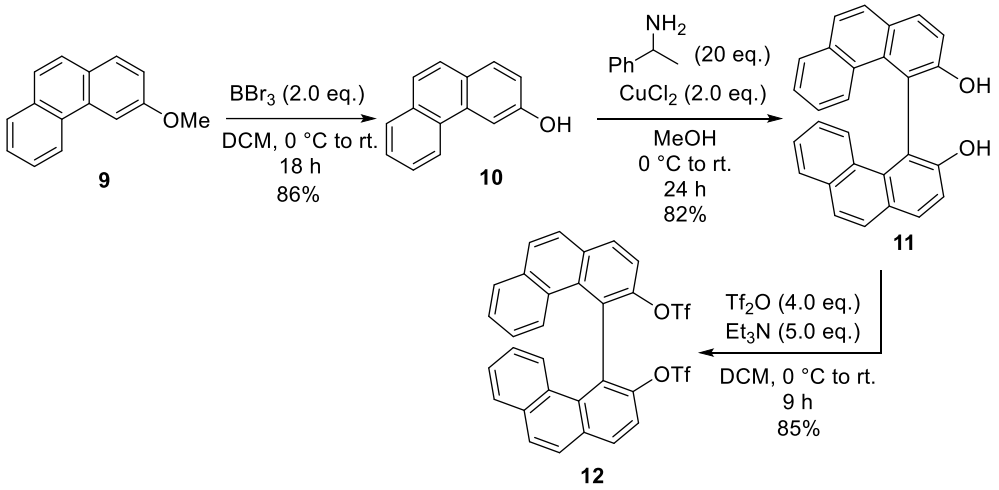
We explored a synthetic pathway to monomethyl ester **4** of biphenanthryl dicarboxylic acid. Firstly, it was intended to prepare 3-methoxyphenanthrene **9**. A versatile method[16] has been developed by Kwong in 2017, which is a three-component cross-coupling of aryl halides, 2-haloarylcarboxylic acids, and nobornadiene. According to this method, compound **9** was directly obtained with the yield of 64% in large scale under almost the same conditions in Kwong's paper except for changing reaction temperature 130 °C to reflux in dioxane (**Scheme 2-2**).



Scheme 2-2. Synthesis of 3-methoxyphenanthrene **9**

With large amount of **9** in hand, racemic ditriflate (*dl*)-**12** of biphenanthrenediol can be furnished smoothly through the demethylation by BBr_3, oxidative coupling in the presence of

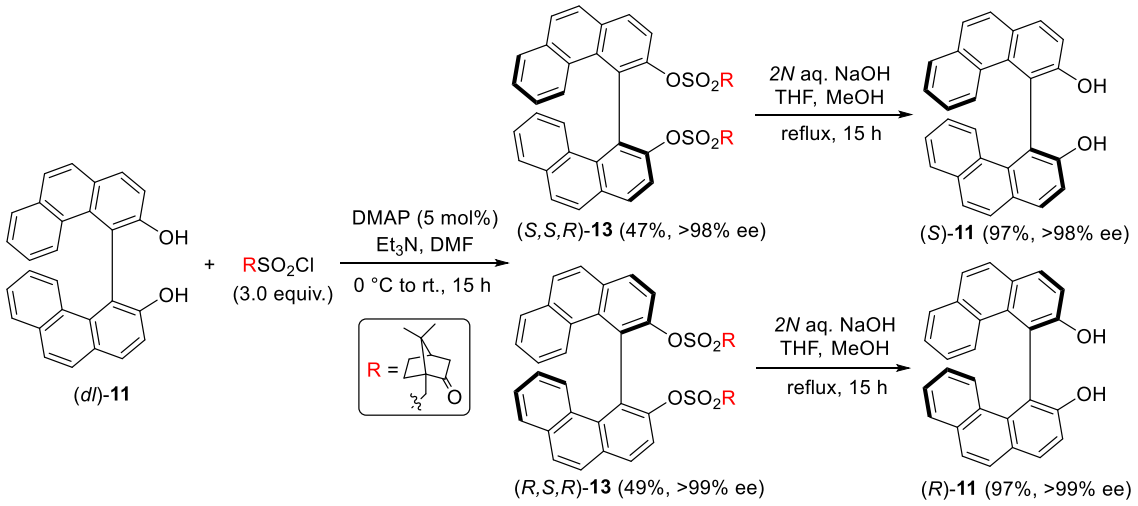
$CuCl_2$ and phenylethylamine, and the triflation with Tf_2O in pyridine according to the reported method as shown in **Scheme 2-3**.[17]



9 **10** **11** **12**

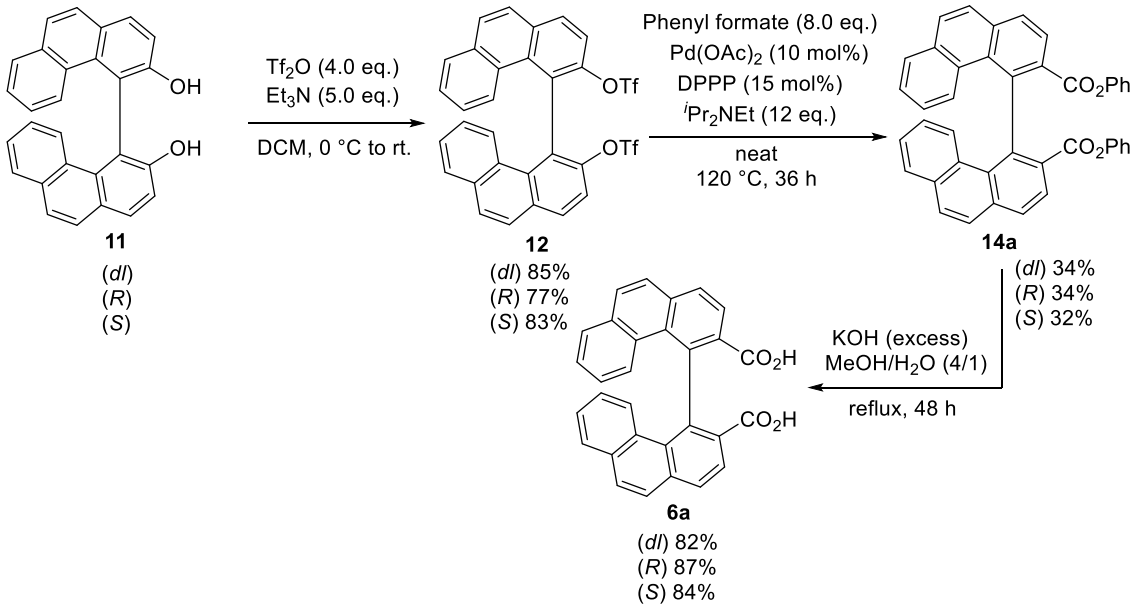
Scheme 2-3. Synthesis of (*dl*)-ditriflate **12**

The optical resolution of (*dl*)-diol **11** was conducted according to the literature procedure by the use of (1*S*)-10-camphorsulfonyl chloride as chiral resolution reagent (**Scheme 2-4**).[18] The diastereomers of **13** was readily separated by column chromatography (SiO_2, toluene : AcOEt = 10 : 1). Then hydrolysis of the camphor ester gave (*S*)-**11** and (*R*)-**11** respectively in enantiopure form. The absolute configuration of compounds **11** has been determined by comparing with the reported ^{1}H NMR data of corresponding compound **13**.[18]



Scheme 2-4. Optical resolution of (*dl*)-**11**

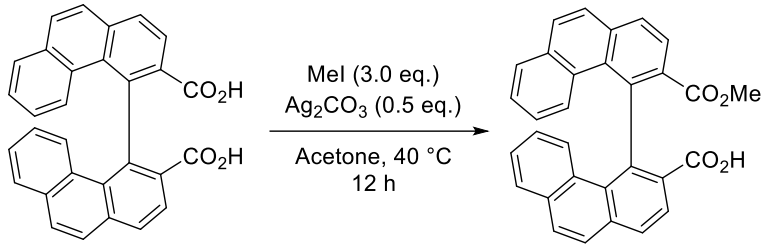
Related to synthesis of the dicarboxylic acid from the ditriflate, Manabe reported a practical synthetic method,[19] palladium-catalyzed external CO-free carbonylation reaction with phenyl formate as a CO surrogate. Claiming the prepared biphenanthryl ditriflate substrate **12**, diphenyl ester **14a** was synthesized. Then, desired dicarboxylic acid (*dl*)-**6a** was obtained by hydrolysis (**Scheme 2-5**).



Scheme 2-5. Optimization for synthesis of dicarboxylic acid **6a**

With dicarboxylic acid (*dl*)-**6a** in hand, selective monomethylation was easily achieved with controlled equivalence of MeI (3.0 equiv.) and Ag_2CO_3 (0.5 equiv.) developed by our group in

54% yield (**Scheme 2-6**),[12b] The same procedure afforded (*R*)-**4** and (*S*)-**4** in 40% and 43% yields, respectively.



6a
(*dl*)
(*R*)
(*S*)

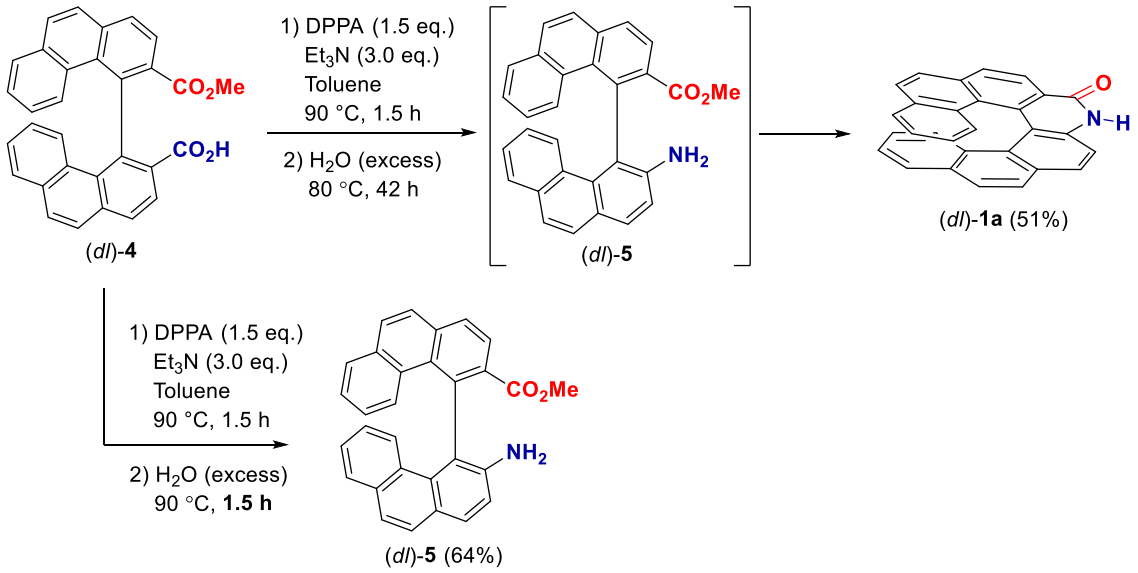
4
(*dl*) 54%
(*R*) 40%
(*S*) 43%

Scheme 2-6. Selective monomethylation of biphenanthryl dicarboxylic acids (*dl*)-, (*R*)-, and (*S*)-**6a**

2.2 Transformation to amide-functionalized [7]helicene-like molecules via lactamization

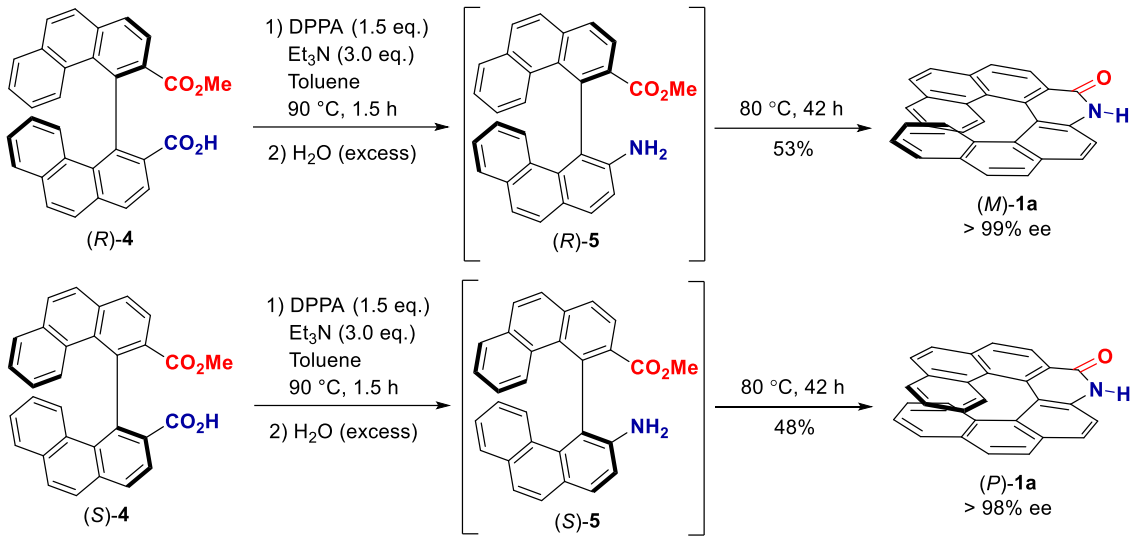
With monomethyl ester **4** in hand, the cyclization reaction via lactamization of *in-situ* generated δ-amino acids **5** prepared from the Curtius rearrangement was conducted (**Scheme 2-7**). Treatment of **4** with DPPA (1.5 equiv.) and Et_3N (3.0 equiv.) in toluene at 90 °C completed the Curtius rearrangement. Subsequently, H_2O was added to hydrolyze the isocyanate intermediate to furnish the intermediate **5**. And finally the target amide-functionalized helicene-like molecule **1a** was obtained after further hearting and stirring for 42 hours in 51% yield.

In order to confirm intermediate **5**, the reaction of (*dl*)-**4** was stopped in 1.5 hours after adding H_2O. Compound **5** was successfully isolated in 64% yield. This proved that the cyclization to **1a** proceeded through lactamization of **5**.



Scheme 2-7. Synthesis of (*dl*)-**1a** via lactamization and isolation of (*dl*)-**5**

Under the same Curtius rearrangement and lactamization procedure, the optically pure (*M*)- and (*P*)-amide-functionalized [7]helicene **1a** were obtained respectively (**Scheme 2-8**). It has been proved that there's no racemization taking place during the lactamization procedure based on the high ee value (> 99% ee for (*M*)-**1a**; >98% ee for (*P*)-**1a**) of each isomer of resulted **1a**. The specific rotation of (*M*)-**1a** was also measured to show large value as described in **Chapter 4** ($[\alpha]_D^{20}$ = -1336, c = 0.01, $CHCl_3$).



Scheme 2-8. Synthesis of optically pure **1a** via lactamization

2.3 The X-Ray analysis of racemic mixture of amide-functionalized [7]helicene-like molecule

An X-Ray diffraction analysis of racemic helicene-like molecule **1a** has been conducted. Although significant disorder over two different geometries of the molecules was observed as shown in **Figure 2-1(A)**, the helicene-like structure of **1a** was clearly confirmed. To make the discussion simple, one of the disordered structure was extracted and depicted in **Figure 2-1(B)**.

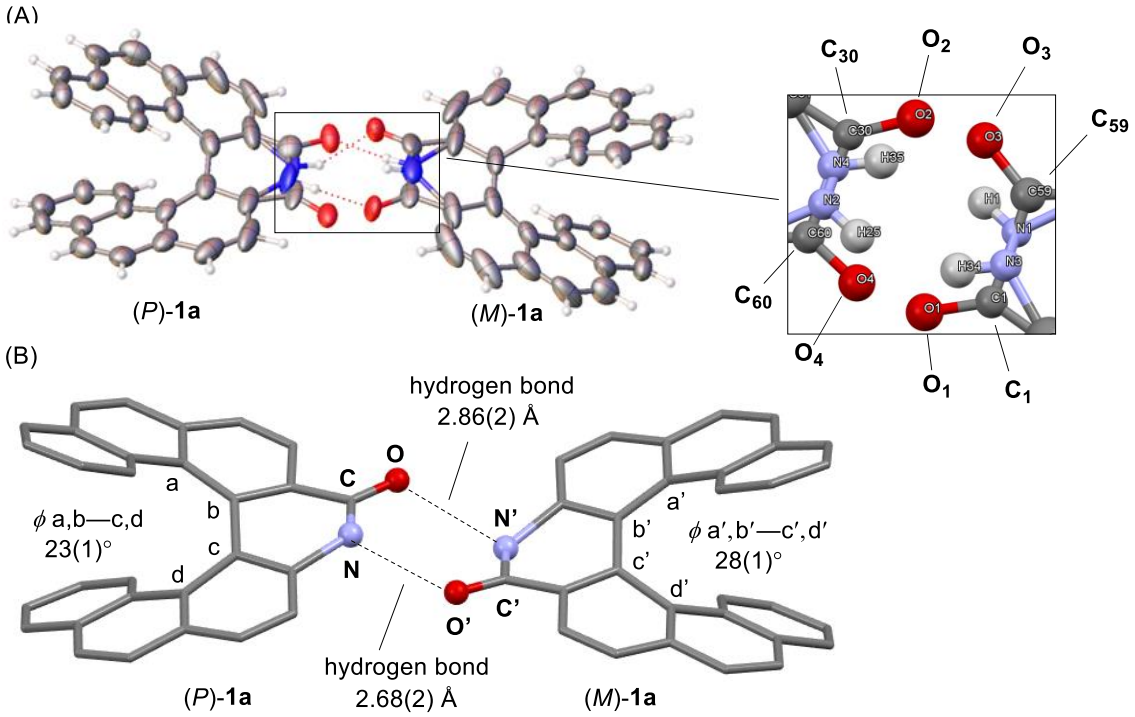


Figure 2-1. The crystal structure of (*dl*)-**1a**. (A) The disordered structure of associated pair of (*P*)- and (*M*)-**1a** through hydrogen bonding. (B) One of the disordered structure.

In **Figure 2-1(B)**, it is clearly confirmed that **1a** revealed a typical helicene structure with a twisted π-system (ϕa,b–c,d: 23(1)° for the (*P*)-enantiomer and ϕa',b'–c',d': –28(1)° for the (*M*)-enantiomer) and an amide group as a constituent moiety of the molecular framework. It is worth noting that the amide group functions as a molecular recognition moiety that manifests in pairwise association between the (*P*)- and (*M*)-enantiomers via hydrogen-bonding interactions (O···N' = 2.86(2) Å; O'···N = 2.68(2) Å).

This paired complex furthermore forms alternatingly aligned *M, P, M, P* columnar packs (**Figure 2-2A, B**), in which each column is created by the π-π stacking of a homochiral enantiomer (**Figure 2-2C**). Generally, π-π stacking interaction plays an important role in the self-assembly behavior of helicenes. In our case, it is typically supported by short contacts between the π-faces

of a homochiral enantiomer such as (*P*)-**1** (e.g., 3.19(2) Å and 3.49(1) Å) (**Figure 2-2C**), acting as one of the foundational driving forces toward aggregations.

Thus, along *a* axis, in a lengthwise way of the packing form, the single enantiomer aggregates vertically based on regular π-π stacking interactions to give the columnar packing constructed by homo chiral molecules. Rarely, along *b* axis, in a crosswise way, each homochiral column is connected horizontally by hydrogen bonding interactions between the amide groups in pairwise enantiomers, leading to an uncommon aggregation style. Hydrogen bonding functionalized packing structure with a particular width makes the racemic mixture of amide-functionalized helicene-like molecule **1a** to form a wider and larger molecular network which is different from usual single columnar aggregations of most helicenes.

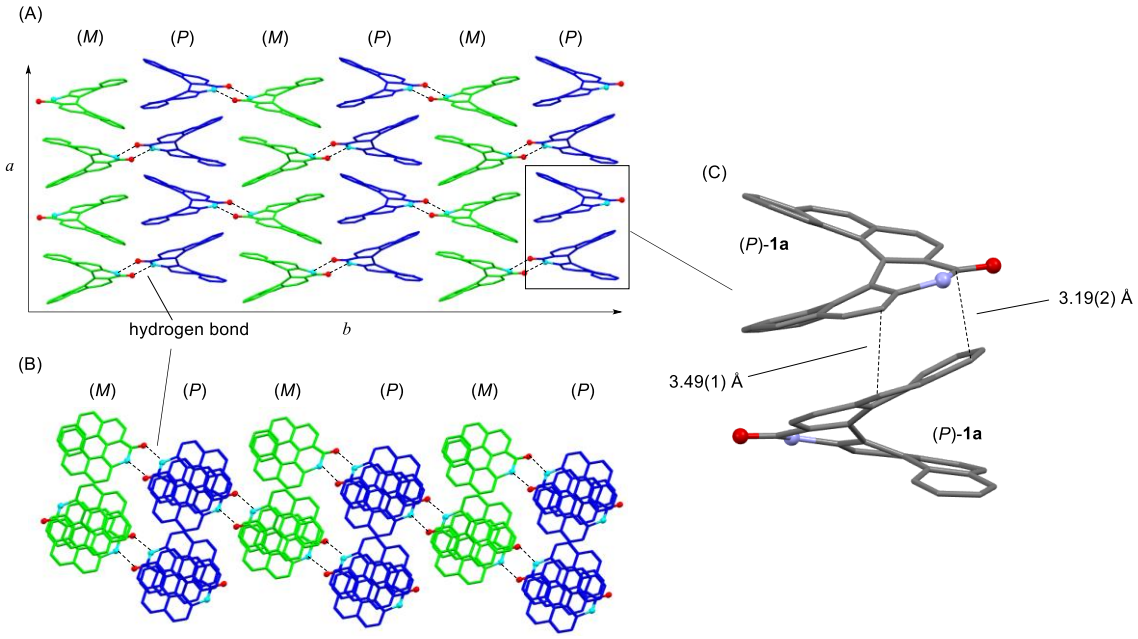


Figure 2-2. The packing diagram of (*dl*)-**1a**

The formation of homochiral or heterochiral dimers of helicene compounds have been studied by Yamaguchi and Wùrthner.[20] The [4]helicene (**Figure 2-3**) dimers might be in an alternating-orientation arrangement (*anti*) or a same-orientation arrangement (*syn*), especially that the *syn*-homochiral dimer is the most stable form (**Figure 2-3**). With regard to chiral recognition phenomenon in noncovalent bonding interactions (π-π stacking interaction in helicene case), the summary was also provided by Prof. Yamaguchi's study: The interactions between helical molecules show a tendency for pairs of the same configuration of the helicenes to form more stable complexes than pairs of enantiomeric helicenes. There was also a finding that in π-π

stacking dimerization of perylene bisimides (PBIs) with π-core, chiral self-recognition (*PP* and *MM* homodimer formation) prevails over self-discrimination (*PM* heterodimer formation).

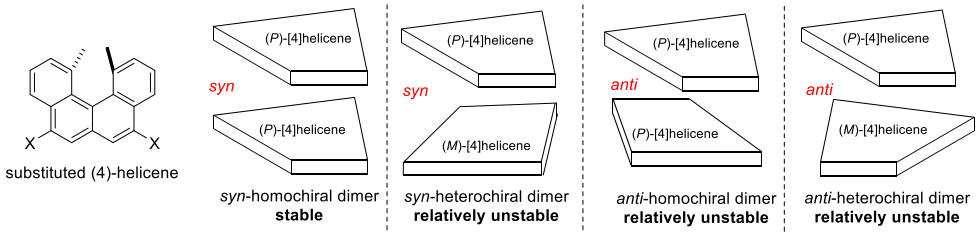


Figure 2-3. *Syn*- and *anti*-dimer aggregation of helicenes with flexible π-core

However, the model used by Prof. Yamaguchi is basically [4]helicenes without large steric repulsion at terminal rings. In the case of **1a** which is much sterically hindered at terminal part, the situation of π-π stacking interactions and aggregation behavior is totally different as discussed below.

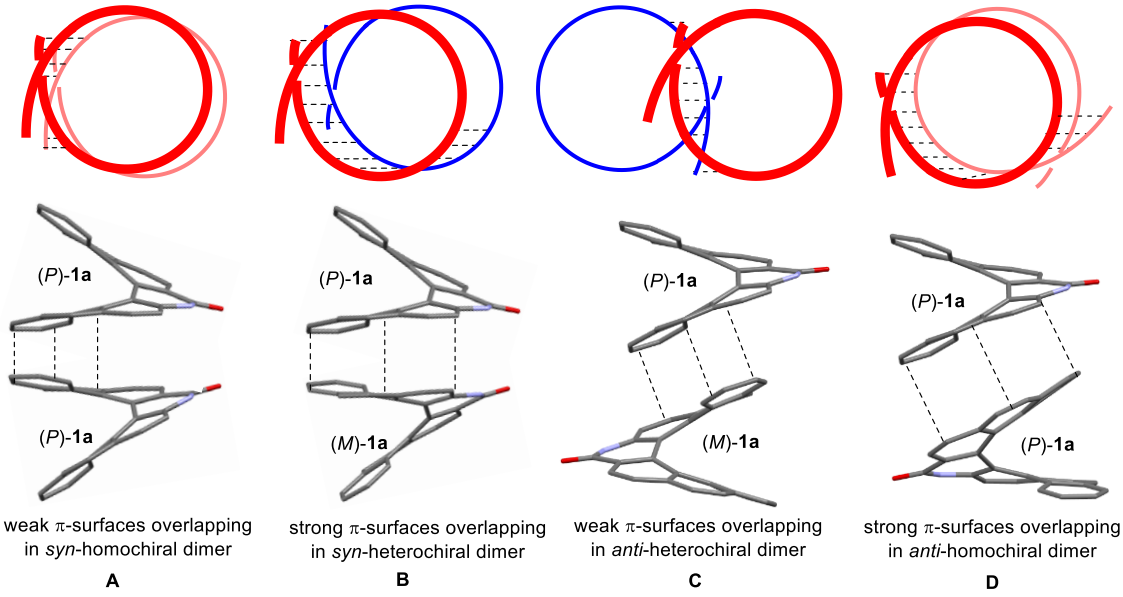


Figure 2-4. π-Overlapping analysis of *syn*- and *anti*-dimers of **1a** ((*P*)-**1a** red; (*M*)-**1a** blue)

***Syn*-dimer form:**

With a sterically hindered terminal part, the π overlapping area of *syn*-homochiral dimer of **1a** is less tight. Since the directions of radians are opposite between the close two π-faces, the overlapping is worst in *syn*-homochiral dimer (**Figure 2-4A**). In *syn*-heterochiral dimer form, the overlapping of the close two π-surfaces is strong (**Figure 2-4B**). However, in this form, only ordinary columnar packing along *a* axis (lengthwise way) is formed by the paired complexed

dimers with associated (*P*)- and (*M*)-enantiomers by hydrogen bonds at amide groups. Since *syn*-dimers are formed, amide groups will be located tightly in the center of each packing column, failing to align molecules in *b* axis (crosswise way). Therefore, it's difficult for *syn*-heterochiral dimers to form aggregation net. In my opinion, the separated columnar packing form should be less stable than the staggered combined net construction as shown in **Figure 2-2** (formed by *anti*-homochiral dimers) because of weaker π-π stacking interactions in separated column form. Further powerful evidences or special-purpose calculation are needed to prove the idea.

***Anti*-dimer form:**

In *anti*-heterochiral dimer form, between the close two twisted π surfaces, the directions of radians are also opposite. Thus, a relatively weak π overlapping extent is formed. The stability of *anti*-heterochiral dimer is still relatively low (**Figure 2-4C**). Finally, in *anti*-homochiral dimer, the two directions of radians in close π-faces are the same, leading to a large π overlapping area. At the same time, because of *anti*-dimer formation, they can further be connected by hydrogen bonds along *b* axis (crosswise way) to form an aggregation net (**Figure 2-2**). Thus, the highest stability is formed (**Figure 2-4D**).

In conclusion, *anti*-homochiral dimer arrangement is the best aggregation way.

The similar molecular assembly through hydrogen-bonding interaction has also been reported by Branda with amide-functionalized helicene bearing amide groups at the ends of the twisted backbone (**Figure 2-5A**).[7d] **Figure 2-5C** shows the packing diagrams. In these molecular assembly, there's a diastereoselective recognition process and only homochiral dimers where the acetyl groups exist exclusively in a *cis*-relationship appear in the crystal. Homochiral dimers arrange into offset racemic columns with face to face π-stacking interactions.

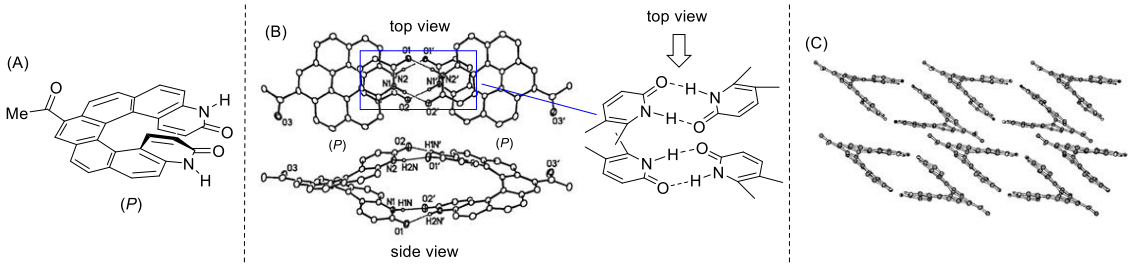


Figure 2-5. (A) Structure of acetyl group and amide-functionalized [7]helicene; (B) Side and up views of the X-Ray diagram of one of the enantiomerically pure hydrogen-bonded dimers (N···O distance of 2.740 and 2.829 Å); (C) Packing diagram (an average distance of 3.64 Å) (see ref. 7d)

Our X-Ray results and this reported observation indicated that molecular assembling property was considered as a typical feature of amide-functionalized helicenes and helicene-like molecules.

Furthermore, the columnar assemblies of helicene have been recognized to be the source of unusual optical properties in helicene-type materials as well as to be a key for potential applications in material chemistry. Especially, one-dimensional stacked chiral columnar aggregations of helicens are particularly attractive due to their unique chiroptical properties in the crystalline state.[4a,4b,4f]

The helicenebisquinone derivative (**Figure 2-6A**)[4b] were reported to form one-dimensional columnar aggregates with the aid of long alkyl side chains. The donor-acceptor interactions between the electron-rich inner rings of one molecule and the electron-poor outer rings of another might stabilize a columnar stack. This aggregate might contribute to the application of electro-optical functional material for helicenebisquinone molecules.

The use of dipole-dipole interactions with inherent π-π stacking interactions in helicenes can also produce a one-dimensional columnar arrangement. One of the examples is the columnar aggregation of λ^5-Phospha [7]helicene with one-way chirality (**Figure 2-6B**).[7c] The dipole moment vectors that are perpendicular to the helical axis compensate with each other by the two interacting molecules, while in the orientation of being parallel to the helical axis, the vectors are aligned in one column. The most notable is that each column has a single enantiomer of either (*P*) or (*M*) in the packing of racemate. Other example was found in coumarin-fused [6]helicene (**Figure 2-6C**).[7a] The packing structure of enantiopure (*M*)-coumarin-fused helicene in the single crystals exhibits a one-dimensionally stacked columnar alignment resulted from antiparallel face-to-tail π-π stacking interactions (**Figure 2-6C**). In the helical axis, the dipole moment vectors compensate for each and the vectors which are parallel to the helical axis are aligned into one column.

The one-dimensionally stacked columnar organization was also found in carbo[5]helicene containing bromide substituted benzylmaleimide group (**Figure 2-6D**).[7b] The peripheral benzyl groups result in weak steric interactions that are responsible for the formation of columnar stacked arrangements by keeping less steric clash at terminal rings as well as the interaction between bromine and oxygen. The formation of (*P*)- and (*M*)-racemic dimers in its unit cell from the pair of bromine and oxygen leads to an alternating array of (*P*)- and (*M*)-columns.

In the author's amide-functionalized helicene-like molecule, the columnar packing was found to be caused from the interactions not only through the π-π interaction between the π-faces, which is well known for helicene molecular assembly, but also through the hydrogen-bonding interactions via the amide groups (**Figure 2-6E**). This indicated that the amide functional group modified at the outer sphere of the helicene and/or helicene-like molecules would also be a promising way to have these special packing modes. Foreseeable, our columnar, as well as row packing of racemic **1a** would thus represent an attractive starting point for potential applications in chiral organic materials.

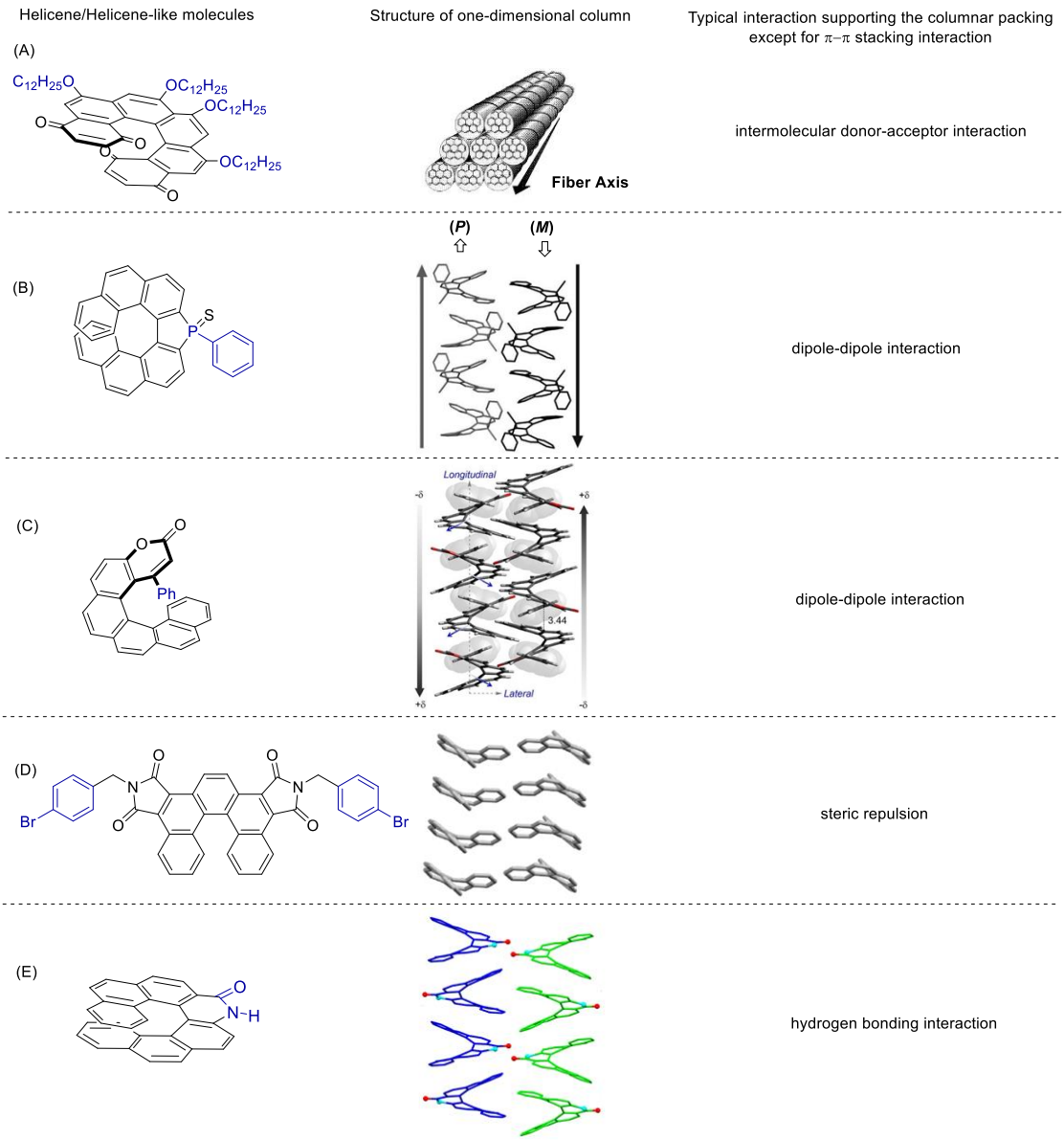


Figure 2-6. (A) Chemical structure of helicenebiquinone and schematic representation of columns of stacked helicene molecules as observed in solid bulk samples. (The side chains have been deleted for clarity, and the first helicenes are arbitrarily shown to be in the same rotational phase) (See ref. 4b) (B) Structure of λ^5 -phospha[7]helicene and columnar arrangement of (*P*) and (*M*) in the single-crystal structure of racemate. (The closest intermolecular contact between homochiral dimers is 3.35 Å.) (See ref.7c) (C) Structure of coumarin-fused helicene and one-dimensionally stacked packing structure of (*M*)-coumarin-fused helicene. (The closest intermolecular contact between homochiral dimers is 3.44 Å) (See ref. 7a) (D) Chemical structure of *p*-bromobenzylmaleimide functionalized carbo[5]helicene and the packing diagram. (The *p*-bromobenzylmaleimide groups and hydrogen atoms are omitted for clarity) (See ref.7b) (E) Packing diagram of **1a**

Furthermore, the discussion on the amide functionalized groups at the terminal rings exist as pyridin-2(1*H*)-one moiety or 2-hydroxypyridine would be important. However, the crystal structure of racemic **1a** is disordered over two positions actually, shown in **Figure 2-1(A)**. Two possible directions, located in the associated structure for each (*P*) or (*M*) enantiomer result in the mixed outcome which might bring some deviation into the crystal data. For example, the bond lengths of C–O bonds were obtained from the X-Ray analysis as following: C1–O1 (124 pm), C60–O4 (124 pm), C59–O3 (129 pm), C30–O2 (127 pm) (**Figure 2-1A**). Based on general experience, it should be predicted that the C–O bond in **1a** is double bond.[21] However, the data might not be reliable or accurate because of its severe disordered structure. Besides, In the case of 2-pyridone, oxo- form **B** mainly exists in both weakly polar solvent (e.g. $CHCl_3$) or polar solvent (e.g. DMSO) (**Figure 2-7**).[21] However, the substituents show large effects on the equilibrium. There's no study for the amide-[7]helicene so far. For the time being, detailed discussion on such tautomeric structures is quite difficult. Further study is needed to make sure the structural details. 2-pyridone form is used in DFT calculation of racemization barrier (**Chapter 4**).

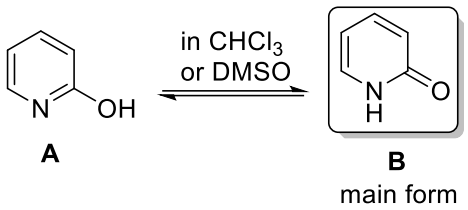
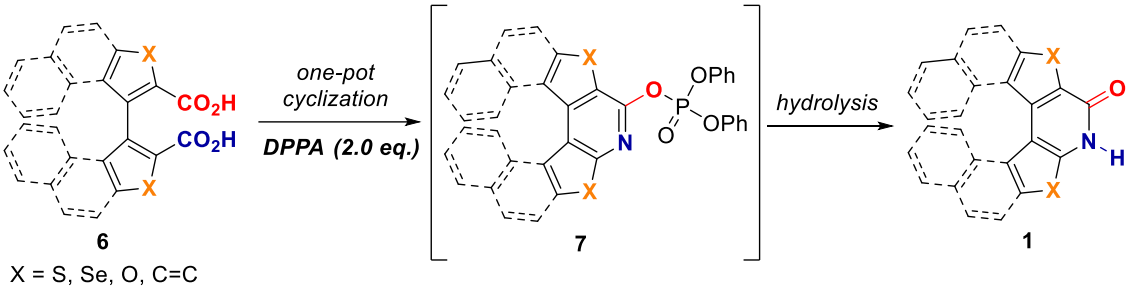


Figure 2-7. Tautomerization of 2-pyridone and 2-hydroxypyridine

In summary, since such special and interesting properties of **1a** shown by an X-Ray analysis have been discovered for the first time, our attentions were drawn even more to its unique molecular behaviors and added promising chiroptical properties of amide-functionalized [7]helicene-like molecules are expected to be checked. Thus, a demand of more efficient, easier and broader synthetic method towards various amide-functionalized [7]helicene-like molecules remains.

Chapter 3
One-pot access to amide-functionalized [7]helicene-like molecules and phenanthridinone derivatives from biaryl dicarboxylic acids

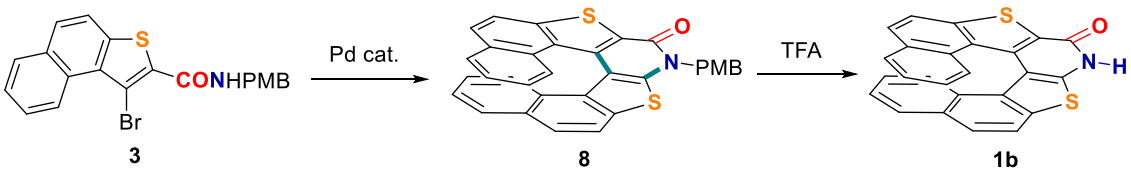
The author envisioned that direct cyclization from the dicarboxylic acid to helicene-like molecules as well as phenanthridinone derivatives would be possible, if the *in-situ* generated amino group undergoes cyclization with the alternative carboxy group under Curtius reaction conditions. By the survey of the reaction conditions, use of 2 equivalents of DPPA gave the desired product. These conditions were applicable to the biaryl dicarboxylic acid derivatives to furnish phenanthridinone derivatives bearing a variety of substituents.



This reaction conditions can be applicable to the preparation of optically active (*M*)- and (*P*)-amide-functionalized [7]helicene-like molecules including sulfur containing derivatives from the corresponding (*R*)- and (*S*)-biaryl dicarboxylic acids. During the survey of the conditions, the author noticed that the phosphate ester derivatives were generated prior to treatment of the basic conditions in the case of the substrates including chalcogen atoms. An X-Ray analysis of this phosphate ester derivatives indicated the helically twisted structures.

Chapter 4
Preparation of amide-functionalized helicene-like molecules by palladium-catalyzed domino reactions

In the above chapters, the key intramolecular amide bond formations were proceeded from the biaryl substrates prepared in prior to the cyclization. Further straightforward way to access amide-functionalized helicene-like molecules would be the domino process through the biaryl formation and the intramolecular amidation. The author envisioned that the Pd catalyzed domino process previously developed in our laboratory could be applicable to this strategy. After the survey of the reaction conditions, sulfur containing amide-functionalized [7]helicene-like molecule was obtained from the aryl bromide bearing PMB-amide group through subsequent C–C and C–N bond formations. The PMB-protecting group was readily deprotected to give the amide-functionalized helicene-like molecule.



The racemization barriers of these amide-functionalized helicene-like molecules were also investigated. Experimental and calculated racemization barriers of the prepared derivatives indicated that [7]helicene-like molecules have enough racemization barriers to be stable as optically active forms in ambient temperature, although [5]helicene-like derivatives showed low racemization barriers. The chiroptical properties, the optical rotations and the CD spectra of these amide-functionalized helicene-like molecules were also discussed.

Conclusion and perspective

In summary, two cyclization methods from biaryl substrates with retention of optical purity was developed to synthesize amide-functionalized [7]helicene-like molecule **1a**, which is optically pure and configurationally stable, showing a special self-assembly behavior caused by common π-π stacking interactions and unusual hydrogen bonding function together in helicene aggregation. The unique aggregation construction is quite promising in material chemistry, presenting special properties and applications.

Sulfur containing amide-functionalized [7]helicene-like molecule **1b** was synthesized through one-pot cyclization and a more direct palladium-catalyzed domino reaction with following deprotection of PMB group, which could be further modified chemically such as sufficient oxidation of sulfur atoms. The sterically hindered and electron withdrawing sulfonyl groups inserted in helical structure might not only improve the acidity of amide group but also function as new hydrogen bonding recognition site.

For newly prepared helicene-like molecules, the racemization barrier energies were revealed to show that amide-functionalized [7]helicene-like molecules are configurationally stable in umbient termperature. CD spectra might be used for deducing the absolute configuration of similar amide-functionalized helicene-like molecules.

Besides, a variety of biologically important phenantheridinone derivatives were prepared by direct one-pot cyclization, during which, increased stability of phosphate derivatives generated in the first stage was turn out to be originated from the combination of chalcogen bonding interaction and pnictogen bonding interaction.

The author expects that more efficient and applicable methodologies to prepare amide-functionalized helicene-like molecules could be developed and more interesting properties and applications of these molecules would be discovered.

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