CHEMICAL REVIEWS

REVIEW

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# Helicenes: Synthesis and Applications

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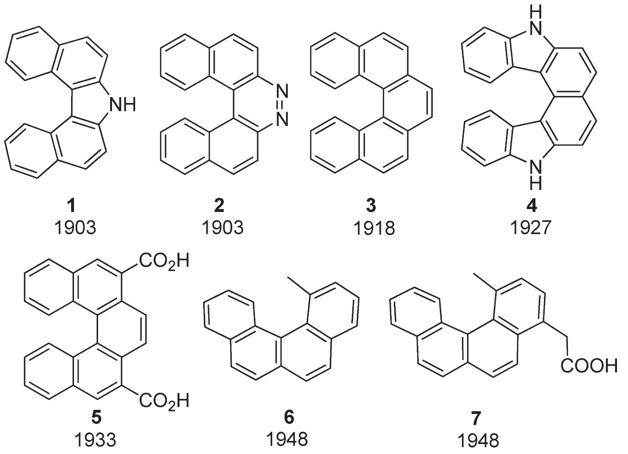
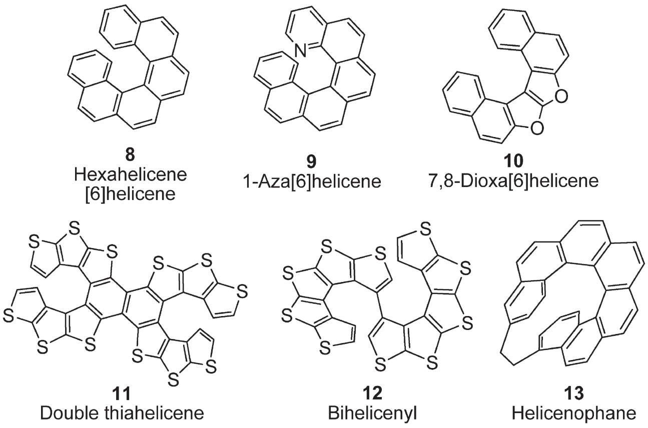


**1** 1903 **2** 1903 **3** 1918 **4** 1927

**5** 1933 **6** 1948 **7** 1948

**Figure 1.** Some helicenes prepared before 1950.



**8** Hexahelicene [6]helicene

**9** 1-Aza[6]helicene

**10** 7,8-Dioxa[6]helicene

**11** Double thiahelicene

**12** Bihelicenyl

**13** Helicenophane

**Figure 2.** Nomenclature of helicenes.

## 1. INTRODUCTION

Helicenes are polycyclic aromatic compounds with nonplanar screw-shaped skeletons formed by ortho-fused benzene or other aromatic rings.[1,2] The first helicenes **1** and **2** (Figure 1) were synthesized by Meisenheimer and Witte in 1903.[3] During the next few decades, little was discovered about the chemistry of helicenes, except for the synthesis of some different helicenes **3**−**7**.[4] After Newman and co-workers reported[5] the synthesis and resolution of hexahelicene in the 1950s, however, the study of the chemistry of helicenes really took off. During the following 30 years, Wynberg,[1a,6] Martin,[1b,7] Laarhoven,[1c,8] and Katz[9] carried out pioneering studies of the synthesis, spectral properties, and structures of helicenes. In the 1990s, the Diels−Alder synthetic approach after Martin's photochemical methods brought another important breakthrough in the preparation of helicenes on a large scale,[10] and based on this approach, a large number of helicene derivatives have been synthesized.[11] Since the late 1990s, more and more new strategies for the synthesis of helicenes with good yields and enantioselectivities have been developed,[1i,j] especially by utilizing organometallic catalysts.[12] Moreover, with the help of the theoretical studies using a variety of methods,[1k,13] the properties of helicenes have also become much clearer.

In order to simplify the IUPAC nomenclature, Newman and Lednicer first introduced the name hexahelicene for phenanthro[3,4-*c*]phenanthrene in 1956.[5b] Adding a Greek prefix or using a number, *n*, in brackets [*n*] before the helicene name was also adopted: thus, pentahelicene = [5]helicene.[1b,d,5b] The prefix or number denotes the number of aromatic rings in the helical backbone. Carbohelicenes are composed solely of benzene rings in the backbone, while heterohelicenes contain at least one heteroatom in the screw skeleton.[1b] When the heteroaromatic rings are thiophenes, pyrroles or pyridines, or furans, they are named thia[*n*]helicenes, aza[*n*]helicenes, or oxa[*n*]helicenes, respectively. In some cases, they are named [*n*]heterohelicenes, hetero[*n*]helicenes, or [*n*]helicenes for simplicity and clarity. Double helicenes are composed of two fused screw structures, which may be the same or different.[1b,d] Bihelicenyls involve two distinct helicene moieties connected by a single bond,[1b,d] and helicenes in which two terminal rings are linked by an alkyl chain, like a clamped helicene, are called helicenophanes (Figure 2).[1d] All helicenes discussed in this review are named using Newman's nomenclature.

A number of reviews and monographs discussing the synthesis and properties of different helicenes have been published.[1c,i,j] Urbano reviewed nine methods for the preparation of carbohelicenes,[1i] while Collins et al. reported several methods for the synthesis of thiaheterohelicenes.[1j] In a recently published book, Stará and Starý provided a comprehensive review of the synthesis of carbohelicenes.[1t] Dumitrascu et al. described the synthesis of azahelicenes,[1r] and some photochemical approaches for the synthesis of helicenes have also been reviewed.[1o,s] However, to date there has been no comprehensive survey of the synthesis or, especially, applications of helicenes, which motivated us to prepare this review. We first briefly describe the general properties of helicenes and then discuss in detail the synthesis of (functionalized) helicenes and their applications. The literature from the 1900s to the early 2011 is covered. In order to provide a complete overview of the chemistry of helicenes, some material in earlier reviews is also included.

## 2. GENERAL PROPERTIES

The defining property of a helicene is its helical structure. Because of the steric hindrance of the terminal rings, helicenes can wind in opposite directions and have a $C_2$-symmetric axis, which is perpendicular to the helical axis (Figure 3a). This renders them chiral even though they have no asymmetric carbons or other chiral centers. On the basis of the helicity rule proposed by Cahn, Ingold, and Prelog in 1966, a left-handed helix is designated "minus" and denoted by *M* whereas a right-handed one is designated "plus" and denoted by *P* (Figure 3b).[14] Furthermore, according to the results of ORD and CD spectroscopy, there is a general relationship between the absolute configuration and the chirality: (*P*)-helicenes are dextrorotatory, while (*M*)-helicenes are levorotatory.[6d,15] As the number of fused rings increases, the helicene spirals up along the helical axis to form a cylindrical structure with a constant pitch (in both the inner and the outer helixes).[1d] For helicenes composed of six-membered aromatic rings, it takes nearly six rings to cover a complete 360° rotation of a screw,[15c] while four thiophene and three benzene units are required for thiahelicenes,[16] because of the smaller in-plane turn $(\theta)$ that the thiophene units contribute to the helical structure[6c] (Figure 3c). If other five-membered aromatic rings are incorporated into the skeleton, one complete 360° rotation also requires more rings.

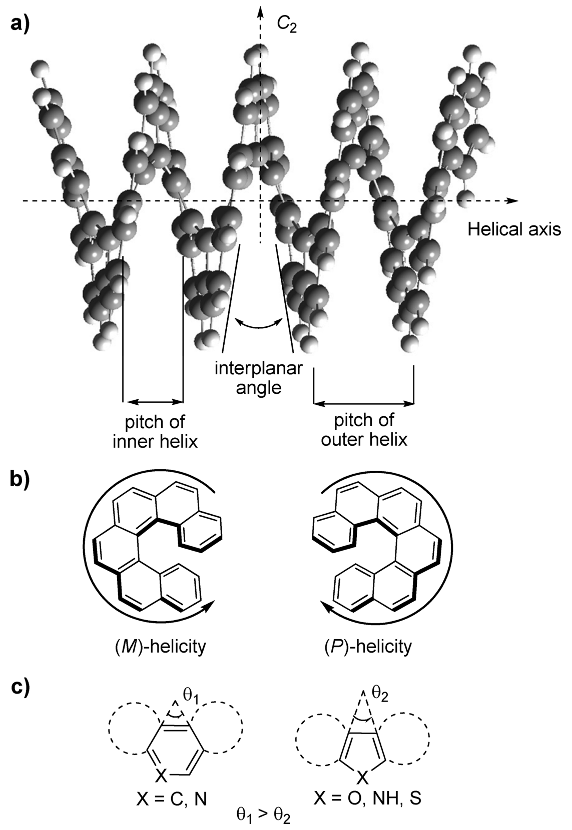


**Figure 3.** (a) Ball and stick model of [25]helicene, (b) schematic representation of helicity, and (c) comparison of the in-plane turn ($\theta$) of different rings.

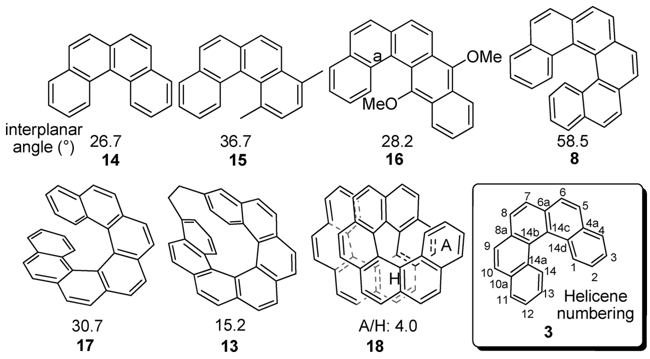


**Figure 4.** Some structural parameters of different helicenes and the helicene numbering scheme.

The nonplanar structure arises because the connections between the rings are twisted. The interplanar angles (or the dihedral angles) of the two terminal rings depend on the lengths of the helicenes and the substituents present. For example, the interplanar angles of carbohelicenes (Figure 4) increase as the helicenes are elongated from [4]helicene (26.7°) to [6]helicene (58.5°) but decrease with further elongation (for [11]helicene **18**,[17] the angle between the rings A and H is only 4.0°).[1c] Moreover, if the terminal rings are linked by a short alkyl chain such as in **13**, the angle also tends to be reduced.[18] According to the interplanar angles, a comparison of **14**[19] with **15**[19] and **16**[20] suggests that the extent of steric hindrance is Me > MeO > H. In addition, overlap of the rings as well as the van der Waals interactions between nearby groups have been demonstrated by observing shielding and deshielding effects in the $^{1}$H NMR spectra of these helicenes.[1b,c]

As a result of torsional strain, the bond lengths in the skeleton are different, with different C−C bonds having features of a single bond or a double bond. In comparison with the bond length of benzene (1.393 Å),[21] the average bond length of the C−C bonds in the inner helix is lengthened to about 1.430 Å while the average length of the ones on the periphery is shortened to about 1.360 Å.[1c,d] The bond *a* in **16** even elongated to 1.480 Å.[20] Surprisingly, numerous studies of the crystallographic structures of helicenes[6a,12b,15c−15e,16,18−20,22] have also always shown that there is a lack of $C_2$ symmetry, not only because of the bond lengths but also because of the torsional angles between the inner carbon atoms, although the atoms on the same ring are approximately coplanar.[1c] This is still not well understood.[22c] In **3**, the torsional angles C(14)−C(14a)−C(14b)−C(14c), C(14a)−C(14b)−C(14c)−C(14d), and C(14b)−C(14c)−C(14d)−C(1) are 33.5°, 8.1°, and 36.5°, respectively.[22m] This suggests that each of the arenes is distorted to a different extent. Furthermore, it has been variously reported that the torsional strain is accommodated by the central ring or shared by each ring of the backbone.[22n] However, different carbohelicenes have a nearly constant inner pitch of 3.20 Å, while the pitch of the outer helix varies with the substituents and lengths of the helicenes.[1c,d]

Compared with the corresponding phenacenes, helicenes show a greater departure from planarity. However, little loss of the local aromaticity has been found,[13m,q] showing that the $\sigma-\pi$ interactions do not significantly interfere with the $\pi$-electron delocalization[13e,23] and the two terminal rings of helicenes are the most aromatic.[13h] Moreover, helicene ions can be prepared by either chemical[24] or electrochemical[9e,25] methods. Interestingly, the antiaromaticity of the $4n\pi$ helicene dianion system, with paratropicity, might be quenched by its distorted structure.[26] In addition, a carbon−sulfur [7]helicene radical cation with a chiral structure was found to be configurationally stable even at room temperature.[25a] Furthermore, different computational and experimental studies have indicated that the transannular interaction between the two superimposed ends is unfavorable[13e,23] or that it can reduce the HOMO−LUMO gap via through-space delocalization.[9e] Thiaheterohelicenes have a smaller HOMO−LUMO gap than carbohelicenes, whereas carbon−sulfur helicenes have a larger gap than both by virtue of the lack of effective conjugation.[13s,27]

Helicenes, like other polycyclic aromatic compounds, are good $\pi$-donors and can form charge-transfer complexes with many $\pi$-acceptors;[5a,28] these have been employed for the optical resolution of helicenes with chiral $\pi$-acceptor reagents through an enthalpy-driven process. In addition, the $\pi-\pi$ interactions play an important role in determining both the properties[29] and the self-assembly behavior[30] of helicenes in either the solution or the solid state. Some other interactions in crystals, such as hydrogen bonding,[31] CH−$\pi$ interactions,[22t,v] S−S interactions,[22x] and H−H interactions,[13h] have also been reported. For some helicenes, recrystallization spontaneously affords homochiral conglomerates[32] or enantioenriched crystals,[6g,7b] which is indicative of a strong interaction between the homochiral helicenes, and allows optical resolution by crystal picking. Moreover, some unusual behavior of helicenes has been observed in confined environments such as micelles[28h,33] and vesicles.[34] In aqueous SDS micelles, 2-hydroxymethyl[5]thiaheterohelicene formed a 1:2 charge-transfer complex with TAPA. After sonication, a 1:1 complex with a reverse

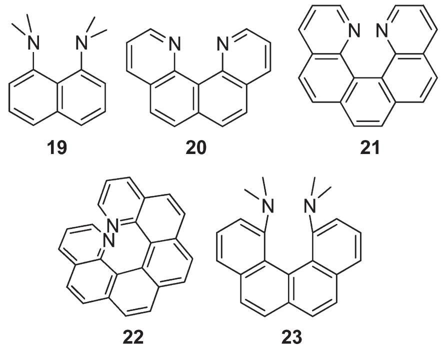


**Figure 5.** Some helical 'proton sponges'.

Cotton effect was observed.[28h] If the thiaheterohelicene was incorporated in chiral (L)-DMPC vesicles, the equilibrium of the transformation between (*P*)- and (*M*)-enantiomers was affected and an enantiomeric excess of *M* was observed according to the CD spectra.[34b]

Some helicenes display high 'proton sponge' basicity by forming linear N···H···N hydrogen bonds, which releases the steric strain (Figure 5).[35] On the basis of transprotonation experiments,[37] **20** ($\mathrm{p}K_\mathrm{a} \sim 12.8$) shows a stronger basicity than **19** ($\mathrm{p}K_\mathrm{a} \approx 12.1$)[36] while the basicity of **21** is 2 orders of magnitude smaller than that of **20**.[38] However, **22**, with a similar basicity to pyridine, did not show 'proton sponge' properties because the two nitrogen atoms are not able to form a strong linear hydrogen bond.[39] In the case of **23**, the steric strain is not released significantly after protonation and its basicity is also negligible.[40]

The solubility of helicenes is much higher than that of similar planar polycyclic aromatic systems, although some helicenes still suffer from low solubility.[41] Fortunately the solubility can be improved by introducing appropriate substituents—alkoxyl and alkyl groups have hitherto been found to be the most effective.[11b,h]

The racemization of helicenes is another intriguing property.[1b−d,6h,42] In an attempt to understand the racemization process, two transition states (TS) of pentahelicene have been proposed as shown in Figure 6.[13d,ah] In one TS, with $C_{2v}$ symmetry, the rings stretch outward but all the atoms are coplanar, while the other TS has $C_s$ symmetry with the terminal rings bending to the same side. The TS with $C_s$ symmetry has been adopted in most of the reported theoretical calculations.[13k,t,w,ah] These suggest that the structure of an unsubstituted pentahelicene in the ground state (GS) first twists into the nonchiral $C_s$-TS, and the subsequent transformation to (*P*)- or (*M*)-configuration with equal probability releases the torsional strain and the repulsion and results in racemization.

This suggests that fixing one or both of the terminal rings or introducing bulky substituents on the terminal rings are two practical methods of hindering the racemization by increasing the racemization barrier (even longer helicenes, like [9]helicene, $t_{1/2}$ = 123 min at 293.5 °C,[7d] undergo racemization via a more complicated process in which more than one TS might be involved[13t,43]). For example, the former can be achieved by forming metallocenes[24c] or by introducing two methyl groups at the 1,1′-positions of hexahelicene, in which case the half-life of racemization ($t_{1/2}$) is increased from 13.4 min at 221.7 °C[7c] to 444 min at 270 °C.[8d] In contrast, substitution at the 2,2′-positions of helicenes does not have a significant effect on the racemization.[15e] On the basis of this principle, introducing chiral auxiliaries by reaction at the 1- or 1′-position has become the most common strategy for optical resolution of helicenes by HPLC or column chromatography. However, if an aryl group is incorporated into the 1- or 1′-position, another method of racemization is feasible.[8f,13o] In comparison with 1-methyltetrahelicene, the rotation around the single bond between the two aryl units of 1-phenyltetrahelicene accelerated the racemization process.[8f] If the terminal rings of the helicene are connected by an alkyl chain, the rate of racemization is increased greatly.[44] Sometimes even the electronic effects of different substituents on the backbones may affect the racemization barrier.[13o,45]

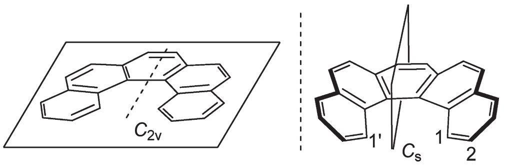
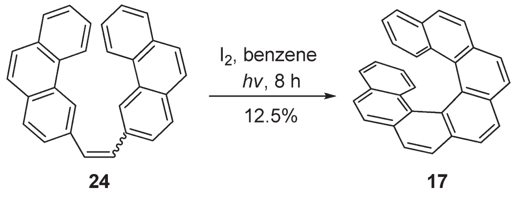
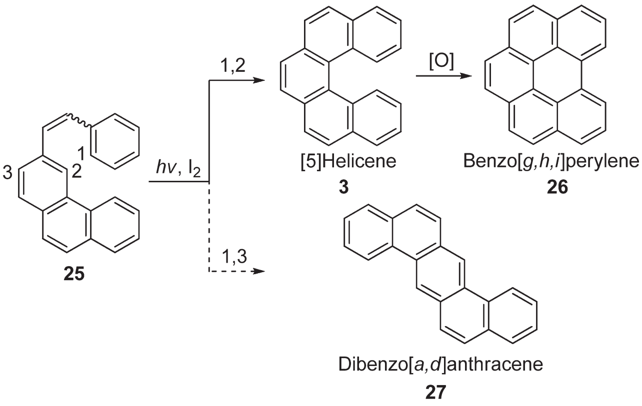


**Figure 6.** Two different transition states for racemization of pentahelicene **3**.

### Scheme 1



### Scheme 2

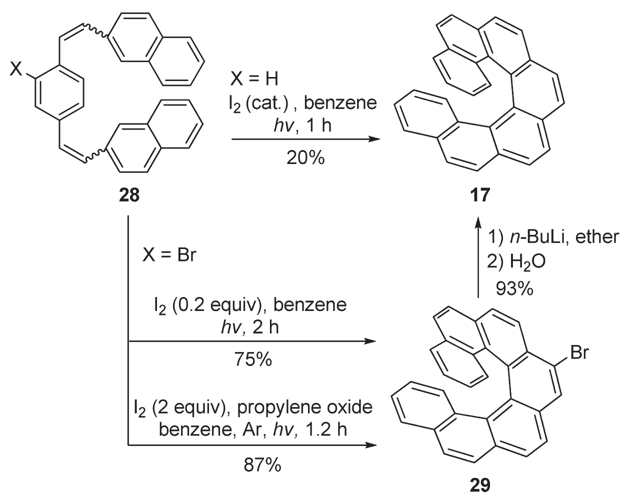


## 3. SYNTHESIS OF CARBOHELICENES

### 3.1. Photocyclization

In 1967, Martin and co-workers reported the first photoinduced synthesis of heptahelicene **17** (Scheme 1).[7a] Since then, photocyclization has become one of the most important methods for the synthesis of many helicene homologues (from [5]- to [14]helicene) and derivatives, because the stilbene-type precursors are easily prepared by Wittig olefination and the helicenes can be obtained in relatively few steps.[1a−d]

**Scheme 3**



Two aspects of the process need to be considered: (i) photocyclization can take place at either the 2- or the 3-position of the precursor **25**, for example, resulting in isomers which are sometimes difficult to separate (Scheme 2); (ii) the HI produced by the cyclization reaction might cause reduction of the double bond.[46] In some cases, further cyclization of the newly formed helicene has been found to occur.[47]

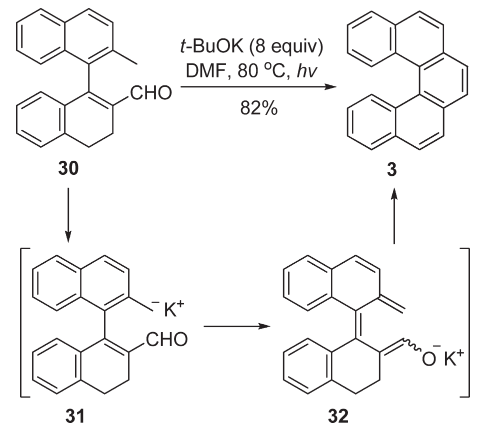
In order to control the regioselectivity, Katz and co-workers[9a,b] developed an efficient bromine-directed photocyclization method in which helicenes can be selectively produced in 75% yield (Scheme 3). Katz et al.[48] also developed another impressive strategy using excess propylene oxide plus a stoichiometric amount of iodine in an inert atmosphere, which not only enhances the yields greatly compared with the traditional conditions for the photocyclization of stilbenes but also prevents photoreduction or photooxidative side reactions of the double bonds. This strategy has become the standard procedure for the photocyclization of stilbenoid precursors. Moreover, the bromine atom in **29** can also be converted to other functional groups after Li/Br exchange.

In 2004, de Koning and co-workers[20] described another type of precursor for the preparation of [5]helicene **3** in good yield (Scheme 4). The mechanism is believed to involve abstraction of one proton of the methyl group by *t*-BuOK, followed by transformation into the enolate **32**, which undergoes photocyclization through isomerization.[49]

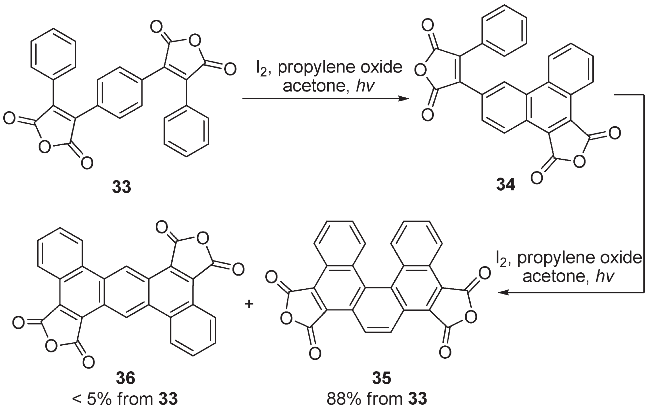
HMO studies of the selectivity of reaction sites have been carried out. For the appropriate atoms, *r* and *s*, in the excited-state cyclizations, Scholz, Mühlstädt, and Dietz proposed the free valence ($F^*_r$) and the localization energy ($L^*_{r,s}$) methods as a means of analysis.[50] Laarhoven and co-workers[51] demonstrated that (i) photodehydrocyclizations do not occur unless $\Sigma F^* > 1.0$, and (ii) other products may be formed if $\Delta\Sigma F^* < 0.1$ for different cyclization processes. In the absence of HMO calculations, a simple empirical rule to predict the major product is that the preferred route is the one that forms the largest number of the benzene rings in the structure.[52] Experimental studies with highly dilute solutions to avoid intermolecular dimerization, which resemble the systems studied theoretically, have been reported by Mattay and co-workers.[22l]

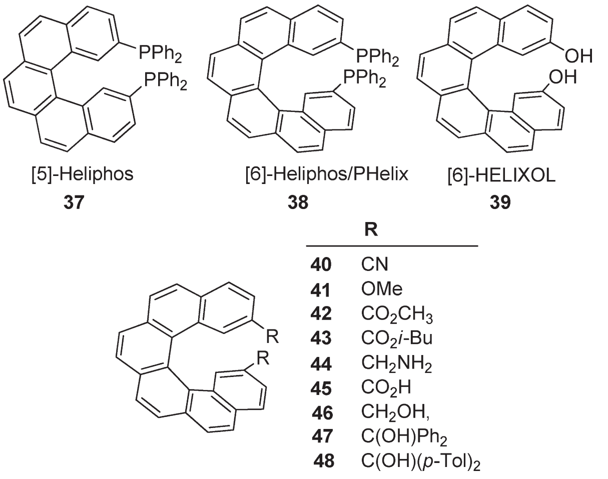
On the basis of this methodology, several helicene derivatives have been synthesized. As shown in Scheme 5, the photoreaction of 1,4-phenylene bis(phenylmaleic anhydride) **33** afforded **35** in 88% yield; the product is a potential monomer for polymerization.[22j] The first helical phosphane ligands Heliphos **37** and **38**, which have become important ligands in asymmetric catalysis, were prepared independently by Brunner's group[53] and

**Scheme 4**



**Scheme 5**





| | R |
|---|---|
| 40 | CN |
| 41 | OMe |
| 42 | $CO_2CH_3$ |
| 43 | $CO_2i$-Bu |
| 44 | $CH_2NH_2$ |
| 45 | $CO_2H$ |
| 46 | $CH_2OH$, |
| 47 | $C(OH)Ph_2$ |
| 48 | $C(OH)(p\text{-}Tol)_2$ |

**Figure 7.** Some 2,2′-disubstituted helicenes prepared by photocyclization.

### Table 1. Synthesis of Helicenes by Diels−Alder Reactions

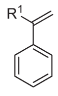
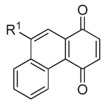
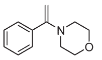
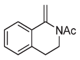
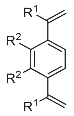
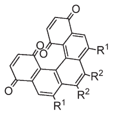
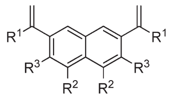
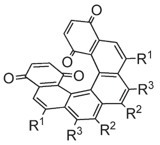
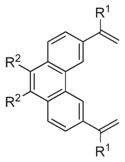
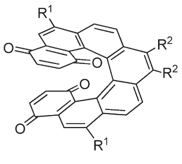
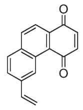
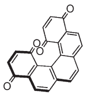
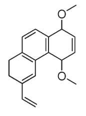
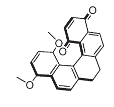
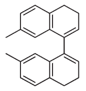
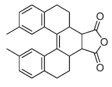
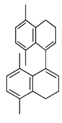
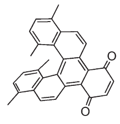
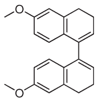
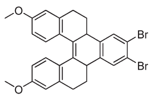
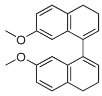
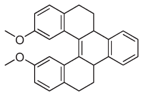
| Entry | Substrate[a] | Cond.[b] | Time (h) | Product[c] | Yield (%)[d] | ref |
|---|---|---|---|---|---|---|
| |  | | |  | | |
| | **49** | | | **50** | | |
| 1 | **a** $R^1$=H | **A** | 48 | **a** | 31 | 11a |
| 2 | **b** $R^1=OCH_3$ | **A** | 48 | **b** | 57 | 11a |
| 3 | **c** $R^1=O(CH_2)_2On$-Bu | **A** | 48 | **c** | 51 | 11a |
| 4 | **d** $R^1=SCH_3$ | **A** | 48 | **d** | 43 | 11a |
| 5 |  **e** | **A** | 24 | **NA** | / | 11a |
| 6 |  **f** | **A** | 2 | **NA** | / | 11a |
| |  | | |  | | |
| | **51** | | | **52** | | |
| 7 | **a** $R^1=R^2$=H | **B** | 33 | **a** | 17 | 10,11b |
| 8 | **b** $R^1$=H, $R^2=OCH_3$ | **B** | 54 | **b** | ≤17[e] | 11b |
| 9 | **c** $R^1$=H, $R^2=O(CH_2)_{1/2}$ | **B** | 66 | **c** | ≤13[e] | 11b |
| 10 | **d** $R^1$=H, $R^2=On$-$C_{12}H_{25}$ | **B** | 33 | **d** | 24 | 11b |
| 11 | **e** $R^1=On$-$C_{12}H_{25}$, $R^2$= H | **C** | 62 | **e** | 50 | 9c,11b |
| 12 | **f** $R^1$= OTIPS, $R^2$= H | **C** | 108 | **f** | 74 | 11b |
| |  | | |  | | |
| | **53** | | | **54** | | |
| 13 | **a** $R^1= R^2= R^3$=H | **B** | 12 | **a** | 6 | 9c,11b |
| 14 | **b** $R^1= R^2$=H, $R^3=OCH_3$ | **B** | 13.5 | **b** | ≤13[e] | 11b |
| 15 | **c** $R^1= R^2$=H, $R^3=On$-$C_{12}H_{25}$ | **B** | 21 | **c** | ≤11[e] | 11b |
| 16 | **d** $R^1=OCH_3$, $R^2= R^3$=H | **C** | 66 | **d** | 47 | 9c,11b |
| 17 | **e** $R^1=O(CH_2)_2On$-Bu, $R^2= R^3$=H | **C** | 65 | **e** | 45-47 | 9c,11b |
| 18 | **f** $R^1=On$-$C_{12}H_{25}$, $R^2= R^3$=H | **C** | 49 | **f** | 54 | 11b |
| 19 | **g** $R^1$=OTBDMS, $R^2= R^3$=H | **C** | 72 | **g** | 42 | 11b |
| 20 | **h** $R^1= R^3=On$-$C_{12}H_{25}$, $R^2$=H | **C** | 40 | **h** | 15 | 11b |
| 21 | **i** $R^1$=OTBDMS, $R^2$=OPiv, $R^3$=H | **D** | 22.5 | **i** | ≤16 | 11e |
| 22 | **j** $R^1= R^2$=OTIPS, $R^3$=H | **D** | 6.5 d | **j** | 40 | 64 |
| |  | | |  | | |
| | **55** | | | **56** | | |
| 23 | **a** $R^1$=OEt, $R^2=O(Ph_2C)_{1/2}$ | **D** | 48 | **a** | 10 | 11c |
| 24 | **b** $R^1$=OTIPS, $R^2=O(Ph_2C)_{1/2}$ | **D** | 63 | **b** | 22 | 11c |
| 25 | **c** $R^1$=OTIPS, $R^2$=OTBDMS | **D** | 86 | **c** | 37 | 11c |
| 26 | **d** $R^1$=OTIPS, $R^2$=OMe | **D** | 72 | **d** | 23 | 11g |
| 27 | **e** $R^1$=OTIPS, $R^2=On$-$C_{12}H_{25}$ | **D** | 96 | **e** | 20 | 11g |
| 28 |  | **E** | 7 d |  | 22 (ee 80%) | 11d |
| | **57** | | | (*M*)-**52a** | | |

**Table 1. Continued**

| Entry | Substrate[a] | Cond.[b] | Time (h) | Product[c] | Yield (%)[d] | ref |
|---|---|---|---|---|---|---|
| 29 | <br>**58** | **F** | 18 | <br>(*P*)-**59** | 72 (ee 72%) | 65e |
| 30 | <br>**60** | **G** | 3 | <br>**61** | 73 | 4c |
| 31 | <br>**62** | **H** | 98 | <br>**63** | 62 | 66b |
| 32 | <br>**64** | **I** | 6 | <br>**65** | 26 | 68 |
| 33 | <br>**66** | **J** | 6 | <br>**67** | 71 | 69 |

[a] TIPS = (*i*-Pr)$_3$Si, TBDMS = *t*-BuMe$_2$Si, Piv = pivaloyl. [b] Conditions: **A**, 6−6.5 equiv of *p*-benzoquinone, toluene, reflux; **B**, 12−14 equiv of *p*-benzoquinone, toluene, reflux, $CCl_3CO_2H$, $N_2$ atmosphere; **C**, 12−14 equiv of *p*-benzoquinone, toluene, reflux, basic alumina; **D**, 15−20 equiv of *p*-benzoquinone, toluene, reflux, $N_2$ (or Ar) atmosphere; **E**, 3 equiv of (*SS*)-(2-*p*-tolylsulfinyl)-1,4-benzoquinone, 4 kbar, $CH_2Cl_2$; **F**, 3 equiv of (*S*,*S*)-(2-*p*-tolylsulfinyl)-1,4-benzoquinone, $CH_2Cl_2$, 20 °C; **G**: 3 equiv of maleic anhydride, xylene, reflux; **H**: 10 equiv of *p*-benzoquinone, toluene, reflux; **I**: 1.15 equiv of 1,2,4,5-tetrabromobenzene, Ar atmosphere, 1.59 equiv of *t*-BuLi, toluene, −20 °C; **J**: 2 equiv of 2-carboxybenzenediazonium chloride, $(CH_2Cl)_2$, 2-methyloxirane, reflux. [c] Only one enantiomer is shown; NA = not available. [d] Isolated. [e] Not fully purified.

Reetz's group[54] in 1997 (Figure 7). Four years later, Reetz and Sostmann reported another important ligand HELIXOL **39**.[55] Similarly, other helicene derivatives **40**−**48** have also been synthesized as shown in Figure 7.[22l,p,v,56]

Photocyclization is difficult to employ in large-scale preparation and also lacks tolerance to some functional groups, such as $NH_2$ and $NO_2$, which accelerate intersystem crossing and prevent cyclization.[46b,57] However, it is still a convenient method for the synthesis of a variety of helicenes due to the easy preparation of the stilbenoid precursors and mild reaction conditions.

## 3.2. Diels−Alder Reactions

Since the Diels−Alder reaction was established in 1928,[58] it has become one of the most useful tools in organic synthesis.[59] The breakthrough in large-scale preparation of helicenes was made by the pioneering work of Katz and Liu in 1990 utilizing this methodology (Table 1, entry 7).[10] They obtained [5]helicene **52a** with two quinone moieties in reasonable yield and gram-scale quantities by the Diels−Alder reaction between *p*-divinylbenzene and *p*-benzoquinone. Moreover, the presence of four carbonyl groups in the resulting [5]helicene allows for convenient functionalization of the terminal rings.[10]

According to FMO theory, the presence of strongly electron-donating substituents on the diene[60] and electron-withdrawing groups on the dienophile[61] should result in more rapid and efficient Diels−Alder reactions reactions.[62] However, because the cycloaddition reactions are sensitive to steric effects, bulky substituents at the termini of the dienes hinder the approach of the dienophiles and thus decrease the rate of reactions.[63] Therefore, dienes with substituents at the *β*-carbon have become the best choice for the synthesis of helicenes since dienophiles such as *p*-benzoquinone, maleic anhydride, and benzyne can be easily obtained. This methodology has been well established by Katz,[9c,11a−11c,11e,11g,64] Carreño and Urbano,[11d,45,65] and their co-workers. Electron-donating substituents have been introduced in different sites of dienes, and a variety of helicenes have been synthesized by Diels−Alder reactions.

As shown in Table 1, dienes with electron-donating groups (entries 2−4, 11−12, 16−19) gave much higher yields of products than unsubstituted dienes (entries 1, 7, 13). However, in some cases, no reaction occurred when the substituents were, for example, amino and amide groups (entries 5 and 6). The presence of basic alumina was generally found to be more effective than trichloroacetic acid (entries 7−20). Although the substituents on the benzene rings of the precursors had little effect on the reaction yields (entries 24−27), they are of great importance in both the subsequent functionalization of the helicenes and in determining their solubility.[11b,c,f,66] By utilizing a chiral benzoquinone, Carreño, Urbano, and co-workers reported the asymmetric synthesis of helicenes with good ee values (entries 28 and 29).[11d,65e]

Besides vinyl-substituted dienes, 3,3′,4,4′-tetrahydro-1,1′-binaphthyl-derived precursors are another type of widely used substrate. This kind of Diels−Alder reaction was first employed by Newman in the preparation of coronene in 1940, where disubstituted [5]helicenes were produced in an overall yield of about 38% (entry 30).[4c] Similarly, Minuti et al. reported the synthesis of [5]helicene **63** in 62% yield from the reaction between diene **62** and *p*-benzoquinone in the presence of a Pd/C catalyst (entry 31).[67] This type of tetrahydrobinaphthyl precursor can also react with benzyne to give helicenes in situ. In 2003, Mandal and Sooksimuang[68] described a route utilizing benzyne obtained by treatment of 1,2,4,5-tetrabromobenzene with *t*-BuLi (entry 32), and Chen et al.[69] recently reported a new and convenient method for the synthesis of helicenes in good yields by utilizing 2-carboxybenzenediazonium chloride as the precursor of benzyne (entry 33).

The Diels−Alder reaction is an effective method to construct helical frameworks by virtue of its ability to be used in large-scale synthesis and its moderate to good yields. Moreover, the functional groups on the dienes and dienophiles can be utilized for other purposes such as enhancing the solubility, optical resolution, and modifying the electronic properties. However, since the presence of electron-donating functional groups in the diene is a prerequisite, the scope of the transformation remains limited and little help is provided in the direct C−H functionalization of the helical backbone.

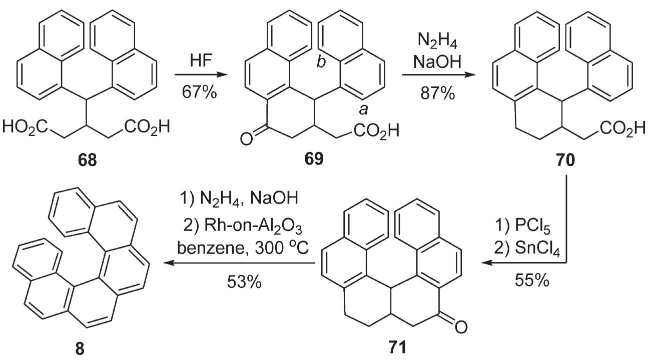
### 3.3. Friedel−Crafts-Type Reactions

The synthesis of 1,12-dimethylbenzo[*c*]phanthrene and hexahelicene by double Friedel−Crafts acylation was first reported by Newman and co-workers.[5b,70] As shown in Scheme 6, the ketoacid **69** prepared by cyclization of malonic acid derivative **68** in the presence of anhydrous hydrogen fluoride was reduced to the carboxylic acid **70** using the Huang−Minlon procedure, and subsequent acylation was accomplished by stannic chloride. After reduction of the ketone and a hydrogen transfer reaction over rhodium-on-alumina, the final hexahelicene **8** was obtained in moderate yield. Because the structure bearing the keto function is more rigid than that with the methylene group, reduction of the ketoacid, thus lowering the energy of the transition state, is essential in order to avoid the second acylation occurring at the *b* position rather than the *a* position.

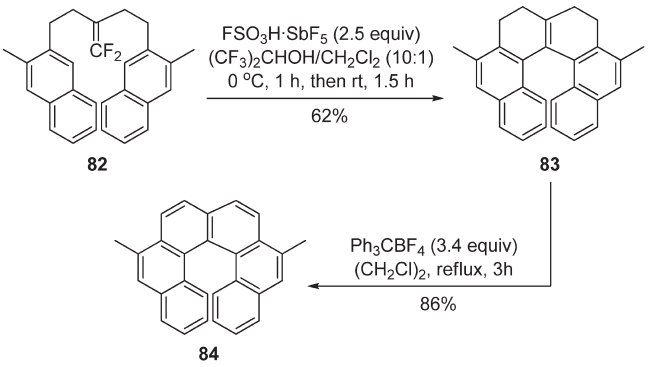
In 1996, Yamaguchi and co-workers reported a similar procedure to prepare 1,12-disubstituted [4]helicenes **81a**−**c** (Scheme 7).[71] Compared with Newman's synthesis, Yamaguchi's synthesis used the R substituents as blocking groups which not only directed the acylation to occur at the specific position but also slowed down the rate of racemization. A new method was adopted to convert ketones **80a**−**c** to [4]helicenes **81a**−**c** with higher yields and simpler experimental procedures than the one in Scheme 6. Thus, after Friedel−Crafts acylation, the diketones **80a**−**c** were treated with $Me_3SiCN$, $POCl_3$, and hydrochloric acid to give the dinitrile, which underwent hydrolysis under basic conditions.[72] Then, after acidification, different 5,8-dicarboxylic acids could be obtained, which could be optically resolved by forming diastereoisomer camphorsultam derivatives or recrystallization with quinine.[71]

Another Friedel−Crafts-type sequence was described by Ichikawa and co-workers (Scheme 8).[73] The presence of two ortho-methyl groups in **82** is important to facilitate the domino cyclization. They not only direct the reaction to form a helical structure but also enhance the nucleophilicity of the aromatic moieties. With the help of magic acid and $Ph_3CBF_4$, double ring closure and dehydrogenation proceeded efficiently, giving

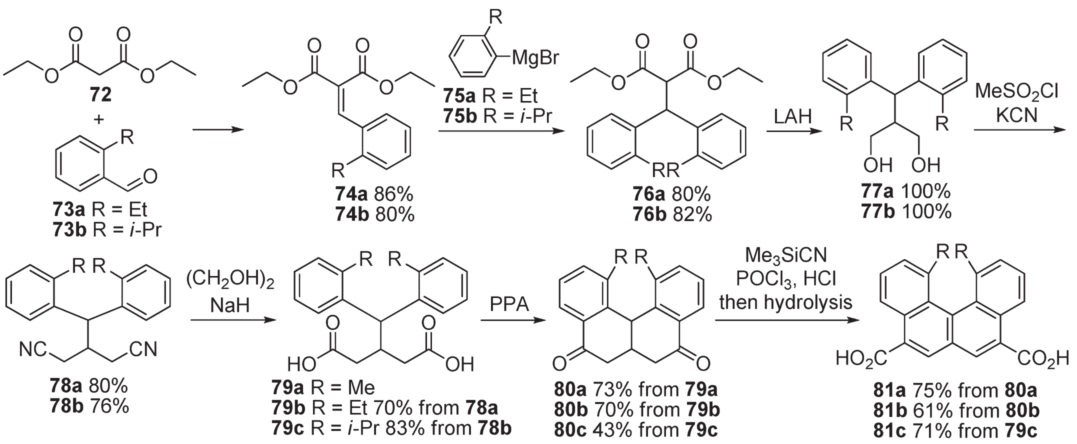
**Scheme 6**



**Scheme 8**



**Scheme 7**



6,11-dimethyl[6]helicene **84** in good yield. On the basis of this route, different helicenes can be conveniently synthesized by varying the aryl groups.

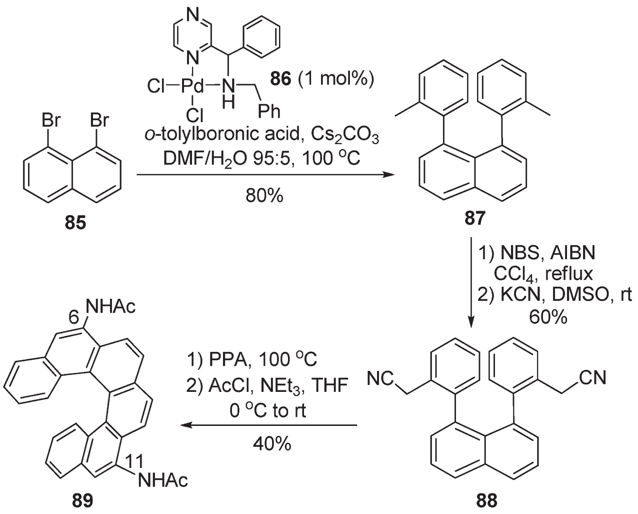
Recently, Gaucher and co-workers reported the synthesis of an unusual 6,11-diamino-[6]helicene via a Friedel−Crafts-type reaction.[74] As shown in Scheme 9, diarylnaphthalene **87** was obtained by Suzuki−Miyaura coupling between 1,8-dibromonaphthalene **85** and *o*-tolylboronic acid followed by bromination and cyanation to afford the dinitrile **88**. The subsequent double cyclization took place in the presence of PPA and AcCl, giving helicene **89** with two amino substituents at the C(6) and C(11) positions in 40% yield.

As shown above, these transformations have the following features: (i) two benzene rings are constructed in one step (except in the first example) in moderate to good yields; (ii) to form the helical frameworks, functional blocking groups are needed to direct the cyclization; and (iii) polar unsaturated bonds, including carboxyl, carbonyl, and cyano groups, should be incorporated in the precursors. However, this strategy is not so useful in practice because methods for the preparation of Friedel−Crafts-type precursors are limited and only symmetric helicenes have been synthesized so far by this methodology.

## 3.4. Metal-Catalyzed Cyclizations

**3.4.1. Pd-Catalyzed Coupling Reactions.** Several routes for the synthesis of helicenes by Pd-catalyzed coupling reactions have been reported.[75] A double C−H arylation reaction was employed in the synthesis of [5]- and [6]helicenes **91**−**92** in moderate to good yields under the optimized conditions (with $Ag_2CO_3$ as the additive, $PCy_3 \cdot HBF_4$ as the ligand) (Scheme 10).[75a] This approach has a good tolerance for the presence of electron-withdrawing substituents at the 3- and 12-positions, and two methoxy groups are required to direct the cyclization reactions to afford the helical framework. Unfortunately, [7]helicene could not be prepared by this method. Using 2,2′-dibromo-1,1′-binaphthyl, Scott and Xue reported the use of a double Stille coupling to prepare benzo-[5]helicene **95** in good yield (Scheme 11).[75b] Another annulation with *vic*-bis(pinacolatoboryl)alkenes via a double Suzuki−Miyaura coupling introducing two phenyl groups at the 7- and 8-positions of [5]helicene **97** was described by Shimizu and co-workers (Scheme 12).[75c] Although these three methods are convenient and the precursors can be easily obtained, the products are difficult to functionalize further and the synthesis is limited to [5]- and [6]helicenes.

**Scheme 9**

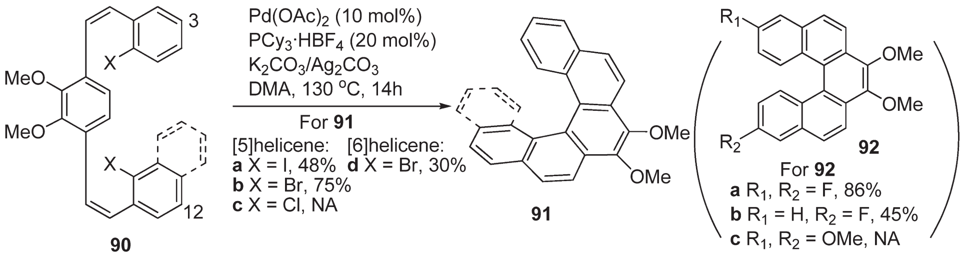


**3.4.2. Ring-Closing Metathesis.** In 2006, Collins and coworkers reported the synthesis of helicenes in 78−93% yield by the ring-closing olefin metathesis method (Scheme 13).[76] Two different routes, *a* and *b*, were utilized. Route *a* is very fast (24 min) but requires a high temperature (100 °C) which can result in pyrolysis; route *b* occurs under mild conditions (40 °C), accommodating the presence of sensitive functional groups, but requires a longer time (24 h). From readily modified 1,1′-binaphthyl framework, this method—with good tolerance and high efficiency—was found to be a facile way to prepare substituted [5]-, [6]-, and [7]helicenes.

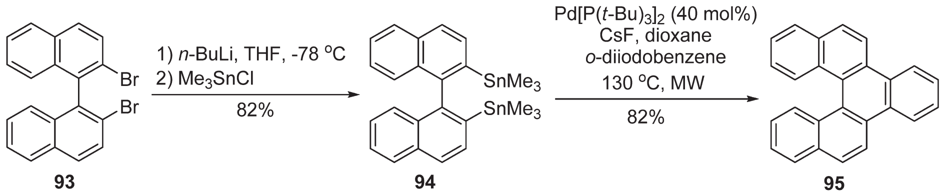
**3.4.3. Metal-Catalyzed [2 + 2 + 2] Cyclizations.** Pérez, Guitián, and co-workers developed a method of palladium-catalyzed intermolecular [2 + 2 + 2] cycloaddition of arynes and alkynes.[12b,77] The precursors, dimethyl acetylenedicarboxylate (DMAD), 1,2-didehydronaphthalene, 3,4-didehydrophenanthrene, 9,10-didehydrophenanthrene, and 1,2-didehydrotriphenylene, were synthesized in situ. Combining the precursors with $Pd_2(dba)_3$ and CsF, several polycyclic aromatic compounds **99**−**103** containing (multiple) helicene structures were prepared (Figure 8). If more than one aryne was used, the structures of the products were found to be uncontrollable because of the modular assembly character of the cycloaddition.

A novel strategy for the synthesis of helicenes by Co/Ni-catalyzed intramolecular [2 + 2 + 2] cycloisomerization was developed by Starý, Stará, and co-workers.[43,78] In 1998, Starý's group first examined this methodology for preparation of helicene-like compounds **105**−**107** (Scheme 14).[78a] After this discovery, they utilized the approach to synthesize (functionalized) tetrahydrohelicenes and helicenes. Tetrahydrohelicenes **109**−**111** were conveniently synthesized in 64−72% yields using a $CpCo(CO)_2/PPh_3$ catalyst (Scheme 15).[78b] If $Ni(cod)_2/PPh_3$ was used, the same products were obtained in similar yields at ambient temperature without visible light irradiation.[78b] The dehydrogenation affording the parent helicenes was achieved either by DDQ or by $Ph_3CBF_4$. In addition, [5]-, [6]-, and

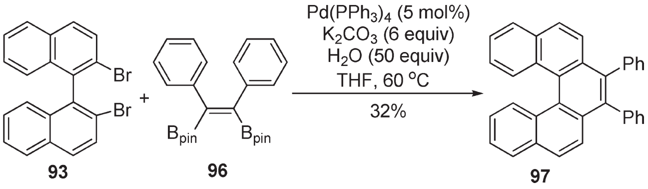
**Scheme 10**



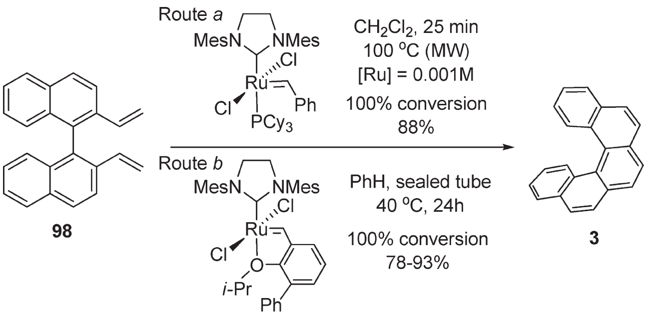
**Scheme 11**



**Scheme 12**



**Scheme 13**



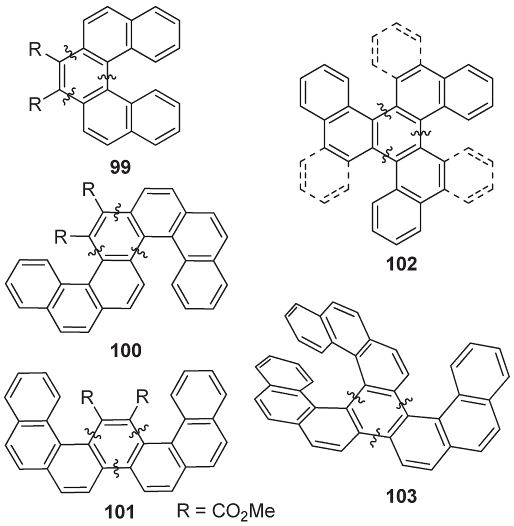


**Figure 8.** Helicenes synthesized by [2 + 2 + 2] cycloaddition.

[7]helicenes were prepared in one step by the cycloisomerization of *cis,cis*-dienetriynes in the presence of Ni(0) or Co(I) catalysts in up to 86% yield (Scheme 16).[78c] Recently, anthra[11]helicene **120**[7e,22z,79] was prepared in one step in nearly 40% yield by double cycloisomerization involving the building of six new rings (Scheme 17).[43] This methodology is very practical not only because of the high efficiency (100% atom economy, good to excellent yields, rapid reaction) but also because of the modular assembly character whereby different functional groups can be introduced in the aromatic and alkyl moieties[80] to afford non-symmetric and multifunctionalized (tetrahydro)helicenes. Consequently, many substituted helicenes[78g,i,81] and helicene-like molecules, such as Vollhardt's heliphenes,[2] Tanaka's [9]helicene-like molecule,[82] Teplý's helquats,[83] and Carbery's helicenoidal DMAP catalyst,[84] have been synthesized using this approach.

A Ru-catalyzed double cyclization through a naphthoannulation procedure based on 1,1-diaryl-2,2-diethynylethylenes **124a**, **b**, was disclosed by Scott and Donovan in 2004.[85] Through Corey−Fuchs olefination, Sonogashira coupling, and a desilylation procedure, diphenyl ketones **121a**,**b** were transformed into **124a**,**b** which isomerized to form **14** and **125** in the presence of a Ru$^{II}$ catalyst in 60% yield (Scheme 18). An empirical distance rule was proposed for successful closure, namely, that both the distances (*D*) between the atoms to be joined should be less than 3.4 Å. Therefore, this method can be applied for the synthesis of longer helicenes.

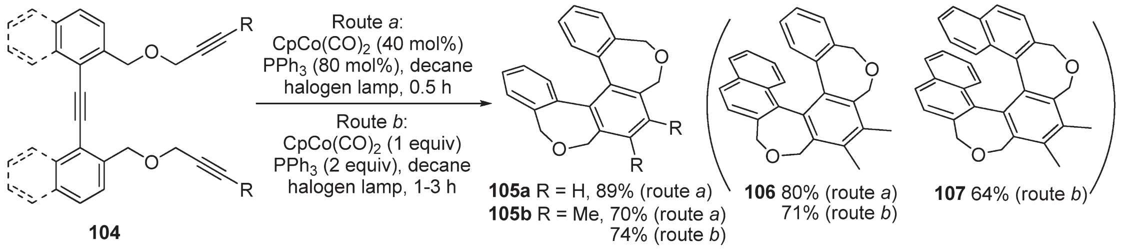
Recently, Storch and co-workers reported another strategy to prepare hexahelicenes **127a**,**b** in good yields via double [2 + 2 + 2] cycloisomerization of biphenylyl-naphthalenes **126a**,**b**, synthesized by a convergent and modular assembly method (Scheme 19).[86a] These easily prepared building blocks allow introduction of substituents at the most sterically hindered position of the helical backbone. Similarly, mono [2 + 2 + 2] cycloisomerization was utilized by Fürstner's group for the synthesis of tetra- and pentahelicene using a $PtCl_2$ catalyst.[86b]

### 3.4.4. Other Metal-Induced Reactions.

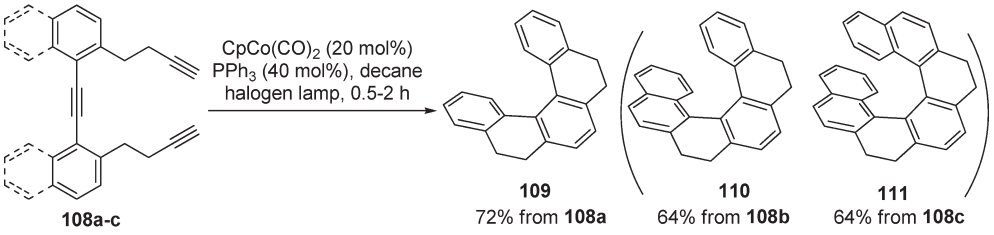
A novel lithium-induced cyclization of tribenzocyclyne **128** was described by Tessier, Youngs, and co-workers.[87] As shown in Scheme 20, the dianion **130** containing two cyclopentadienyl moieties was prepared in high yield in the presence of lithium. Two intermediates **129** were proposed in the reaction. After the dianion was protonated by THF, addition of *n*-BuLi gave a sandwich-like system **132** with lithium atoms bound to two $\eta^5$-$Cp^-$ rings.[87] This method is a highly efficient (4 steps with 85% overall yield) way of constructing benzo[5]helicene. Furthermore, the two TMS substituents can be replaced by other functional groups, and the presence of two Cp moieties in the backbone might have potential utility in the preparation of new materials.

In addition to the Wittig olefination, Pd-catalyzed coupling, and ring-closing metathesis, the McMurry reaction is another convenient method to build carbon−carbon double bonds. As shown in Scheme 21, Gingras and Dubois utilized McMurry coupling to form a benzene ring in the synthesis of carbohelicene.[88] After bromination of BINOL **133** by $Ph_3PBr_2$, the bromide was converted into dialdehyde **134** through Li/Br

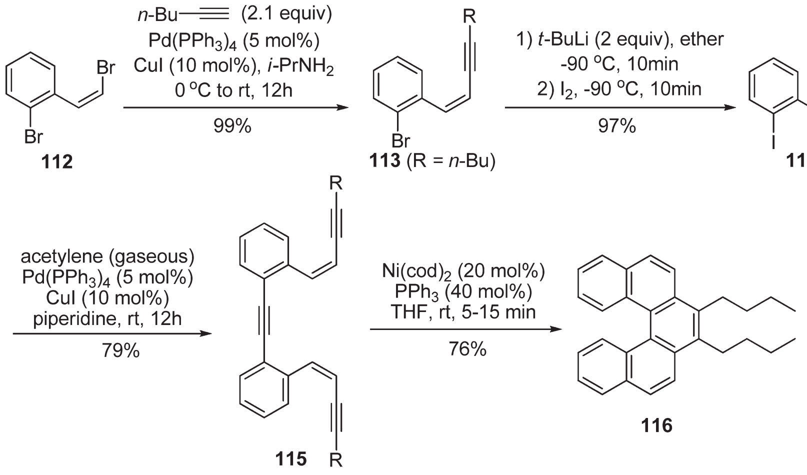
Scheme 14



Scheme 15



Scheme 16



exchange, followed by formylation. The benzene ring was formed using reduction of $TiCl_3$ in DME in the presence of a zinc—copper couple. This three-step approach is a convenient way to construct a [5]helicene framework, but it is not so practical because of the relatively low yield and extreme conditions.

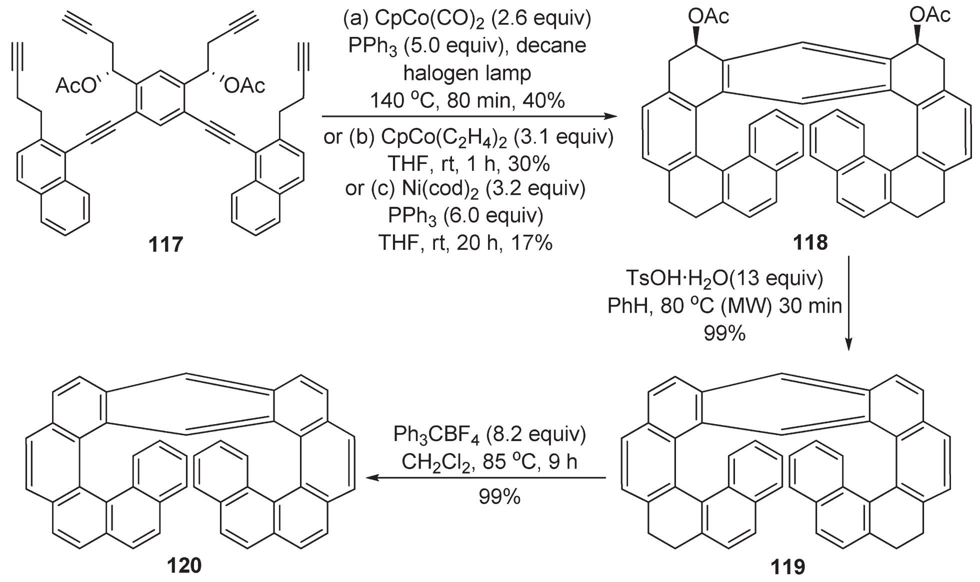
In this subsection, 11 different types of metal-catalyzed cyclizations have been introduced, most of which involve the use of precious metals, including cross-coupling reactions, ring-closing metathesis, [2 + 2 + 2] cycloaddition, and [2 + 2 + 2] cycloisomerization. These cyclizations are of practical utility not only by virtue of the small number of steps (building several rings in one step), relatively high yields, and good functional group tolerance, but also because such modular synthesis allows construction of a variety of helicenes (even long helicenes). The [2 + 2 + 2] cycloisomerization, in particular, has been accepted as a general synthetic strategy.

## 3.5. Radical Cyclizations

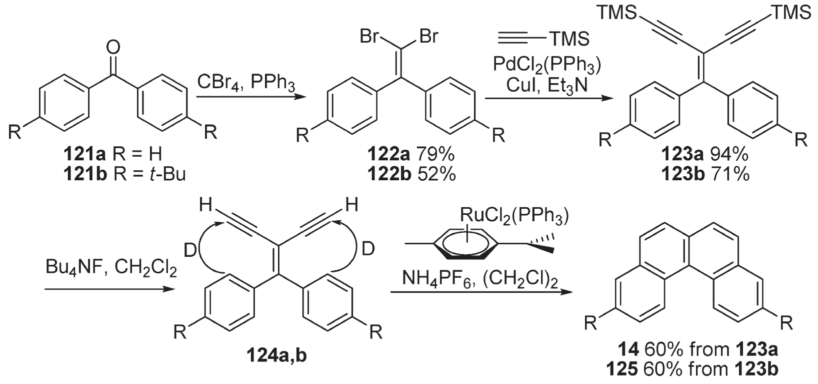
Harrowven and co-workers described an intramolecular aryl radical addition reaction for the synthesis of helicenes with reasonable yields (Scheme 22).[22n,89] After Wittig olefination and treatment of **137** with tributyltinhydride, a radical cyclization took place. This cyclization was controlled by the 6-exo/endo-trig regioselectivity, with preferential reaction at C(5) rather than C(7) of the stilbene owing to the stronger SOMO—LUMO interaction.[89a] The precursor **135** was prepared using a similar procedure.

On the basis of the above iterative radical cyclization approach, another efficient tandem radical cyclization was developed by the same group.[22n,89b] The two ortho-methoxy groups on the dialdehyde precursor not only controlled the diastereoselectivity with moderate *Z,Z*/*Z,E* ratio (7:1—4:1) but also efficiently

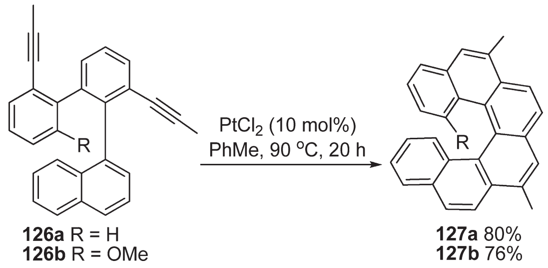
**Scheme 17**



**Scheme 18**



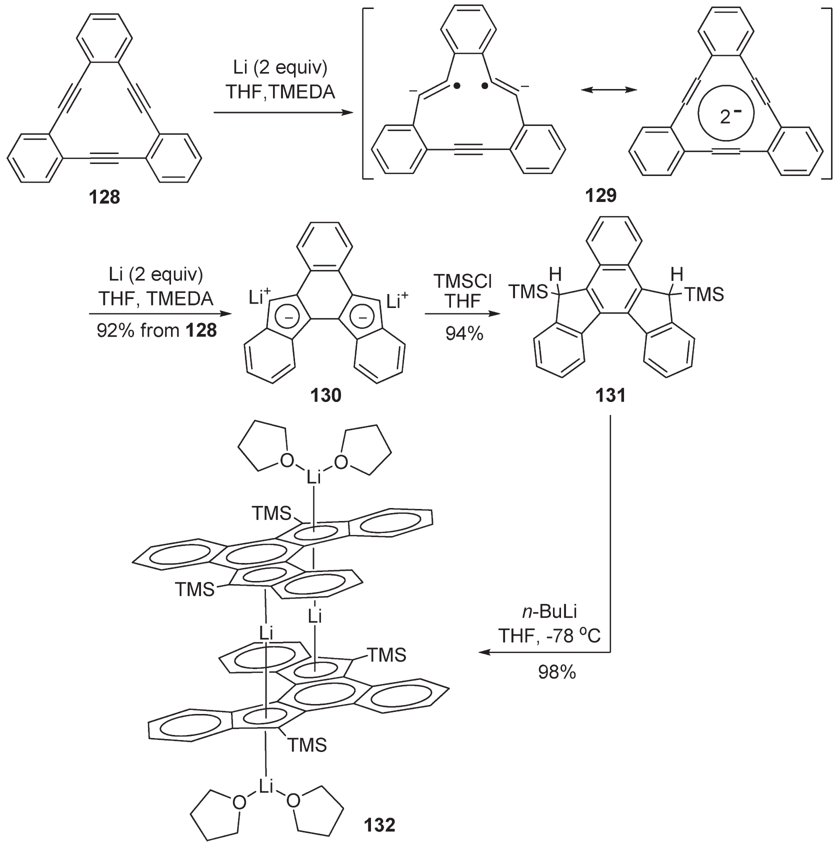
**Scheme 19**



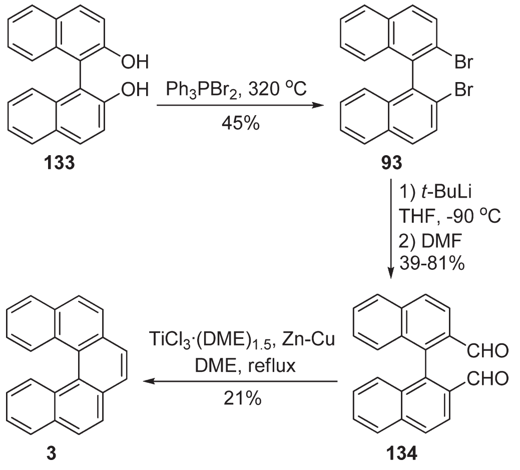
directed the cyclization to give the helical skeleton (Scheme 23). Using this approach different substituted helicenes were prepared in 53−86% yields.[22n] This two-step strategy is an alternative to the previous Pd-catalyzed coupling where sensitive functional groups are present and can also be extended by replacing the aryl groups on the bis(stilbene).

Another radical double-cyclization approach for the synthesis of helicenes was reported by Wang and co-workers.[22w,90] The reaction between 3,6-dipivalophenanthrene **144**, obtained by treating 3,6-phenanthrenedicarboxylic acid **143** with *tert*-butylcopper, and 2 equiv of lithium acetylide afforded the benzannulated enediynyl alcohol **145**. The diol **145** was subsequently reduced to the benzannulated enediyne **146** by silane and TFA. After cascade biradical coupling through a Schmittel cyclization reaction,[91] helicene **150** was prepared in 47% yield (Scheme 24). This approach not only provides helicenes bearing aryl substituents at the most sterically hindered positions but also extends the helical framework by fusing two indene moieties at the terminal rings of the backbone.[22w,90] Using this kind of structure with ortho-fused Cp rings in the backbone, an interesting ring enlargement was also disclosed by Wang's group.[92] When **152** was treated with LDA and then reacted with paraformaldehyde, **153** was obtained in good yield which, after an expeditious Wagner−Meerwein rearrangement in the presence of $P_2O_5$, gave **154** in which the five-membered ring has been expanded to a benzene moiety (Scheme 25).

Scheme 20



Scheme 21



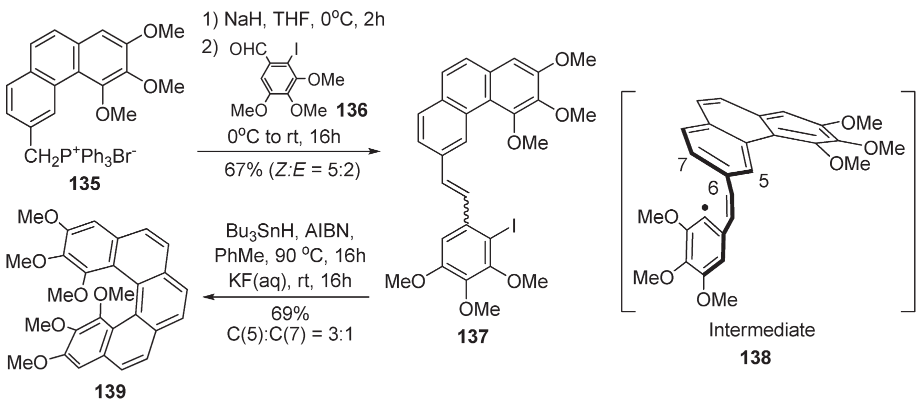
Although radical cyclization is a convenient approach to construct helicenes because of the easy preparation of the precursors and the moderate to good yields, it has not been widely utilized due to its low regioselectivity and functional group tolerance.

### 3.6. Other Cyclization Reactions

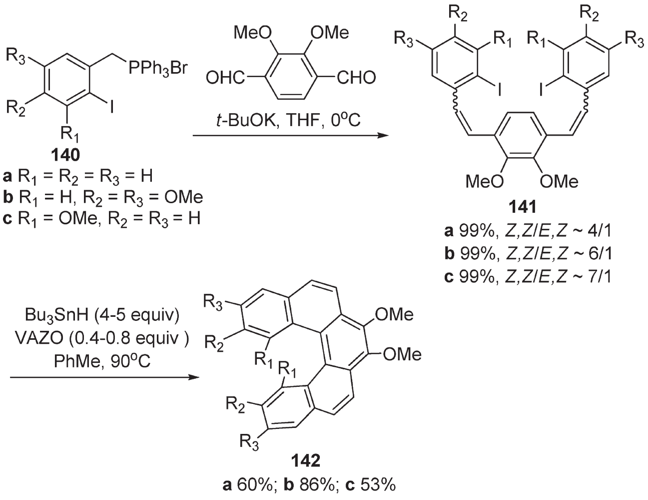
In addition to the above metal-catalyzed strategies, several other approaches with 1,1′-binaphthyl derivatives as precursors have been reported. In 1998, Gingras and Dubois described the carbenoid coupling reactions of bromo-substituted 2,2′-dimethyl-1,1′-binaphthyls in the presence of appropriate lithium reagents.[88,93] On the basis of this approach, [5]- and [7]helicenes were synthesized in moderate yields (Scheme 26). Multiple bromo-substituted binaphthyls **155a**−**c** were treated with LiHMDS or PhLi to produce 7-bromo[5]helicene **156**, 7,8-dibromo[5]helicene **157**, and [7]helicene **17**, respectively. Similarly, [5]helicene **3** and 7,8-dihydro[5]helicene **160** were obtained from dibromomethyl-substituted binaphthyl **159** (Scheme 27). An improved route to synthesize functional helicenes via benzylic (dibromo)methine coupling was recently developed by the Gingras' group.[94] As shown in Scheme 28, the precursor 2,2′-bis(dibromomethyl)-1,1′-binaphthyl **155b** was prepared by bromination of **161** with excess NBS and benzoyl peroxide. Ring closing occurred spontaneously in the presence of *t*-BuOK to give 7,8-dibromo[5]helicene **157**, which was converted into 7-bromo[5]helicene **156** by subsequent reduction. These methods are a practical way to prepare helicenes: (i) the precursors are easily obtained either by coupling reactions or from 1,1′-binaphthyl derivatives; (ii) the reagents used are all inexpensive; (iii) the rates of reactions are extremely rapid (10−15 min at 0 °C); and (iv) the yields of products are high, up to 96%.

In 2005, Piers and co-workers reported a convenient one-step synthesis of [5]helicene **163** in 59% yield through Li/Br exchange, followed by quenching with 1 equiv of $C_6F_6$ (Scheme 29).[22o] Compared with the two-step synthesis of **163** starting from **93**, the one-step route has the advantages of higher

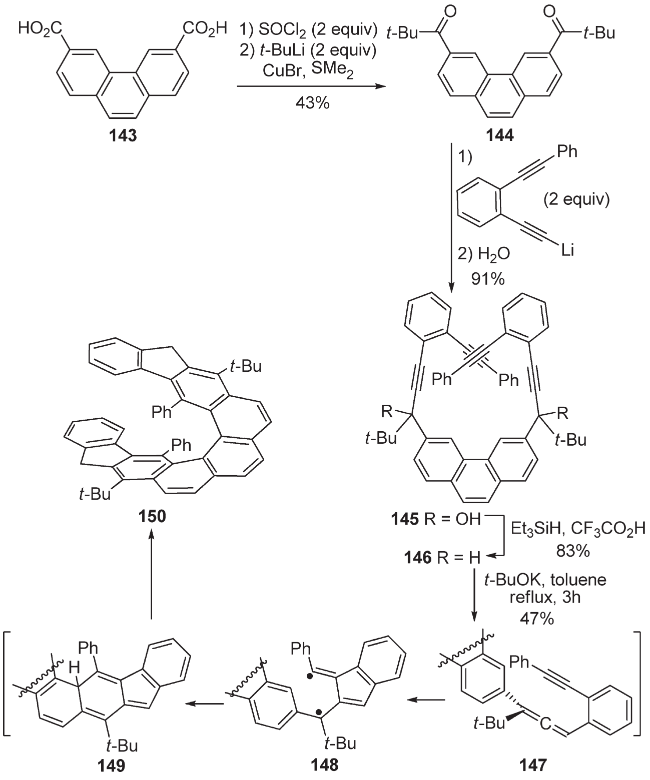
Scheme 22



Scheme 23



Scheme 24



yield, simpler procedures, and lower cost. Moreover, electron-withdrawing substituents can also be introduced by this method.

Larock et al. reported an efficient synthesis of [4]helicenes in moderate to excellent yields by electrophilic cyclization under mild reaction conditions (Scheme 30).[95] The precursors, 2-(1-alkynyl)biaryls **164a**,**b**, were prepared by Sonogashira coupling reactions between terminal alkynes and the corresponding 2-iodobiaryl. On treating **164a**,**b** with the electrophile ICl, cyclization took place via a cationic intermediate to give products **165a**,**b**. The higher yield of **165a** compared with that of **165b** was attributed to the electron-donating character of the methoxy group. The products can be converted into more complex compounds by subsequent Pd-catalyzed reactions.

In the reactions discussed in this subsection, all helicenes were obtained by constructing one benzene ring using 1,1′-binaphthyl derivatives. These reactions do not require expensive noble metal organometallic catalysts and usually involve less than four steps with good to excellent yields, and some reactions are extremely rapid. Nonetheless, most of these strategies focus on the synthesis of pentahelicenes, which are not optically stable at room temperature.

## 4. SYNTHESIS OF HETEROHELICENES

### 4.1. Synthesis Involving Construction of Six-Membered Rings

**4.1.1. Photocyclizations.** Just as in the synthesis of carbohelicenes, photoinduced synthetic routes based on several modified stilbene-type precursors (Figure 9) have been widely used in the synthesis of heterohelicenes. However, there are some differences between the two cases because the heteroatoms on the aryl moieties can have an effect on the reactions.[96] For example, in type B (below), the N atom can direct the ring closure occurring at the carbon site of the pyridine ring (Scheme 34) or can become involved in the photocyclization to give a quaternary ammonium cation in the helicene backbone (Scheme 35).

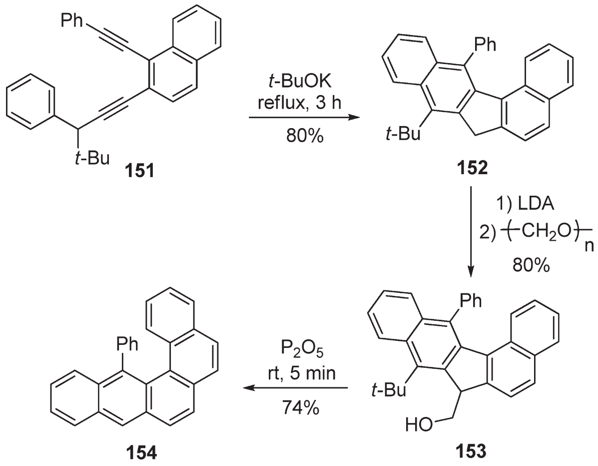
For types D and E, the low reactivity of the S atom similarly acts as a block, leading to unidirectional ring closure at the $\beta$-C atom of thiophenes (Schemes 41−43).

*4.1.1.1. Type A.* In these reactions, no heteroatom is present in the stilbene unit but the heterorings in the aryl groups of the precursors can affect the cyclization process. Castle and co-workers synthesized thiahetero[5]helicene **167** by a photocyclization method. Unlike in the preparation of carbo[5]helicene, where the yield of the linear product **27** was negligible,[97] reaction of **166** gave two isomers **167** and **168** in 50% and 37% yields, respectively (Scheme 31).[98] This low regioselectivity might result from the smaller energy gap of the reaction (8.6 kcal/mol; the energy gap for photocyclization of the corresponding carbohelicene is 17.4 kcal/mol).[99] When the thiophene ring was replaced by a benzene ring, the selectivity was much better (Scheme 32).[100] Accordingly, pyranone-annulated helicenes have been recently synthesized by Moorthy and co-workers.[22ae] After reaction between **172** and a Grignard reagent, **173** was obtained (Scheme 33). This method introduces two substituents at the terminal ring by breaking the pyranone ring, and moreover, the product displays good photochromic properties.

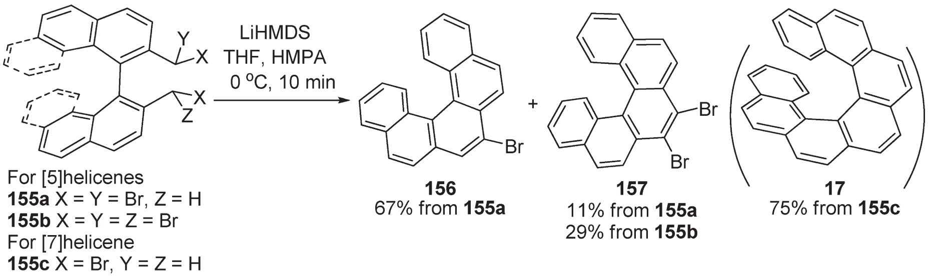
*4.1.1.2. Type B.* In 2005, Caronna and co-workers reported the synthesis of 6-aza[5]helicene **176** in moderate yield (Scheme 34).[22ac] By photocyclization of **177**, Arai et al. developed a novel route to synthesize azoniahelicenes **178a,b** bearing quinolizinium systems in moderate yields; the products might have bioactivities (Scheme 35).[101] Recently, Hassine and co-workers utilized $\beta$-styrylpyridine as one aryl moiety to give two helicene isomers **181** and **9** after Mizoroki−Heck coupling and a photocyclization (Scheme 36).[102] These three reactions clearly show that the nitrogen atom in the type B precursors can play different roles as a blocking group, as a participant in the cyclization, or as a regulator to control the regioselectivity.

*4.1.1.3. Type C.* This type of photocyclization has been less widely utilized for the synthesis of helicenes. Only two successful syntheses of stilbenoid precursors by isomerization of amides have been described. As shown in Scheme 37, after a condensation reaction **184** was transformed into a $\gamma$-lactam in 86% yield and the unsubstituted 6-aza-3,4-dithia[6]helicene **188** was obtained after three extra steps.[103] When the amino substituent on phenanthrene was at C(4), the double-helicene **197** was obtained instead (Scheme 38).[104] Caronna and co-workers

Scheme 25

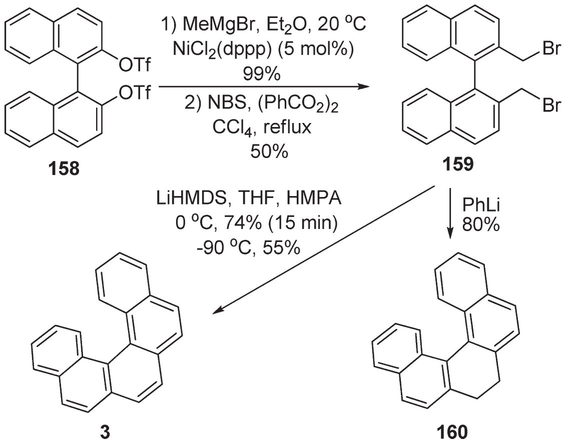


Scheme 26

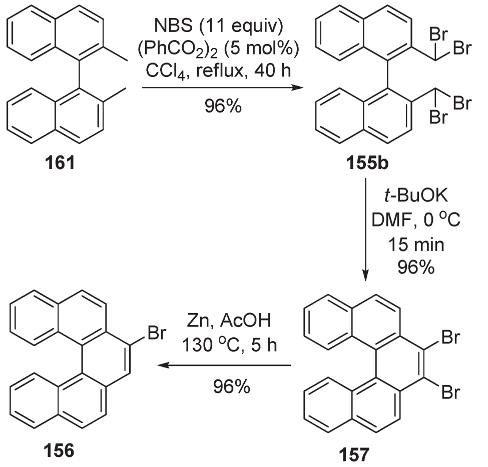


For [5]helicenes
**155a** X = Y = Br, Z = H
**155b** X = Y = Z = Br
For [7]helicene
**155c** X = Br, Y = Z = H

Scheme 27



Scheme 28



performed the ring closure of the Schiff base **198** under acid conditions and found that the yield of diazahelicene **199** was rather low (Scheme 39).[105] The same authors also found that compound **202**, described in one report in the earlier literature,[106] could not be prepared even under the most drastic conditions (Scheme 40).[22ac,100]

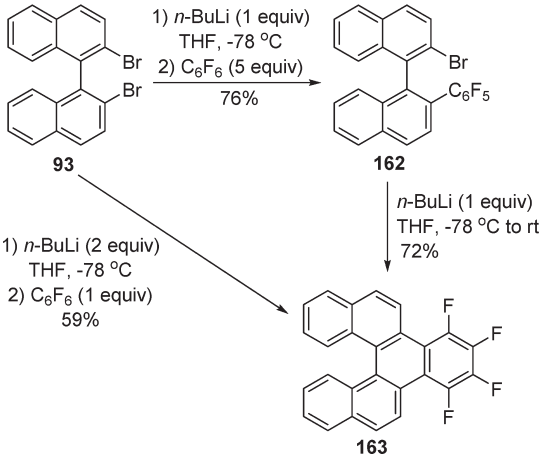
*4.1.1.4. Type D.* Arai and co-workers reported a new type of stilbene-type precursor for the synthesis of helicenes bearing bridgehead quaternary N atoms at the periphery of the helical structure.[24a] After reduction and elimination, the quaternary ammonium salt **205** was transformed into a stilbene-type structure, which underwent photoinduced ring closure to give compound **208**. The helicenium cation **210** was prepared after Knoevenagel condensation and subsequent photocyclization with a total yield of 73% for the two steps (Scheme 41).

*4.1.1.5. Type E.* Pioneering work on the synthesis of thiaheterohelicenes via mono (Scheme 42) or double (Scheme 43) photocyclization was carried out by Wynberg and co-workers, in which the precursors were prepared by Wittig olefination in moderate to good yields.[6c,i] Since then, a wide variety of thiaheterohelicenes have been prepared by this simple and easy approach.[22r,s,x,aa,24a,103,107]

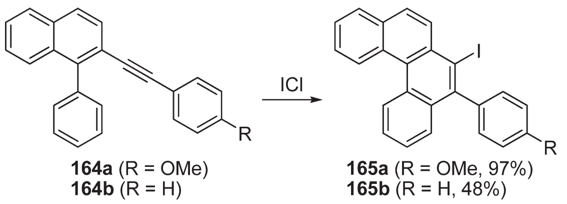
**4.1.2. Substitutions.** Different amine reagents have been employed in the synthesis of heterohelicenes using substitution reactions. In 1970, Vogel and Teuber reported the synthesis of azaheterohelicene **221** from hydrazine derivative **220** (Scheme 44).[108] Another two-step approach to synthesize the diazaheterohelicene **225** in nearly quantitative yield, involving substitution of arenediazonium salts and subsequent cyclization under acid conditions (attempted photocyclization resulted in failure), was described by Schuster and Rau (Scheme 45).[109] In 1999, Katz and Fox reported a novel route to extend the helical skeleton by adding two pyrazine aromatic rings to **54e**, during which the absolute configuration of the helicene was retained (Scheme 46).[110]

In 2002, Caronna and co-workers described two approaches for the synthesis of 6,9-diaza- and 2,13-diaza[5]helicenes by cyclization of an amine and a Schiff base, although the yields were low (<5%).[105] Recently, the same group reported a very simple method to prepare 7,8-diaza[5]helicene by oxidation of 2,2′-diamino-1,1′-binaphthyl **229** in the presence of *m*-CPBA.[111] A mixture of diazahelicene **2** and its *N*-oxide **230** and *N,N*′-dioxide **231** (Scheme 47) were obtained, but the oxides could be easily reduced by LAH to provide **2** in good yields.

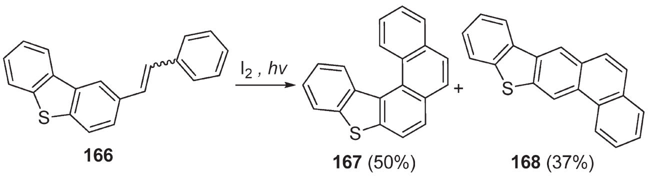
Scheme 29



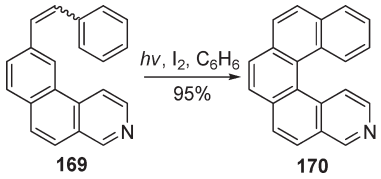
Scheme 30



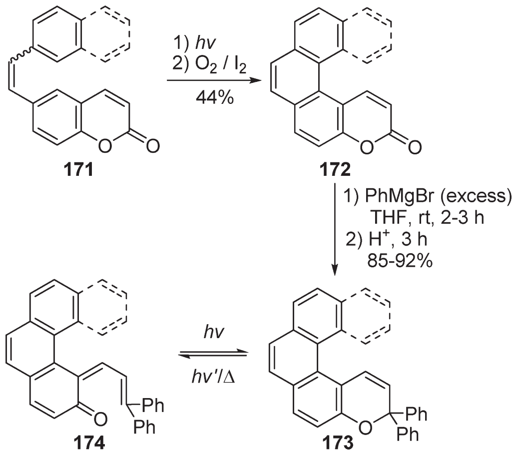
Scheme 31



Scheme 32



Scheme 33



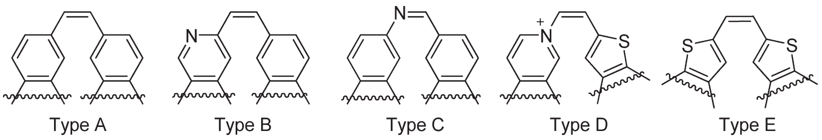
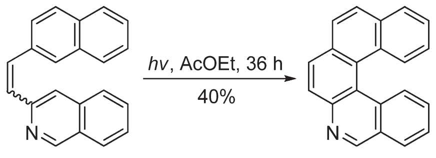


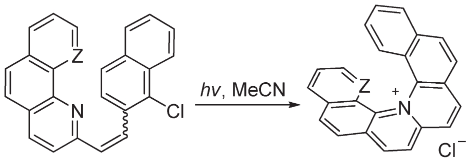
**Figure 9.** Different stilbene-type precursors for photocyclizations.

### Scheme 34



**175** **176**

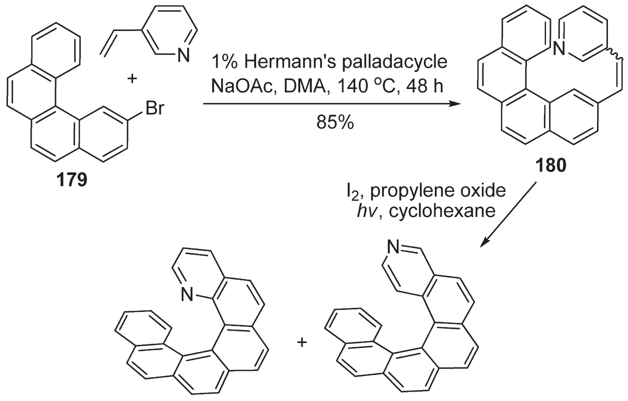
### Scheme 35



**177a** (Z = CH)
**177b** (Z = N)

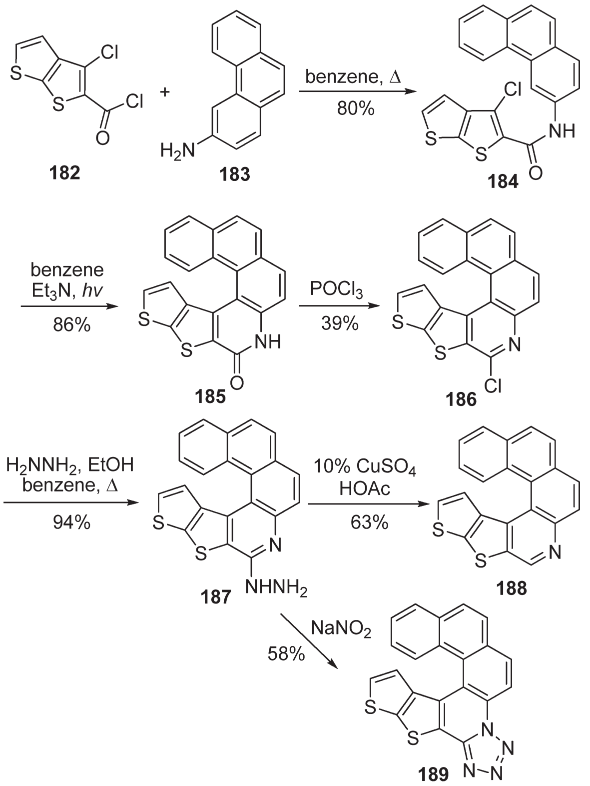
**178a** (Z = CH, 40%)
**178b** (Z = N, 32%)

### Scheme 36



**179** **180** **9** (7%) **181** (50%)

### Scheme 37



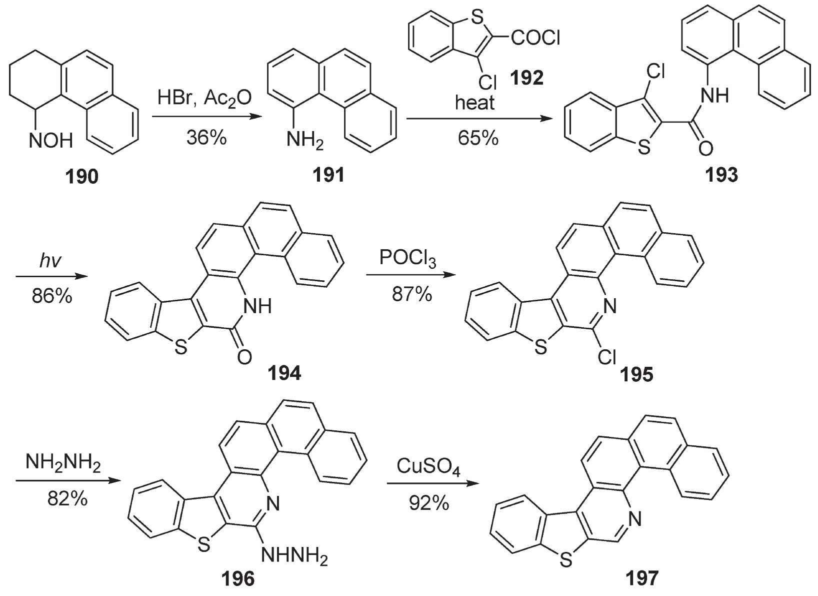
**182** **183** **184** **185** **186** **187** **188** **189**

In addition to hydrazine and the primary and secondary amines, triarylamines have also been utilized to construct helicenes with a bridgehead nitrogen atom. In 2003, Venkataraman et al. established a three-step method to construct helicenes bearing a bridgehead nitrogen atom in moderate yields.[22u] As shown in Scheme 48, the triarylamine **234**, prepared by copper-catalyzed Ullmann coupling, was converted to the corresponding acid chloride via hydrolysis followed by treatment with oxalyl chloride. Subsequent Friedel–Crafts reaction in the presence of $SnCl_4$ afforded the helicene **235**. Because of the steric hindrance in the coupling step, the overall yields depended greatly on the size of the aryl groups in the amines: when Ar = Ar′ = Ph, the overall yield was 66%, while when Ar = Ar′ = naphthyl, the overall yield was only 14%. Although this method requires a long time to reach completion, the presence of the two carbonyl groups in **235** facilitate convenient functionalization and the tertiary amine group in the helical backbone might also provide some new properties.

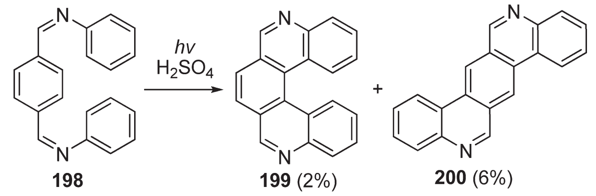
Recently, a practical method to synthesize thia-bridged triarylamine heterohelicenes was described by Menichetti and co-workers.[112] By changing the aryl substituents of the amines, several [4]- and [6]heterohelicenes were obtained in 46–72% yields by reaction with PhtNSCl with or in the absence of a Lewis acid.[112,113] For the synthesis of **237**, the four successive electrophilic aromatic subsititution ($S_EAr$) processes were facilitated by the trimethoxy-substituted benzene units and the possibility of protonation at the N atom of the sulfonamide (Scheme 49). This is a highly efficient means (63% yield) of constructing a helical core with nine alkoxy groups, which would be difficult to achieve by other approaches. Surprisingly, the [4]helicene **238**, prepared by a similar procedure in 71% yield, had a barrier of racemization even larger than that of parent [5]helicene, and its optical resolution could be achieved by HPLC.

Interestingly, several approaches to construct helicenium cations by intramolecular substitution have been disclosed. In 2003, Laursen, Lacour, and co-workers prepared a novel heterohelicenium cation **240** by a series of nucleophilic aromatic substitution ($S_NAr$) reactions between **239** and propylamine (Scheme 50).[24b] This helical cation, bearing a twisted helical structure, was stabilized by forming two 6$\pi$-aromatic rings. The cation **240** which has a higher barrier of racemization (41.3 kcal/mol at 200 °C) than that of [6]helicene (36.2 kcal/mol at 27 °C)[7d] was resolved by forming diastereoisomers with BINPHAT anions. Recently, the intermediate **242**, adopting the [4]helicene configuration, was isolated by Lacour and co-workers in the synthesis of the trioxatriangulenium cation (TOTA$^+$) **243** (Scheme 51).[114] The barrier of racemization of **242** was determined to be 27.7 kcal/mol at 20 °C, which is smaller than that of **240**, indicating that two bridging oxygen atoms bring a larger degree of flexibility than two nitrogen atoms.

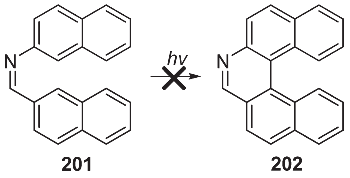
Scheme 38



Scheme 39



Scheme 40



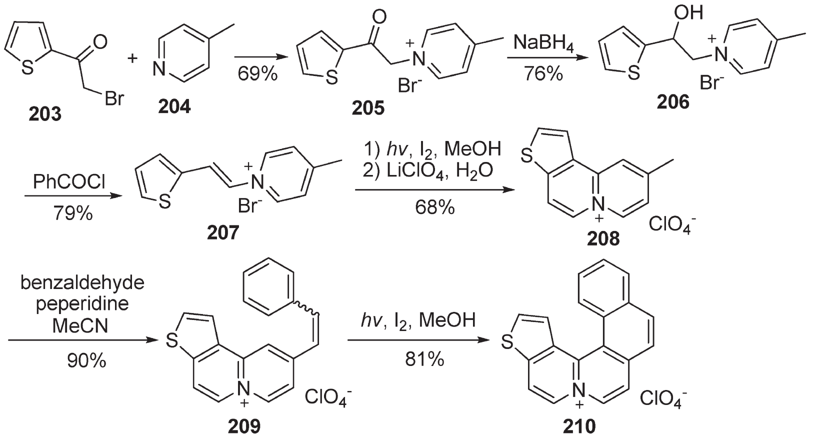
As an alternative to photocyclization (section 4.1.1.4), a new strategy for the synthesis of the helicenium cation was described by Ihmels and co-workers.[115] Cyclization occurred under different reaction conditions after ion exchange. Interestingly, if PPA was used, the major product was **251**, while if the reaction took place in the presence of HBr, the regioselectivity was reversed (**250** became the major product) and the overall yield was lower (Scheme 52).

**4.1.3. Metal-Induced Synthesis.** Staab and co-workers reported the use of Stille−Kelly coupling to synthesize 1,16-diaza[6]helicene **22** in 52% yield in the presence of hexamethyldistannane (Scheme 53).[39] Takenaka and co-workers developed a similar method to construct 1-azahelicene **9** in 61% yield (Scheme 54).[116] The precursor is easily prepared by a highly *Z*-selective Wittig reaction of the halogen substituents. This synthetic strategy is of considerable practical utility, since different helicenes can be easily prepared using different Wittig reaction precursors.

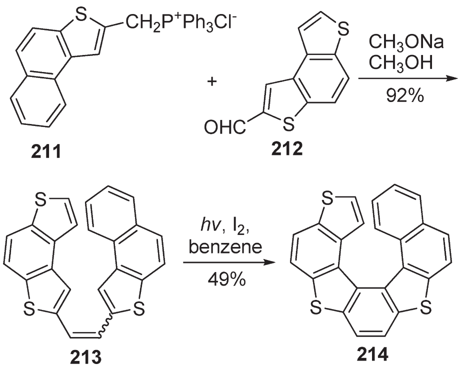
Starý, Stará, and co-workers also extended the cycloisomerization of triynes approach used for the synthesis of carbohelicenes[78c] to the preparation of heterohelicenes (Scheme 55).[117] The bromopyridine derivative **255**, obtained from **254** by treatment with 1-(triisopropyl)-1-silylpropyne and *n*-BuLi, underwent Sonogashira coupling to give **256a** in 86% yield in the presence of a Pd$^0$/Cu$^I$ catalyst. After desilylation the key step, [2 + 2+2] cycloisomerization of **256b**, took place smoothly in the presence of a Co$^I$ catalyst to afford the tetrahydrodiazahelicene **257**. Subsequent oxidation of **257**, the most difficult step in the approach, was achieved by utilizing MnO$_2$ under microwave irradiation to give 1,14-diaza[5]helicene **21** in 41% yield. Using this method, 1- and 2-aza[6]helicene were also synthesized from the corresponding triynes in 47−53% yields.

On the basis of Starý and Stará's [2 + 2 + 2] cycloisomerization of triynes, Teplý and co-workers synthesized a series of helquats.[118] In the presence of the triflate-substituted butyne **259**, the precursors **258a**−**c** underwent two successive nitrogen quaternizations giving triynes **260a**−**262a** in moderate to good yields.[118a] Subsequent cycloisomerization of the triynes was carried out with a rhodium catalyst affording [5]-, [6]-, and [7]helquat in 69−99% yields (Scheme 56).[118a] Because the first nitrogen quaternization produces a pyridinium-type cation which deactivates the second quaternization by virtue of its strong electron-withdrawing effect, nonsymmetric helquats can be obtained using different triflates.[118b] Moreover, different functional groups can also be incorporated in the precursors **260**−**262** and **266**. Using this efficient and highly modular assembly strategy, symmetric and nonsymmetric helquats were obtained in good to excellent yields (Figure 10).[118] With their unique extended diquat skeletons, [5]helquats have similar electrochemical properties to diquats.[119] Furthermore, **268** ($R_1$, $R_2$, $R_3$, $R_4$ = Me) was easily resolved by crystallization after forming diastereoisomeric salts with (*R*,*R*)-dibenzoyltartrate anions.[120]

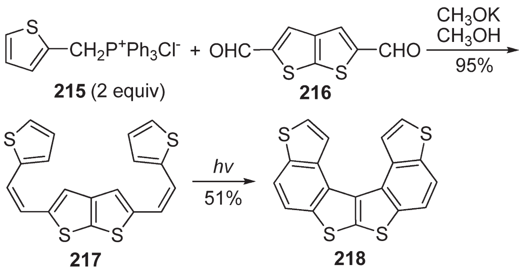
Scheme 41



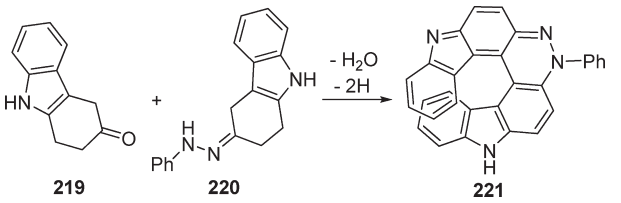
Scheme 42



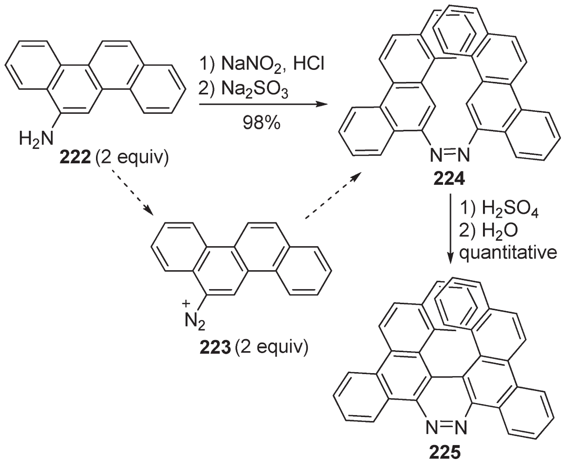
Scheme 43



Scheme 44



Scheme 45

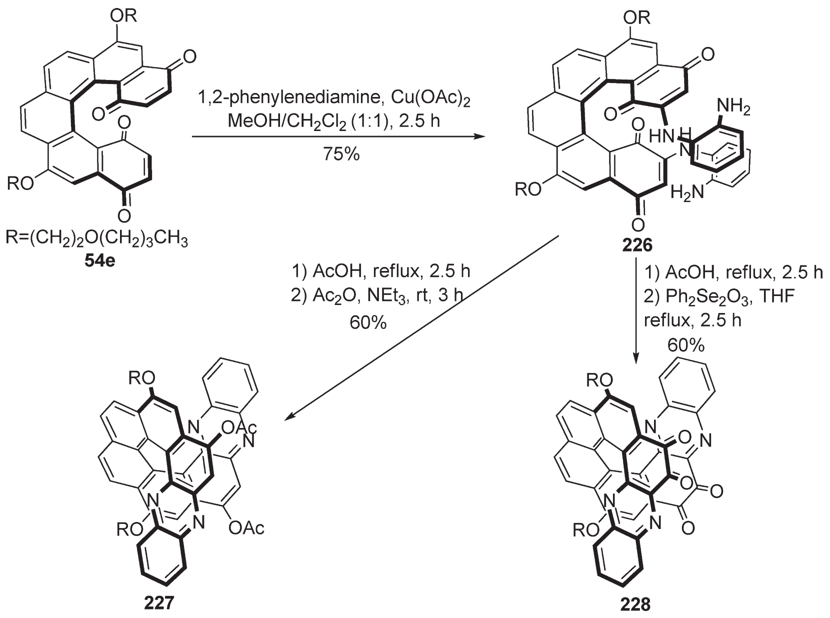


Recently, Storch and co-workers used double cycloisomerization of the nitrogen-containing biphenylylnaphthalene **268** to synthesize azahetero[6]helicene **269** in 80% yield in the presence of PtCl$_4$ and InCl$_3$ (Scheme 57).[121] Besides the above three-ring and two-ring closure methods, a McMurry reaction has also been utilized to construct benzene rings in the skeleton of heterohelicenes.[22y,122] As shown in Scheme 58, Rajca and co-workers utilized McMurry coupling to prepare the thiaheterohelicene **271** in 38% yield.[22y] Similarly, a double helicene **273**, obtained in 80% yield from diketone **272**, was recently reported by Wang and co-workers (Scheme 59).[122]

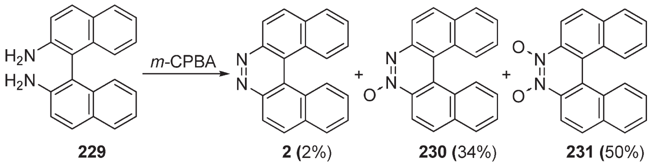
**4.1.4. Other Cyclizations.** In addition to the photoinduced cyclization of stilbene-type precursors, two routes to construct the thiahelicene **275** involving either electrochemical or anhydrous FeCl$_3$ oxidation have been reported by Larsen and Bechgaard (Scheme 60).[123] The latter is preferred by virtue of the simpler workup procedure. However, neither of the approaches is appropriate for large-scale preparation (being limited to a scale of ~$10^{-4}$ mol).

In a more practical synthesis, the Diels–Alder reaction between *p*-benzoquinone and dienes bearing heteroaromatic rings was utilized by Katz and co-workers to prepare heterohelicenes on a gram scale and in reasonable yields (Schemes 61 and 62).[99,124] The rates of reactions were much faster than those in the preparation of carbohelicenes, and the two *p*-benzoquinone

Scheme 46



Scheme 47



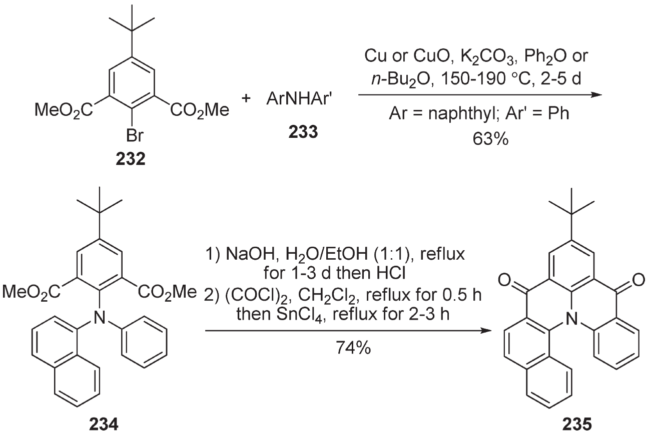
moieties in **277a**−**d** and **279** can be utilized for both further functionalization and optical resolution.

The Ramberg−Bächlund rearrangement, another way to build benzene rings, was employed by Staab and co-workers to prepare the heterohelicene **21**.[22ab] As shown in Scheme 63, the bis(quinoline) **281** prepared from the diamine **280** by double Skraup reaction underwent oxidation with trifluoroperoxyacetic acid to give the *S*,*S*-dioxide **282**. The subsequent rearrangement took place in *t*-BuOH in the presence of KOH and $CCl_4$ producing 1,14-diaza[5]helicene **21** in 13% yield.

In 2005, Rajca and co-workers reported the synthesis of a novel $\pi$-conjugated conjoined double helicene by a simple and efficient synthetic method.[125] As shown in Scheme 64, diamine **284** was obtained by C−N coupling[126] of the bromide **283** and 4-*tert*-butylaniline in the presence of a $Pd^{II}$ catalyst. The planar diamine **285**, prepared by a $S_EAr$ reaction of **284** in the presence of $H_3PO_4$, was converted into the configurationally stable azaheterohelicene **286** in good yield by three oxidative homocouplings using benzoyl peroxide in dichloromethane solution.

Harrowven et al. prepared several azahelicenes using homolytic aromatic substitution reactions of a stilbene-type precursor to build C−C bonds (Scheme 65).[22n] The stereoselectivity of the Wittig reaction was controlled by the cooperative ortho effects, which afforded a 16:1 ratio of the *Z* and *E* isomers. Subsequent homolysis of the carbon−iodine bond directed the cyclization to produce 5-azahelicene **291** in 75% yield. Similarly, Caronna and co-workers reported the radical cyclization of bromo-substituted stilbene to give,2-azahelicene, but the yield was low.[100]

Scheme 48

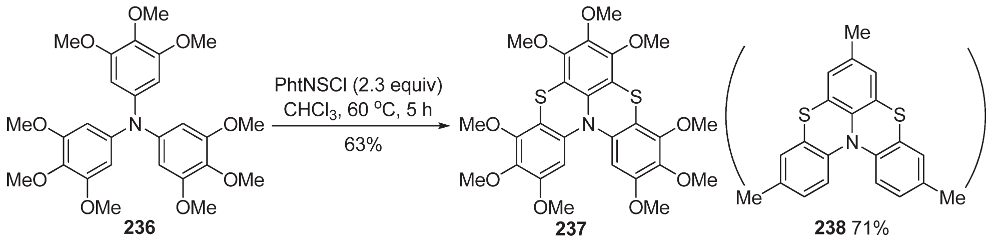


In this subsection, syntheses of heterohelicenes based on construction of six-membered rings have been discussed. Although most of the methodologies are similar to those used in the synthesis of carbohelicenes, the differences between the properties of the heteroatoms and carbon provide some new perspectives. For example, a nitrogen atom can donate a lone pair of electrons to form helicenium cation species; the lower reactivity makes a sulfur atom a good blocking group to direct the cyclization; the $\alpha$-carbon atom of the thiophene ring can be easily and selectively substituted; due to the nucleophilicity or electrophilicity of the heteroatoms, cyclization can be achieved by aromatic substitution reactions; and the presence of the heteroatoms might affect the activation energies of the reactions.

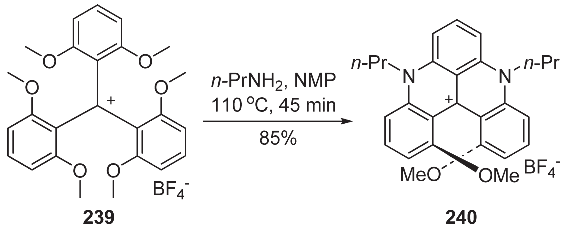
### 4.2. Synthesis Involving Construction of Five-Membered Rings

Since the majority of the ortho-fused hetero five-membered rings in helicene frameworks are furan, imidazole or pyrrole, or

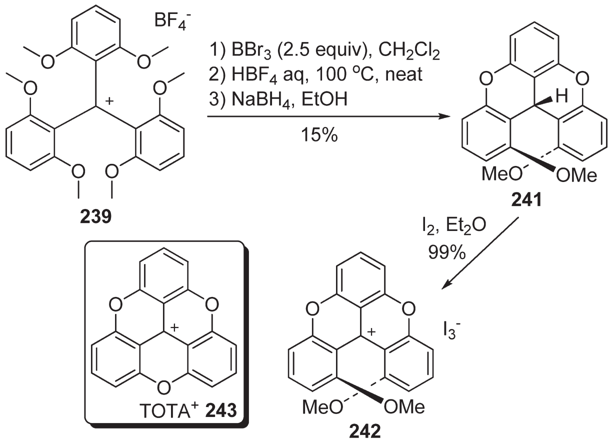
Scheme 49



Scheme 50



Scheme 51



thiophene units, the following discussion is based on this classification.

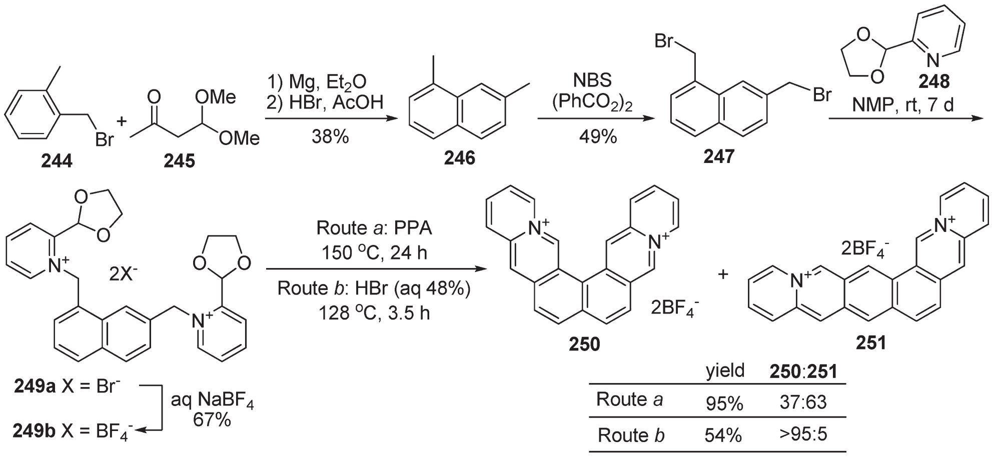
**4.2.1. Construction of Furan Rings.** Nearly all the approaches to build furan rings start from different BINOL analogues. In 1973, Högberg prepared diol **294** from dibenzofuran **292** via Ullmann coupling, demethylation, and subsequent acidification. Prolonged heating in a sealed tube resulted in ring closure producing the oxahelicene **295** in 54% yield (Scheme 66).[127] In 1999, Dötz and co-workers reported a much simpler method for the synthesis of the furan-fused helicene **297** in 36% yield by adding excess TMSI to cleave the ether, followed by intramolecular nucleophilic substitution (Scheme 67).[22ad] Moreover, Dötz et al. also synthesized 7-oxapentahelicene **299** by acid-promoted ring closure in a 43% yield (Scheme 68);[128] the resulting product can be further functionalized after Li/Br exchange. A more efficient sequence which could be easily scaled up to synthesize 2,12-disustituted-7-oxa[5]helicenes **303a**−**e** from cheap commercially available materials was reported by Thongpanchang and co-workers in 2004.[129] As shown in Scheme 69, 1,1′-binaphthyl-2,2′,7,7′-tetraol **301** was obtained in 96% yield by the oxidative coupling of **300** with $FeCl_3$. After substitution and subsequent ring closure, five oxahelicenes **303a**−**e** were prepared in good yields using different nucleophiles. In addition, Bechgaard and co-workers synthesized 7,8-dioxa[6]helicene **10** in 35% yield by dehydrogenation of dihydrohelicene[4b] in the presence of NBS under illumination by sunlight.[28i]

**4.2.2. Construction of Imidazole and Pyrrole Rings.** Two approaches have been reported for incorporation of an imidazole ring in the helical backbone. In 1990, Leonard and co-workers disclosed a method to synthesize tetraazaoctahelicene. As shown in Scheme 70, diarylamine **306**, obtained by reaction between benzo[*h*]quinolin-2-amine **304** and chloroketene diethyl acetal **305**, was converted into helicene **307** in 47% yield via oxidative ring closure in the presence of iodobenzene diacetate.[130] In addition, Böhm et al. described another strategy to prepare azahelicene by ferricyanide oxidation (Scheme 71).[131] Pyridinium salts **310a**−**c**, synthesized by reaction between amines **308a**−**c** and 2,4,6-triphenylpyrylium perchlorate **309**, were oxidized to afford [4]helicenes **311a**−**c** and pyrrole derivatives **312a**−**c**, although the mechanism of the reaction remains unclear.

In 1996, Vögtle and co-workers reported that 5,10-diaza-[6]helicenes could be obtained by reaction between naphthalene-2,7-diol and phenylhydrazine leading to construction of two pyrrole rings in the helical backbone.[132] Moreover, a one-pot reaction to synthesize azahelicenes via *N*-ylide 1,3-dipolar cycloaddition has been developed by Dumitrascu and co-workers.[133] As shown in Scheme 72, the salt **313**, obtained by treating the corresponding pyridine derivatives with 2-bromoacetophenones, underwent cycloaddition with acetylenic dicarboxylates in the presence of $NEt_3$ and (tetrakispyridino)cobalt(II) dichromate (TPCD) affording aza[4]helicenes **314** in good yield. Another convenient method for preparation of [5]helicenes with two pyrrole units was developed by Maghsoodlou and co-workers.[134] When the phenanthroline derivatives **315** were treated with acetylenic esters in MeOH, different pentahelicenes **316** were obtained in moderate yields (Scheme 73).

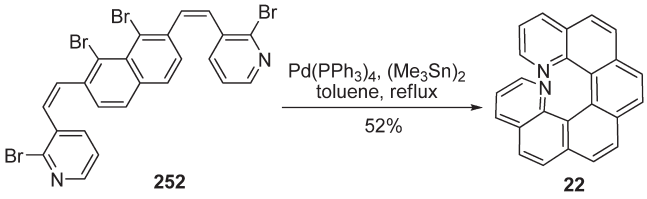
**4.2.3. Construction of Thiophene Rings.** A practical iterative approach for the synthesis of carbon−sulfur helicenes was developed by Rajca and co-workers.[22q,135] As shown in Scheme 74, desilylation of **317** gave compound **318** in 80% yield, and subsequent mono Li/Br exchange followed by oxidation with $CuCl_2$ gave compound **319**. Finally, reaction of the two $\alpha$ positions in **319** with LDA followed by annelation in the presence of $(PhSO_2)_2$ afforded thia[7]helicene **320**. Although the precursor **317** could be prepared from 3,4-dibromothiophene using this approach, [15]helicene could not be synthesized by

Scheme 52

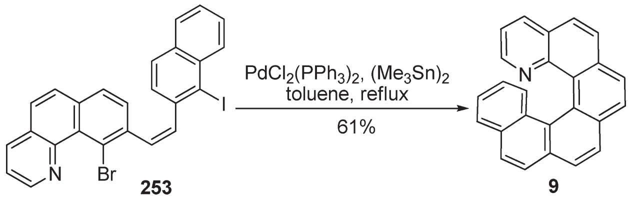


|  | yield | **250**:**251** |
|---|---|---|
| Route *a* | 95% | 37:63 |
| Route *b* | 54% | >95:5 |

Scheme 53



Scheme 54



another iteration from **320** because of the diminished reactivity in the 1- and 1′- positions resulting from steric hindrance and the rigid conformation.[136]

Starting from 7,7′-dibromo-2,2′-dihydroxy-1,1′-binaphthyl **298**, Dötz and co-workers synthesized 7-thiahelicene **322** in 36% yield by a Newman−Kwart rearrangement. Moreover, helicene **322** could be further extended to hexa- or heptahelicene by Dötz benzannulation reactions at the terminal rings (Scheme 75).[128]

Recently, Nenajdenko and co-workers reported two new strategies for the synthesis of thiaheterohelicenes.[137] Reaction of the bromothiophene **325** with LDA and sulfur followed by treatment with $CH_2Br_2$ afforded thioether **326**. After formylation with carbamate, 10*H*-bisthienodithiocin-10-one **327** was obtained. Subsequent cyclization took place by deprotonation followed by reaction with $BF_3 \cdot Et_2O$ (Scheme 76). In the other strategy, ketone **332**, synthesized by reaction between the carboxamide **330** and the Grignard reagent **331**, was converted into dichloroethene **333** by a phosphorus ylide. Heterohelicenes **334** and **335** were then obtained under different conditions (Scheme 77).

Helicenes prepared by constructing five-membered heterorings have been less utilized (except for Rajca's carbon−sulfur helicenes) because of the limited transformations available for cyclization. Thus far, only two general strategies have been utilized as practical methods, namely, aromatic substitution for furan and thiophene rings and [2 + 3] cycloaddition for imidazole and pyrrole rings.

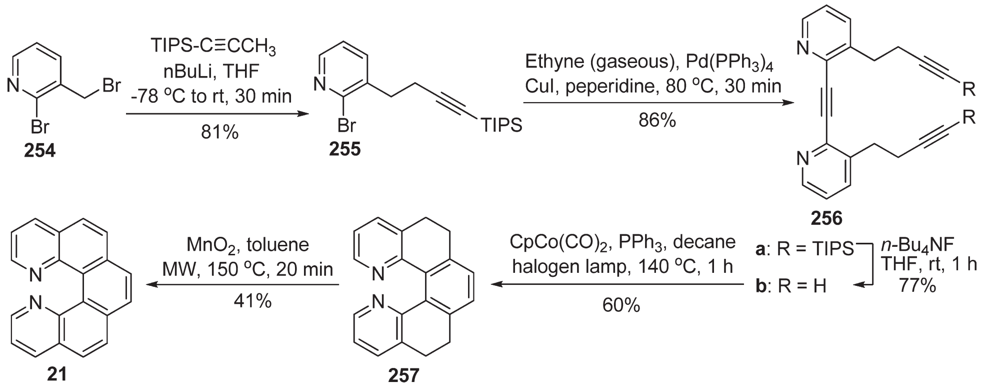
## 4.3. Total Synthesis of Helical Natural Products

Helicene moieties are also found in some marine products. In 1993, Chan isolated a purple compound purpurone **340b** from the marine sponge *Iotrochota* sp. which had an inhibitory effect on ATP-citrate lyase.[138] Soon afterward, a similar marine alkaloid ningalin D **340a** produced by *Didemnum* sp. was reported by Fenical and Kang.[139] In 2005, Boger and co-workers described the first total synthesis of **340a** in 19% overall yield by Diels−Alder cycloaddition and subsequent reduction to establish a pyrrole moiety, followed by Dieckmann condensation and Suzuki coupling (Scheme 78).[140]

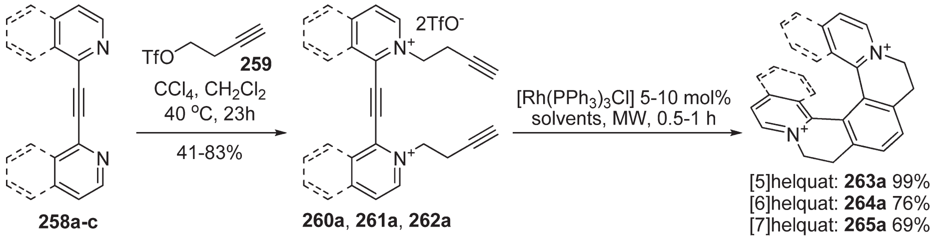
Dictyodendrins, another class of tetracyclic helical compounds, were isolated from *Dictyodendrilla* sp. by Sato and co-workers in 1993.[141] It was found that these compounds could completely inhibit telomerase at concentrations as low as 50 $\mu$g/mL.[142] Fürstner and co-workers achieved the first total synthesis of dictyodendrins B, C, and E.[143] The chalcone **342**, obtained by condensation of **341b** with *p*-$MeOC_6H_4CHO$, was transformed via reactions with TosMIC and NaH into pyrrole **343a**, which was reduced to give aniline **343b**. Subsequent treatment with the acid chloride **344** afforded amide **345**, which was converted into the indole **346** on exposure to titanium−graphite. The dictyodendrin core **347** was synthesized by 6$\pi$-electrocyclization and aromatization with Pd/C and nitrobenzene in one step with a yield of 81%. Dictyodendrins B, C, and E were further prepared using several extra steps (Scheme 79). Recently, another efficient approach for the synthesis of dictyodendrin A and B was reported by Tokuyama and co-workers involving an unprecedented one-pot indoline synthesis and cross-coupling sequence.[144] Moreover, Álvarez and co-workers prepared a simplified dictyodendrin core, pyrrolo[2,3-*c*]carbazole **354**, via a two-step convergent method involving Suzuki cross-coupling and 6$\pi$-electrocyclization (Scheme 80).[145]

In summary, it is difficult to develop a general approach for the preparation of heterohelicenes since both the type and the position of the heteroatom in the helical backbone have a significant effect on

Scheme 55



Scheme 56



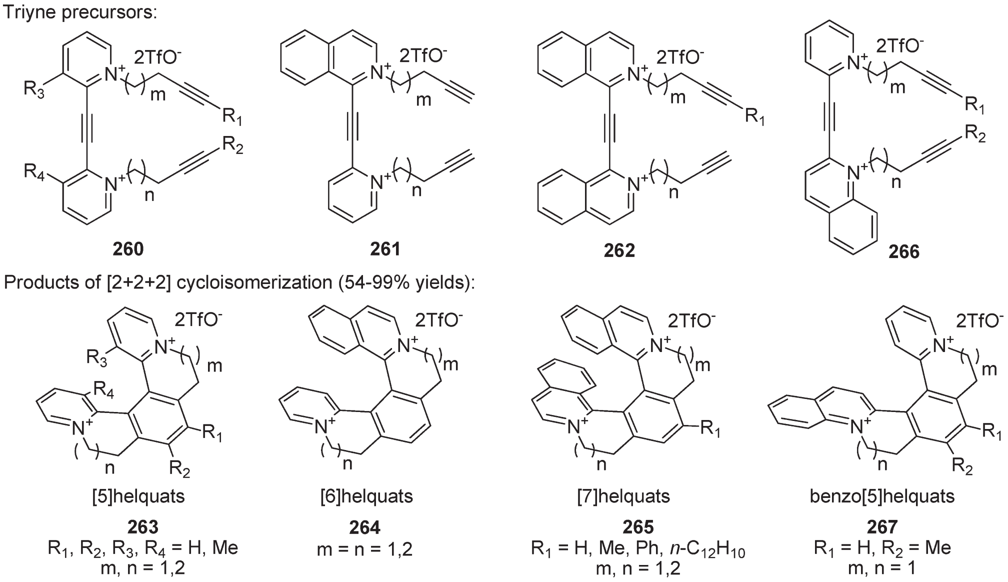


**Figure 10.** Helquats prepared by [2 + 2 + 2] cycloisomerization of different triynes.

the synthesis. Fortunately several practical approaches have been discovered, including metal-catalyzed methods, Katz's Diels−Alder approach, and aromatic substitution for oxa- and thiahelicenes.

## 5. ASYMMETRIC SYNTHESIS AND OPTICAL RESOLUTION

### 5.1. Asymmetric Synthesis

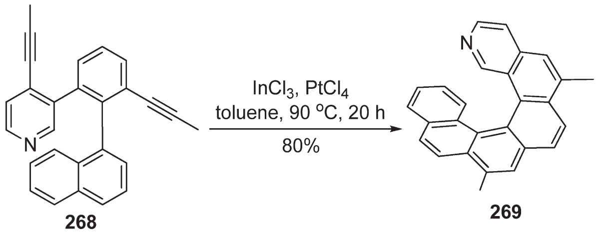
**5.1.1. CPL-Induced Asymmetric Photocyclization.** In the 1970s, Kagan, Kelvin, and co-workers investigated the asymmetric synthesis of helicenes by CPL.[146] Three mechanisms were proposed: (i) asymmetric photodestruction,[147] in which the enantiomerically enriched helicenes were produced by preferential destruction of the other enantiomer induced by CPL; (ii) partial photoresolution,[148] such that when the racemic dihydrohelicene formed after cyclization one enantiomer might have a stronger absorption and revert to the olefin, thus making the subsequent oxidation slower and leading to optical activity; and (iii) asymmetric synthesis,[149] based on unequal amounts of different conformations of precursors under certain CPL conditions, resulting in enantioenriched products.[146d]

Comparing the photosynthesis with the photodestruction of hexahelicene (**355a** and **8**) in Table 2, the magnitudes of opposite rotations are very similar under the same right-CPL (r-CPL)[146b] and no optical rotation was detected when the racemic hepta- and octahelicenes were irradiated with CPL.[146d] Therefore, optical activity obviously does not result from an asymmetric photodestruction mechanism.

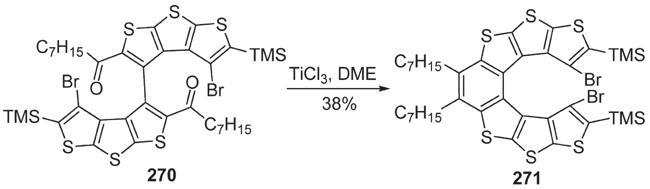
Partial photoresolution involves a photostationary state in which the dihydrohelicene enantiomers are converted into diarylethylene at different rates under CPL. However, according to Muszkat and Fisher, since the conversion cis ↔ trans is faster than the subsequent cyclization and oxidation and the rates of cyclization (**355** to **357**) and oxidation (**357** to **356**) were comparable, dihydrohelicene could not be accumulated.[150] Thus, the mechanism partial photoresolution is also an unlikely explanation.

Hammond pointed out that the excitation is localized at the large aryl group for the lowest excited singlet ($S_1$) state of the stilbene in the photocyclization procedure.[151] For **355**, the excitation was localized in the benzophenanthryl moiety, but the phenyl group could rotate freely along the phenyl—ethylene

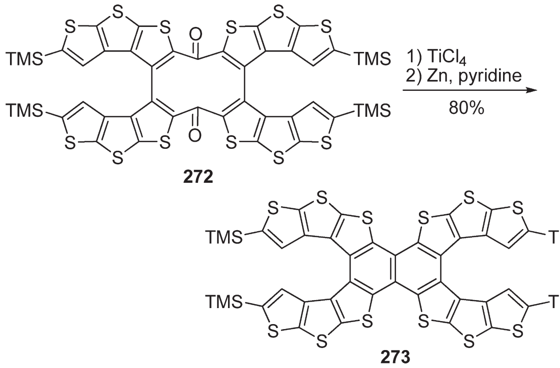
### Scheme 57



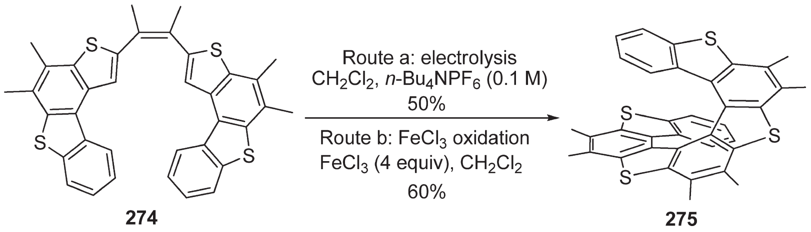
### Scheme 58



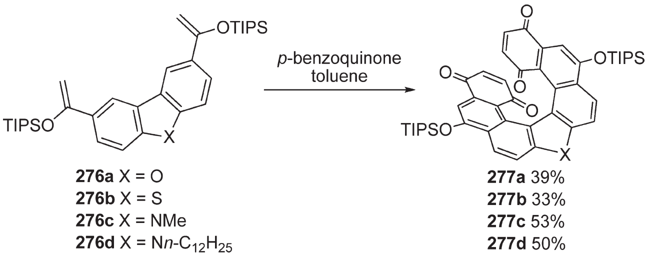
### Scheme 59



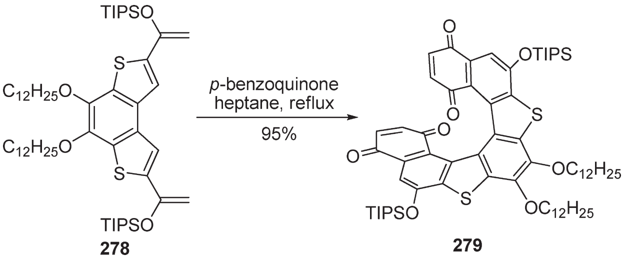
### Scheme 60



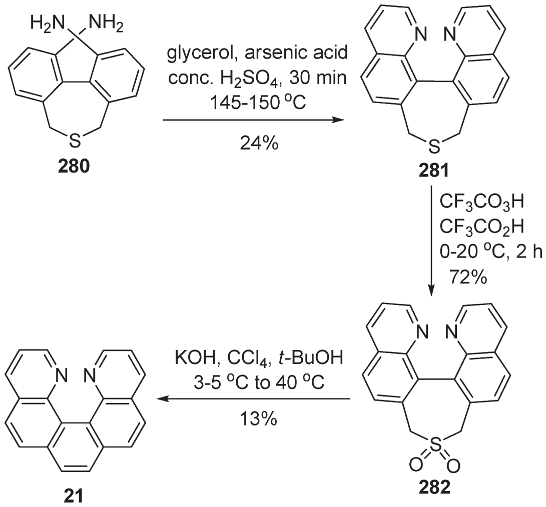
### Scheme 61



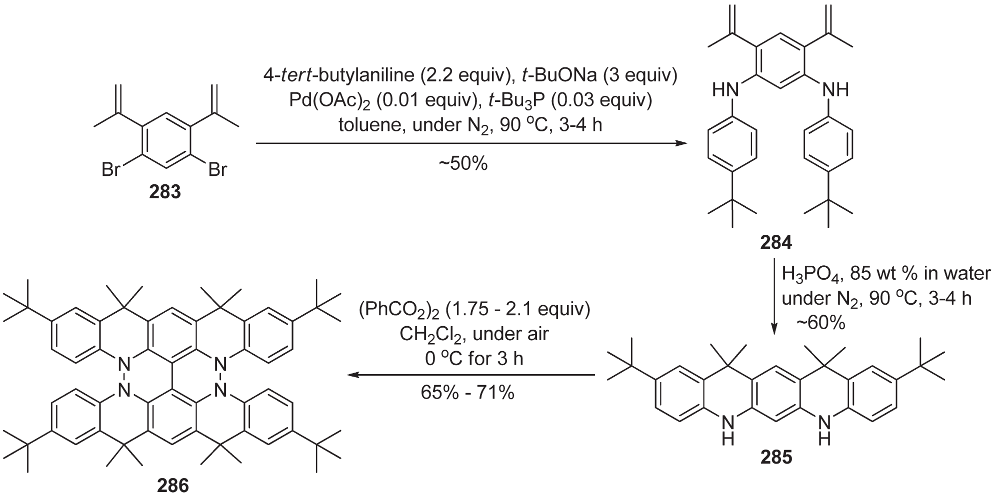
### Scheme 62



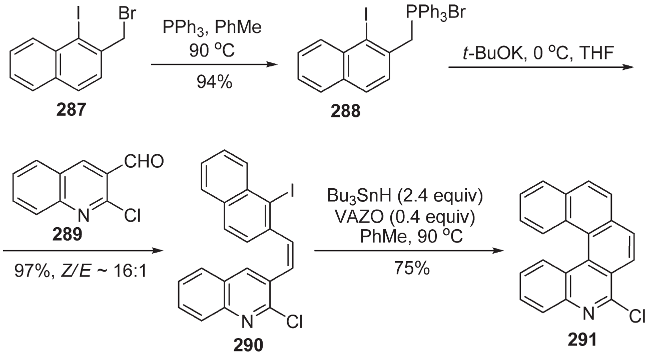
### Scheme 63



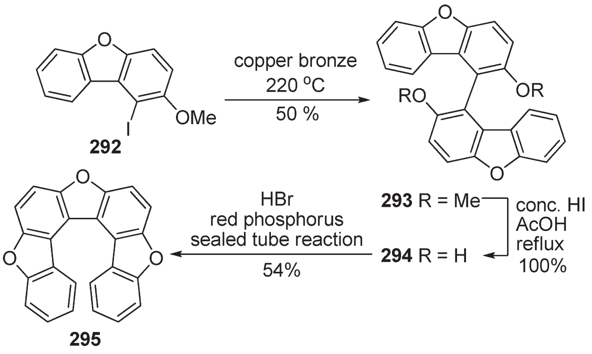
Scheme 64



Scheme 65

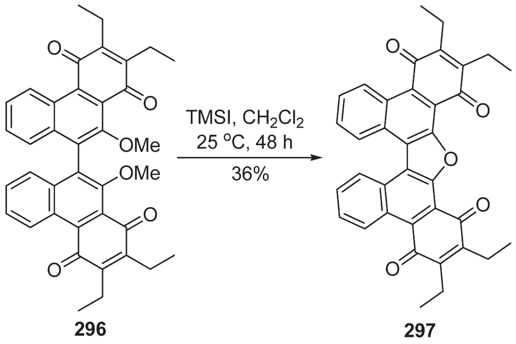


Scheme 66

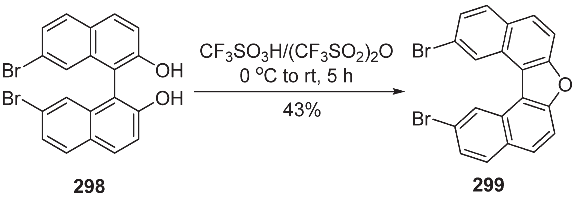


bond (~180°), while the naphthyl group had less freedom to rotate due to its asymmetry in stilbene **358** (Scheme 81).[146d] This explains why the optical activity using **358** ($[\alpha]^{23}_{436} = -30.0 \pm 0.3°$, $c$ 1.29)[146b] was much higher than that observed using the precursor **355a** under the same conditions. Consequently, asymmetric synthesis seems the most plausible of the three proposed mechanisms.

Scheme 67



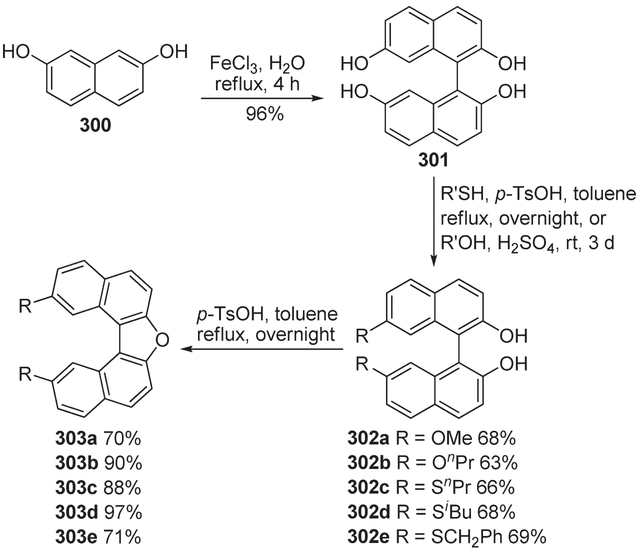
Scheme 68



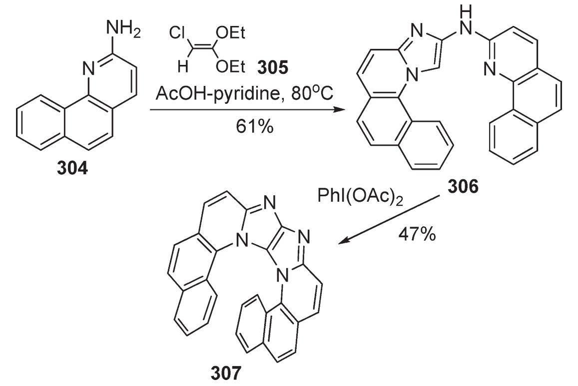
Structural effects in the CPL-induced asymmetric synthesis of hexahelicene were investigated by Buchardt and co-workers.[146c,e] For entries 1−5 in Table 2, optical yields increased as the R$^2$ functional group became larger. Comparing entries 2 and 5 with entries 6 and 7, it is obvious that R$^1$ has a larger hindrance to the rotation of the phenyl moiety in the excited state and entries 2 and 5 provide strong evidence for the asymmetric synthesis mechanism.[146e]

**5.1.2. Chemically-Induced Asymmetric Photocyclization.** Besides asymmetric photosynthesis induced by CPL, introduction of bulky chiral groups into the terminal rings has also been employed, since one terminal ring stacks on the other. As shown in Scheme 82, Katz and Sudhakar introduced a large

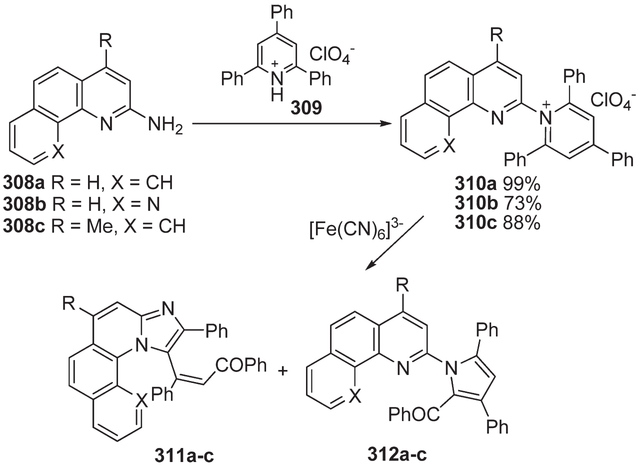
Scheme 69



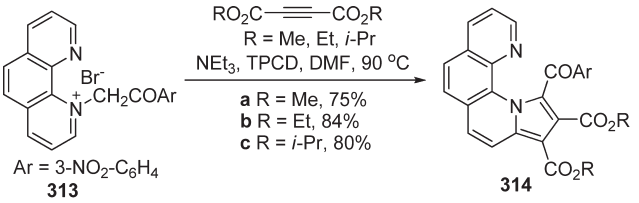
Scheme 70



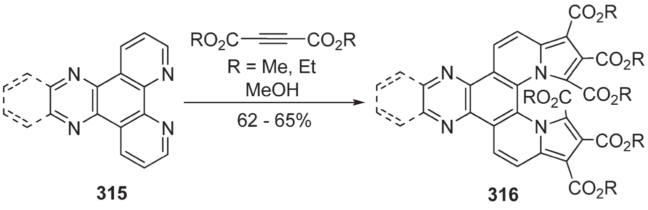
Scheme 71



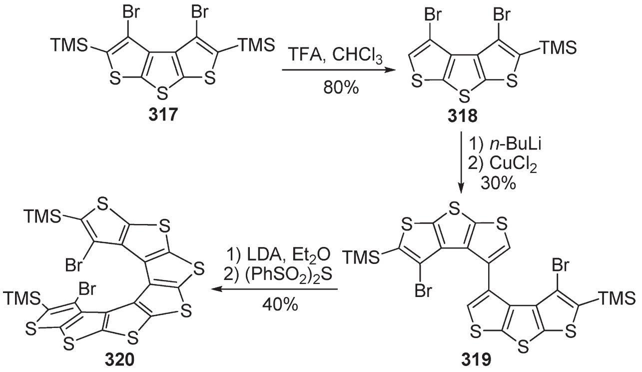
Scheme 72



Scheme 73



Scheme 74



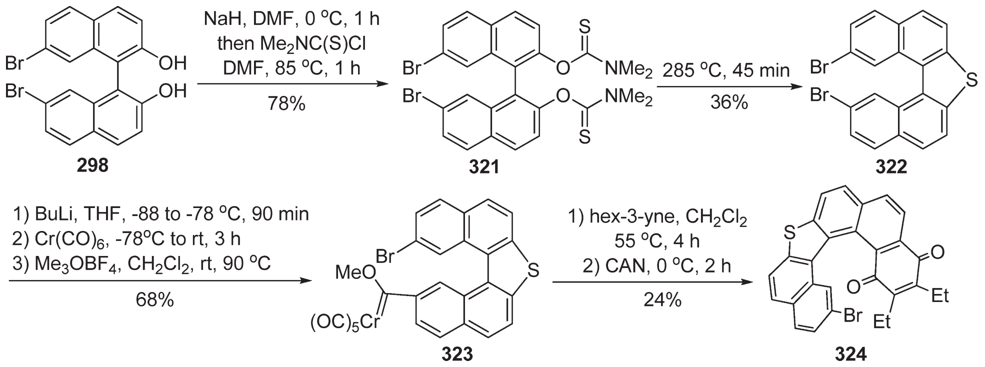
*tert*-butyl-dimethylsilyloxy group at the C(1) position on one terminal ring of **359** which directed the cyclization by keeping the bulky silyloxy substituent outside to lower the activation energy. When the stilbene was wound into a helical structure, (*M*)-helicene **361** bearing two cyclopentadiene moieties was obtained with good yield and enantioselectivity and can be used to build helical metallocenes.[9a]

Another route using diastereoselective photocyclization of bis(stilbene) via menthyl esters was developed by Carbery and Pearson.[152] As shown in Scheme 83, the bis(stilbene) **364**, which was prepared by Wittig olefination, underwent a cyclization directed by two (−)-menthyl groups on the termini with a good diastereomeric ratio. However, if only one chiral auxiliary was incorporated, there was little diastereoselectivity.

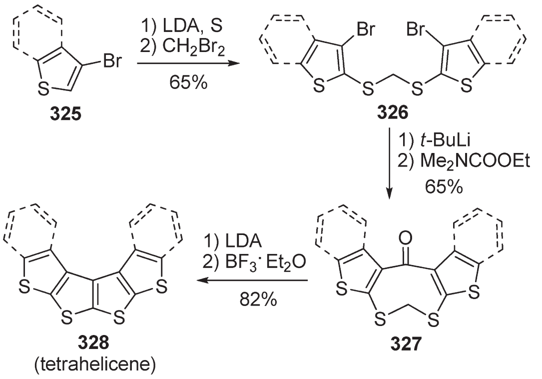
Osuga and co-workers utilized 3-amino-2-hydroxybornane as a chiral auxiliary to control the diastereoselectivity in a photocyclization process (Scheme 84).[153] Although the yield was good, the diastereomeric ratio was low, which suggests that only one chiral auxiliary is not sufficient and that a better result might be achieved if the carboxamide unit was at the most sterically hindered position.

**5.1.3. Metal-Catalyzed Asymmetric Synthesis.** In 1999, Starý, Stará, and co-workers first disclosed the asymmetric synthesis of tetrahydrohelicene using a $Ni^0$ catalyst with Hayashi's ligand[12a] **372** (Scheme 85).[78b,e,154] The helicity of

**Scheme 75**



**Scheme 76**



(+)-tetrahydro[6]helicene was successfully controlled by asymmetric [2 + 2 + 2] cycloisomerization. This one-step, efficient route made the enantioenriched precursors of the helicenes easily accessible in moderate yields with 42−48% ee.

Starý, Stará et al. also reported a helicity-controlled strategy for the asymmetric synthesis of [7]helicene-like molecules.[154,155] As shown in Scheme 86, an asymmetric carbon is present in the triyne **373**. During cyclization under catalysis by CpCo(CO)$_2$/PPh$_3$, the stereogenic chirality was transferred to helical chirality.[154,155] Interestingly, the functional group R had a marked impact on the diastereoselectivity: when R = H, (*M*,*S*)-**374a** was the major product (with a diasteromeric ratio of 92:8), while the diastereoselectivity was reversed and became higher for R = *o*-tolyl.[154,155] For CpCo(C$_2$H$_4$)$_2$-mediated cycloisomerization at room temperature, a loss of diastereoselectivity was observed.[155b] However, for **374c**, the diastereoselectivity could be enhanced by raising the temperature, indicating that a thermodynamic-controlled process was involved.

In addition to Starý's asymmetric synthesis of helicene-like molecules controlled by the stereogenic carbon in the precursor, Tanaka and co-workers recently utilized chiral bidentate phosphine ligands with [Rh(cod)$_2$]BF$_4$ to synthesize [5]-, [7]-, and [9]helicene-like molecules.[82,156] In the cyclization of triynes, (*R*,*R*)-Me-Duphos and (*S*)-xyl-Segphos were examined. Triyne **375** gave the best result with a Rh(I)/**378a** catalyst, affording (−)-**376** in 71% yield and 85% ee. Interestingly, in addition to the [2 + 2 + 2] product **376**, the [2 + 1 + 2 + 1] product **377** was found in 10% yield as a result of a C≡C triple bond cleavage process (Scheme 87).[156] Later, Tanaka and co-workers developed a novel strategy to construct enantioenriched [7]- and [9]helicene-like molecules via double [2 + 2 + 2] cycloaddition between different tetraynes **379a**,**b** and dialkynylketones **380a**,**b** in the presence of [Rh(cod)$_2$]BF$_4$ and the ligand **378b** (Scheme 88).[82] This method, producing enantioenriched helicene-like molecules in up to 60% ee, is highly efficient in terms of building five rings in one step.

Similarly, asymmetric [2 + 2 + 2] cycloaddition involving arynes for the preparation of helicenes was reported by Pérez, Guitián, and co-workers (Scheme 89).[12b] Several isomers were obtained, and the enantiomeric excesses of helicenes varied from 0% to >90% with different yields as the reaction conditions were changed.

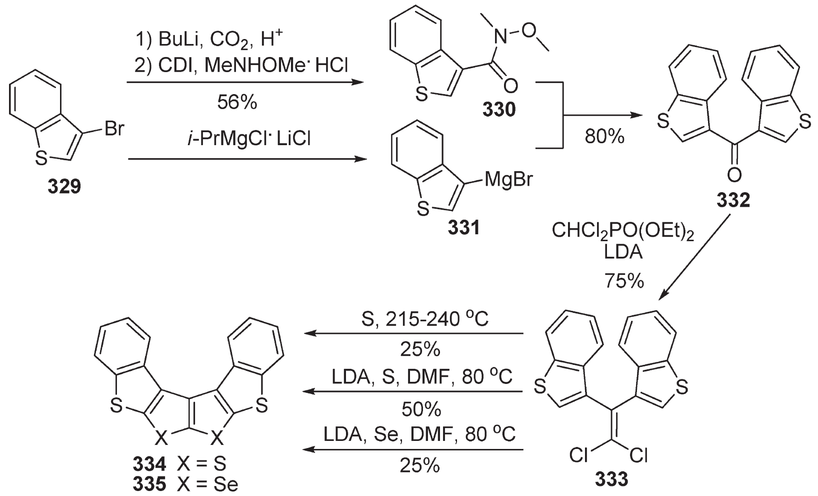
Besides the addition reactions of arynes and alkynes, biaryls are also important precursors to enantioenriched helicenes and the absolute configurations of the precursors determine the enantioselectivity of the reaction.

Recently, Collins and Grandbois achieved the enantioselective synthesis of [7]helicene in high ee by asymmetric ring-closing metathesis (Scheme 90).[12c] In this approach, adding the achiral olefin additive vinylcyclohexane—which enables the reversible binding between the catalyst and the substrate by controlling the propagation procedure—and using hexafluorobenzene as a solvent were important factors in enhancing the kinetic resolution.

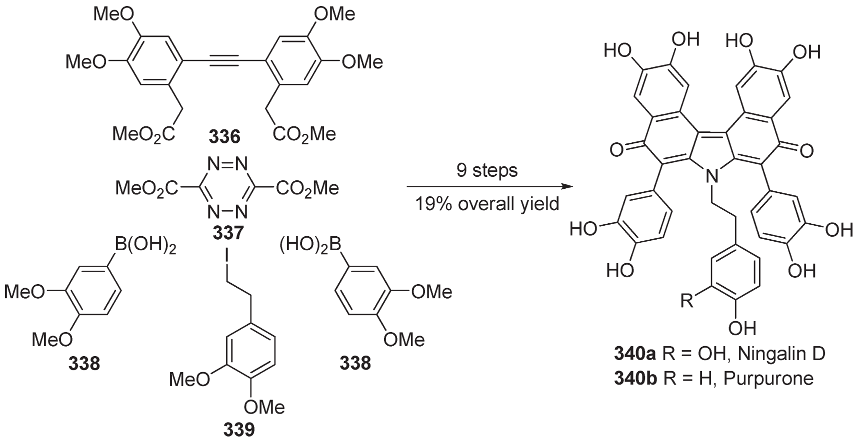
An efficient Pd-catalyzed synthesis of aza- and oxahetero[7]helicene has been described by Nozaki and co-workers utilizing double *N*-arylation and intramolecular *O*-arylation in high ee (Scheme 91).[12d] Given that the high temperature would be expected to facilitate racemization, helicene **389** was prepared using shorter reaction times (20% ee, 96 h, 100 °C; 94% ee, 13 h, 100 °C) whereas helicene **388** could be obtained after longer reaction times (>99% ee, 123 h, 100 °C), indicating that it had a higher barrier to racemization than **389**. The dibromo- and tetrabromo-9-aza[7]helicenes were easily prepared by regioselective bromination in reactions with 2 and 4 equiv of NBS.

In 1997, Tanaka, Suzuki, and Osuga prepared the thiahetero[7]helicene **395** in 99% ee via asymmetric Ullmann coupling and subsequent intramolecular McMurry coupling by means of which the central chirality was successfully transformed into axial chirality and helical chirality (Scheme 92).[157] The oxazoline substituents play a key role not only in the enantioselectivity but also in providing an atropisomeric biaryl **393** with stable $C_2$ symmetry, which subsequently is converted into a dialdehyde for the further coupling reaction.

Scheme 77



Scheme 78

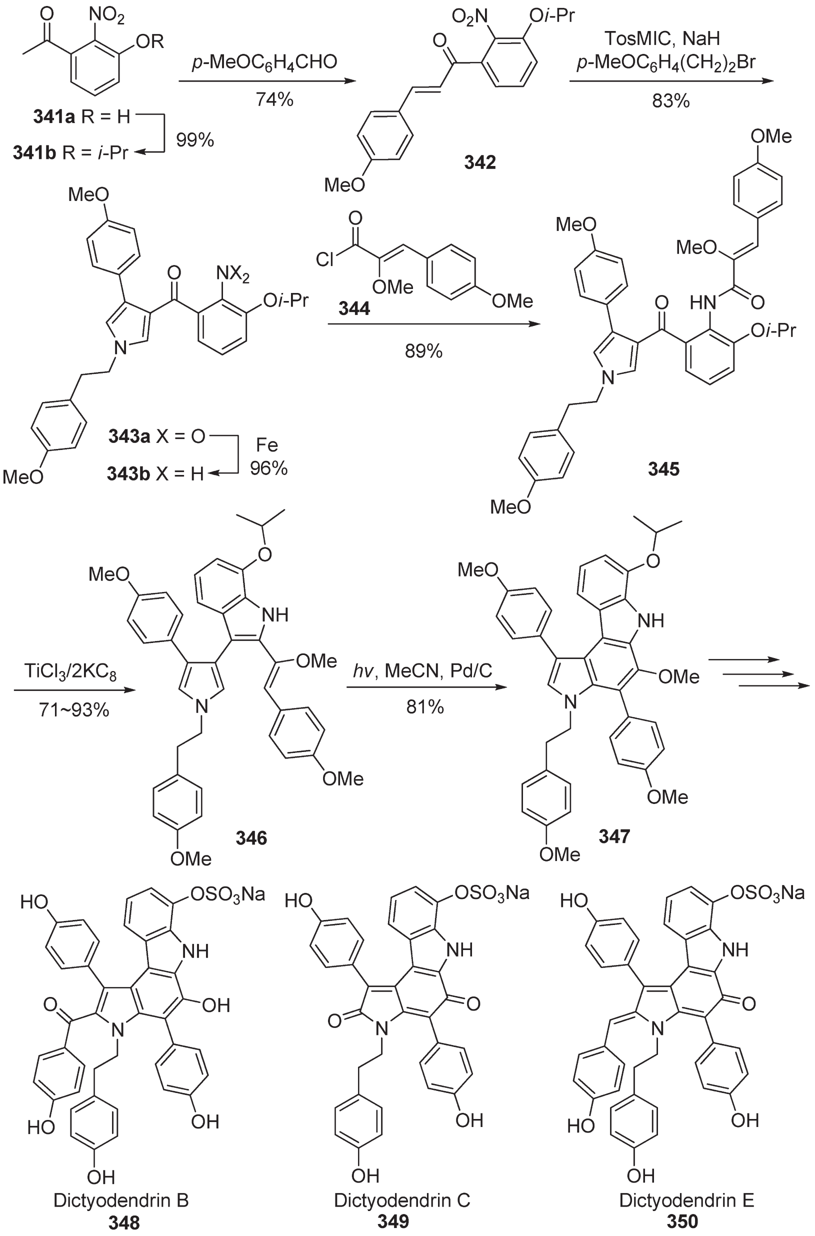


In addition, use of an optically pure 1,1′-binaphthyl derivative **159** to prepare pentahelicene via a lithium-induced synthesis was reported by Both and Bestmann.[15f] As shown in Scheme 93, the bisphosphonium periodate **397**, obtained after reaction between the (*S*)-binaphthyl derivative **159** and $PPh_3/NaIO_4$, underwent ring closure affording the optically active [5]helicene **3** in the presence of LiOEt. Thus, the absolute configuration of the helicene can be easily deduced from the configuration of (*S*)-binaphthyl **159**. The reaction was carried out at low temperatures (−5 to 0 °C) because [5]helicene is not optically stable at room temperature.

**5.1.4. Asymmetric Diels–Alder Reactions.** Carreño, Urbano, and co-workers, employing (*SS*)-(+)-(2-*p*-tolylsulfinyl)-1,4-benzoquinone **398** as the dienophile, prepared a variety of dihydro[4]helicenequinones, dihydro[5]helicenequinones, and tetrahydro[7]helicenequinones which can be easily oxidized to helicenes.[11d,45,65] In 1999, Carreño's group reported the first example of the enantioselective synthesis of (*P*)-[5]helicene with 80% ee (Table 1, entry 28).[11d] Since high pressure was needed, another route with milder conditions was subsequently developed (Scheme 94).[65e] The optimized conditions were found to be as follows: (i) to obtain good enantioselectivity, the synthesis should be carried out at low temperatures; (ii) to reduce the reaction time, the dienes should be modified by electron-donating substituents to lower the activation energy; (iii) to facilitate the aromatization procedure, electron-rich dienes are preferred.[45,65c,65f] Mono- or double-Diels–Alder cycloaddition processes afford the helicenes with good enantioselectivity from 84% to >99% ee (Scheme 95).[65b,e]

Recently, the same authors described an efficient and convergent approach to synthesize (2-biphenyl)-substituted configurationally stable dihydro[4]helicene **405** in 100% diastereoisomeric excess via dynamic kinetic resolution (DKR) (Scheme 96).[1p,65a,158] The chirality was transformed from the central chirality to axial chirality and then to helicity. The optical yields of this one-pot approach, based on the domino asymmetric cycloaddition, sulfoxide elimination, and oxidative aromatization as key steps, are determined by the first step, while the absolute configuration of the helicenequinones is influenced by the oxidizing agent employed.[65c]

Scheme 79



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**5.1.5. Asymmetric Rearrangements.** An interesting one-step method to synthesize optically active pentahelicene by a Stevens rearrangement was described by Závada and co-workers.[159] As shown in Scheme 97, the (*S*)-binaphthyl quaternary ammonium salt **406** was first converted into an amine by treatment with *n*-BuLi, which then underwent an elimination reaction to give helicene **3** in >99% ee. Low temperatures must be employed, because the product is not optically stable at room temperature.

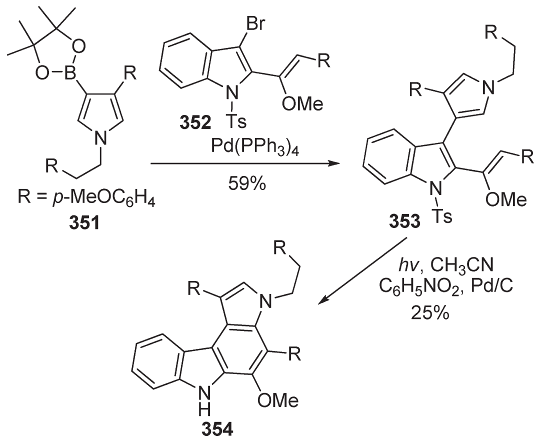
Furthermore, synthesis of pentahelicene using an oxy-Cope rearrangement was disclosed by Karikomi and co-workers in 2002.[160] The authors later found that this method had good enantioselectivity. The precursor **409**, prepared as a major product from (−)-**407**, was rearranged to give **410**, which was transformed to (*P*)-pentahelicene **411** in four steps in >98% ee (Scheme 98).[22m]

**5.1.6. Chiral Additives.** In 2004, Rajca and co-workers first disclosed the asymmetric synthesis of carbon−sulfur [7]helicene by adding (−)-sparteine, a chiral additive,[161] which is widely used in regio-, diastereo-, and enantioselective lithiation substitutions.[162] Reaction of bis($\beta$-trithiophene) **319** with LDA in the presence of (−)-sparteine **412** followed by addition of bis(phenylsulfonyl)sulfide at −78 °C gave (*M*)-helicene **320** in 19−47% ee (Scheme 99). However, it is still not clear whether the enantioselectivity results from kinetic resolution via the asymmetric deprotonation or in the subsequent ring closure reaction. The yield and enantiomeric excess are not high,[22z,136] but this one-step approach is still of great value.

In addition, a new kinetic resolution utilizing (−)-B-chlorodiisopinocampheylborane **414** to reduce one carbonyl group of (+)-**270** with 50% conversion was reported by the same authors (Scheme 100).[22y] After separation and subsequent PCC oxidation, enantioenriched **270** was obtained in reasonable yields and 56−71% ee and was then converted into the corresponding optically active tetrathia[7]helicene by a subsequent McMurry reaction.

Twenty different types of asymmetric synthesis of helicenes and helicene-like molecules, with low to excellent enantioselectivity or diastereoselectivity, have been discussed above. Of these, asymmetric rearrangement and use of chiral additives are not generally applicable for preparation of other helicenes because of the unavailability of suitable precursors; asymmetric synthesis accomplished by photocyclization is difficult to scale up for large-scale preparation, and the methods for the synthesis of [5]-helicenes are also not practical since the products undergo racemization at room temperature. In general, metal-catalyzed approaches and asymmetric Diels−Alder methods, affording helicenes (or helicene-like molecules) in moderate to good yields with excellent enantioselectivity (diastereoselectivity), are the most practical, although the latter generally require long reaction times (usually several days).

Scheme 80

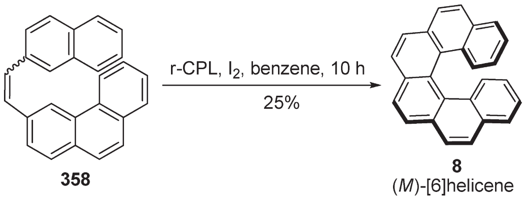


## 5.2. Optical Resolution

Helicenes undergo racemization easily at high temperatures and in some cases even at room temperature. From section 5.1, it can be clearly seen that the products of asymmetric synthesis do not have satisfactory optical purity. Therefore, to investigate and utilize helicenes, efficient ways for optical resolution are of great significance since they are still the most practical way to obtain optically pure helicenes. Since the first reports of the resolution of 1-methyl[4]helicene **6**[4d] and hexahelicene **8**[5a,b] by L-menthol and 2-(2,4,5,7-tetranitro-9-fluorenylideneaminooxy)propionic acid (TAPA) **416** (Figure 11),[163] respectively, several new approaches for optical resolution have been discovered.

**5.2.1. Crystal Picking and Recrystallization.** In early research, recrystallization in the presence of a chiral reagent and crystal picking were the principal methods employed for

Scheme 81



Scheme 82

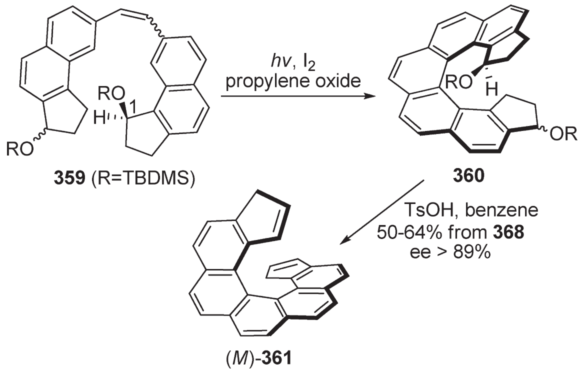
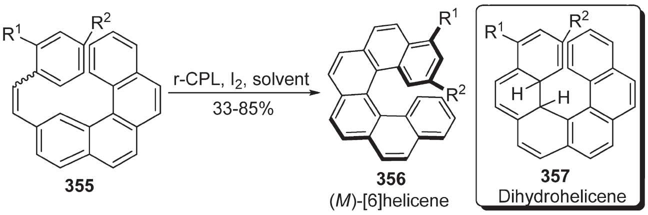


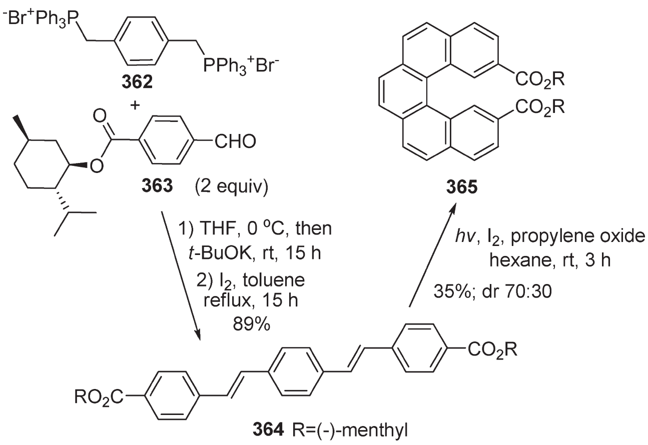
Table 2. Optical Rotations for Photosynthesis and Photodestruction of [6]Helicenes



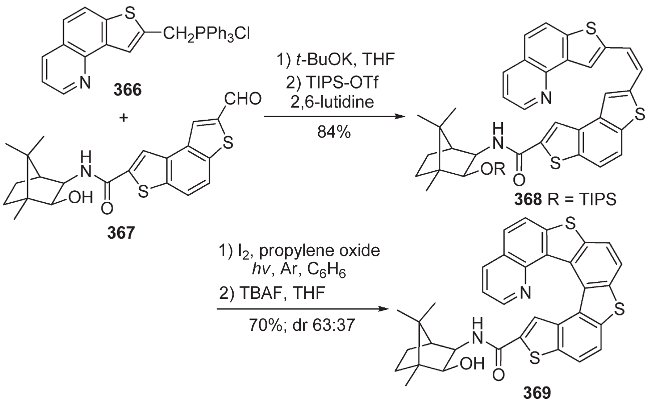
| entry | precursor stilbene **355** | product [6]helicene **356** | cond.[a] (time) | $[\alpha]^{20}_{436}$ in deg (conc.)[b] **356** | photodestruction | $[\alpha]^{23}_{436}$ in deg (conc.)[b] | ref |
|---|---|---|---|---|---|---|---|
| 1 | **a**: $R^1 = R^2 = H$ | **8** | A (6 h) | −7.6 ± 0.4 (1.29)[c] | **8** (rac) | + 7.5 ± 0.3 (1.99) | 146b |
| | | | B (24 h) | −8.0 ± 0.8 (5.91) | | | 146e |
| 2 | **b**: $R^1 = H, R^2 = F$ | **b** | B (24 h) | −10.5 ± 0.9 (5.54) | | | 146e |
| 3 | **c**: $R^1 = H, R^2 = Cl$ | **c** | B (24 h) | −16.4 ± 0.8 (6.60) | | | 146e |
| 4 | **d**: $R^1 = H, R^2 = Br$ | **d** | B (24 h) | −23.8 ± 0.9 (5.85) | | | 146e |
| 5 | **e**: $R^1 = H, R^2 = Me$ | **e** | B (36 h) | −36.4 ± 1.0 (5.03) | | | 146e |
| 6 | **f**: $R^1 = F, R^2 = H$ | **f** | B (36 h) | −31.5 ± 1.2 (4.10) | | | 146e |
| 7 | **g**: $R^1 = Me, R^2 = H$ | **g** | B (24 h) | −35.6 ± 1.0 (5.08) | | | 146e |

[a] Conditions: A benzene, B toluene. [b] Concentration (mg/mL), $CHCl_3$. [c] $[\alpha]^{23}_{436}$.

Scheme 83



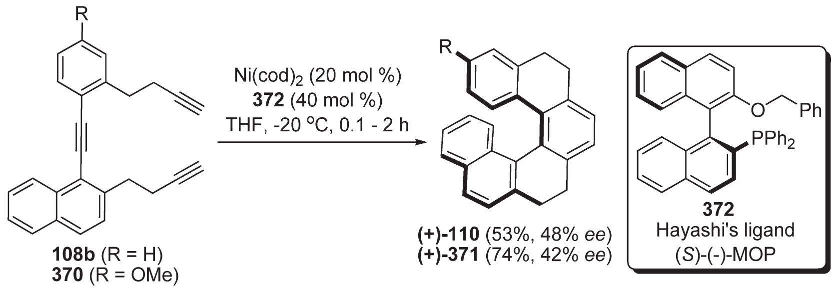
Scheme 84



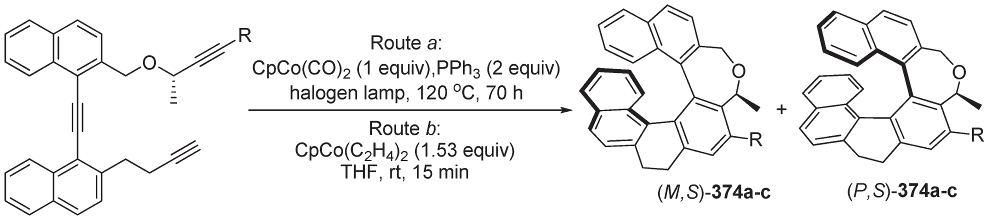
optical resolution.[6c,g,7b] Because the latter approach suffers from limitations of scale,[6b] the former tended to be favored, although low optical purities were sometimes found.[6c] Both (+)- and (−)-TAPA have been widely used to separate helicene enantiomers, because they form charge-transfer complexes,[5a,b] in which (*S*)-(+)-TAPA has a stronger interaction with (*M*)-(−)-helicenes and vice versa.[28d,g,164] The racemates of [6]- to [14]-helicene were resolved using TAPA. Moreover, Starý's group used (+)-tartaric acid derivative **417** to resolve 1-aza[6]helicene giving the (+)-enantiomer in 75% ee;[117] Newman utilized cinchonidine **419** for the optical resolution of 1,12-dimethyl-[4]helicene-5-acetic acid;[5c] Yamaguchi's group found that the quinine **420** has a stronger interaction with (*P*)-**81a**, leaving the (−)-enantiomer in the mother liquid;[72a] and Wang's group used brucine **421** for the optical resolution of 1-nitrotetrahydro-[5]helicene anhydride by recrystallization.[165] In addition, a chiral environment, for example, using (−)-α-pinene **418** as a solvent, can also facilitate the resolution of helicenes.[6b,8c,8e]

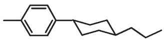
**5.2.2. Direct Resolution by HPLC.** Optical resolution of helicenes by HPLC was first studied by Mikeš and co-workers in 1976.[28d,166] With short silica gel (7 μm) columns coated with optically active TAPA or TABA (10−25%) and cyclohexane−$CH_2Cl_2$ as the mobile phase, the enantiomers of [5]- to [14]helicene were resolved based on the charge-transfer interactions.[28d] Later, Kawazura's group reported better results using a silica gel (5 μm) column (30 cm) bonded with 11% (*S*)-(+)-TAPA and 50% hexane−$CH_2Cl_2$ as the mobile phase.[28g,42] Since then, a variety of chiral stationary phases have been utilized to separate the enantiomers of different helicenes. The optical resolution of hexa- and pentahelicene crown ether was achieved by HPLC using a column packed with (+)-poly(triphenylmethyl methacrylate),[167] while 2,13-dicyano-[5]helicene was resolved by means of a column packed with

Scheme 85



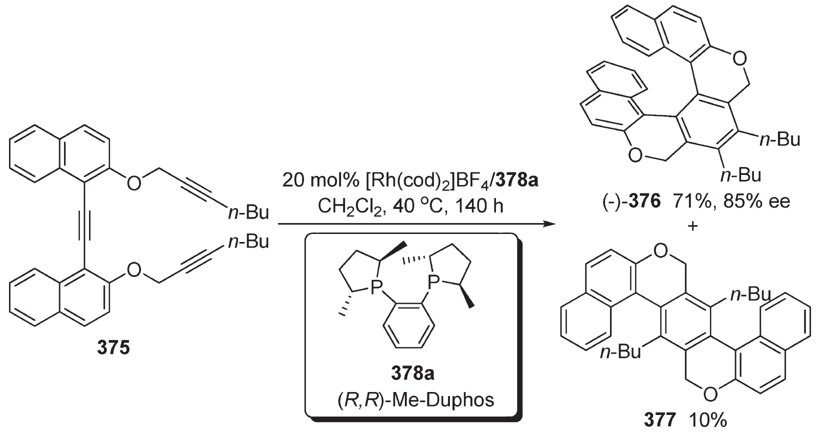
Scheme 86



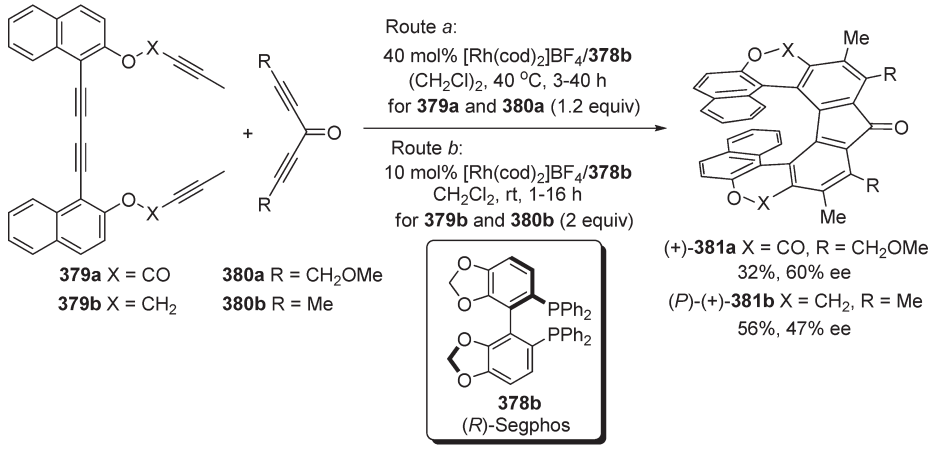
| Route | | R | yield | dr (*M*,*S*)-**374**:(*P*,*S*)-**374** |
|---|---|---|---|---|
| *a* | **374a** | H | 63% | 92:8 |
| | **374b** | *o*-tolyl | 66% | 0:100 |
| *b* | **374c** |  | 75% | 56:44<br>19:81 |

heating

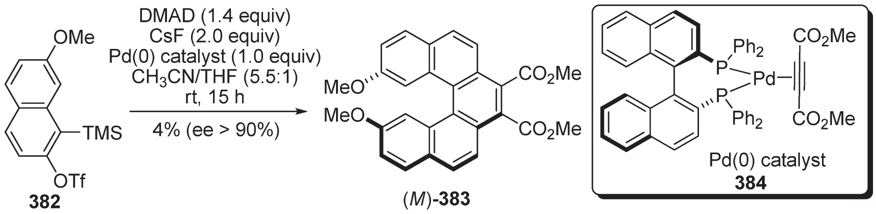
**Scheme 87**



**Scheme 88**



**Scheme 89**



γ-cyclodextrin.[22l] With the help of Chiralcel OD columns, [5]-helicene **3**[168] and [7]helicene **17**,[169] Carreño's helicenequinones,[65e,f] Yamaguchi's [4]helicene diacid **81a**,[71] azahelicenes such as 4-, 5-, and 6-aza[5]helicene,[13w] 1- and 2-aza[6]helicene,[117] aza[6]helicene diyne,[170] thiaheterohelicenes including 2,13-bis(trialkylsilyl)tetrathia[7]helicene[22aa] and **395**,[157b] Starý's helicene-like molecules,[155b] and Takenaka's *N*-oxide catalysts[116] were all resolved. Chiralpak AD columns were used for optical resolution of 14-methoxy-3-aza[6]helicene,[171] **40** and **41**,[13v] and Rajca's thiaheterohelicenes.[22y] In addition, Lacour's [4]helicenium cation **240** was also resolved using Chiralcel OD-RH[172] or Chiralpak AD-H columns.[24b]

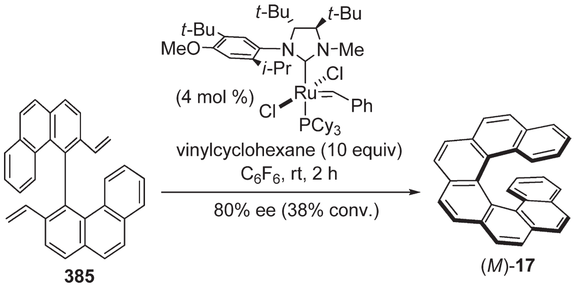
**5.2.3. Chiral Auxiliaries.** Different chiral auxiliaries for optical resolution of helicenes by HPLC or column chromatography have been reported (Figure 12). Some of these can also be used as probes to determine the absolute configuration. Lacour and co-workers introduced BINPHAT **422b** and (*R*)-(+)-methyl-*p*-tolylsulfoxide **423b** to separate [4]heterohelicenium dyes, since the former gives complexes with helicenium cations while the latter reacts with the cations to give diastereoisomers.[24b,173]

(*R*)-**424b** can be used in the case of helicenes containing hydroxyl groups.[174] Because of the rigid and bulky structure of bornane, several different chiral auxiliaries had been developed based on this species. Katz and co-workers utilized (*S*)-camphanoyl chloride **425b** to separate bis(quinone) systems which had been first reduced by Zn[11c,99,124] or $Na_2S_2O_4$ with water.[11e,g,66a,175] **426b** was used by Yamaguchi and co-workers to resolve [4]helicene dicarboxylic acid,[72a] and **427c** was utilized by Tanaka and co-workers for resolution of heterohelicenes.[22r,153,176] Simple pyrrolidine and menthol skeletons bearing chiral centers have also been investigated. The anhydride **428b** was incorporated onto the termini of the bis(quinone) helicenes, similar to **425b**, to produce diastereoesters.[11b] In the case of **429b** and **430b**, the former can be substituted at the $\alpha$-position of the termini of thiaheterohelicenes[161] while the latter acts as a strong base reacting with acids or acyl chlorides to give diastereoisomers.[177]

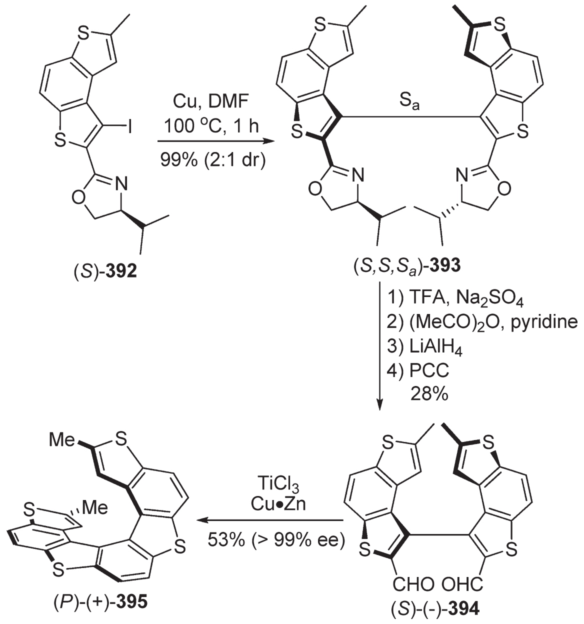
As an alternative to organic chiral auxiliaries, Hassine et al. described a new method for resolution of 2-(diphenylphosphino)heptahelicene **432** with the help of a chiral Pd reagent (Scheme 101).[56a] After coordination, diastereomers were produced, which could be separated by column chromatography. The optically pure helicene ligand was released by reaction between the diastereomers and dppe.

**5.2.4. Enzymatic Resolutions.** In 1990, Liu and Katz reported an enzymatic hydrolysis method which afforded the optically active helicene **52a** in 62% ee (Scheme 102).[10] The method involved conversion of a hemiketal, prepared using sodium dithionite, into an acetate analogue by reaction with acetic anhydride. The key step, kinetic resolution, was achieved with the aid of bovin pancreas. Optically active **434** was obtained, which was readily oxidized to **52a**, leaving the enantioenriched

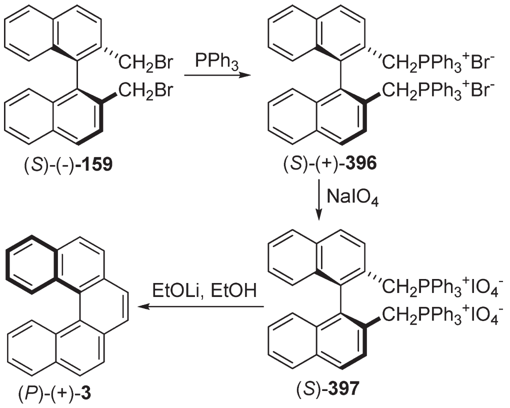
Scheme 90



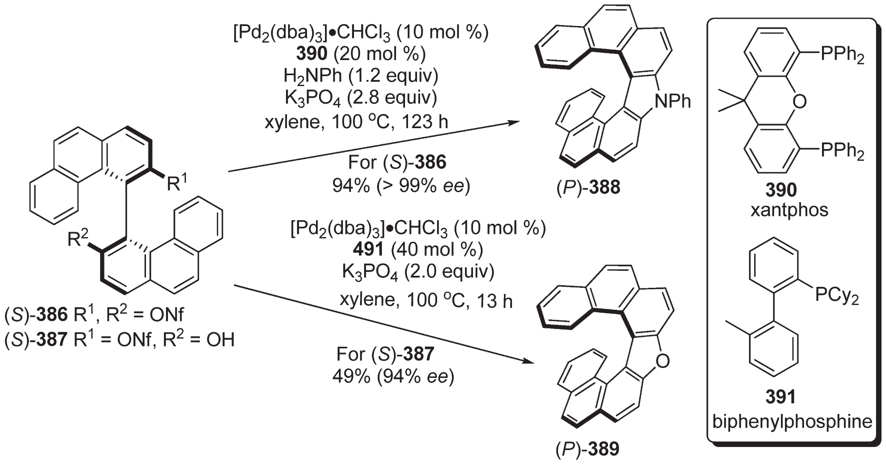
Scheme 92



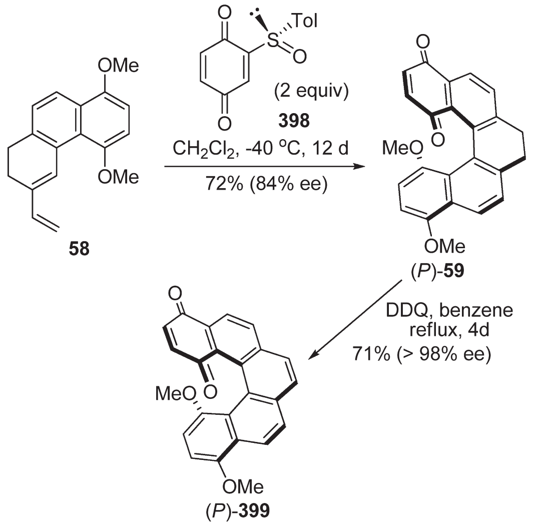
Scheme 93



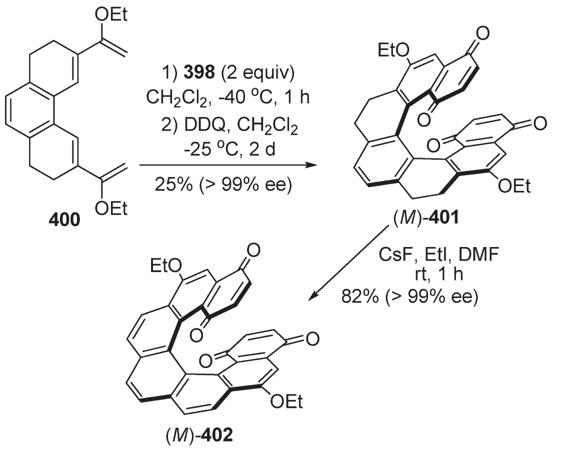
Scheme 91



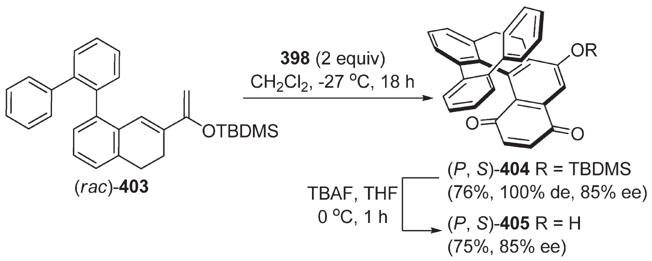
Scheme 94



Scheme 95

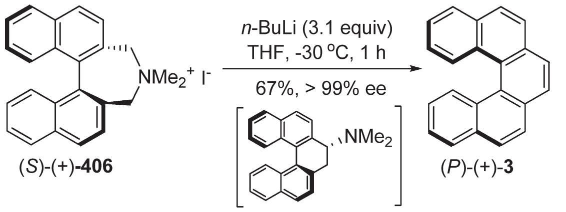


Scheme 96

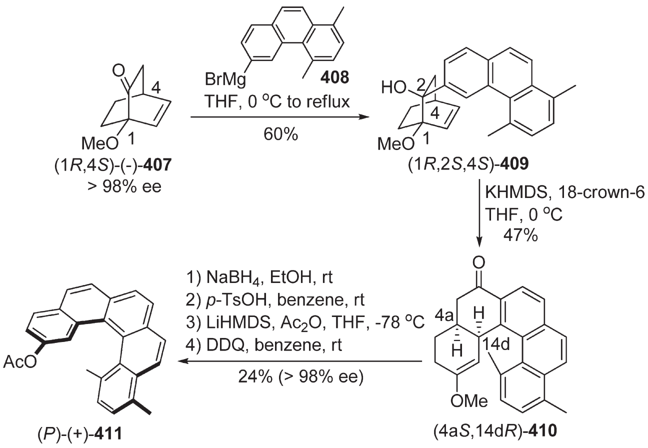


acetate **435** in 76% ee. Later, Yamada and co-workers used the protein bovine serum albumin (BSA) to convert the racemic 2-hydromethyl-trithia[5]helicene into the (*P*)-enantiomer utilizing the chiral recognition between the helical substrates and BSA.[178]

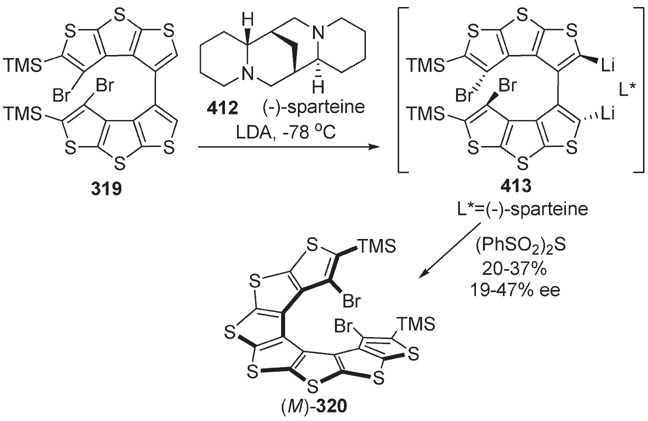
Scheme 97



Scheme 98

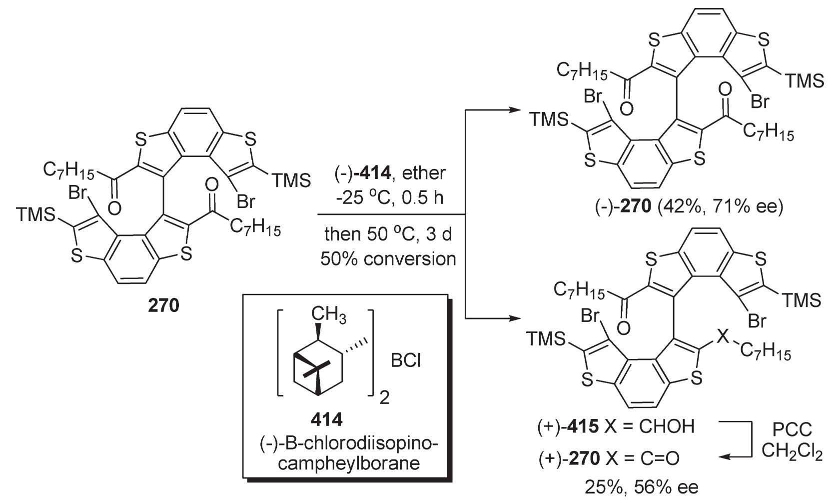


Scheme 99



Moreover, Tanaka and co-workers utilized lipase-catalyzed (*Pseudomonas cepacia* and *Candida antarctica*) enantioselective transesterification of the racemic heterohelicene **436** to achieve its optical resolution (Scheme 103).[179] **436** was transformed into the (*M*)-acetate and (*M*)-diacetate in the presence of *P. cepacia* and vinyl acetate, leaving (*P*)-**436** in 98% ee; (*M*)-**436** was regenerated by hydrolysis of the (*M*)-acetate and (*M*)-diacetate in 77% and 94% ee, respectively. When the *C. antarctica* lipase was used, the reaction gave (*M*)-**436** in 92% ee.

Scheme 100



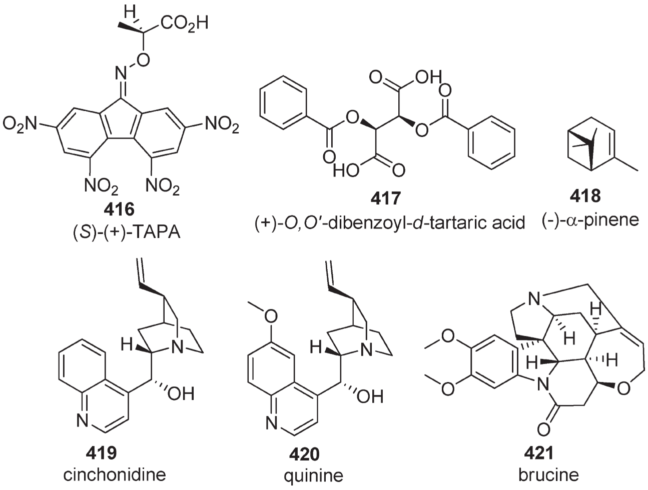


**Figure 11.** Some chiral reagents used for optical resolution of helicenes.

## 6. CHEMICAL REACTIONS AND TRANSFORMATIONS

### 6.1. Intramolecular Cyclization

As shown in Scheme 2, helicenes can undergo further cyclization by dehydrogenation in the presence of oxidizing agents, giving dehydrohelicenes as a result of forming an aryl−aryl carbon−carbon bond. For example, pentahelicene gives benzo[*ghi*]perylene **26** in the presence of iodine (Scheme 104).[9b] Surprisingly, photocyclization of the stilbenoid precursor **439** did not give helicene but rather the dehydrogenation product **440** (Scheme 105).[24a] The different behavior of precursors **439** and **209** (no further cyclizations were observed, Scheme 41) might be a result of the longer distance between C(1) and C(13) in **209**. However, **441** (Scheme 106) and **35** (Scheme 107) did not give similar products, because of the antibonding character of the newly formed carbon−carbon bond.[8a,22j] Interestingly, in the photoreaction of 1-fluoro[5]helicenes an unusual rearrangement was observed by Mallory and co-workers (Scheme 108).[47]

Several nonphotochemical strategies for preparing dehydrohelicenes have been reported. Chen et al. recently prepared **450** by treating the benzo[5]helicene **449** with DDQ and trifluoroacetic acid (Scheme 109).[69] Yamamoto's group and Scott's group reported cyclization of helicenes by thermal cyclodehydrogenation induced by flash vacuum pyrolysis (FVP) (Schemes 110 and 111).[75b,180] Moreover, dehydrogenation of [5]- and [6]helicene was achieved by the Scholl reaction (Scheme 112),[6c,f,i,150,181] and four different methods for cyclization of dibromothiahelicenes have been developed by Rajca and co-workers (Scheme 113).[27,182]

### 6.2. Reduction and Oxidation

There have been very few reports of the reduction of helicenes. In 2008, Thiel and co-workers prepared the metallocene $[(Dbf)_2Fe]$ **465**, which underwent selective hydrogenation under a pressure of 60 bar of hydrogen with a Pd/C catalyst (Scheme 114).[183]

Helicenebisquinones could be reduced by $Na_2S_2O_4$ (Scheme 115) or zinc with acid (Scheme 116), affording two hydroxyl groups at the most sterically hindered positions of the helicenes, which were optically resolved with the help of chiral auxiliaries.[11f,g] In addition, a semiketal **434** was obtained during the reduction of [5]helicene in the presence of $K_2CO_3$,[10] and the reduced products can be oxidized into bisquinones by CAN or benzeneseleninic anhydride as shown in Scheme 116.[11f]

Oxidation of [6]helicene with chromic acid at room temperature can produce the quinone **472** in which the electron-donating groups on the helicene accelerate the oxidation process.[8g] A subsequent benzylic acid rearrangement took place in the presence of NaOH to give **473**. After a Wolff−Kischner reduction, helicene **474**, bearing a five-membered ring, was obtained which could be converted into a chiral ligand after deprotonation (Scheme 117).[184]

### 6.3. Rearrangement

Acid treatment of 1-hydroxylmethyl[6]helicene **475** gives a spiro-compound **477**, in which a carbocation species may be formed (Scheme 118).[185] Furthermore, a similar product **481** was obtained by heating 1,3,14,16-tetramethyl[6]helicene **478** through an antarafacial 1,7-hydrogen shift, disrotatory electrocyclic reaction, and rearrangement via a 1,2-phenyl shift or a $[\pi_{2s} + \sigma_{2a}]$ reaction with subsequent 1,3-hydrogen shifts (Scheme 119).[186] Moreover, ring expansion of the helical backbone was disclosed by Martin and co-workers. The product **484** was obtained after an

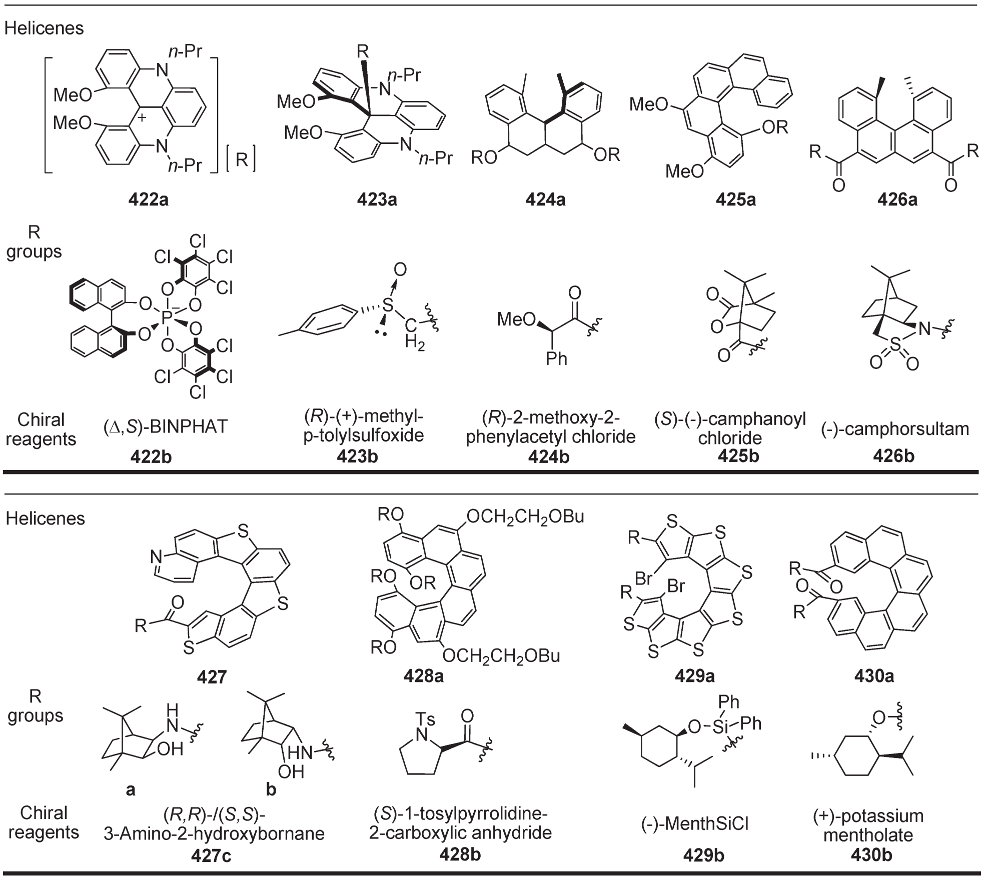
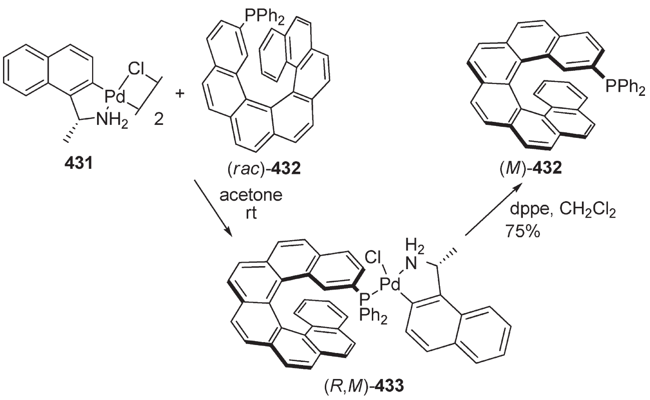
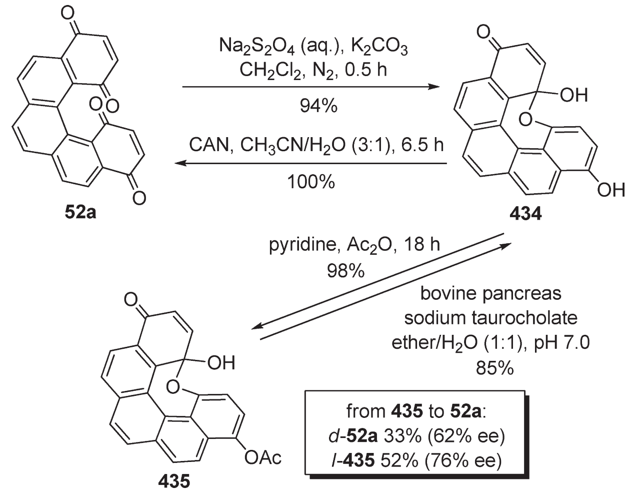


**Figure 12.** Some representative chiral auxiliaries for the optical resolution of helicenes.

**Scheme 101**



**Scheme 102**

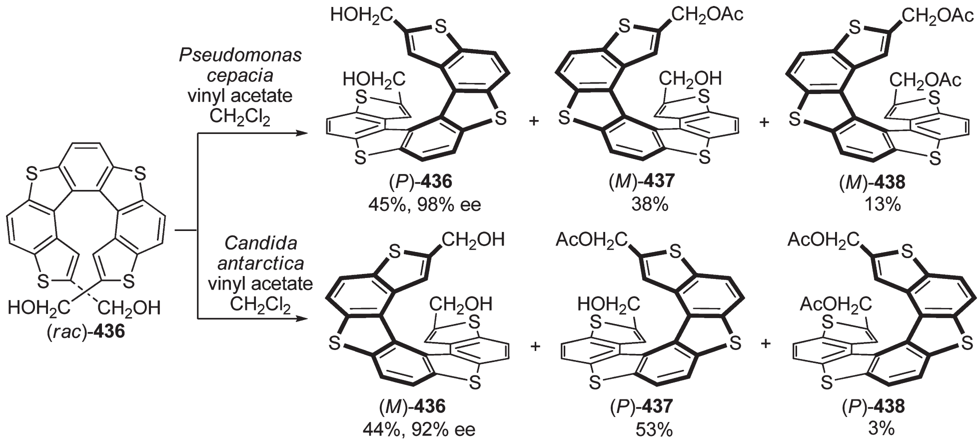


insertion reaction in which a carbene was formed in situ by heating **483** in the presence of NaH, giving a seven-membered ring (Scheme 120).[187]

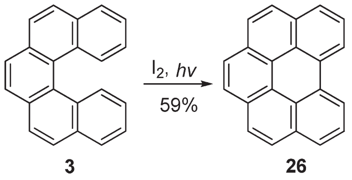
### 6.4. Intramolecular Addition

The Diels–Alder reaction of [6]helicene, giving a coronene ion, was first reported by Dougherty in 1968 based on its mass spectrum.[188] Martin et al. described another type of Diels–Alder reaction in 1975 (Scheme 121).[189] After **485** was reacted with a phosphorus ylide for 12 h, two isomers of **487** were obtained. When the reaction was carried out at room temperature, only **487a** was obtained. In 2004, Katz et al. reported the synthesis of two benzynes bearing helicene skeletons, which underwent intramolecular addition in situ (Scheme 122).[190] Treatment of **488** with tetramethylammonium fluoride gave benzyne by elimination of TMSOTf, which added to ring **F** together with one furan moiety affording **489** as an intermediate. Brief acid

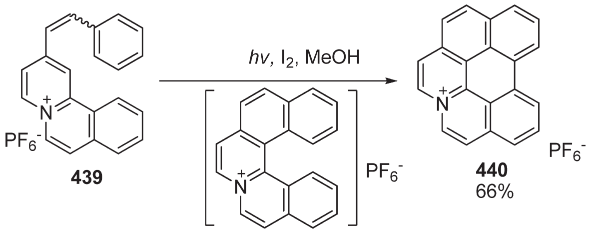
Scheme 103



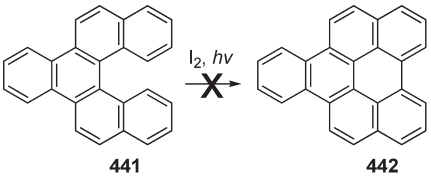
Scheme 104



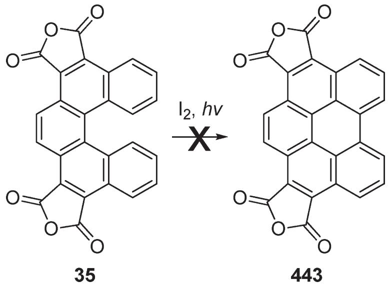
Scheme 105



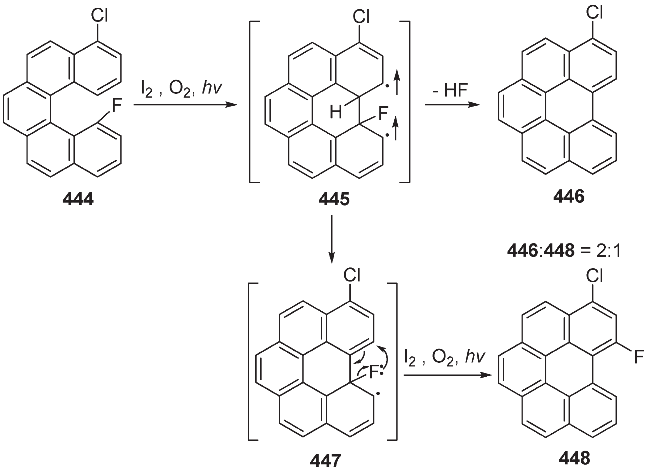
Scheme 106



Scheme 107

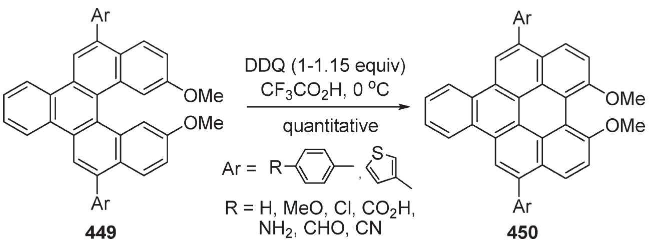


Scheme 108

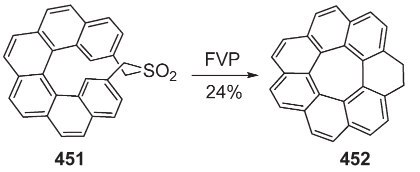


hydrolysis of **489** gave the ketone **492**, while hydrolysis for a longer time gave **490** and **491** instead. In addition to [4 + 2] addition an unusual [2 + 2] addition was described by Garcia and co-workers in 2009 (Scheme 123).[191] With the loss of the ligand $PPh_3$, the change in the coordination of the nitrile group allowed the metal center to interact with the hydrogen atom at the other terminal thiophene ring in **494**. The subsequent nucleophilic attack induced addition, in which the nitrile group reverted from side-on back to end-on coordination, which together with the coordination of $PPh_3$ afforded the organometallic compound

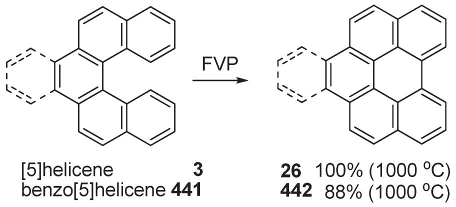
Scheme 109



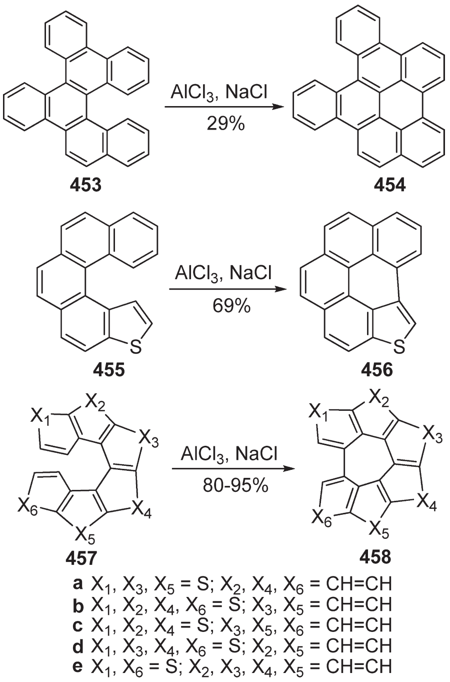
Scheme 110



Scheme 111

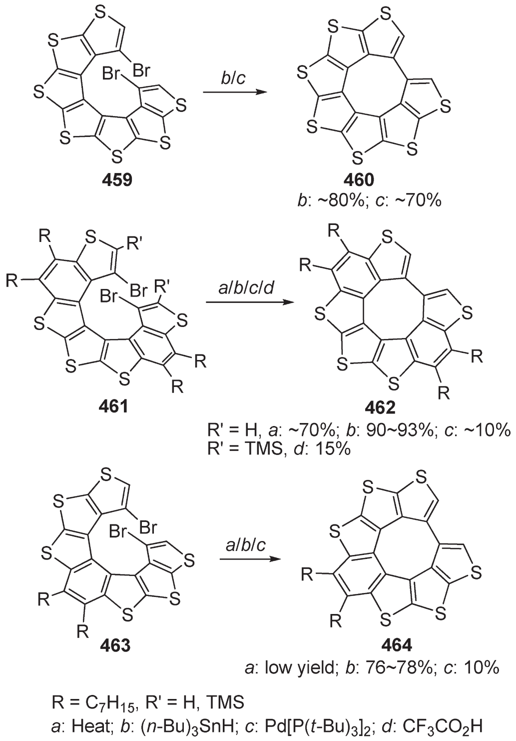


Scheme 112

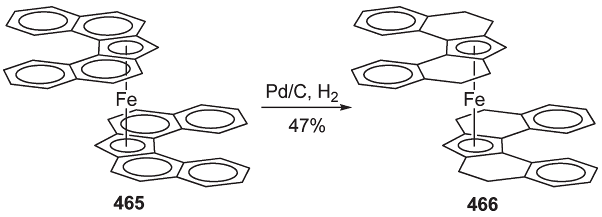


**496**. These intramolecular addition reactions indicate that some rings of helicenes are less aromatic than benzene.

Scheme 113



Scheme 114



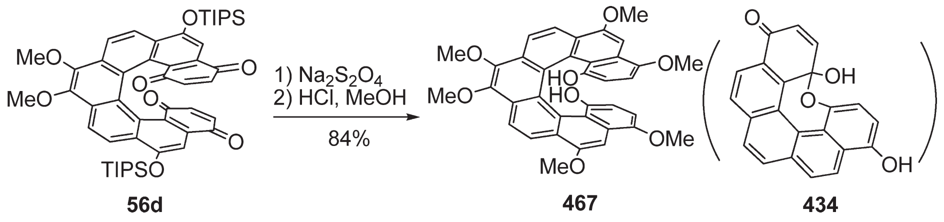
## 6.5. Dimerization

Two different BINOL analogues have been synthesized by the Katz's group and the Yamaguchi's group. In 2000, Katz et al. first reported the synthesis of [5]HELOL **500** (Scheme 124).[11f,192] By means of a Russig–Laatsch reaction, **497** was conveniently transformed into the dimethyl ether **498**. After optical resolution, the resolved **498** was treated with freshly prepared $Ag_2O$ and triethylamine to give the dimer **499**. By reducing **499** with zinc dust and acetic acid, (+)- and (−)-**500** were obtained in high enantiopurities and yields. Yamaguchi et al. reported a similar method for the synthesis of bihelicenols **505** (Scheme 125).[193] The aldehyde **502** was prepared by reduction of the acid **501**. Subsequent Baeyer–Villiger oxidation and hydrolysis of **502** gave the helicenol **503**. In the presence of the Cu–TMEDA complex in air, (*Z*,*P*,*P*)-**504** was prepared selectively and subsequent stereoselective hydrogenation produced (*P*,*P*,*R*)-**505** in quantitative yield.

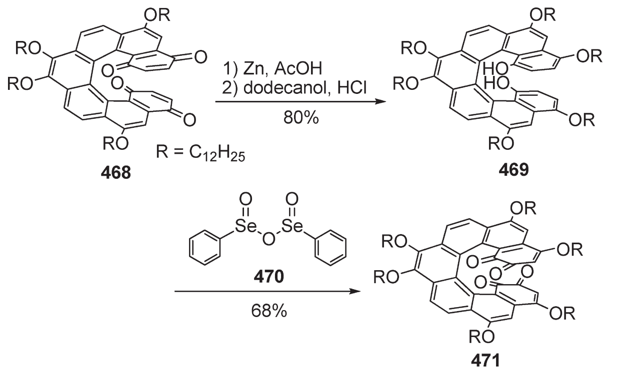
## 6.6. Direct C–H Functionalization on the Helical Backbone

Early studies of bromination, nitration, and acetylation reactions showed that the C(5) atom of [6]helicene is the most

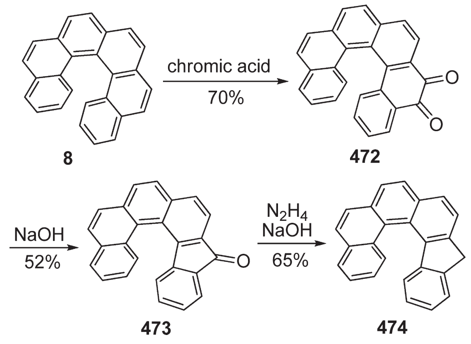
### Scheme 115



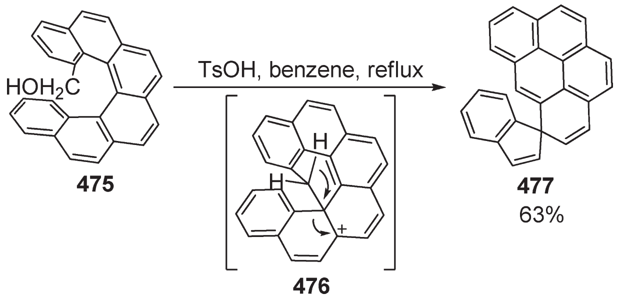
### Scheme 116



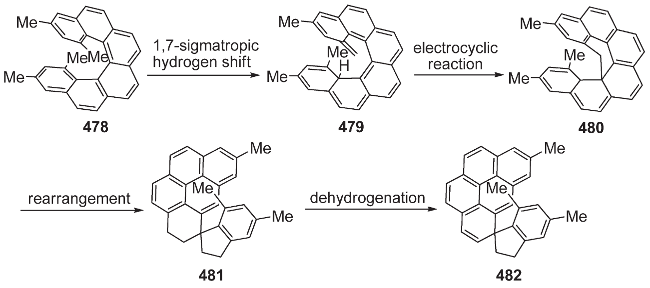
### Scheme 117



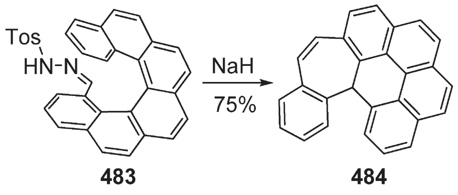
### Scheme 118



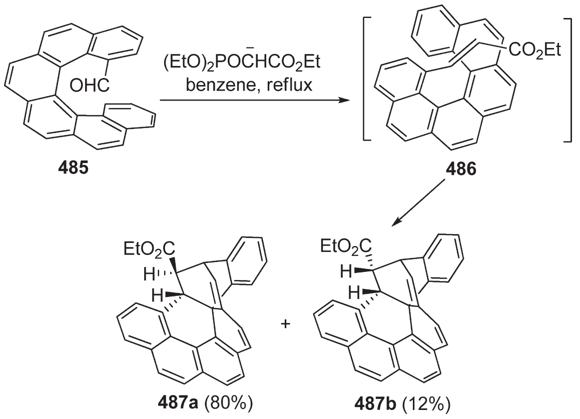
### Scheme 119



### Scheme 120

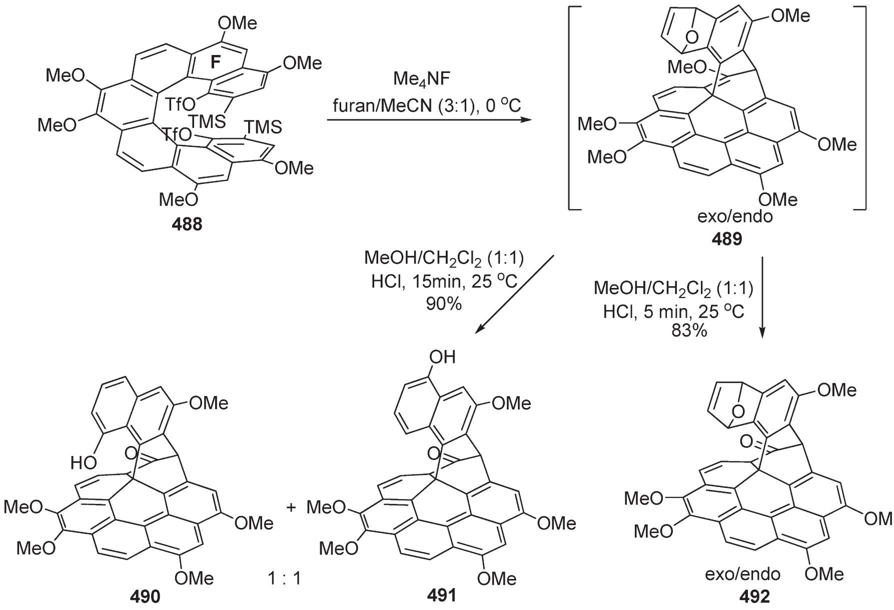


### Scheme 121

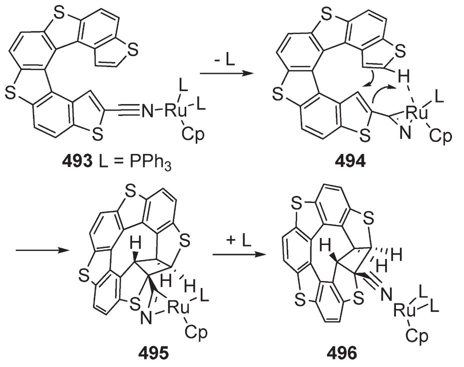


reactive position for electrophilic substitution, while detritiation experiments suggested the second most reactive site is C(7).[1c] Moreover, the reactivity of helicene homologues increases in the order phenanthrene < [4]helicene < [5]helicene < [6]helicene.[194] For the bromination of benzo[5]helicene **506** (Scheme 126) and [7]helicene **388** (Scheme 127) using NBS, attack at C(5) and C(5′) was preferred,[12d,69] while C(7) and C(7′) had the second highest reactivity.[12d]

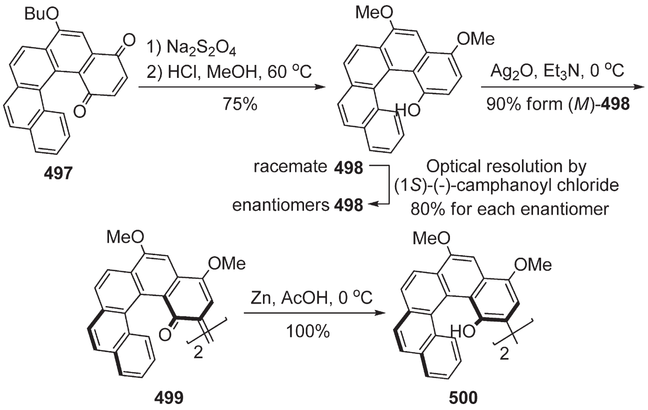
Scheme 122



Scheme 123



Scheme 124



Yamaguchi and co-workers synthesized a series of polynitro[4]helicenes by direct nitration reactions. Treatment of **510** with fuming $HNO_3$ gave the tetranitrohelicene **511** and the trinitrohelicene **512**; if acetic acid was added, dinitrohelicenes **513a,b** and **514a,b** were obtained (Scheme 128).[28f] For the dinitrile helicene **515**, nitration reactions gave similar products.[28e] However, the nitro groups could be selectively substituted at C(2) and C(11) at low temperature affording **518**, which underwent further nitration to give the tetranitrohelicene **519** (Scheme 129).

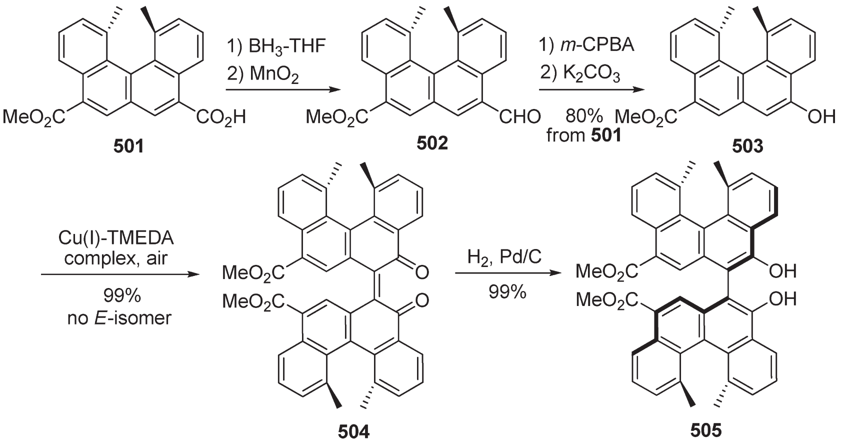
Direct formylation of the thiaheterohelicene **520** was examined by Maiorana and co-workers.[195] It was found that treatment of **520** with $Cl_2CHOMe$ in the presence of $SnCl_4$ gave the unique 1-formyl bridged helicene **521**. Moreover, the 2-formyl helicene **522** could be prepared by Vilsmeier–Haack formylation or via deprotonation followed by treatment with DMF (Scheme 130).

Direct substitution at the terminal rings of helicenebisquinones and hexamethoxyhelicenes was investigated by Katz and co-workers. For the bisquinone **54e**, direct bromination occurred at C(2) and C(2′) of **523**; in contrast, when **54e** was reduced to **525**, treating with $Br_2$ resulted in bromination at C(3) and C(3′), affording the dibromohelicene **526** (Scheme 131).[196] Treating **54e** with 40 equiv of $SOCl_2$ and 110 equiv of pyridine in boiling benzene gave the tetrachlorohelicene **527**. Moreover, if 36 equiv of methyl carbamate was added to the reaction mixture, the thiadiazole **528** was obtained.[197] In addition, direct amination was achieved in the presence of a Cu catalyst in an $O_2$ atmosphere giving **529**, which could be used for analysis of the absolute configuration of the helicene.[11b] **531** was converted in high yield into the dibromohelicene **532** in the presence of NBS. Monoformylated **533** and diformylated **534** were obtained in 59–61% yield by changing the reaction conditions, while monoacylation and diacylation took place at 0 and 25 °C, respectively, affording **535** and **536** in good yields (Scheme 132).

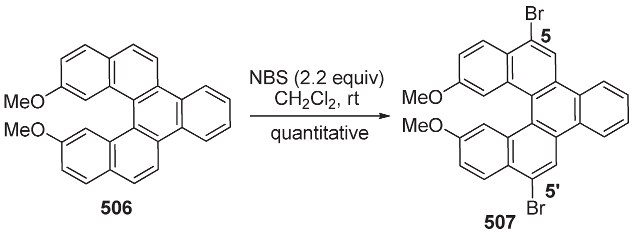
## 6.7. Transformation of the Functional Groups

This subsection discusses transformations of functional groups which have been incorporated into helicenes. Using bromo-substituted helicenes as precursors is a good choice for

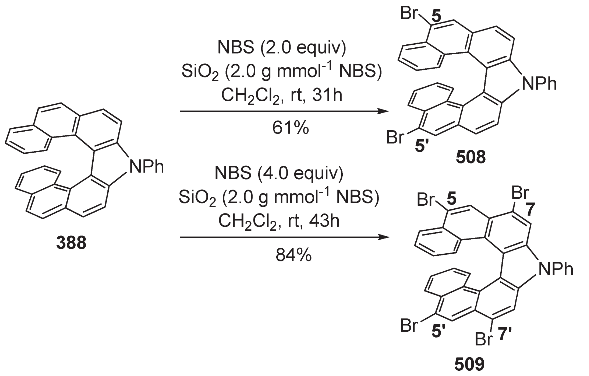
Scheme 125



Scheme 126



Scheme 127



preparing other functionalized helicenes. As shown in Scheme 133, bromohelicenes **156**−**157** underwent Sonogashira cross-coupling with alkynes to give alkynyl-substituted helicenes **537**−**539**.[94] By treating **539** with MeOH and $K_2CO_3$, 7-ethynyl[5]helicene **540** was prepared. In addition, bromohelicenes were conveniently converted into iodohelicenes **541**−**542** in the presence of CuI and KI, and thioethers **543**−**544** were prepared with NaSMe and a Pd catalyst. Moreover, thioether **544** was transformed into the thiol **545** in quantitative yield. Likewise, dinitril[5]helicene **546** was synthesized by the reaction between dibromohelicene **157** and CuCN.[94] By Suzuki−Miyaura cross-coupling, diaryl-substituted [5]helicenes could be prepared from the dibromohelicene **507** (Scheme 134)[69] and dichlorohelicene **547** (Scheme 135)[78g] in moderate to good yields.

Furthermore, based on Li/Br exchange, other varieties of functionalized helicenes have been synthesized: aldehydes **552** (Scheme 136)[167] and **533** and **534** (Scheme 137)[11h] were obtained by formylation with DMF; acyl chloride **553** was prepared in the presence of dry ice followed by treatment with $SOCl_2$;[167] phosphines **38** and **550** were synthesized by reaction with $ClPPh_2$;[167] the phosphine oxides **551**[167] and **555**[11h] were obtained either by direct reaction with $ClP(O)PPh_2$ or by oxidation of the corresponding phosphines; ketones **535**−**536** were prepared by treatment of **532** with BuLi and *N*-methoxy-*N*-methylacetamide;[11h] and ester **556** was prepared in moderate yield by reaction with $ClCO_2Me$ (Scheme 138).[12d]

Aldehydes are also useful precursors. The diol **46** was obtained by reduction of the dialdehyde **552** (Scheme 136),[167] while hydroxyl[4]helicene **558** was prepared from **557** by Baeyer−Villiger oxidation involving breaking of the bond between the formyl group and the helicene unit (Scheme 139).[193] By treatment with $NH_2OH{\cdot}HCl$ and $Ac_2O$, the aldehyde **522** was converted into the nitrile **559** (Scheme 140).[191] Moreover, after a Wittig reaction followed by reaction with MeLi, alkyne **554** was synthesized in high yield from **552** (Scheme 136).[167]

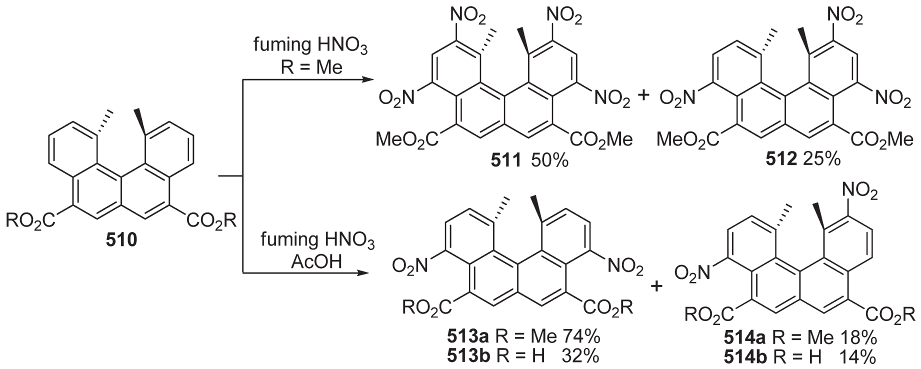
Nitrile **515** could be transformed into amine **560** by hydrogenation with a Pd/C catalyst (Scheme 141).[198] 3-Hydroxyl-[6]helicene **562**, prepared by treating **561** with $BBr_3$, gave the *O*-thiocarbamate **571** in the presence of $Me_2NC(S)Cl$, and the *S*-thiocarbamate **572** was obtained by the Newman−Kwart rearrangement (Scheme 142).[78e] Moreover, TfO- and NfO-substituted helicenes **563** and **564** were prepared from **562** by treatment with *n*-BuLi/$Tf_2O$ and NaH/NfF, respectively (Scheme 142).[78e]

The triflate derivative **563** is another excellent precursor. By using different Pd catalysts, the ester **565**, primary and secondary amines **568** and **566**, Schiff base **567**, and phosphine oxide **569** were prepared in moderate to good yields. Moreover, the phosphine **570** was obtained by reduction of **569** in the presence of $HSiCl_3$ and $NEt_3$ (Scheme 142).[78e] In addition, amides **574** and **576**, synthesized by treating ester **573** with different lithium amides, were transformed into dinitrile **575** by substitution and amine **577** by reduction (Scheme 143).[22l]

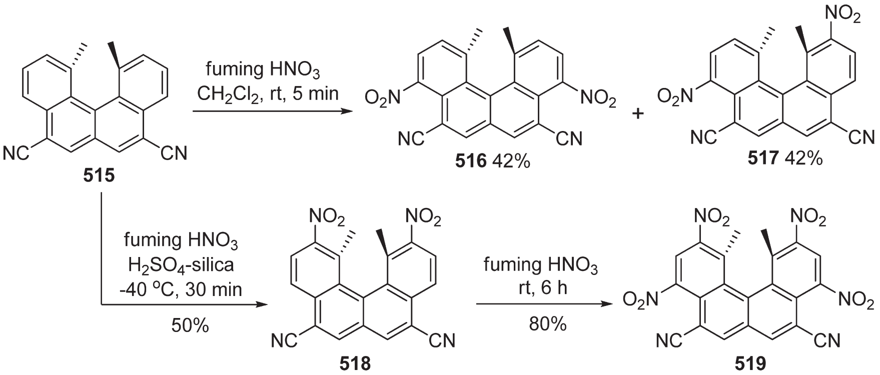
## 6.8. Organometallic Compounds with Helical Ligands

Recently, some novel organometallic compounds bearing enantiopure helical ligands have been prepared (Figure 13).

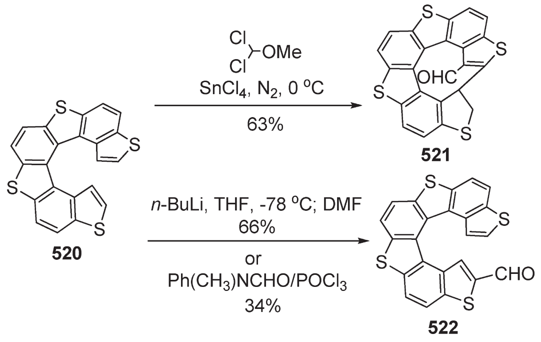
Scheme 128



Scheme 129



Scheme 130



Hassine and co-workers first reported the complex **433** in their optical resolution of 2-(diphenylphosphino)heptahelicene.[56a] They also synthesized other Ru and Pd complexes **578**−**580**, which might have catalytic activity.[56c] Tetrathia[7]helicene nitrile derivatives were used as ligands to prepare Fe/Ru complexes **493** and **581** by Garcia's group.[191] Recently, Réau et al. developed a series of helical bidentate ligands.[170,199] When the chiral *P*,*N*-bidentate ligands were coordinated to the metals Cu and Pd in **582** and **583**, two different types of coordination mode were observed. Moreover, the metal center can interact with the helicene moiety and significantly influence the chiroptical properties of the complex, resulting in a stereoselective coordination process.[199c] Metallahelicenes **586** and **587**, in which the metals are incorporated into the $\pi$-conjugated skeleton of helicenes, were synthesized and shown to have large and tunable chiroptical properties.[199b] The electronic interactions between the metal center and the helical $\pi$-system might provide new perspectives for helicenes.

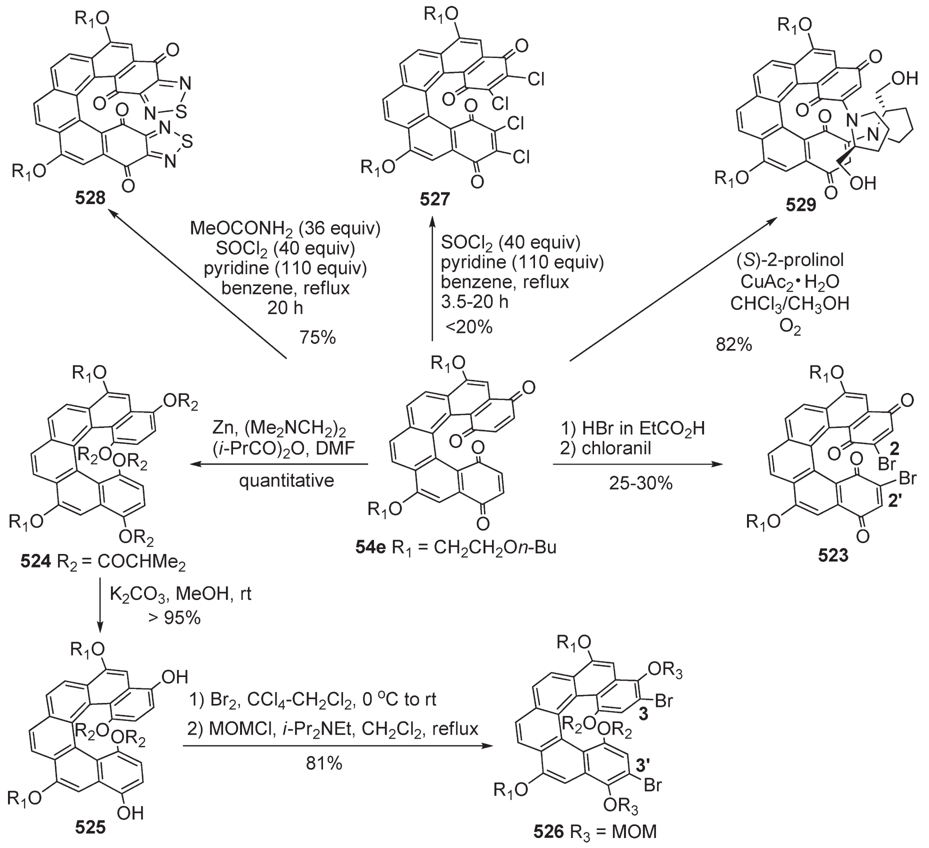
## 7. APPLICATIONS

### 7.1. Asymmetric Catalysis

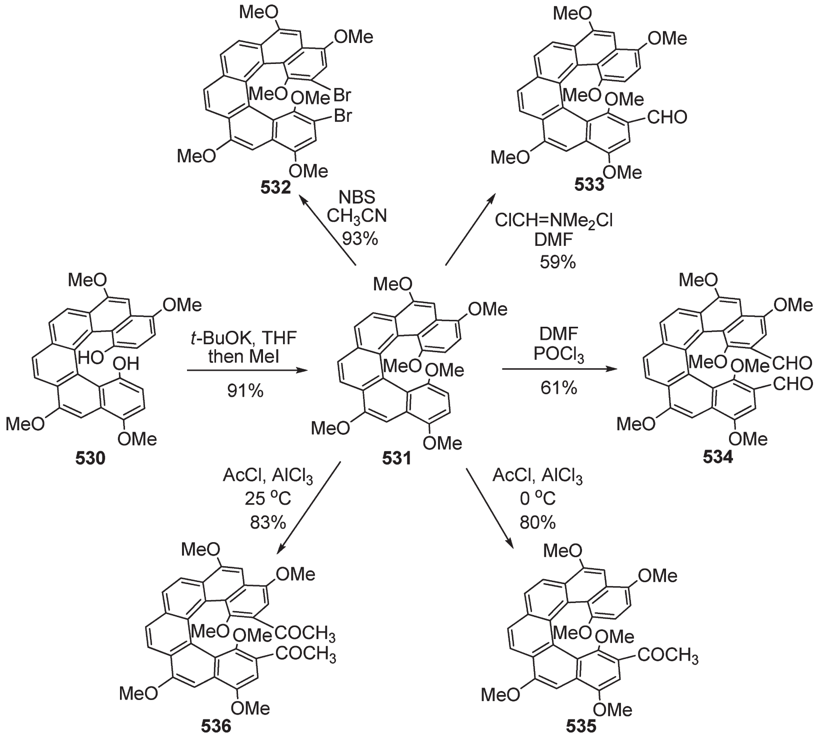
Since Bredig first reported the preparation of mandelonitrile in <10% ee by utilizing quinine as a catalyst, asymmetric catalysis has continued to develop over nearly 100 years.[200] Although many different kinds of chiral ligands and chiral catalysts have been developed so far (Figure 14), it is surprising that no ligands bearing helical chirality were used in asymmetric catalysis until 1997.[54] Before that, however, Martin and co-workers utilized substituted [7]helicenes as chiral auxiliaries or chiral reagents in five different diastereoselective reactions, including reduction of $\alpha$-keto esters,[201] hydroxyamination[202] and epoxidation (Scheme 144)[203] of olefins, synthesis of atrolactic ester,[204] and the ene reaction.[205]

In 1997, Reetz and co-workers reported the first catalyst based on a helical chiral ligand.[54] The catalyst was synthesized in situ by the stoichiometric reaction of (*M*)-PHelix **38** and Rh$^+$-(cod)$_2$BF$_4$$^-$; its use in the hydrogenation of the itaconate **595**

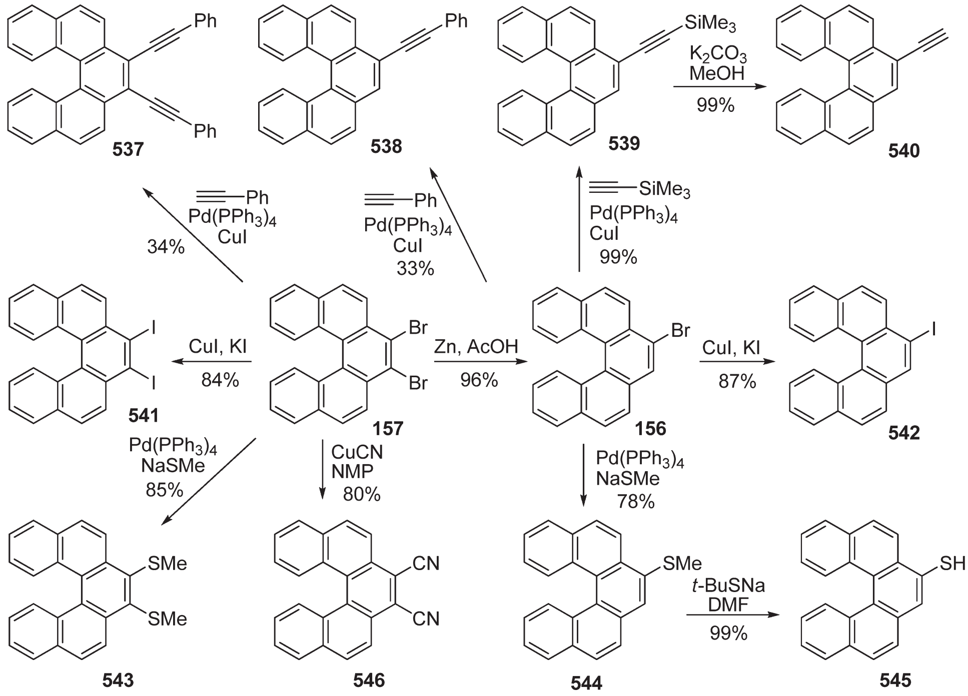
## Scheme 131



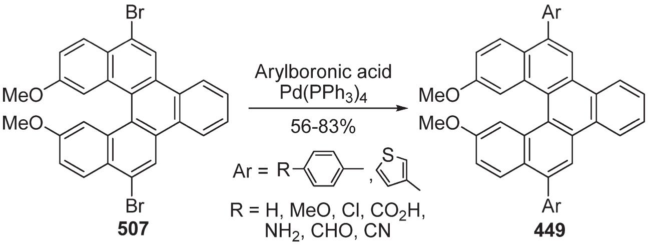
## Scheme 132



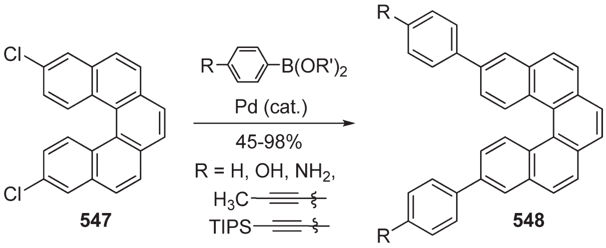
Scheme 133



Scheme 134



Scheme 135



under mild conditions afforded the diester (*S*)-**596** in 54% yield and 39% ee (Scheme 145). This reaction was reexamined by Yamaguchi and Nakano in 2003. By utilizing the bihelicenol phosphite ligand (*M*,*M*,*S*,*l*)-**597**, interestingly they found that a match/mismatch phenomenon existed in the catalytic reaction, and the ligand bearing both (*M*)-helical and (*S*)-axial chirality gave the best result (quantitative yield and 96% ee).[206]

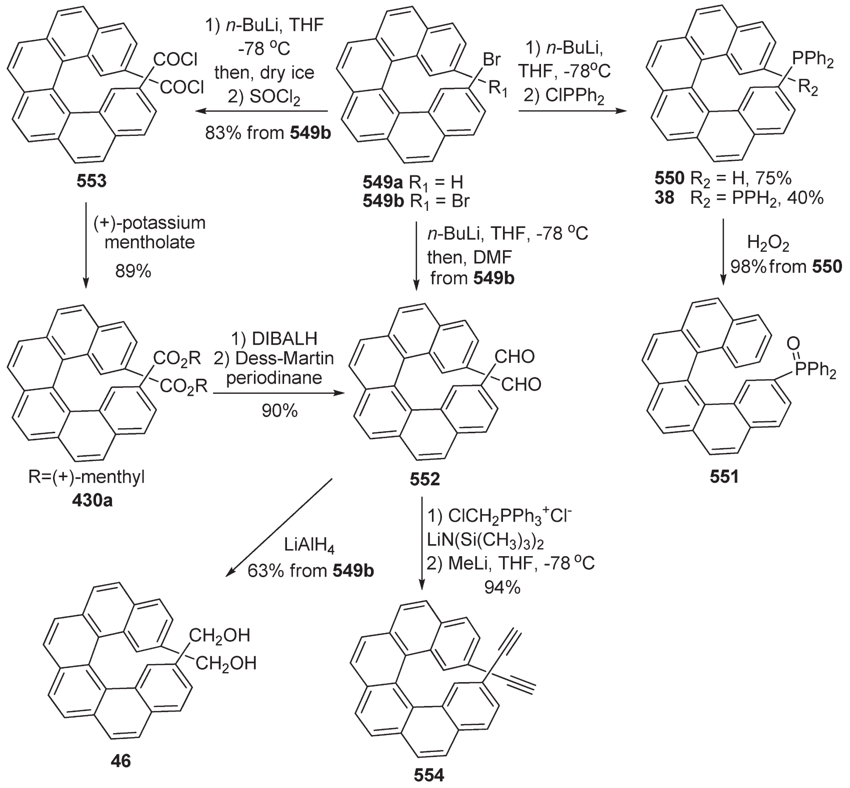
Reetz et al. also tried to utilize (*P*)-(+)-PHelix **38** in the kinetic resolution of **598** by Pd-catalyzed allylic substitution (Scheme 146).[207] In this case, the PHelix behaved only as a chiral monodentate ligand because of the long distance between the two phosphorus atoms (6.481 Å). They found that when the catalyst system with a Pd−PHelix ratio of 1:4 was employed in the kinetic resolution, the reaction (81% conversion) gave (*R*)-**598** in more than 99% ee.

In 1998, Yamaguchi and co-workers reported that the optically pure macrocyclic amide (*P*,*P*)-**603** containing two [4]helicene moieties could be employed in the catalytic asymmetric addition of diethylzinc to aromatic aldehydes, which enabled the synthesis of (*R*)-arylpropanol **602** in 50% ee (Scheme 147).[72a] If the helicene moieties in **603** were all in the (*M*)-configuration, the (*S*)-enantiomer of the product was obtained.

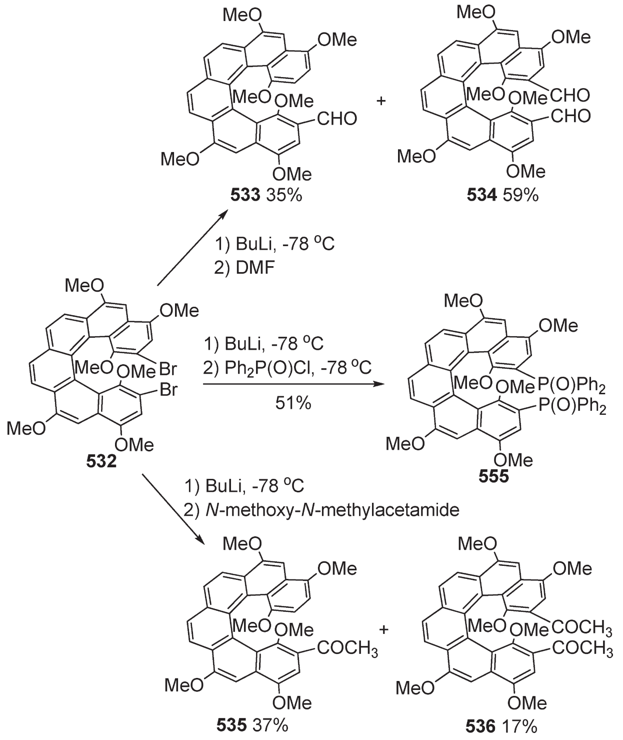
Inspired by the substituted BINOL[208] and vaulted biaryl ligand VAPOL,[209] Katz and co-workers found that (*P*,*P*,*S*)-[5]HELOL **500** with a helical groove could also be used in the catalytic asymmetric addition of diethylzinc to benzaldehyde, which afforded (*S*)-product **606** in 81% ee (Scheme 148).[192] The reaction was suggested to involve intermediate **605**, in which the zinc atom is bound to [5]HELOL and coordinated to the benzaldehyde. Consequently, the *Re* face of the aldehyde is blocked by the bottom helicene, which forces the $Et_2Zn$ to enter the groove from the other side.

In 2001, Soai and co-workers found that hexahelicene **8** could be used as an asymmetric trigger for the autocatalytic reaction[210] between dialkylzinc and the pyrimidyl aldehyde **607** (Scheme 149).[168] Similarly, the tetrathia[7]helicene **609** was also found to induce the autocatalytic reaction.[211] In these reactions, all (*P*)-helicenes induced formation of the (*S*)-alcohol in high ee through either route *a* or route *b*. Interestingly, even if helicenes with very low ee were used, for example, (*P*)-**8** in nearly

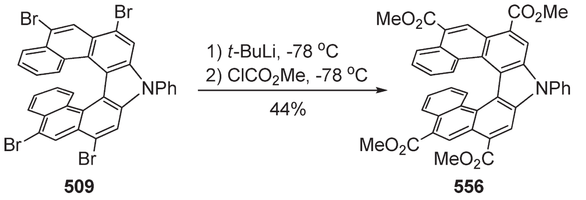
Scheme 136



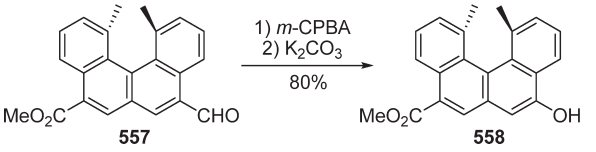
Scheme 137



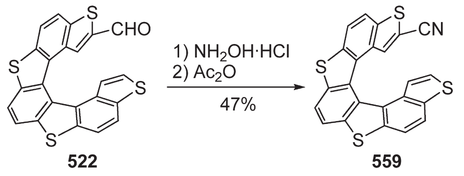
Scheme 138



Scheme 139



Scheme 140



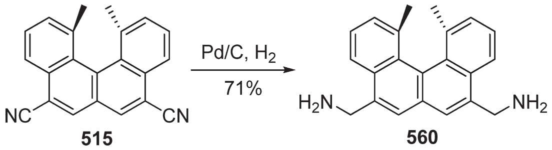
0.13% ee and ($P$)-**609** in 2% ee, the reactions still gave products with 56% and 83% ee, respectively.

Recently, Takenaka and co-workers reported two novel series of asymmetric catalysts based on the unique properties of 1-azahelicenes.[116,212] Initially, they synthesized the helical chiral pyridine *N*-oxides **611**−**613** by oxidation of the corresponding 1-azahelicene in the presence of *m*-CPBA and found that the *N*-oxides could perform as a Lewis base in the catalytic enantioselective ring opening of the *meso*-epoxide **593**. The reaction is thought to involve a cationic species that enables the chloride anion to add from the less hindered side and gave **610** in up to 94% ee (Scheme 150).[116,213] Furthermore, modification of the helical pyridine *N*-oxides can increase both the substrate scope and the enantioselectivity. More recently, another new kind of helicene **617** bearing a 2-aminopyridinium terminal ring was prepared and shown to be an efficient dual-hydrogen-bond donor catalyst for the addition reaction of dihydroindole **614** and nitroalkene **615** at low temperature; the reaction proceeds with high enantioselectivity (Scheme 151).[212]

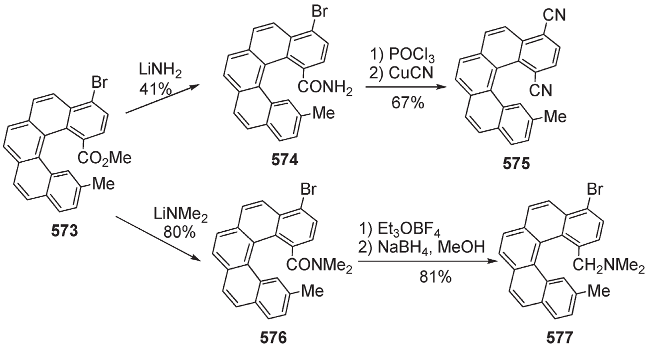
Starý, Stará, and co-workers utilized (*P*)-1-aza- and (*M*)-2-aza[6]helicene as organocatalysts in the asymmetric acyl transfer reactions of *rac*-1-phenylethanol (Scheme 152).[214] The authors found that (*P*)-1-aza[6]helicene had low activity (<5% conversion), which might be a result of the limited accessibility because the *N* atom is at the most sterically hindered position. However, 2-aza[6]helicene (*M*)-**620**, with high proton affinity[96] and a p$K_a$ (in $H_2O$) of 5.28 ± 0.25,[215] showed good catalytic efficiency, affording (*R*)-**618** in 99% ee with up to 72% conversion when the reaction was carried out using $(i\text{-PrCO})_2O$ as the anhydride and $i\text{-Pr}_2NEt$ as the base.

Recently, the kinetic resolution of secondary alcohols was reexamined by Carbery and co-workers (Scheme 153).[84] They designed a helicenoidal DMAP analogue **623** bearing a dialkylaminopyridine unit and helical scaffold as a Lewis base catalyst, which afforded (*R*)-**621** in 98% ee and (*S*)-**622** in 92% ee (51% conversion). This organocatalyst showed high levels of selectivity (selectivity factor *s* up to 116) and excellent reactivity

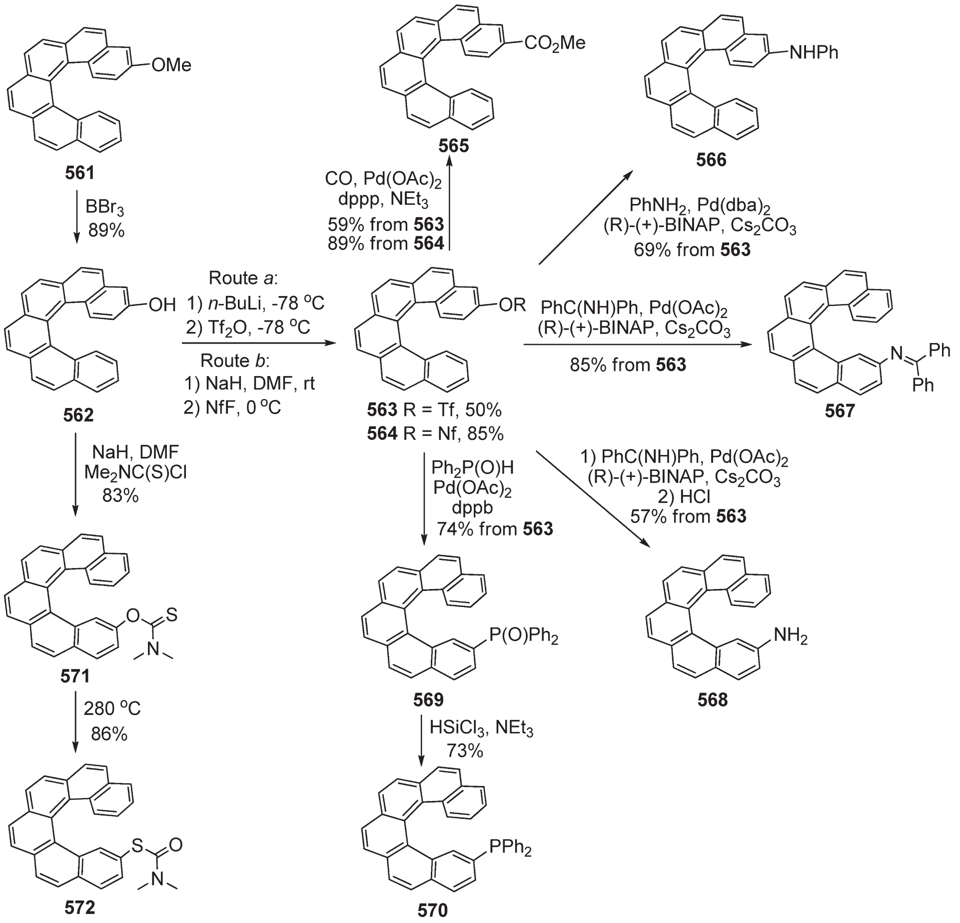
## Scheme 141



## Scheme 143



## Scheme 142



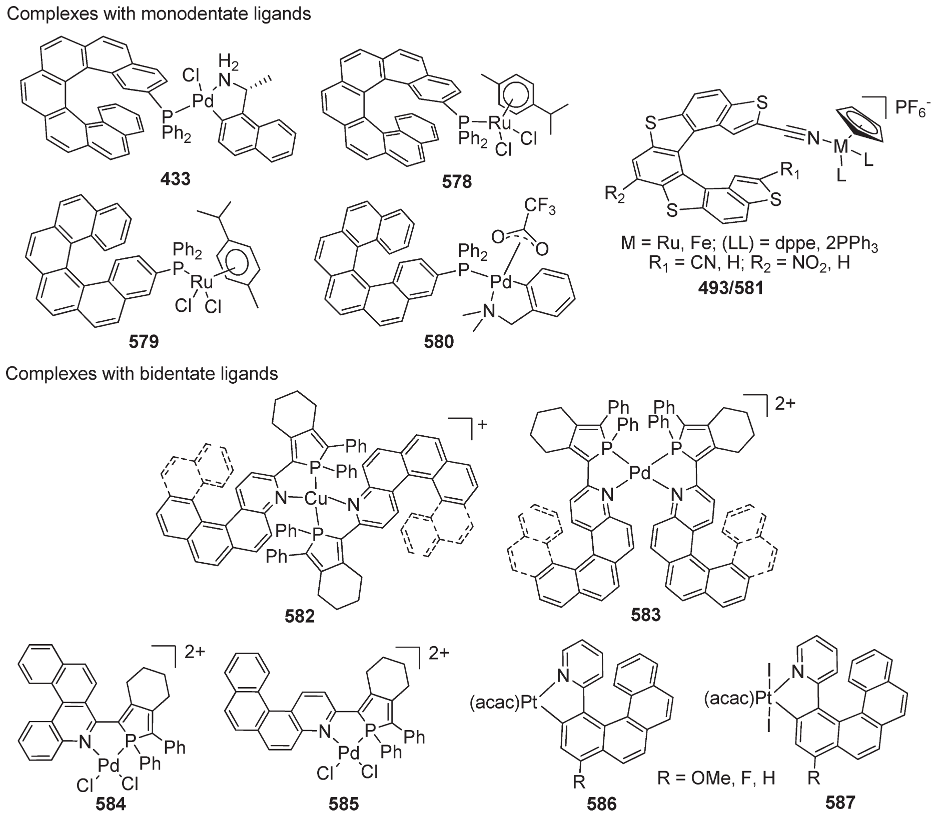


**Figure 13.** Some organometallic compounds with helical ligands.

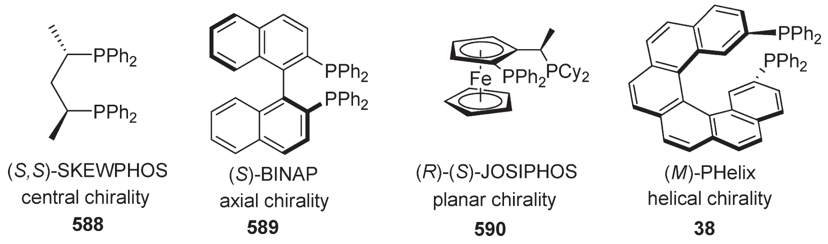
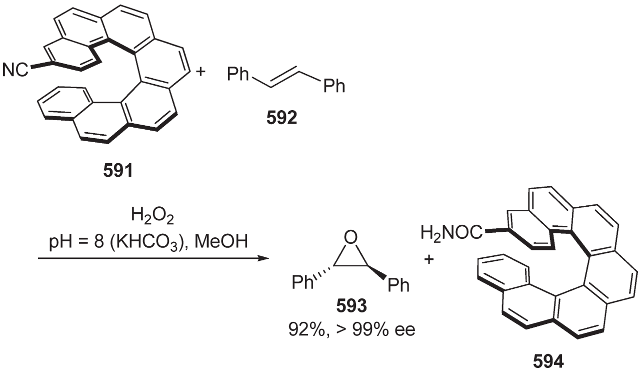


**Figure 14.** Some diphosphine ligands with different types of chirality used in asymmetric hydrogenation.

**Scheme 144**



(exceptionally low catalyst loading, as low as 0.05 mol % or 1 mg in one example).

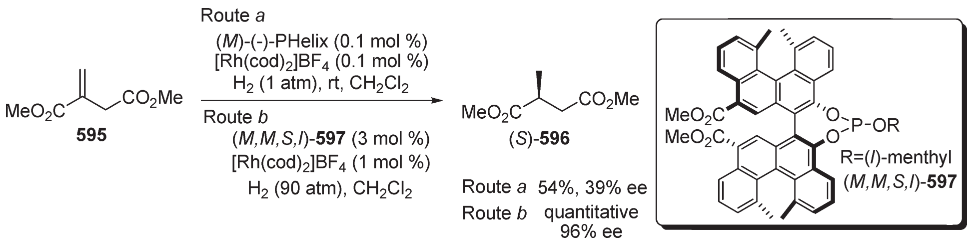
Starý, Stará, and co-workers subsequently studied four helicene-based phosphate species (Figure 15) as ligands in asymmetric Rh-catalyzed hydroformylation and Ir-catalyzed allylic amination.[216] For the Rh-catalyzed hydroformylation, excellent regioselectivity (up to 99:1) and low enantioselectivity (up to 32% ee) were observed. For example, hydroformylation of **625** gave **626** in 29% ee (96% conversion) with a regioselectivity of 93:7 in the presence of Ru(acac)$(CO)_2$/(*P*,*S*)-**624c** (Scheme 154). The Ir-catalyzed asymmetric allylic amination showed both excellent regioselectivity and enantioselectivity (Scheme 155). The best results were obtained using a $[Ir(cod)Cl]_2$/(*P*,*S*)-**624b** catalyst, which afforded **630a** and **631a** with >99:1 regioselectivity in 92% and 94% ee, respectively.

## 7.2. Molecular Machines

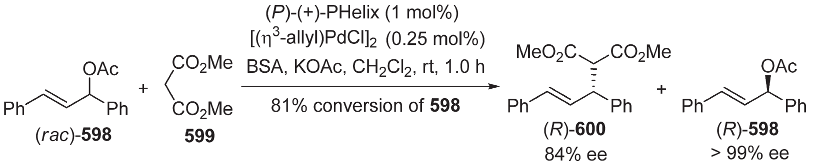
### 7.2.1. Molecular Ratchet.

Kelly and co-workers designed and synthesized a novel ratchet **632** by employing a triptycene as a toothed wheel and a [4]helicene as the pawl and the spring (Figure 16).[217] Slow rotation of the triptycene was observed based on the peak broadening in $^1H$ NMR spectra recorded at 160 °C, while spin polarization transfer NMR results indicated a

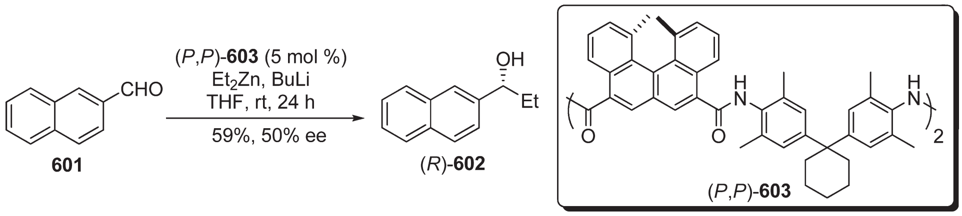
Scheme 145



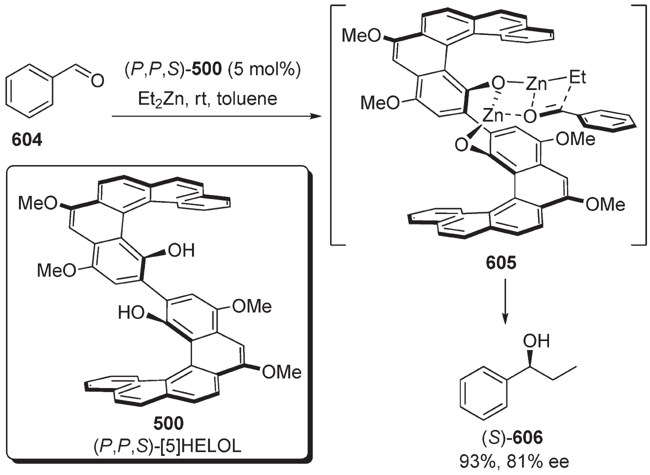
Scheme 146



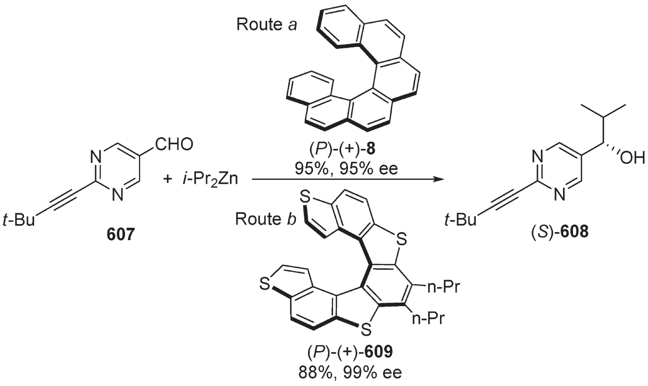
Scheme 147



Scheme 148



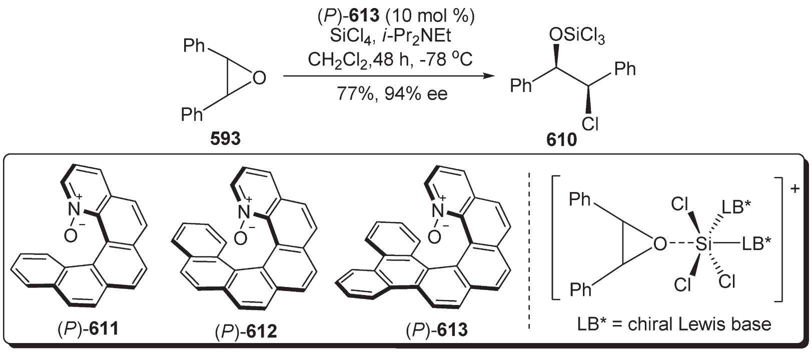
Scheme 149



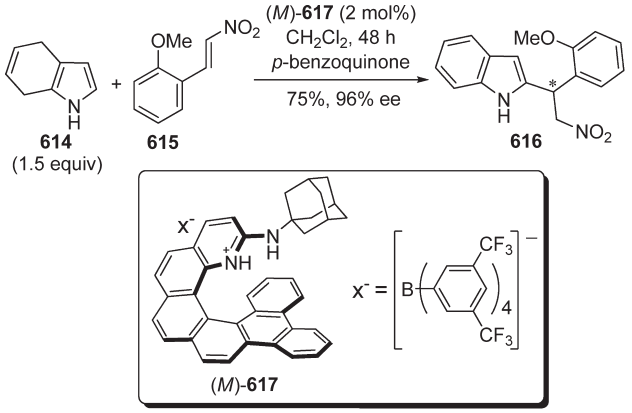
bidirectional rotation to the same extent. This is as required by the second law of thermodynamics and the principle of microscopic reversibility, although an asymmetric calculated energy curve was obtained as the toothed wheel rotated. The experimental results as well as the theoretical and thermodynamic analyses all demonstrated that **632** cannot be utilized as a unidirectional ratchet itself in an isothermal environment.[217b,c,218]

To realize this challenging objective, Kelly and co-workers made an intelligent improvement: introducing a tether on the helicene unit **633** and using carbonyl dichloride (phosgene) as a chemical energy provider, like ATP in biological activities, enabled successful rotation by 120° unidirectionally around the single bond between the two units (Scheme 156).[219] Carbamoyl chloride was formed by adding carbonyl dichloride to **633**, which was readily converted into the isocyanate **636** in the presence of triethylamine. This activation of the ratchet is the basis of the unidirectional rotation, not only by fostering the clockwise

Scheme 150



Scheme 151



rotation to form urethane by the reaction of isocyanate and a hydroxyl group (otherwise the two groups are too far away to react) but also by lowering the activation energy ($\Delta E_{act}$) of the rotation (clockwise rotation from **II** to **III**) by raising the energy of the rotamer **633**; this also results in the counterclockwise route (from **III** to **II**) requiring a higher $\Delta E_{act}$. The rotation is the rate-determining step (the half-life was nearly 3 h), and **633** (**IV**) was obtained by urethane cleavage. Thus, the unidirectional, chemically powered rotation was realized.

On the basis of this successful design, the Kelly group attempted to obtain repeated rotations and achieve a continuous unidirectional rotation by modifying the triptycenyl helicene system.[220] For this purpose, (i) three blades of the triptycene unit are required to be selectively bonded, (ii) there should be a transporter to capture the phosgene and then transport it to a certain blade, (iii) the urethane should be readily formed and cleaved, and most important (iv) all the modifications, if not facilitating the rotation, should not inhibit the procedure.

Kelly and co-workers found that DMAP was a good delivery agent which directed the phosgene molecule exclusively to the nearest amino group.[220a] Therefore, they constructed **634** and later **635** as plausible candidates.[220b] However, disappointingly, the process could not be realized; subsequent work showed that this was because of unexpected Bürgi–Dunitz[221] or covalent interactions.[220b,c]

### 7.2.2. Molecular Springs.

Helicenes, due to the crowded helical framework, are inherently helical and the dihedral angles of the helical structures, like a spring, vary with the change in the number of the rings and the substituents on the skeleton.

By X-ray analysis of the self-assembly of thiahetero[7]helicene, Tanaka and co-workers found that the conjugated $\pi$-framework is flexible and acts as a molecular spring (Figure 17, Table 3).[222] The interplanar angles for enantiopure (entry 1) and racemic (entry 2) helicene **436** were different (the latter was larger by 10.9°). When the helicene formed clathrates with different guest molecules (entries 3–5), the interplanar angle (without guest, entry 2, 44.7°) decrease to as low as 38.0° (entry 4) or increased to as high as 54.5° (entry 5). Later, Tanaka and co-workers synthesized a series of bridged helicenes **639** and **640** with different dihedral angles of the terminal thiophene rings (entries 6–10). As expected, the angles were wider (from 21.9° to 59.2°) when the bridges were longer. Moreover, the wider the dihedral angle, the longer the distance between atom C(1) and atom C(18). As a result of the relatively flexible alkyl chain and the more rigid helical skeleton, the increase became much smaller as the bridge length increased. Therefore, helicenes are excellent ligands in asymmetric catalysis since the distance between the terminal rings can be tuned in order to optimize the coordination with a metal center. According to Hartree–Fock calculations, the stiffness of the nanospring can be modulated by varying the length of the helicene and the electron density.[223] Moreover, a recent theoretical study showed that the elasticity decreased as the helicene became longer.[13r]

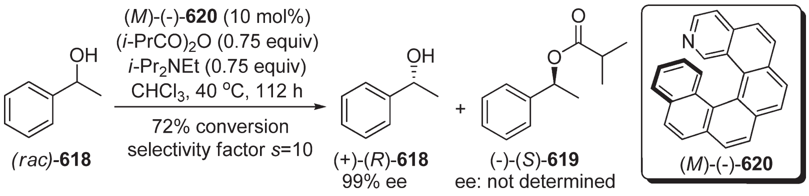
### 7.2.3. Molecular Switches.

Photochromism has been studied for a long time because of its potential applications in devices such as switches and optical memories.[224] Branda and co-workers described the reversible formation of a dimethyl[7]helicene in which irradiation of the open form **641** (yellow) in $CH_2Cl_2$ at 410 nm afforded a PSS consisting of the closed form **642** (orange) and the open form in a ratio of 74%:36%. In the reverse process, irradiation of **642** by light with $\lambda > 458$ nm regenerated **641** through a rapid ring-opening process (Scheme 157).[225]

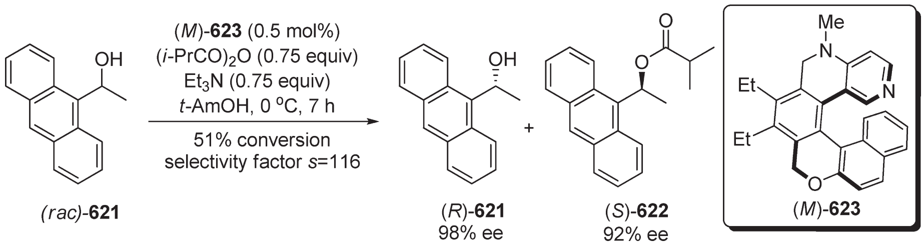
Later, Branda's group reported chiral discrimination phenomena in such photochromic thiahelicenes (Scheme 158).[226] Comparing **643** with **641**, the key difference is the remote chiral moiety, which introduces steric hindrance, making (*M*)-**644** the major product of photolysis of **643** at 400 nm. (*M*)-**644** can be photobleached by irradiation with light of $\lambda > 434$ nm. Even though photolysis of **643** gave just 40% conversion to (*M*)-**644**, this system is still a good candidate for a chiroptical photoswitch not only because of its thermal stability but also by virtue of the large difference in the optical rotation ($\Delta[\alpha] = 8698°$).

Yokoyama and co-workers reported the photochromic behavior of **645** in which the ring closure was directed by the chiral

Scheme 152



Scheme 153



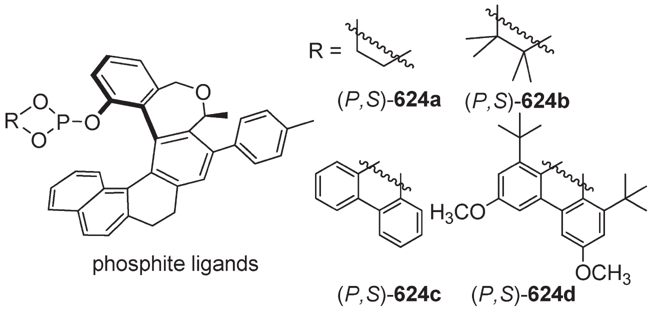
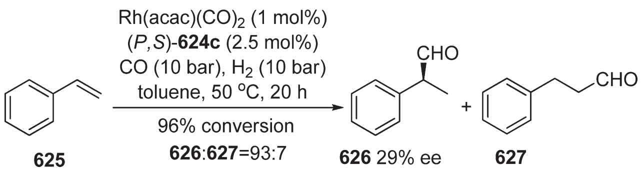


**Figure 15.** Helicene-based phosphite ligands.

(methoxymethoxy)ethyl group[227] on the benzothiophene (Scheme 159).[107c] Irradiation by light at 405 nm gave (*M*)-**646** in 47% de in the PSS (**645**:**646** = 36/64). At 589 nm, where both PSS and open state have no absorption, the difference in the optical rotation ($[\alpha]_D = -1370°$ for PSS and $[\alpha]_D = -69°$ for the precursor, respectively) in ethyl acetate was 1300°.

In 2001, Suzuki and co-workers constructed the first example of redox switches with a dramatic chiroptical response based on dihydro[5]helicene and induced by electron transfer.[228] Because the redox pairs are stable and no racemization occurred at room temperature, optically active (*P*)-**647** and (*S*)-**648** were utilized to examine the electrochemical response (Scheme 160). Interestingly electrochromism, with a vivid color change, was detected by UV−vis spectroscopy. Moreover, a drastic change in $\Delta(\Delta\varepsilon)$ (= 140 $mol^{-1}$ $dm^3$ $cm^{-1}$ at 290 nm) was observed with a negative ellipticity growing in the long-wavelength region. Several other electrochiroptical switches have also been developed by the same group.[229] Recently, they reported multi-input/multioutput molecular switches based on the tetraaryldihydro[5]helicene (*P*)-**649** (Scheme 161).[230] Upon reversible interconversion by electrochromism or dynamic redox behavior, the system showed changes in its UV−vis, CD, and fluorescence spectra. In addition, solvatochromic behavior in the UV−vis and CD spectra of (*S*)-**650** was also detected.

Scheme 154

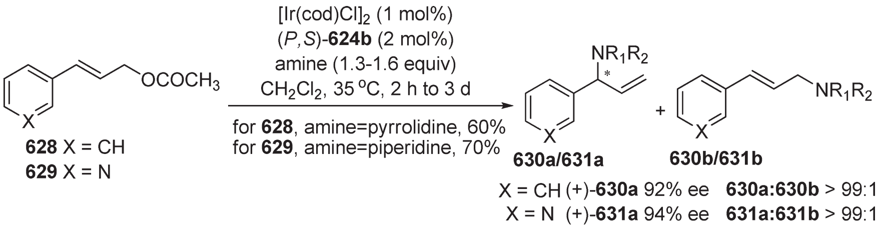


## 7.3. Dye Materials

Because of their unique structure, metallocenes bearing helicene moieties might have unusual magnetic, conductive, and optical properties.[231] Cyclopentadiene rings can be incorporated into the helicenes either in the body or at the termini and can be easily deprotonated to give cyclopentadienyl anion units. Therefore, [4]- and [5]helicene dianions were prepared by Katz and co-workers, and subsequent reactions with metal cations produced metallocenes **651**−**653** (Figure 18).[24c] If the helicenes are intended to be polymerized, the terminal rings should be superimposed.[24c] Therefore, optically active [7]helicenes were prepared and treated with *tert*-butyllithium followed by appropriate metal reagents affording two novel helical metallocenes **654a**,**b**, in which the metal atoms are centered between the terminal rings.[232] Furthermore, metallocene oligomers **655a**,**b**, which were extremely robust and stable with high optical activity under normal conditions, were successfully prepared by the reaction between the optically active [9]helicene dianion and the cobalt salts. The degrees of polymerization were 3.5 and 5.3 for **655a** and **655b**, respectively.[9d,233] Metallocene **655a** was reduced to form a conductive film for charge transfer, and its cyclic voltammogram showed weak interactions between adjacent units.[233b] Other metallocenes containing one or two helicenes have also been reported.[9d,87,183]

In 1999, Katz and co-workers prepared the first novel optically active helicene-fused octaazaphthalocyanine dyes **656a**,**b** which aggregated in 75% EtOH−25% CHCl₃ (as indicated by their

Scheme 155



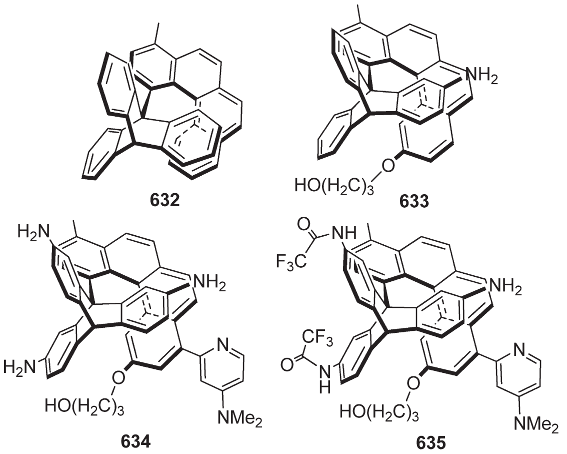
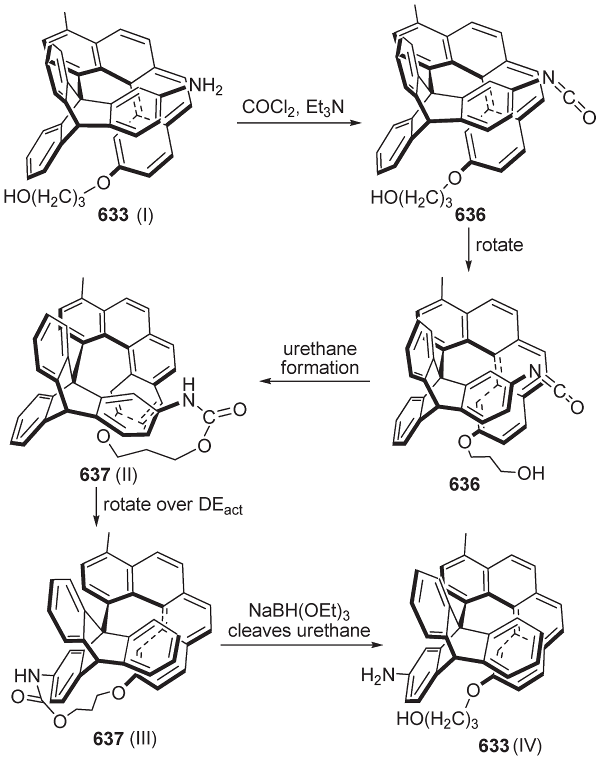


**Figure 16.** Rational design of a molecular ratchet.

Scheme 156



UV−vis and CD spectra).[234] According to a molecular mechanics computational study of a bimolecular aggregate, the optimized distance between the cores was ca. 3.4 Å with an anticlockwise rotation of about 35°. AFM analysis revealed that the isolated stacks of the dyes were perpendicular to the surface of a mica substrate, while in chiral LB films the aggregates stacked with their axes parallel to the surface. Later, another three [5]helicene-fused phthalocyanines **657a**−**c** were synthesized by Mandal and Sooksimuang.[68] Interestingly, **657c** was observed to form dimeric assemblies over a wide range of concentrations:[235] in the UV−vis spectrum of the dimer a new broad band at 525 nm was observed, and the fluorescence spectrum of **657c** exhibited two bands at 500 and 900 nm.[235] The absorption spectra of these five phthalocyanine dyes covered the entire visible spectral region, indicating that they could be utilized for harvesting solar energy (Figure 19).[68,234,235]

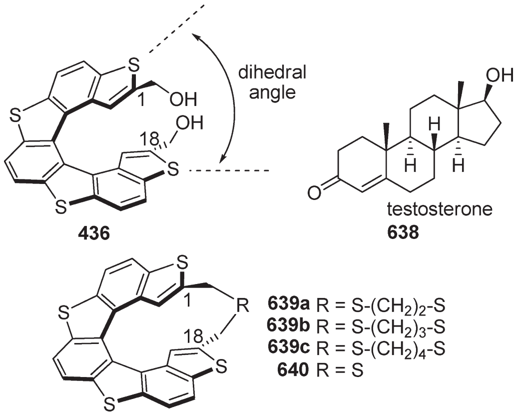


**Figure 17.** Some thiahelicenes as molecular springs.

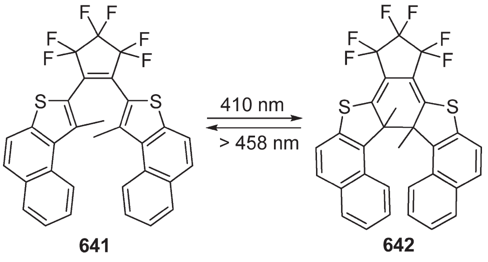
With increasing public awareness of energy shortages, dye-sensitized solar cells (DSSCs)—as the next-generation solar cells—have attracted considerable attention by virtue of their low-cost processes, high performance, and ease of production.[236] Grätzel and O'Regan reported the first DSSCs in 1991.[237] Because of the high expense of the Ru dyes involved, several environmentally friendly, easily prepared organic donor−acceptor $\pi$-conjugated (D−$\pi$−A) dyes have been investigated as alternatives.[238] Harima and co-workers synthesized a series of D−$\pi$−A dyes **658** and **659** using a heterohelicene as a building block taking advantage of its conjugation framework and helical backbone (Figure 20).[239] Some photovoltaic performances are listed in Table 4. Although entry 2 has a larger adsorption loading than entry 1 on the TiO$_2$ surface, the efficiency of the cell decreased, which was ascribed to the $\pi$−$\pi$ interactions between large $\pi$-conjugated systems.[239b,c] From entries 3 and 4 it can be concluded that the alkyl substituent on the nitrogen atom can not only separate the molecules effectively but also enhance the

Table 3. Some Crystallographic Data for Thiahetero[7]helicenes in Self-Assemblies

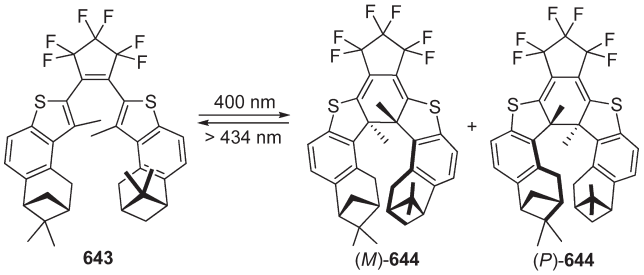
| entry | host[a] | guest | dihedral angle (deg) | C(1)−C(18) distance (Å) | ref |
|---|---|---|---|---|---|
| 1 | *P*-**436** | | 33.8 | 3.65 | 222b |
| 2 | (*PM*-**436**) | | 44.7 | 4.03 | 222b |
| 3 | *M*-**436** | **638** | 46.2 | 4.05 | 222b |
| 4 | (*PM*-**436**) | EtOH | 38.0 | 3.83 | 222b |
| 5 | (*PM*-**436**)$_2$ | DCE[b] | 54.5/52.2[c] | 4.32/4.32[c] | 222b |
| 6 | (*PM*-**639a**) | | 53.5 | 4.33 | 222c |
| 7 | (*PM*-**639b**) | | 57.8 | 4.48 | 222c |
| 8 | (*PM*-**639c**) | | 59.2 | 4.60 | 222c |
| 9 | (*PM*-**640**)$_4$ | benzene | 22.5/21.9[c] | 3.29/3.27[c] | 222c |
| 10 | *P*-**640** | | 26.2 | 3.29 | 222c |

[a] *P*, (*P*)-helicene; *M*, (*M*)-helicene; (*PM*)$_n$, the newly formed clathrate bearing *n* (*P*)- and *n* (*M*)-helicenes. [b] 1,2-Dichloroethane. [c] Two independent molecules of helicenes exist in the crystal lattice.

Scheme 157

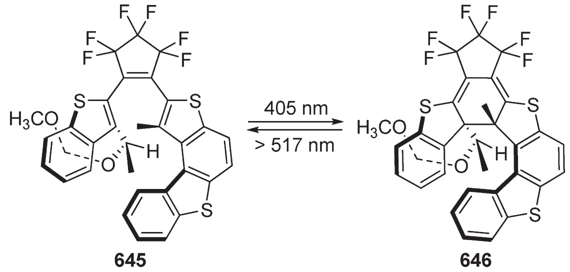


Scheme 158

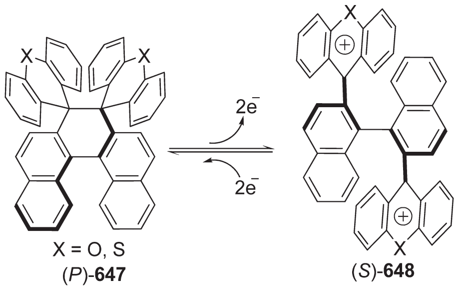


performance of the cell.[239b] To evaluate electron communication between the surface and the dyes, the authors constructed dyes **659a**−**f** using a cyano group as an electron acceptor and a carboxyl group as an anchoring group.[239d,f] Entry 5 had a low adsorption loading, which might be caused by the short anchoring group. Entries 6−10 showed that the carboxyl groups were not necessary to act as electron acceptors and that because of the flexibility of the alkyl chain the cyano substituent could be located close to the surface and transfer electrons (Figure 21). More recently, Harima and co-workers found that the intramolecular charge-transfer (ICT) process depends on the electron acceptor and donor−acceptor $\pi$-conjugation system.[239h] Thus, to develop new effective organic sensors, the dyes should have (i) good light-harvesting character, (ii) an appropriate arrangement on the $TiO_2$ surface, and, most importantly, (iii) a strong interaction between the electron acceptor moieties on the dyes and the $TiO_2$ surface.[239e]

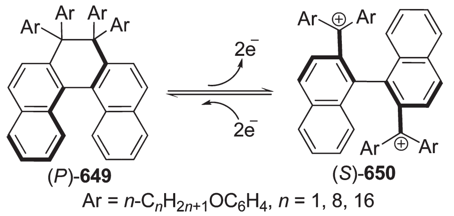
Scheme 159



Scheme 160



Scheme 161



## 7.4. Polymers

### 7.4.1. Ladder Polymers.

Katz and co-workers described the first synthesis of two novel ladder polymers **661** and **663** bearing heptahelicene connected by nickel salophen units in which the square planar geometry made the $\pi$-conjugation extend from the helicenes to the whole polymer. The chirality and optical activity are determined by the intrinsic helical structure (Schemes 162 and 163).[196,240] To synthesize the salophen ligands using 1,2-phenylenediamine, the formyl groups were at either the 2-,15-positions of **660** or the 3-,14-positions of **662** according to Katz's Diels−Alder synthetic approach. As a result, two different types of polymers were obtained by virtue of the strong coordination between ligands and metal centers. Polymer **661** is wound in a single direction due to the binding units preserving the helicity of the helicene units. However, since the salophen units were outside the helicene moieties, polymer **663** has two winding directions with the nickel−salophen units having a right-handed helix and the helicene units having the opposite helicity.

Polymers **661** and **663**, with number-average molecular weights of ca. 7000, had good solubility in a variety of organic solvents. Moreover, their CD spectra were generally similar to those of the helicene precursors, with only a slight bathochromic shift, except that polymer **661** showed a large CD intensity at a wavelength ca. 600 nm.

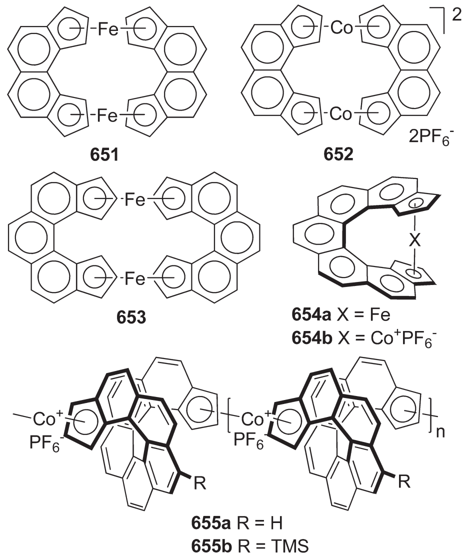
Recently another novel type of ladder polymer forming a one-dimensional wire, constructed from fused benzothiophene rings, was described by Nishide and co-workers (Scheme 164).[241] In previous theoretical simulations they found that the conductivity of a helical molecular wire (like **669**) could be greatly improved by chemical doping.[242] The stiff poly(thiaheterohelicene) **668** (Figure 22) was prepared from **664** and **665a**−**c** via Suzuki−Miyaura coupling, oxidation, and intramolecular cyclization (the molecular weights for Poly-S were $M_n = 1.1 \times 10^4$, $M_w/M_n = 1.2$ for **666a**; $M_n = 7.5 \times 10^3$, $M_w/M_n = 1.4$ for **666b**; and $M_n = 4.4 \times 10^3$, $M_w/M_n = 1.7$ for **666c**). The helicity of **668a** was induced by the chiral substituents on Poly-SO **667a** and fixed in the ring-closing step. Under basic conditions **668a**−**c** in the film state could be dealkylated to give the rigid, helical $\pi$-conjugated polymer **669** in which the electrical conductivity was enhanced by iodine doping.

### 7.4.2. Other Polymers.

Besides the above ladder polymers which have helical skeletons themselves, helicene units can be introduced into macromolecules by either directly synthesizing helicenes or utilizing helicene monomers.

As an example of the former strategy, for example, Wang and Douglas reported a simple method to construct helicene-based polymers by using Lawesson's reagent to achieve the chemical transformation from the poly(ether ketone) **670** to **671**, which had a weight-average molecular weight of $8.2 \times 10^4$ ($M_w/M_n = 2.0$) and showed a high glass transition temperature ($T_g = 265$ °C) because of the newly formed rigid [5]helicene (Scheme 165).[243]

Examples of the latter approach include those based on several monomers containing [5]helicene or tetrahydro[5]helicene **672**−**676** (Figure 23) prepared by Wang and co-workers.[244]

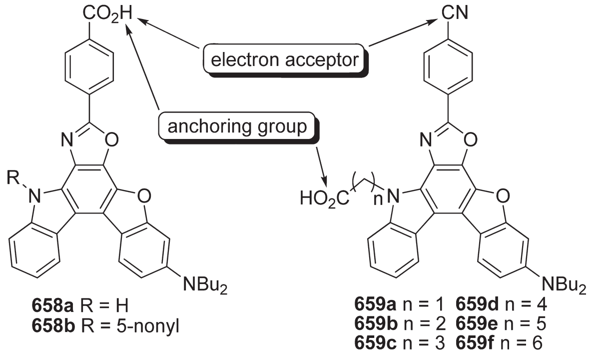


**651** **652** **653**

**654a** X = Fe
**654b** X = Co$^+$PF$_6^-$

**655a** R = H
**655b** R = TMS

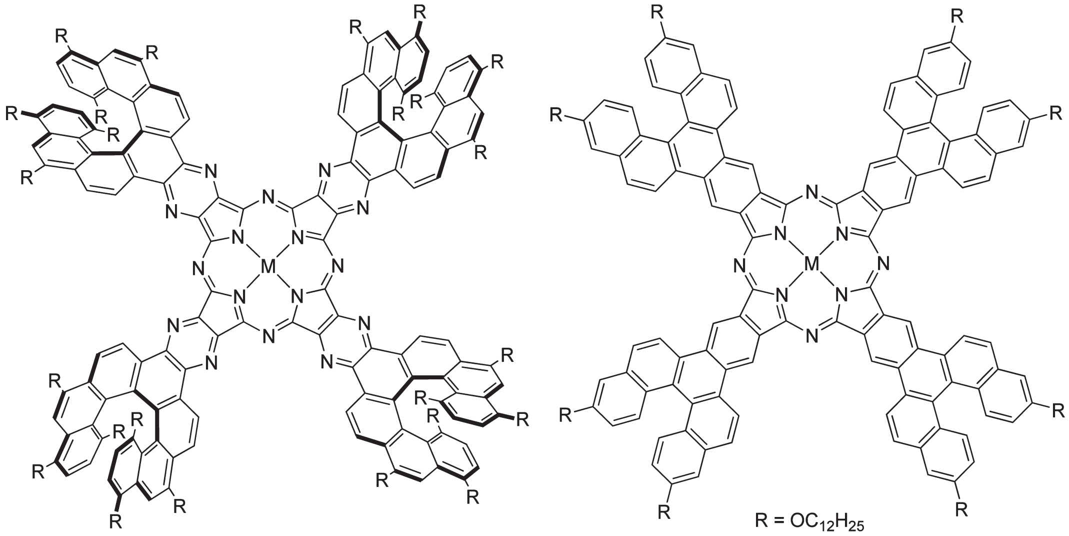
**Figure 18.** Examples of metallocenes incorporated in helicenes.



**658a** R = H
**658b** R = 5-nonyl

**659a** n = 1 **659d** n = 4
**659b** n = 2 **659e** n = 5
**659c** n = 3 **659f** n = 6

**Figure 20.** Some organic D−$\pi$−A dyes.



(M)-[7]helicene-fused octaazaphthalocyanine
**656a** M = Cu
**656b** M = Ni

[5]helicene-fused phthalocyanine
**657a** M = Zn
**657b** M = Pb
**657c** M = 2H

**Figure 19.** Phthalocyanine dye materials.

Table 4. Photovoltaic Performance of Some DSSCs[a]

| entry | dye | adsorption[b] (molecules·cm$^{-2}$) | $J_{sc}$ (mA·cm$^{-2}$) | $V_{oc}$ (mV) | *ff* | $\eta$ (%) | ref |
|---|---|---|---|---|---|---|---|
| 1 | **658a** | $6.8 \times 10^{16}$ | 2.12 | 508 | 0.57 | 1.00 | 239c |
| 2 | **658a** | $1.39 \times 10^{17}$ | 2.00 | 504 | 0.54 | 0.89 | 239b |
| 3 | **658b** | $2.3 \times 10^{16}$ | 1.73 | 536 | 0.58 | 0.88 | 239b |
| 4 | **658b** | $6.5 \times 10^{16}$[c] | 2.17 | | | 1.02 | 239b |
| 5 | **659a** | $4.4 \times 10^{15}$ | 0.12 | 216 | 0.42 | 0.02 | 239d |
| 6 | **659b** | $6.6 \times 10^{16}$ | 2.06 | 500 | 0.57 | 1.00 | 239d |
| 7 | **659c** | $5.5 \times 10^{16}$ | 2.10 | 548 | 0.56 | 1.00 | 239d |
| 8 | **659d** | $7.8 \times 10^{16}$ | 1.88 | 524 | 0.53 | 0.86 | 239d |
| 9 | **659e** | $7.2 \times 10^{16}$ | 2.00 | 468 | 0.55 | 0.84 | 239d |
| 10 | **659f** | $7.4 \times 10^{16}$ | 1.91 | 520 | 0.57 | 0.90 | 239d |

[a] A 7 $\mu$m thick $TiO_2$ electrode, Pt-coated glass as a counter electrode, a solution of 0.05 M iodine, 0.1 M lithium iodide, and 1,2-dimethyl-3-*n*-propylimidazolium iodide in acetonitrile as electrolyte; the photocurrent−voltage characteristics were measured under a simulated solar light (AM 1.5, 61 mW·cm$^{-2}$). [b] Adsorption amount per unit area of the $TiO_2$ film. [c] Using a thicker $TiO_2$ electrode (ca. 10 $\mu$m); values of $V_{oc}$ and *ff* were not given.

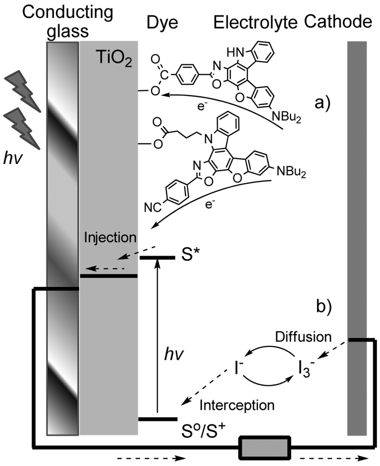


**Figure 21.** (a) Different ways of electron communication between a dye and the $TiO_2$ surface; (b) operational principle of DSSCs.

It was found that polymerization of **673** only gave insoluble oligomers,[244b] but when **672** (which has good solubility in a variety of solvents) was used as the monomer, the high molecular weight polymer **677** was obtained. Dehydrogenation of **677** either by chemical or by thermal transformation further provided the same polymer **678** as that obtained by polymerization of **673** (Scheme 166).[244a,b] Moreover, a transimidization method was established in order to ensure the monomer remained stable during the isolation and purification procedures as shown in Scheme 167.[245] In an effort to improve the solubility of such polymers, several dianhydrides have been used in copolymerization reactions to form diads with helicene units.[244] In addition, in the polymerization of the isocyanides **676** and tetrahydro-**676**, the remote chirality could be transferred during the process, which afforded polymers with optical rotation $[M]_D^{22}$ +228.0° (*c* 0.32, $CHCl_3$) and +139.0° (*c* 0.29, $CHCl_3$), respectively.[246]

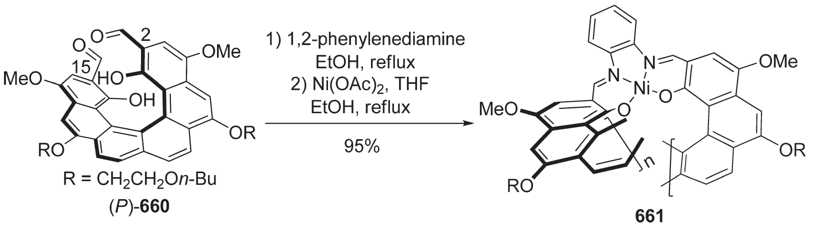
By Pd-catalyzed coupling between *o*- or *p*-diiodobenzene and the diethynyl[6]helicenes **681a**,**b**, Fox and co-workers reported the synthesis of cyclophanes **684** ($M_w = 1.40 \times 10^4$, $M_w/M_n = 1.68$) and helical acetylene-bridged polymers **685** ($M_w = 1.11 \times 10^4$, $M_w/M_n = 1.54$) (Scheme 168).[177] Interestingly, according to the UV and CD spectra, compared with **681b** and **684**, bathochromic shifts were observed for **685** at $\lambda$ = 369 and 355 nm, indicating that the conjugation was extended between the helicenes but not in the cyclophane **684** because of the twisted structure.

Optically stable [4]helicene has been employed by Yamaguchi and co-workers to prepare copolymers.[30a,71,72,247] As shown in Scheme 169, optically active [(*n* − 1) + *n*]amides **688** and [*n* + *n*]-cycloamides **603** and **689** (*n* = 1, 3−10), containing *n* or *n* − 1 parts of the (*P*)-helicene moieties **686** and *n* parts of diamines **687** were synthesized under controlled conditions.[71,72,247a] For *n* = 1−4, the CD spectra indicated that all macromolecules had significant ring effects, indicating that the larger ones had more flexible coiled structures. In addition, some cycloamides were found to have interesting characteristics. For example, when *n* = 1, **689** could form stable Langmuir−Blodgett films[248] and the [2 + 2]cycloamide **603** could be used as a catalyst in asymmetric addition reactions.[72a] Similarly, cyclic helicenealkynes **690** (*n* = 3−8) and acyclic helicenealkynes **691** (*n* = 2−9) were prepared (Figure 24).[247b,c,249] For **690**, when *n* = 3−7, the macromolecules were rigid and the [3 + 3]cycloalkyne was dimeric in solution due to the nonplanar $\pi-\pi$ interactions.[247b,249] Moreover, since **691** was a random coil, double-helix formation was observed at low temperatures.[250]

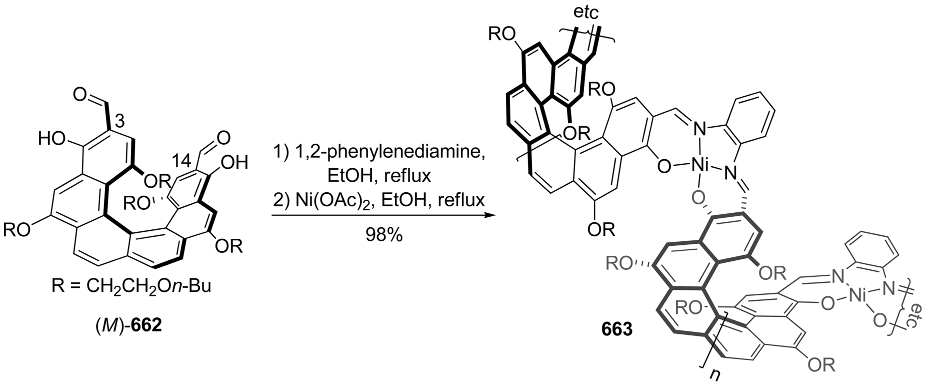
## 7.5. Molecular Recognition

In 1983, Nakazaki and co-workers synthesized two optically active crown ethers with helicene moieties by double-Wittig olefination and photocyclization (Figure 25).[167,251] After optical resolution by HPLC, chiral recognition of the crown ethers **692** and **693** was investigated by the differential transport process.[252] The experiment was carried out using a conventional approach in which the aqueous phases with the guest in the inner glass tube and the outer vessel were separated by a $CHCl_3$ solution containing the crown ether host. At 20 °C, when the organic layer was stirred, the guest in the outer aqueous phase was transported into the inner tube. The results are listed in Table 5.[167,251] **692** was found to give better transport of 1-phenylethylamine hydrochloride and had a higher selectivity for methyl phenylglycinate hydrochloride and 1,2-diphenylethylamine hydrochloride. Corey−Pauling−Koltun (CPK) models showed that the inner methyl substituents of the pentahelicene forced the smallest group of the guest to face inside, while the medium-sized group was located in the less hindered position. For the hexahelicene **693**, the outer methyl groups can affect the recognition, and thus, the selectivity was reversed for crown

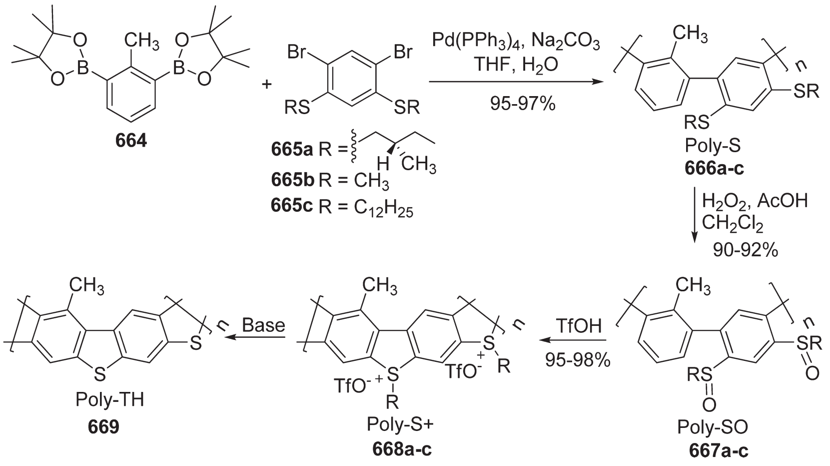
Scheme 162



Scheme 163

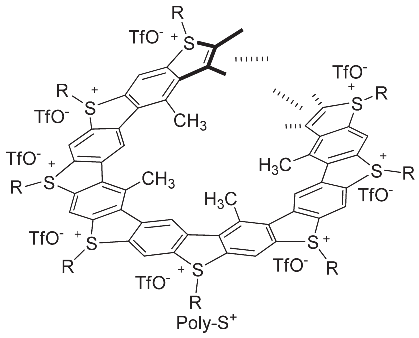


Scheme 164



ethers with the same handedness.[167] The shapes of the guest salts, namely, the degree of complementarity with the hosts, play key roles in both the transport and chiral recognition.

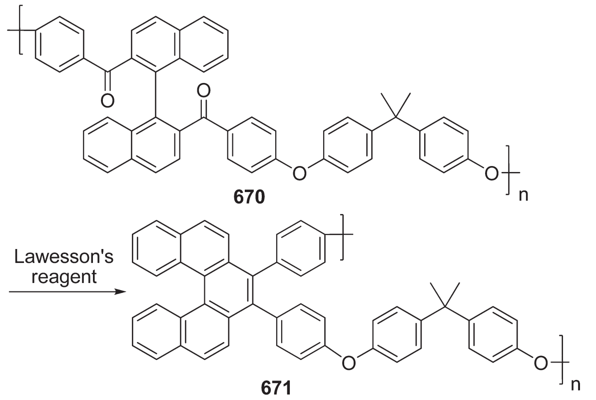
In addition to the above macrocyclic hosts, Diederich and coworkers reported the first helicopodands bearing a helical core in which a preorganized cleft formed at the termini of the helicene-containing hydrogen-bonding functionality (Figure 26).[253] They found that **694** could form stable 1:1 complexes in the presence of $\alpha,\omega$-dicarboxylic acids.[253b] In the crystal packing, (*PM*)-**694** stacked as a dimer by means of hydrogen bonding between helicenes or between a helicene and a CHCl$_3$ molecule. The two helicenes were in different configurations: one of them with the two NH/N moieties both pointing out had an 'out—out' configuration, whereas the other one had the functionality NH/N in an 'in—out' configuration. $^1$H NMR titrations were employed to determine the association constants ($K_a$) between the helicopodand and the diacid guests in CDCl$_3$ at 300 K. Diacid **695** was found to have the largest association constant (5500 ± 810 L/mol). According to theoretical calculations, this probably resulted from the distance between the two carboxyl groups (7.77 Å, separated by the fully staggered conformation) being comparable to that between the two NH/N moieties in the helicopodand (7.98 Å). Incorporation of a cyclohexyl (Cy) group in the derivatives **696**—**698** increased the solubilities of the materials, allowing a more detailed study. Comparing **698** with **697**, the helicopodand had a higher diastereoselectivity with the value of $\Delta(\Delta G°)$ nearly



**668a-c**

**Figure 22.** Thiahelicene-based ladder polymer.

### Scheme 165



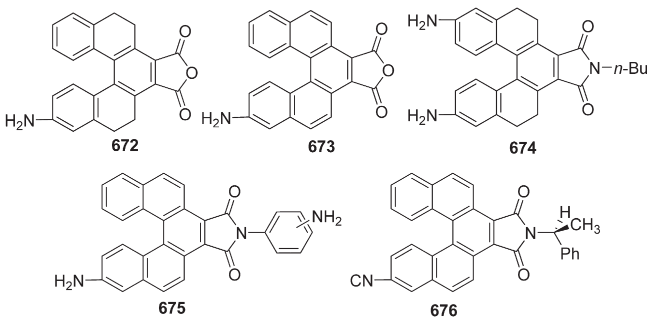
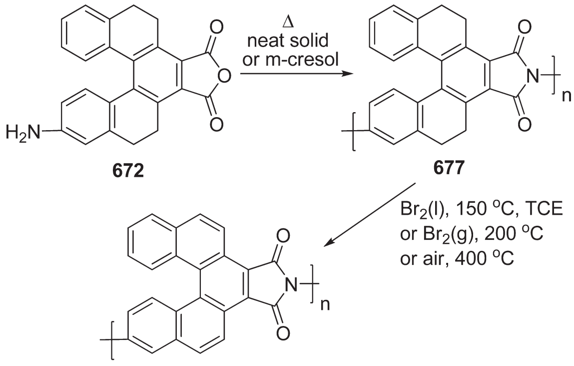


**Figure 23.** Some monomers used in the polymerization of helicenes.

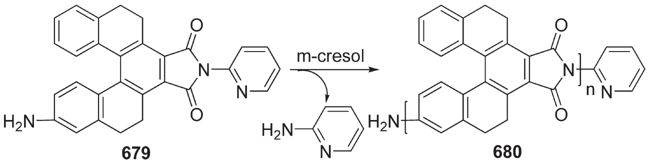
1.4 kcal/mol, indicating that (*E*)-diacid **697** has a better preorganization than its (*Z*)-isomer.

Katz and co-workers reported a novel method to enhance the sensitivity to the remote chiral centers by attaching the molecules to the chiral groove of [5]HELOL chlorophosphite.[254] **500** (or **699**) was treated with $PCl_3$, $Et_3N$, and DMAP followed by addition of chiral reagents such as chiral alcohols, phenols, and amines to the system to afford different diastereomers **700** (or **701**), where the chiral center is connected to the phosphite via a link (Figure 27).[254] Since the link lying in the groove is the alkyl chain, the polarity of the solvent will significantly affect the analysis. Consequently, it is important to choose an appropriate solvent for $^{31}$P NMR spectroscopic analysis based on baseline resolution.[254] In this approach, the ratio of the peak integrals for the corresponding diastereoisomers represents the enantiomeric excess of the previous mixture.[254a] This method is efficient in that **500** and **699** were prepared easily on a large scale and can be employed with a large range of substrates, including alcohols, phenols, amines, and carboxylic acids.

### Scheme 166



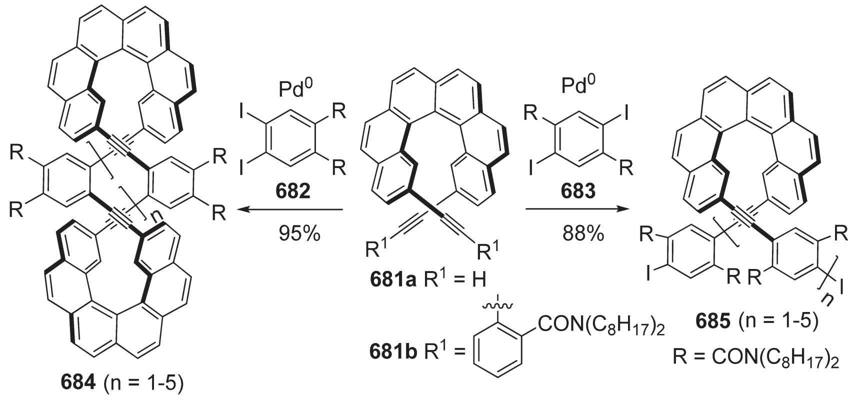
### Scheme 167



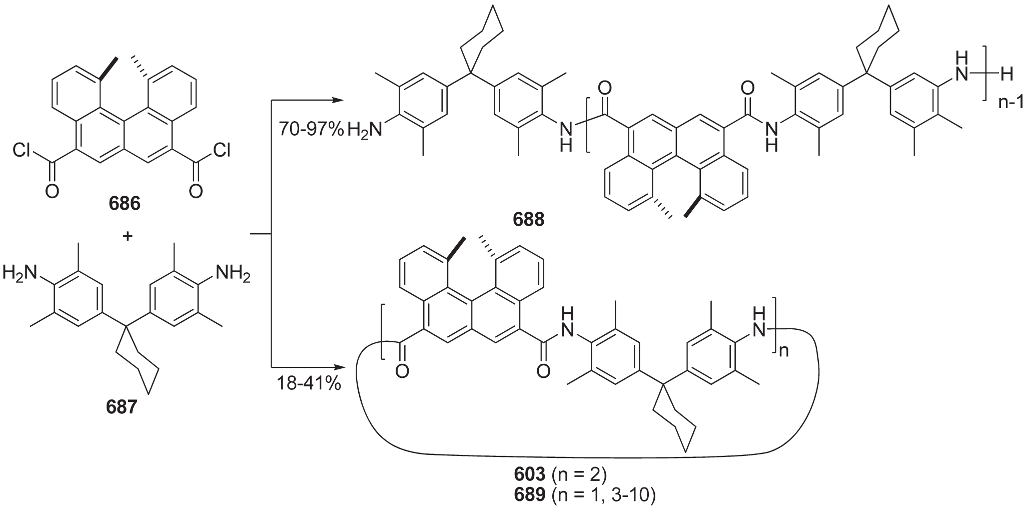
Moreover, in 1997, Kano and co-workers disclosed the chiral recognition between tetrahelicene dicarboxylic acids and oligosaccharides.[255a] By capillary zone electrophoresis (CZE) using different noncyclic oligosaccharides as chiral selectors, enantiomers of the tetrahelicene **81a** could be separated.[255a] Furthermore, based on the retention times, maltotetraose, maltopentaose, maltohexaose, and maltoheptaose favored the (*M*)-enantiomer as a guest; this was attributed to the hydrogen-bonding interaction between the carbonyl anions of the guest and the hydroxyl groups of the hosts via a "three-point attachment mechanism".[255a] Later, the same group also reported that cyclodextrins could recognize the tetrahelicene with high enantioselectivity.[255b,c] The binding constant of the complex (*M*)-**81a**-$\beta$-CD was 18 700 ± 1700 L/mol, which is nearly eight times larger than that of the complex (*P*)-**81a**-$\beta$-CD, whereas $\gamma$-CD formed less stable complexes, and $\alpha$-CD did not interact with **81a** because of its smaller cavity.[255b] The $^1$H NMR spectra and p$K_a$ measurements indicated that the $-CO_2^-$ groups were located outside the $\beta$-CD cavity, while the (*P*)-isomer penetrated deeper into the host. The enantioselectivity of $\beta$-CD for **81a** is mainly controlled by enthalpy changes resulting from the different degrees of penetration.[255c] In addition, the authors assumed that the CDs possessed an induced right-handed helical structure allowing better recognition of the guests bearing axial or helical chirality.[255b,c]

[6]HELIXOL **39** was examined as a fluorescence sensor for chiral aminoalcohols and amines by Reetz and Sostmann.[55] When (−)-**39** was treated with pairs of (*R*)- or (*S*)-enantiomers, different quenching rates were obtained from the Stern−Volmer

Scheme 168



Scheme 169

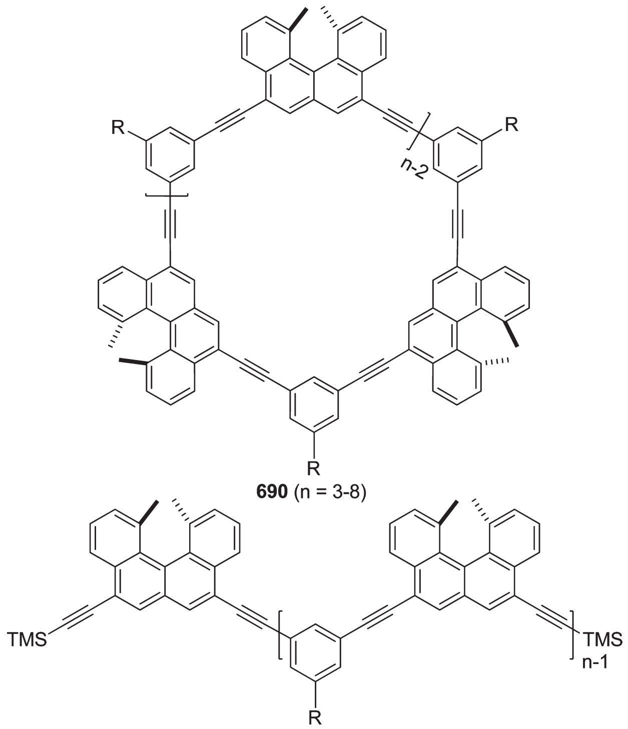


plots, which indicated chiral recognition between (−)-**39** and the quenchers **702**−**709** (Figure 28). Of these, the aminoalcohol **704** gave the highest enantioselectivity with a $K_{SV}(R)/K_{SV}(S)$ value of 2.10. Since the value of $K_{SV}$ can be linearly correlated with the enantiomeric excess of the quencher, optically pure [6]HELIXOL might be a useful enantioselective sensor by virtue of its high fluorescence intensity and high degree of chiral recognition.

## 7.6. Self-Assembly

**7.6.1. Self-Assembly in Solutions and Crystals.** Spontaneous aggregation of the optically active helicenebisquinone **710** (Figure 29) was first reported by Katz and co-workers in 1996.[175] The intensity of the CD spectra was enhanced greatly, and the specific rotation $[\alpha]_D$ increased from 678 to 8400 deg·cm$^2$/g as the concentration of **710** in *n*-dodecane was increased from 2.1 × $10^{-5}$ to 2.1 × $10^{-2}$ M. Interestingly, the precursor **711** was found as isolated molecules in both dilute and concentrated solutions. Cooling the isotropic liquid **710** could form fibers, which exhibited aggregation, with similar CD and UV−vis spectra to those of concentrated solutions, as well as cast films, of **710**.[11e] Similarly, the enantiopure thiaheterohelicene **712** aggregated into columnar structures either in dodecane or in the absence of a solvent, exhibiting good nonlinear optical properties.[124] Recently, Ungar and co-workers disclosed a novel type of self-assembly of the helicene **712** giving $13_2$ hollow six-stranded columns consisting of six-molecule repeat units with a period of 11.2 nm along the column axis.[256] For racemic **712**, an unusual mesoscale racemate was obtained, in which spontaneous resolution occurred and (*M*)-**712** and (*P*)-**712** self-assembled into right- and left-handed helices, respectively, while the enantiomer (*M*)-**712** gave a true hexagonal structure. Because of the steric hindrance at the center of the column, this provides a new approach to chiral porous materials.

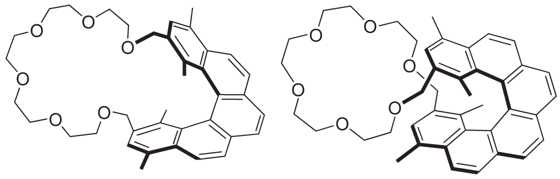
The nonplanar $\pi-\pi$ interactions provide an important method for aggregation of helicenes. Introducing hydrogen-bonding functionality on the periphery of the helical skeleton is an alternative useful method. Tanaka and co-workers found that racemic **436** crystallized from ethanol could form a 1:1 host−guest clathrate by hydrogen bonding.[257] Later, Tanaka and Kitahara reported that (*P*)-**436** self-assembled into a four-leaf clover motif in a left-handed manner.[222a] The authors also described a homochiral dimer of **713** (Figure 29) formed by intermolecular hydrogen bonding in which the nitrogen atom of one helicene was bound to a hydroxyl group on the other helicene.[22r]



**690** ($n$ = 3-8)

**691** ($n$ = 2-9)
R = $CO_2n$-$C_{10}H_{21}$

**Figure 24.** Cyclic and acyclic helicenealkynes.



**692** **693**

**Figure 25.** Two chiral crown ether hosts containing different helicene moieties.

Branda and co-workers described a new helicene **714** bearing two binding sites at each terminal ring. The position of the binding sites allowed formation of enantiomerically pure dimers with handedness (*P*,*P*) or (*M*,*M*) or arrays consisting of alternating *P* and *M* helicenes.[31] $^1$H NMR spectroscopy suggested that cooperativity is the driving force of self-assembly. However, X-ray analysis revealed that only the homochiral dimers were observed, involving two pairs of double hydrogen bonds with two acetyl groups in a cis relationship, as shown in Scheme 170.[31] The packing of the dimers made the crystal racemic. Self-assembly of helicenes by hydrogen bonds has also been supported by one theoretical calculation.[258]

Yamaguchi and co-workers studied the self-assembly of cyclic and acyclic helicenealkynes and their oligomers.[30] The cyclic helicene alkyne **690** ($n$ = 3) was dimerized, even at a concentration of 2 mM, and no higher aggregates were observed.[249] Moreover, the chirality of the helicene units significantly affected the self-aggregation, with the ease of dimer formation decreasing in the order (*M*,*M*,*M*)/(*M*,*M*,*M*) > (*M*,*P*,*M*)/(*M*,*P*,*M*) > (*M*,*M*,*M*)/(*P*,*P*,*P*) > (*M*,*P*,*M*)/(*P*,*M*,*P*). This result suggests that cycloalkynes with the same handedness of helicenes give the most stable dimer.[249] Substitution at positions C(2) and C(11) of the helicene units revealed that introduction of electron-withdrawing substituents resulted in stronger aggregation than electron-donating ones.[247b]

Later, Yamaguchi et al. further investigated the structural effects of different linkers of the oligomers of **690** ($n$ = 3) for which the rigidity and planarity play key roles in controlling the intra- and intermolecular aggregation (Figure 30).[259] When the linker was a flexible alkyl chain like (*P*,*P*,*P*)/(*P*,*P*,*P*)-**715**, strong intramolecular aggregation occurred as shown in Figure 31a, and a planar, rigid linker-induced dimerization was observed as shown in Figure 31b, 31c, and 31e.[259,260] Interestingly, when two cycloalkynes were linked by a *cis*-azo group, (*M*,*M*,*M*)/(*M*,*M*,*M*)-**717** preferentially polymerized by nonplanar $\pi-\pi$ interactions, as shown in Figure 31d, rather than dimerization or intramolecular aggregation.[260] Moreover, the linkers also influenced the strength of the aggregation: for example, a weak equilibrium existed in the self-assembly of (*P*,*P*,*P*)/(*P*,*P*,*P*)-**716**, while (*P*,*P*,*P*)/(*P*,*P*,*P*)/(*P*,*P*,*P*)-**718** formed a strong bimolecular aggregate without any other species.[259]

[*n*]Amines **719** (Figure 32, $n$ = 2−6) containing [4]helicene were synthesized by Yamaguchi and co-workers via condensation

**Table 5. Chiral Recognition of Enantiomeric Molecules in Differential Transport**

| entry | host[a] | guest[b] | time (h) | transport (%) | main enantiomer | optical purity (%) | ref |
|---|---|---|---|---|---|---|---|
| 1 | (*P*)-**692** | A | 6.0 | 6.0 | *R* | 77 | 167,251 |
| 2 | | B | 2.5(5.0) | 5.8(11) | *S* | 29(29) | 167,251 |
| 3 | | C | 5.0 | 6.2 | *S* | 82 | 167 |
| 4 | (*M*)-**692** | A | 6.0 | 6.0 | *S* | 75 | 167,251 |
| 5 | | B | 2.5(5.0) | 5.8(12) | *R* | 26(26) | 167,251 |
| 6 | | C | 5.0 | 6.2 | *R* | 80 | 167 |
| 7 | (*P*)-**693** | A | 10.0(6.0) | 5.8(2) | *S* | 28 | 167,251 |
| 8 | | B | 4.5(4.0) | 6.1(5) | *R* | 18 | 167,251 |
| 9 | | C | 8.0 | 5.9 | *R* | 46 | 167 |
| 10 | (*M*)-**693** | A | 10.0(6.0) | 5.8(2) | *R* | 27(26) | 167,251 |
| 11 | | B | 4.5(4.0) | 6.1(5) | *S* | 20 | 167,251 |
| 12 | | C | 8.0 | 5.8 | *S* | 45 | 167 |

[a] No transport was detected in the absence of the crown ether host. [b] A, methyl phenylglycinate hydrochloride; B, 1-phenylethylamine hydrochloride; C, 1,2-diphenylethylamine hydrochloride.

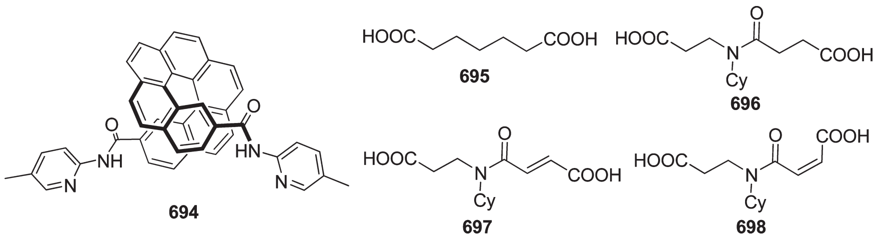
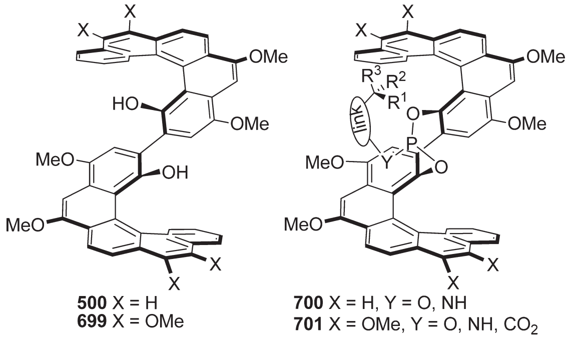
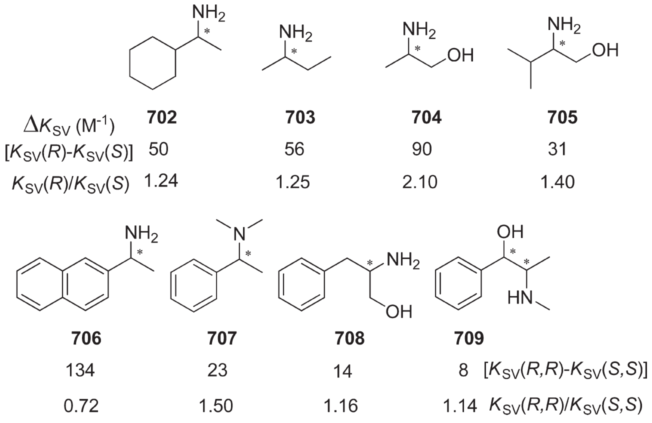


**Figure 26.** Helicopodand **694** is able to interact by hydrogen bonding with several dicarboxylic acids.



**500** X = H
**699** X = OMe
**700** X = H, Y = O, NH
**701** X = OMe, Y = O, NH, $CO_2$

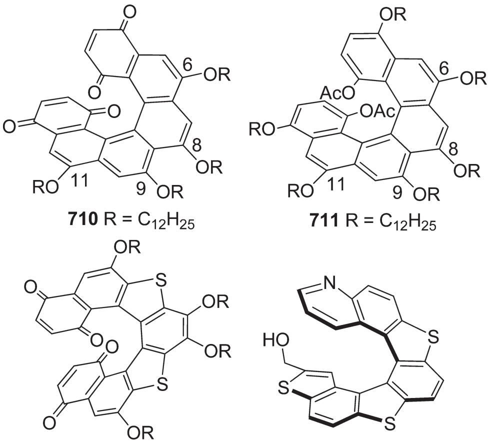
**Figure 27.** Some bihelicenyls bearing chiral grooves.



| | **702** | **703** | **704** | **705** |
|---|---|---|---|---|
| $\Delta K_{SV}$ ($M^{-1}$) $[K_{SV}(R)-K_{SV}(S)]$ | 50 | 56 | 90 | 31 |
| $K_{SV}(R)/K_{SV}(S)$ | 1.24 | 1.25 | 2.10 | 1.40 |

| **706** | **707** | **708** | **709** | |
|---|---|---|---|---|
| 134 | 23 | 14 | 8 | $[K_{SV}(R,R)-K_{SV}(S,S)]$ |
| 0.72 | 1.50 | 1.16 | 1.14 | $K_{SV}(R,R)/K_{SV}(S,S)$ |

**Figure 28.** Different amines and aminoalcohols employed as fluorescence quenchers.



**710** R = $C_{12}H_{25}$
**711** R = $C_{12}H_{25}$
**712** R = $C_{12}H_{25}$
(*P*)-**713**

**Figure 29.** Some helicenes used in self-assembly.

of amines and aldehydes followed by $NaBH_4$ reduction. The amines self-assembled into multilayer structures in water, whereas random coils were formed in methanol.[198,261] For $n$ = 2, the dihelicenetriamine bearing a homochiral helicene unit formed a more stable folded structure compared with the one containing enantiomeric helicenes.[198] When $n$ = 2−6, the helicene moieties stacked at the BC rings to form folded multilayer structures in which, according to $^1H$ NMR studies and theoretical calculations, the helicenes in adjacent layers favored a syn conformation if they were in the same handedness, whereas otherwise an anti conformation was preferred.[198,261]

A new class of acyclic helicenealkynes, $[n + (n - 1)]$alkynes **691** ($n$ = 2−9), has been prepared by Yamaguchi's group, in which the helical units are connected by a rigid linker *m*-phenylene. The CD signals were inverted and greatly enhanced for the alkyne ($n > 6$) compared with those of lower homologues ($n < 7$). In addition, vapor pressure osmometry (VPO) analysis suggested that a bimolecular aggregate or a double helix was formed.[250,262] Furthermore, thermodynamic and kinetic studies showed that the change of the structure from double helix to random coils was strongly influenced by the solvent, temperature, concentration, and absolute configuration of the helicene units.[30b,250,262] For example, the folding of (*P,P,P,P,P,P,P*)-[7 + 6]alkyne was accelerated at higher concentration and lower temperature, while the unfolding rate constant was correlated to the absolute hardness[263] of the solvent. The stability of the double helixes decreased in the order (*P,P,P,P,P,P,P*) > (*M,P,P,P,P,P,M*) > (*P,M,P,P,P,M,P*), indicating that the double-helix bearing helicene units with the same absolute configuration is more stable. In addition, Yamaguchi and co-workers reported that a heterohelix dimer, in which the substituents R on the two helicenealkynes are different (R = $CO_2n$-$C_{10}H_{21}$ and R = $n$-$C_8F_{17}$), was more stable than the homohelix dimer (R = $CO_2n$-$C_{10}H_{21}$).[264]

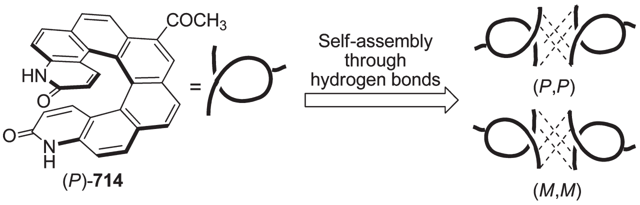
Surprisingly, a two-component organogel was formed by the enantiomers of **691** ($n$ = 3−6),[265] which is unusual for racemates which are poor gelators and easily crystallized.[266] The longer the oligomers were, the lower the concentrations that were needed for gelation and the more stable the gels were. The Cotton effects between 350 and 430 nm were dominated by the longer enantiomer. This new methodology affords a variety of gel systems, since the lengths of the *P* and *M* oligomers and their ratios can be varied.

Both **720** and **721** formed double helixes (head-to-tail or head-to-head) as a result of intramolecular aggregation in $CHCl_3$ (Figure 33).[30a,267] Compared with **691** ($n$ = 7), the unfolding rates of **720** and **721** were slower, with higher activation energies of 133 and 163 kJ/mol, respectively, at 5 × $10^{-6}$ M and 25 °C. Moreover, the UV−vis melting study showed that different processes involve different mechanisms, and two mechanisms, namely, a unimolecular mechanism for the head-to-tail helix and a bimolecular mechanism for a head-to-head one, were proposed.[30a] The processes of folding and unfolding, as for **691**, were markedly affected by the properties of the linkers, the temperature needed for the exothermic pre-equilibrium, and the concentration.[267]

A foldamer **722**, having highly solvent-dependent CD spectroscopic properties for different conformations, was reported by Moore and co-workers (Figure 34).[268] The most pronounced variations in CD features were between 250 and 340 nm, which is the characteristic region of *m*-phenylene ethynylene (*m*PE), where the isodichroic points indicate the changes of conformation. Three different foldamers were proposed: *m*PE arms folded into (i) (*P*)-helixes or (ii) (*M*)-helixes where the helicene was jutting out and (iii) the structure where two (*M*)-helixes wrapped around the helicene moiety.

**7.6.2. Self-Assembly at Metal Surfaces.** Taniguchi and co-workers studied the self-assembly of the thiahetero[11]helicene **723** on different gold surfaces under ultrahigh vacuum (UHV) conditions (Figure 35).[269] The resulting two-dimensional adlayers, prepared by vaporizing helicenes on Au(111), Au(110), and polycrystalline gold, were characterized by scanning tunneling microscopy (STM) and low-energy electron diffraction (LEED). According to STM, the helicene **723** adsorbed in the low-coverage region, and an ordered adlayer was formed on the wide terraces after exposure for long times.[269] For Au(111), the

**Scheme 170**



(*P*)-**714**

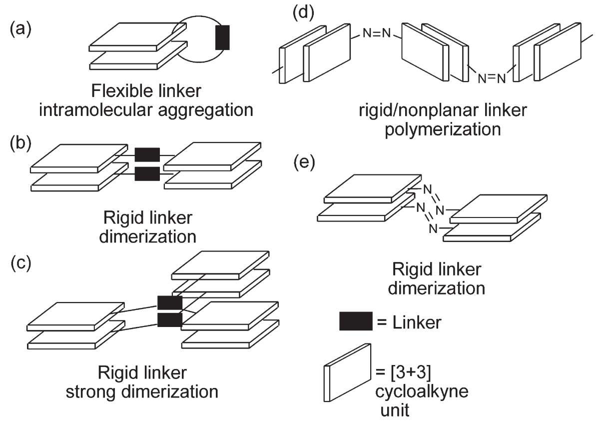
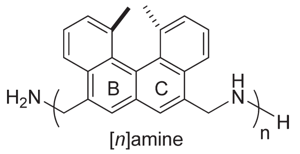
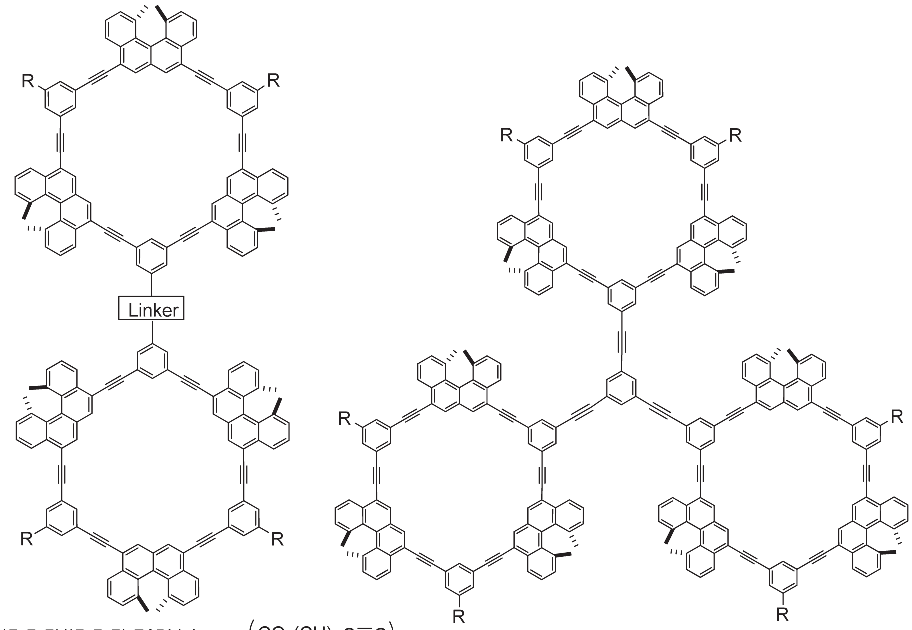


**Figure 31.** Different types of self-aggregation in helicenealkynes.



[*n*]amine
**719**

**Figure 32.** [*n*]Amines bearing helicene units.



(*P,P,P*)/(*P,P,P*)-**715** Linker = $\left( CO_2(CH)_4C{\equiv}C \right)_2$

(*P,P,P*)/(*P,P,P*)-**716** Linker = $\left( C{\equiv}C \right)_2$

(*M,M,M*)/(*M,M,M*)-**717** Linker = —N=N—

(*P,P,P*)/(*P,P,P*)/(*P,P,P*)-**718**
R = $CO_2n\text{-}C_{10}H_{21}$

**Figure 30.** Helicenealkynes connected by different linkers.

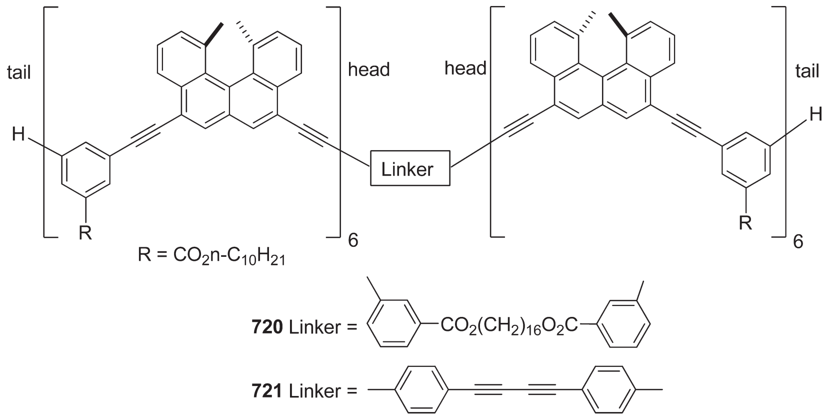


**Figure 33.** Helicenealkynes connected by different linkers.

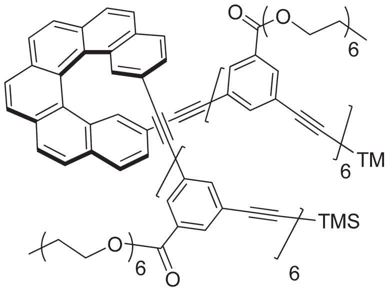
two-dimensional adlayer on the wide terraces was a hexagonal lattice in which the helicenes were randomly arranged without any chiral discrimination in their interactions, while the one on the narrow steps gave enantiomeric arrays of (*P*)- or (*M*)-isomers.[269a] In contrast, for the Au(110) substrate, the [11]-helicene **723** was aligned into chirality-sensitive chains.[269b] Moreover, **723** self-assembled on gold film on mica with a higher index surface, affording arrays with homochirality.[269b] Thus, the structure of the substrate plays an important role in the self-assembly of **723**.

Ernst and co-workers investigated the self-assembly of the [7]helicene **17** on different metal surfaces.[169,270] They found that enantiopure **17** formed a closely packed adlayer on Ni(111), without decomposition, in which the distance between the helicenes was 1 nm. Subsequent physical vapor deposition (PVD) afforded a chiral organic film.[270a] The orientations of the helicenes were determined by near-edge X-ray absorption fine structure (NEXAFS) and X-ray photoelectron diffraction (XPD) studies, which showed that the molecules were bound to the surfaces via $\pi$-orbitals and spiraled away from the substrates.[270b,c] On Ni(100), for a saturated monolayer of (*P*)-**17**, the tilt angle between the helical axis and the substrate surface was ca. 43°.[270b] (*M*)-**17** adsorbed on Cu(111) and Cu(332) with different azimuthal arrangements, in both of which three terminal benzene rings of the helicenes were found to be parallel to the (111) terrace planes.[270c] In particular, the step−molecule interaction rendered the surface chiral in the Cu(332) system.[270c] Moreover, the authors observed that the chirality—directed by the intermolecular steric repulsive forces—was transferred from the single molecule to the two-dimensional homochiral layer on Cu(111) (Figure 36).[169b] Later, Ernst and co-workers observed a unique example of the amplification of chirality.[270e−g] The self-assembly of racemic **17** on Cu(111) did not lead to the expected resolution[169a] but instead formed two enantiomorphous closely packed domains with different supramolecular handedness (left-handed, $\lambda$, and right-handed, $\rho$) in equal probability.[270e−g] If the helicene was enantioenriched, however, the domain sizes changed dramatically. If the amount of (*M*)-**17** exceeded 50%, $\lambda$ domains were favored, whereas an excess of (*P*)-**17** resulted in the preferential formation of $\rho$ domains, indicating that the $\lambda$−*M* and $\rho$−*P* interfaces are energetically favored.[270e] According to molecular mechanics calculations, neither of the domains can incorporate the excess enantiomers, which are expelled to the edges or the residue areas, keeping the main terrace homochiral. Therefore, the boundaries between the two domains have higher energy than those between domains with the same handedness in different orientations.[270e] Consequently, the mirror domain boundary energy and the domain/residual area interface energy are the two factors driving the chiral amplification effect.[270e] Recently, Stará's group found that even on an insulating substrate, namely, calcite, with the help of $\pi$−$\pi$ interactions within the rows and hydrogen-bonding interactions between the rows, racemic heptahelicene-2-carboxylic acid **724** underwent self-assembly into nanowire-like aggregates.[78h,i] Interestingly, the dimers of the acid in the columnar stacks were upright relative to the substrate surface, in contrast to what was observed for studies on metal surfaces.

### 7.7. Langmuir−Blodgett Films

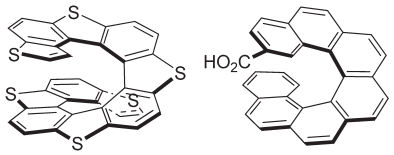
In 1998, Yamaguchi and co-workers described the first chiral Langmuir−Blodgett (LB) films bearing enantiopure helicene units.[248] This new class of LB films was successfully prepared by transferring a stable monolayer of (*P*)-(−)-**689** (*n* = 1) from the water/air surface to solid supports by down and up strokes. UV−vis absorption spectra of the LB films showed a slight bathochromic shift in comparison with that of the solution of (−)-**689** (*n* = 1). As the number of layers increased, the absorbance did not increase in proportion to the number of layers because the transfer ratio gradually decreased. Moreover, as expected, the broad emissions indicate that some excimer species were formed and the LB films had the same Cotton effect as a solution of **689** (*n* = 1). The skeleton of **689** (*n* = 1) was essential to produce stable LB films, and the properties could be improved by *N*-alkylation, which afforded a variety of optically active films.[30a,271]

Katz, Verbiest, and co-workers prepared another novel class of LB films using the optically active helicene **710**.[272] Self-assembly of the nonracemic **710** was shown to form long fibers in both solution[175] and the liquid crystalline material (Figure 37).[273] Similarly, LB films were obtained from parallel columns in which the molecules were perpendicular to the substrate, as demonstrated by atomic force microscopy (AFM) images,[29b] with supporting evidence provided by the linear dichroism, 180 °C periodicity, and X-ray diffraction (XRD) analysis of the films.[272] Moreover, as shown in Figure 37, the long parallel columns stack into lamellae about 2−3 columns high and 60 columns across (ca. 10 nm high and 50−200 nm wide), which can be seen under an optical microscope.[273] The CD and UV−vis spectra of a 10-layer film resemble those of the aggregates in a solution of **710**



(-)-(*M*)-**722**

**Figure 34.** Foldamer-containing helicene core.



**723** **724**

**Figure 35.** Helicenes studied on different surfaces.

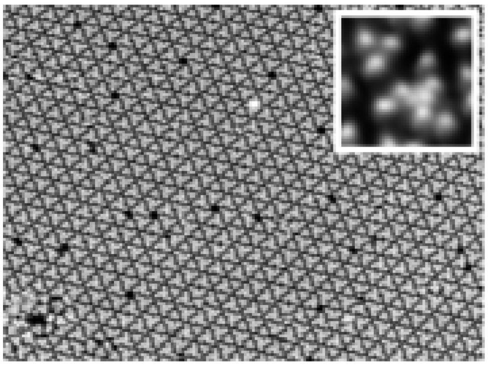


**Figure 36.** STM image of long-range ordered monolayers of (*M*)-**17** on Cu(111) at 50 K. Reprinted with permission from ref 169b. Copyright 2003 John Wiley and Sons.

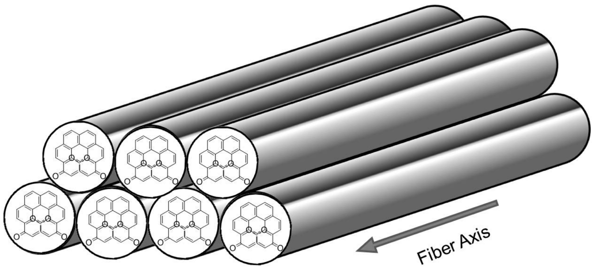


**Figure 37.** Schematic representation of columnar aggregation formed by helicenes (functional groups are omitted for clarity).

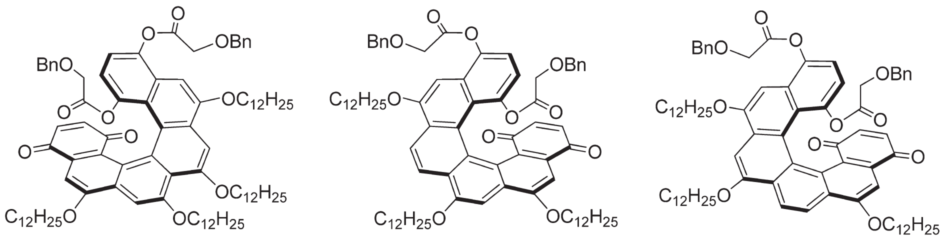
($2.5 \times 10^{-2}$ M) but differ from those of the monomers in highly dilute solution ($1.0 \times 10^{-4}$ M). The CD spectrum and specific rotation of the monolayer were greatly enhanced as a result of aggregation.[272] Surprisingly, the columnar stacking of the optically active helicene **710** showed a susceptibility value of 50 pm/V and a high second-order nonlinear optical response nearly 30 times larger than that of the racemic material which was dominated by the chirality of the organization.[29b] The morphology was improved and the nonlinear optical efficiency doubled by heating the LB films of **710**.[274] These results provide a new approach for fabricating frequency converters by self-assembly of helicenes.[29]

By theoretical and experimental studies of the LB films formed from the thiaheterohelicene **712** the roles played by chirality and anisotropy in the circular-difference effect were elucidated. The former was intrinsic and independent of the process of analysis, whereas the latter depended on the azimuthal angle during characterization.[275] Siltanen and co-workers prepared both X- and Y-type LB films of **712** and found that independent of the thickness and type of the film the overall nonlinear properties originate from the susceptibility tensor components associated with chirality.[276] In addition, a Y-type LB film showed a more ordered columnar aggregation, while a X-type was more randomly oriented.[276] Moreover, Verbiest and co-workers reported that even the spin coating highly asymmetric chiral films could give second-harmonic generation (SHG) with a susceptibility of up to 9 pm/V.[277]

## 7.8. Liquid Crystals

Lovinger, Nuckolls, and Katz reported that when nonracemic helicenebisquinone **710** was cooled from the melt it could organize into liquid crystalline fibers comprised of lamellae (Figure 37).[273,278] The molecules were packed into hexagonal columns, and the long axes of the fibers were parallel to those of the columns. When the bisquinone **710** was converted to (*P*)-**725** (Figure 38) by reduction with $Na_2S_2O_4$ and $H_2O$ and subsequent acylation, a columnar mesophase bearing an optically active helical core was obtained in *n*-dodecane at room temperature.[279] Just as for the bisquinone **710**, XRD demonstrated that **725** aggregated with hexagonal columnar ordering and the order along the lengths with a smaller diameter of 3.3 nm was greater than that for **710**.[279] If the concentration of dodecane was higher than 30 vol %, a nematic liquid crystalline phase could be obtained, while when the concentration was ≤5 vol %, the mixture had a hexagonal columnar phase.[280] Furthermore, enhanced circular dichroism and specific rotation as well as shifted fluorescent emissions were observed compared with the isolated molecules in highly dilute solutions.[279] Because of its large intrinsic dipole moment, **725** can be used as an electro-optical switch with a typical activation energy of 11.90 ± 0.7 kcal/mol.[280] Verbiest and co-workers observed second-order NLO effects in the chiral discotic nematic liquid crystalline phase composed of a mixture of (*M*)-**726** and (*M*)-**727**. Without the orienting electric field, there was no CD effect in the SHG, while in the oriented state the material was polar and CD effects were observed, the signs of which were changed by reversing the polarity of the electric field.[281] Katz and co-workers studied the effects of the side chains at C(6), C(8), C(9), and C(11) in **710** and discovered that all derivatives could aggregate into hexagonal columns.[282] However, formation of the true liquid crystalline mesophases required three unsymmetrically arranged side chains, and their structures markedly affect the properties of the material (Figure 38).[282]

Helicenes, dissolved in achiral liquid crystals could also be chiral dopants and transfer the molecular chirality to the whole phase, as characterized by the helical pitch and the handedness as shown in Figure 39a.[283] The mechanism is depicted in Figure 39b: for example, (*P*)-[5]helicene induced the (*P*)-biaryl rather than the (*M*)-isomer because of the unfavorable steric repulsion in the latter.[283b] Therefore, the deracemization process



(*P*)-(+)-**725** (*M*)-(-)-**726** (*M*)-(-)-**727**

**Figure 38.** Different helicenes forming liquid crystalline mesophases.

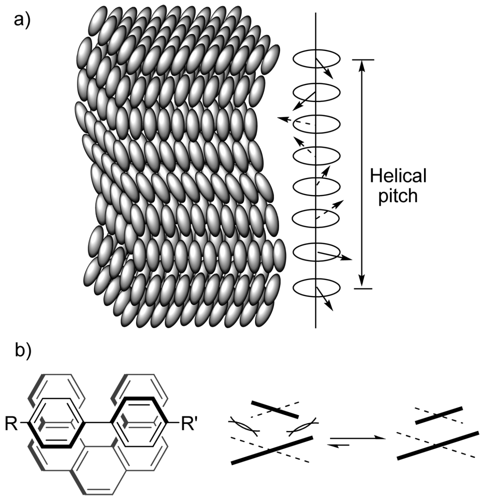


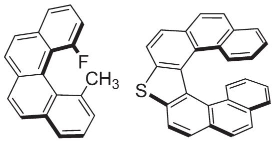
**Figure 39.** (a) Schematic representation of the chiral phase and helical pitch; (b) mechanism for the chirality transfer procedure from the dopant to the whole organization.

occurred by transfer of the chirality from the dopant to the nearby solvent molecules and sample molecules. Spada and co-workers utilized three different (*M*)-helicenes (**8**, **728**, and **729**) as dopants and found that all three rigid chiral probes gave the left-handed cholesteric structures with helical twisting powers of −55, −9, and −20 $\mu m^{-1}$, respectively (Figure 40).[284] The results are in good accordance with a model study of the surface chirality.[285,286] Furthermore, this LC technique can be used to predict the absolute configuration or the enantiomeric excess of the dopants.[284,286]

## 7.9. Biological Applications

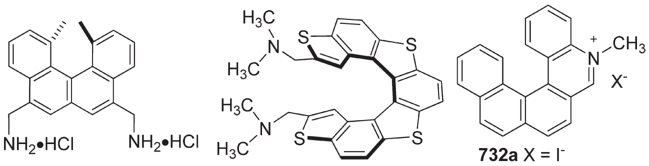
In 2002, Yamaguchi and co-workers first disclosed the chiral recognition between the helicenediamine **730** and B-DNA (Figure 41).[287] The apparent changes in the UV and CD spectra caused by adding calf thymus DNA to the solutions of (*P*)- and (*M*)-**730** suggested that DNA−helicene complexes were formed. According to isothermal titration calorimetry, the binding constant of (*P*)-helicene is slightly larger than that of its enantiomer, whereas the chiral recognition whereby (*P*)-**730** favors right-handed helicity is probably driven by entropy.

That (*P*)-helicene **731** can bind Z-DNA selectively and convert B-DNA into Z-DNA was first reported by Sugiyama and co-workers.[288] However, although (*M*)-**731** exhibited selective binding with Z-DNA, the binding constant of the (*P*)-enantiomer was five times greater. Interestingly, when the amino groups were replaced by hydroxyl groups, the structural selectivity vanished, indicating that the protonated amino substituents were important in binding Z-DNA.



(*M*)-**728** (*M*)-**729**

**Figure 40.** Optically active helicenes as chiral dopants in LC.



(*P*)-**730** (*P*)-**731**

**732a** X = $I^-$
**732b** X = $NO_3^-$
**732c** X = $CF_3CO_2^-$

**Figure 41.** Several helicenes examined in biological applications.

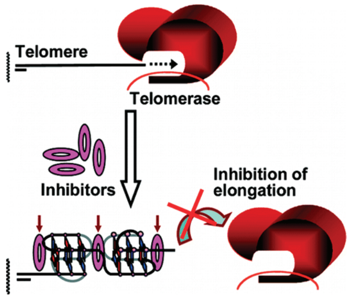


**Figure 42.** Schematic representation of telomerase inhibition. Reprinted with permission from ref 290. Copyright 2010 American Chemical Society.

Recently, Latterini and co-workers reported counterion effects in the binding between helicenes and DNA using the same organic azahelicenium moiety with different anions ($I^-$, $NO_3^-$, and $CF_3CO_2^-$).[289] The counterions affected the interaction greatly: **732c** with $CF_3CO_2^-$ anions had the highest association binding constant ($K_a = 2.4 \times 10^{-4}$ $M^{-1}$), whereas **732b** with $NO_3^-$ ions had the highest number of binding sites ($n = 2.5$). This suggests a mixed mechanism involving intercalation and external binding with **732a** and **732c** favoring formation of intercalation complexes according to CD and AFM studies.

Telomerase inhibition has been considered as a new method of cancer therapy. Sugiyama and co-workers described the first example using a bridged helicene as a chiral wedge to effectively block the access of telomerase to telomeres by association with higher order G-quadruplex structures.[290] The authors employed quadruplex dimers to investigate the enantioselective recognition using the substrates ODN 1 (AGGG(TTAGGG)$_3$TTAGGG-(TTAGGG)$_3$) and ODN 2 (AGGG(TTAGGG)$_3$(TTA)$_6$-GGG(TTAGGG)$_3$), in which the linkers of the two G-quadruplex repeats differ. The former is connected by one TTA repeat, while in ODN2, as a control, the linker is elongated to six TTA repeats. Several different bridged helicenes **639a**, **639b**, and **640** were prepared as inhibitor candidates. Unfortunately, only (*M*)-**640**, with the appropriate dihedral angle and absolute configuration, showed an effective interaction with the substrate. It was proposed that (*M*)-**640** has a better complementary shape to the chiral pocket between the two G-quadruplexes (Figure 42).

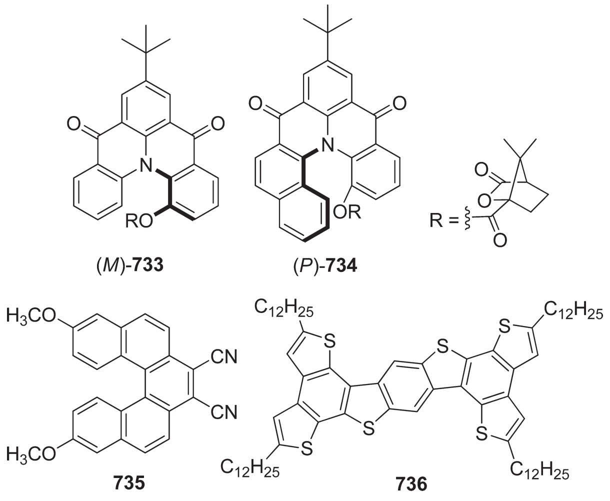


**Figure 43.** Different helicenes employed in organic electronics.

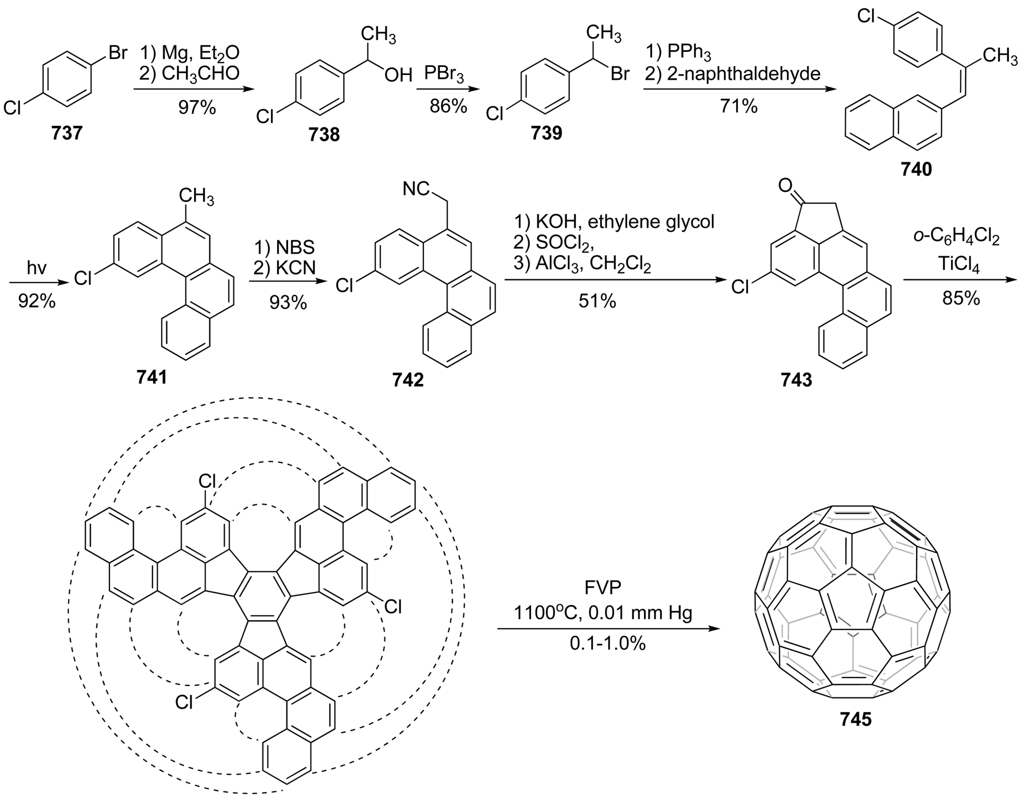
## 7.10. Miscellaneous

### 7.10.1. Organic Electronics.

All chiral luminescent organic molecules are capable of circularly polarized luminescence, but emission of the two polarized light beams differs.[291] In 2003, Venkataraman and co-workers showed that two helicenes bearing triarylamine units (**733** and **734**, Figure 43) were able to absorb and emit the circularly polarized light with different signs. The absorption and emission were determined by the helical chirality, of which the absolute configurations were stabilized by the bulky camphanate substituents at the C(1) position.[292] According to the luminescence spectra, the luminescence dissymmetry ratios $g_{\mathrm{lum}}$, representing the degree of the circularly polarized luminescence, were +0.0009 and −0.0011 at 453 nm for (*P*)- and (*M*)-**733** and +0.0008 and −0.0007 at 478 nm for (*P*)- and (*M*)-**734**, respectively. Furthermore, Barnes et al. observed the chiroptical response of a single molecule of **734**, which might have potential applications in polarized organic light-emitting diodes (POLEDs).[293]

Recently, Sooksimuang and co-workers employed 3,12-dimethoxy-7,8-dicyano-[5]helicene (DDH) **735** as a new organic emissive material in which the pull and push structure results in absorption and fluorescence at longer wavelengths.[294] DDH has an energy gap of ca. 2.6 eV and high thermal stability (mp 307 °C, $T_g$ = 130 °C, decomposition at 330 °C) which might prolong its life span.[294] OLEDs were fabricated with the ITO/PEDOT:PSS (35 nm)/DDH/Ca(10 nm)/Al(100 nm) configuration. For

Scheme 171



thicknesses from 60 to 100 nm the turn-on voltages were the same (3.7 V). The best result was obtained when the DDH thickness was 100 nm, exhibiting maximum brightness, current efficiency, and power efficiency of 1587 cd/m$^2$ (at 8.0 V and 281 mA/cm$^2$), 0.64 cd/A, and 0.29 lm/W, respectively. The CIE coordinates of the OLEDs varied from (0.38, 0.47) to (0.51, 0.44) as the voltage was increased from 5.0 to 8.0 V.

More recently, Pei and co-workers[295] fabricated high-performance organic field-effect transistors based on a single-crystal microribbon which was obtained by directed precipitation of the double thiahelicene **736**; the highest mobility was 2.1 cm$^2$ V$^{-1}$ s$^{-1}$ with a threshold voltage of −7 V and an on/off ratio of 2 × 10$^5$. The properties of these p-channel transistors were greatly improved by enhancing the crystallinity, optimizing the interface between the crystal and the dielectric layer, and utilizing an improved plastic fiber mask method to shrink the channel length, fabricate the asymmetric gold source, and drain electrodes. In addition, 3,6,9,12-tetrathia[7]helicene has also been employed in organic thin-film transistors (OTFTs).[107e]

**7.10.2. Synthesis of $C_{60}$.** Chemical synthesis of fullerenes is of great interest, not only because a controllable process, unlike vaporization of graphite,[296] gives products in isolable quantities but also because chemical methods provide access to new fullerenes and their derivatives.[297] The general approach starts from construction of polycyclic aromatic structures having a fullerene topology which can be rolled up under FVP conditions.[298] Scott and co-workers[299] reported the first chemical synthesis of buckminsterfullerene $C_{60}$. As shown in Scheme 171, **737** was converted into helicene **741** by Grignard addition, bromination, Wittig olefination, and photocyclization. Then, **743** was obtained in moderate yield via bromination, cyano substitution, and Friedel−Crafts alkylation. Trimerization took place in the presence of $TiCl_4$, giving **744** by building a benzene unit. Fortunately, since the 1,2-shifts of hydrogen atom in aryl radicals are generated at a high temperature,[300] three chlorine atoms in **744** initiate cyclization. By a "cascade" effect, this polyarene **744** bearing several helicene units was folded up by FVP without forming any other higher fullerene.[298,299b] The efficiency of the FVP procedure, forming 15 new C−C bonds and 16 new aromatic rings in one step, results in reasonable yields of 0.1−1.0%.

## 8. CONCLUSION AND OUTLOOK

This review has shown that helicenes are an interesting class of molecules with unique helical structure and inherent chirality. During the past century, in particular in the last two decades, enormous progress has been made in understanding the chemistry of helicenes. Not only have more and more new synthetic methods for different kinds of helicenes, including carbohelicenes and heterohelicenes, been developed but the asymmetric synthesis and optical resolution of some helicenes have also been achieved. In particular, a variety of applications of the helicenes in areas such as asymmetric catalysis, molecular machines, molecular recognition and self-assemblies, and materials science have been demonstrated, and some of the results are exciting. However, new strategies for the efficient, low-cost synthesis and functionalization of helicenes still need to be explored. Discovering general routes for the asymmetric synthesis of helicenes, developing new convenient methods for the optical resolution of racemic helicenes, and preparing longer helicenes are the next challenging targets. Undoubtedly, there is also plenty of room for further studies of applications of helicenes in different areas. In short, this promising field is entering its golden age, and we believe that more and more important and exciting progress in the chemistry of helicenes will be made in the near future.

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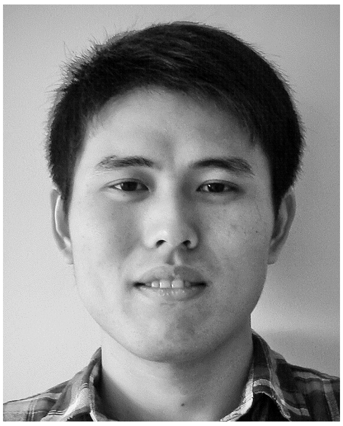

Yun Shen was born in Zhejiang, China, in 1986. He received his B.S. degree in Chemistry from Xiamen University in 2009. He is currently a Ph.D. candidate under the direction of Professor Chuan-Feng Chen at the Institute of Chemistry, Chinese Academy of Sciences. His research focuses on the synthesis of helicenes and their applications in asymmetric catalysis.

Chuan-Feng Chen was born in Anhui, China, in 1965. He graduated and received his B.S. degree from Anhui Normal University in 1986, his M.S. degree from Hangzhou University in 1989, and his Ph.D. degree from Nanjing University in 1994. After working as a postdoctoral fellow at the Institute of Chemistry, Chinese Academy of Sciences for 2 years, he became an associate professor at the same institute in 1996. From 1998 to 2001 he worked as a visiting scientist at the University of New Mexico. Then he was promoted to a full professor of ICCAS in 2001. His current research interests include supramolecular chemistry based on novel synthetic hosts, hydrogen-bond-mediated molecular assemblies, helical foldamer, and helicene chemistry.

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## ABBREVIATIONS

| | |
|---|---|
| A | adenine |
| acac | acetylacetonyl |
| AFM | atomic force microscopy |
| AIBN | 2,2′-azobis(2-methylpropionitrile) |
| Am | pentyl |
| ATP | adenosine triphosphate |
| BINAP | 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl |
| BINOL | 1,1′-bi-2-naphthol |
| BINPHAT | bis(tetrachlorobenzenediolato)mono([1,1′]-binaphthalenyl-2,2′-diolato)phosphate(V) |
| BSA | bovine serum albumin |
| CAN | ceric ammonium nitrate |
| CD | circular dichroism |
| CD | cyclodextrin |
| CDI | carbonyl diimidazole |
| CIE | International Commission on Illumination |
| cod | 1,5-cyclooctadiene |
| Cp | cyclopentadienyl |
| CPK | Corey–Pauling–Koltun |
| CPL | circularly polarized light |
| Cy | cyclohexyl |
| CZE | capillary zone electrophoresis |
| dba | dibenzylideneacetone |
| Dbf | dibenzo[*c*,*g*]fluorenide |
| DCE | 1,2-dichloroethane |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| de | diastereoisomeric excess |
| DEAD | diethyl acetylenedicarboxylate |
| DKR | dynamic kinetic resolution |
| DMA | *N*,*N*-dimethylacetamide |
| DMAD | dimethyl acetylenedicarboxylate |
| DMAP | *N*,*N*-4-dimethylaminopyridine |
| DME | 1,2-dimethoxyethane |
| DMF | *N*,*N*-dimethylformamide |
| DMPC | dimyristoyl phosphatidylcholine |
| DMSO | dimethyl sulfoxide |
| DNA | deoxyribonucleic acid |
| dppb | 1,4-bis(diphenylphosphino)butane |
| dppe | 1,2-bis(diphenylphosphino)ethane |
| dppp | 1,3-bis(diphenylphosphino)propane |
| dr | diastereomeric ratio |
| DSSCs | dye-sensitized solar cells |
| ee | enantiomeric excess |
| FMO | frontier molecular orbital |
| FVP | flash vacuum pyrolysis |
| G | guanine |
| GS | ground state |
| Heliphos | 2,2′-bis(diphenyl phosphino)helicenes |
| HELIXOL | 2,2′-dihydroxylhelicenes |
| HELOL | 2,2′-bihelicenyl-1,1′-diols |
| HMO | Hückel molecular orbital |
| HMPA | hexamethylphosphoramide |
| HOMO | highest occupied molecular orbital |
| HPLC | high-performance liquid chromatography |
| ICT | intramolecular charge transfer |
| KHMDS | potassium bis(trimethylsilyl)amide |
| LAH | lithium aluminum hydride |
| LB | Langmuir–Blodgett |
| LC | liquid crystal |
| LDA | lithium diisopropylamide |
| LEED | low-energy electron diffraction |
| LiHMDS | lithium bis(trimethylsilyl)amide |
| LUMO | lowest unoccupied molecular orbital |
| *m*-CPBA | *meta*-chloroperbenzoic acid |
| Mes | mesityl |
| MIC | methyl isocyanate |
| $M_n$ | number-average molecular weight |
| MOMCl | methyl chloromethyl ether |
| *m*PE | *m*-phenylene ethynylene |
| $M_w$ | weight-average molecular weight |
| MW | microwave |
| NA | not available |
| NBS | *N*-bromosuccinimide |
| NEXAFS | near-edge X-ray absorption fine structure |
| Nf | nonafluorobutanesulfonyl |
| NLO | nonlinear optical |
| NMP | *N*-methyl-2-pyrrolidinone |
| NMR | nuclear magnetic resonance |
| ORD | optical rotatory dispersion |
| OTFTs | organic thin-film transistors |
| PCC | pyridinium chlorochromate |
| PHelix | 2,15-bis(diphenylphosphino)hexahelicene |
| PhtNSCl | phthalimidesulfenyl chloride |
| Piv | pivaloyl |
| PPA | polyphosphoric acid |
| PSS | photostationary state |
| PVD | physical vapor deposition |
| *rac* | racemic |
| r-CPL | right circularly polarized light |
| SDS | sodium dodecyl sulfate |
| $S_E$Ar | electrophilic aromatic subsititution |
| SHG | second-harmonic generation |
| $S_N$Ar | nucleophilic aromatic subsititution |
| SOMO | singly occupied molecular orbital |
| sp | species |
| STM | scanning tunneling microscopy |
| T | thymine |
| TABA | 2-(2,4,5,7-tetranitro-9-fluorenylideneamino-oxy)butyric acid |
| TAPA | 2-(2,4,5,7-tetranitro-9-fluorenylideneamino-oxy)propionic acid |
| TBAF | tetra-*n*-butylammonium fluoride |
| TBDMS | *tert*-butyldimethylsilyl |
| TCE | 1,1,2,2-tetrachloroethane |
| Tf | trifluoromethanesulfonyl |
| TFA | trifluoroacetic acid |
| $T_g$ | glass transition temperature |
| THF | tetrahydrofuran |
| TIPS | triisopropylsilyl |
| TMEDA | *N*,*N*,*N*′,*N*′-tetramethylethylenediamine |
| TMS | trimethylsilyl |
| Tol | *p*-tolyl |
| TOTA$^+$ | trioxatriangulenium cation |
| TPCD | (tetrakispyridino)cobalt(II) dichromate |
| TS | transition state |
| Ts (Tos) | *p*-toluenesulfonyl |
| UHV | ultrahigh vacuum |

| | |
|---|---|
| UV−vis | ultraviolet−visible |
| VAPOL | vaulted 3,3′-biphenanthrol |
| VAZO | 1,1′-azobis(cyclohexanecarbonitrile) |
| XPD | X-ray photoelectron diffraction |
| XRD | X-ray diffraction |

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