Unlocking the potential of thiaheterohelicenes: chemical synthesis as the key

Shawn K. Collins* and Martin P. Vachon

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The possibility of combining the electronic properties of oligothiophenes with potential chiroptical properties has fueled research in the area of thiaheterohelicenes. Recent reports that these molecules also exhibit fascinating interactions with biologically important macromolecules place further emphasis on the need for new synthetic methods to access thiaheterohelicenes. This review highlights the synthetic methods currently being used to prepare thiaheterohelicenes and discusses the role that chemical synthesis plays in the exploration of the properties of these helically chiral molecules.

Introduction

Conjugated molecules continue to be a subject of interest due to their optoelectronic properties. Advancement of the field is often directly linked to the availability of synthetic methods for making new well-defined molecular architectures. This is particularly true in the field of helicene synthesis, where the addition or subtraction of substituents can modify both the electronic and optical properties and influence the solid state organisation of the materials. Unfortunately, the synthetic methods available to make such substitutions are often limited. Helicenes possess an intrinsically chiral helical structure due to their twisted carbon skeleton which results from the ortho-fusion of aromatic rings.[1] These rigid structures are particularly attractive because the chiroptic and electronic properties combine[2] and become more significant with increasing molecular size. The overlapping rings of the large system have the potential for π-interactions and the packing and supramolecular assembly of helicenes in the solid state has been shown to be influenced by the molecular geometry.[1]

The inherent chirality of helicenes has led to their application in asymmetric synthesis as chiral ligands.[3,4] However, it is the unique mesh of chirality and electronic potential[5] that has piqued the interest of chemists for over 30 years.[1] Although the domain has been dominated by carbohelicenes (Fig. 1, A), an emerging trend is the fusion of thiophenes into the helical skeleton of the helicene, giving birth to various thiaheterohelicenes (Fig. 1, B, C and D). The presence of sulfur along the outer ridge of the helicene offers new opportunities to modify the electronic and optical properties due to S–S interactions in the solid state.[6,7]

As the properties of both carbohelicenes and thiaheterohelicenes continue to be investigated, differences between the two classes of helical motifs have emerged. An important difference

Department of Chemistry, University of Montréal, C.P. 6128 Succursale Centre-ville, H3C 3J7, Montréal, Québec, Canada. E-mail: shawn.collins@umontreal.ca; Fax: +1 (514)343 7586; Tel: +1 (514)343 6735

Shawn K. Collins obtained a BSc (Honours) degree from Concordia University in 1996 and his doctoral dissertation in 2001 with Professor Alex G. Fallis at the University of Ottawa. After a NSERC postdoctoral fellowship with Professor Larry E. Overman (University of California, Irvine), he joined the faculty at the Université de Montréal in September 2003 as an Assistant Professor. Professor Collins' research group is interested in the development of new stereoselective methods for the formation of molecules possessing helical, planar or axial forms of chirality.

Shawn K. Collins

Martin P. Vachon

Martin P. Vachon obtained his BSc degree from Université de Montréal in 2004. Martin earned his Masters degree from the Université de Montréal in 2006 working with Professor Shawn Collins exploring new transition metal catalyzed routes to functionalized helicenes.

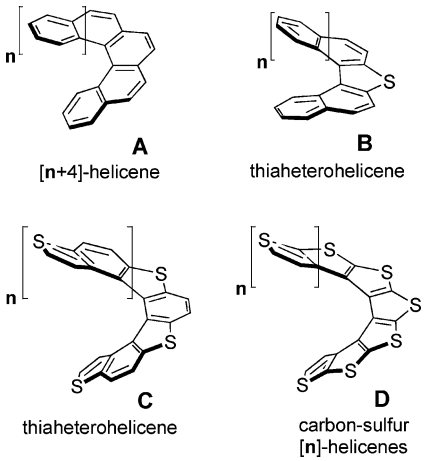


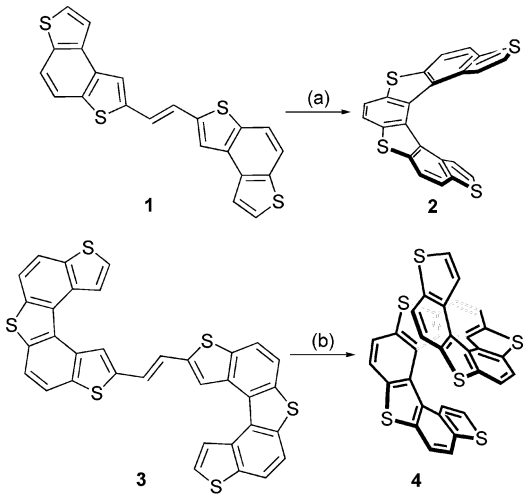
Fig. 1 The structures of [*n*]carbohelicenes, thiaheterohelicenes and carbon–sulfur [*n*]helicenes.

is the synthetic advantage introduced through the inclusion of thiophene rings. The ease of functionalization of the α- and β-positions of the thiophene ring is a valuable asset. Considering the difficulty of modifying the termini of carbohelicenes, it is understandable how interest in the thiaheterohelicene skeleton has flourished. This review aims to highlight the synthetic methods currently being used to prepare thiaheterohelicenes, in both racemic and enantiopure forms. As the majority of the skeletons possess both benzene and thiophene rings, this review has been divided into two sections dealing with protocols for the formation of either a benzene ring or a thiophene ring.

(1) Routes to racemic and enantiopure thiaheterohelicenes involving construction of a benzene ring

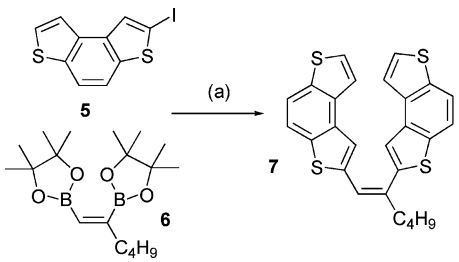
The classic method of carbohelicene synthesis involves a photocyclization of stilbene precursors. Despite the fact that this chemistry was developed over 30 years ago, it remains the most popular method for the preparation of thiaheterohelicenes of various sizes and functionalization. Although the yields are not always high, a mixture of *Z* and *E* olefins can often be used, as an *in situ* isomerization takes place. A recent study has shown that the photocyclization method can be used to prepare the heptahelicene **2** in 85% yield following irradiation (Scheme 1).[8] In fact, the tricyclic units flanking the olefin in precursor **1** can also be prepared *via* photocyclization. Thus, this method can be used repeatedly throughout the preparation of various sizes of thiaheterohelicenes. The changes in yields are often minimal, and the higher homologue **4** could be prepared in 60% yield following irradiation in benzene, in the presence of iodine and propylene oxide.[9]

Stilbenoid precursors are often prepared *via* Wittig reactions or McMurry couplings.[8,9] However, a new method was recently developed by Baldoli and co-workers *via* a stereospecific Suzuki-type reaction using (*Z*)-boronic esters (Scheme 2) that can introduce functionality as well.[10,11] The stilbene precursor **7** can be prepared in 83% yield when two equivalents of the iodide **5** are subjected to Pd-catalyzed cross-coupling with the bis-boronic ester **6**. Following this coupling procedure, the resulting stilbenoid can be subjected to photocyclization to give the corresponding



(a) *hυ*. 350 nm or visible light, 85 %; (b) *hυ*. 350 nm or visible light, 60 %

Scheme 1 Photocyclization of stilbenoid precursors as a route to thiaheterohelicenes.



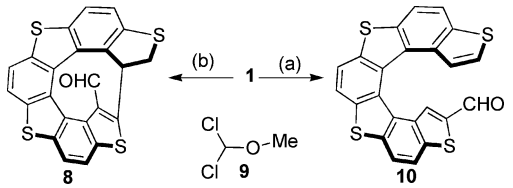
(a) $Pd(PPh_3)_4$ (3 %), 2 M Na_2CO_3, PhMe, EtOH, 65 °C then Δ, 83 % yield.

Scheme 2 Stereospecific Suzuki-type reaction of (*Z*)-boronic esters as a route to constructing thiaheterohelicene precursors.

thiaheterohelicene in 78% yield. An advantage of this method is that the *Z*-alkenes formed are typically more soluble than the corresponding *E*-isomers. In addition, the abundance of the *Z*-isomer also typically leads to increased yields of the photocyclized products. Overall, the photocyclization method is fairly robust and can be used in concert with high pressure mercury lamps or specialized reactors for large-scale preparations.

The ability to easily functionalize both the α and β positions of a terminal thiophene ring can also allow modification of the precursors prior to, or following, photocyclization. Maiorana and co-workers functionalized the terminus of stilbene **1** with a formyl group *via* a simple deprotonation protocol followed by a DMF quench (Scheme 3).[12] Other formylating reagents such as chloroether **9** led to the formation of rearranged products and the fusing of the terminal thiophene rings. The bridging of the thiophene termini has also been investigated by Tanaka *et al.* as a method of building molecular springs from thiaheterohelicenes.[13]

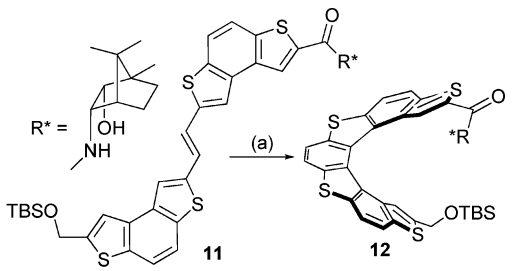
Although the simple preparation of the photocyclization precursors is advantageous, an obvious disadvantage is the lack of enantiocontrol. Classic attempts by Martin and co-workers at inducing enantioexcess (ee) *via* polarized light in the preparation of carbohelicenes resulted in low levels of ee.[14] However, photocyclization using a pendant chiral auxiliary at the terminus of one



(a) *n*-BuLi, THF -78°C then DMF, 66 % yield, (b) **11**, $SnCl_4$, CH_2Cl_2, 0 °C to RT, 63 % yield.

Scheme 3 Functionalizing the α and β-positions of the thiophene termini of thiaheterohelicenes.

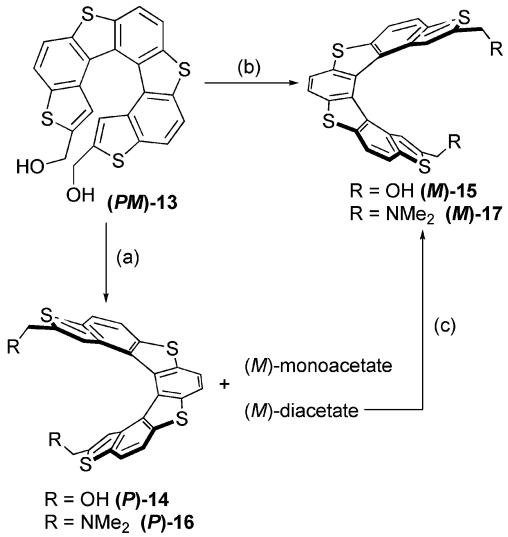
thiophene unit (**11**) resulted in modest diastereoselectivity (38 : 62) (Scheme 4). Unfortunately, due to the crowded steric environment about the helicene unit, removal of the auxiliary in product **12** was problematic.[15]



(a) *hυ*. I_2, propylene oxide, PhH, 77 % yield (62:38 dr)

Scheme 4 Photocyclization using chiral auxiliaries.

Despite the disappointing attempt to induce asymmetry *via* chiral auxiliaries, resolution of thiaheterohelicenes is possible. Some examples of traditional methods include successive recrystallizations of diastereomeric complexes derived from charge transfer complexes of 2-(2,4,5,7-tetranitrofluoren-9-ylideneaminooxy)-propionic acid,[16] crystal selection of conglomerates,[17] recrystallization from a chiral solvent[18] or separation using chiral stationary phases using HPLC techniques.[19] Tanaka and co-workers have developed an enzymatic route to resolving thiaheterohelicenes (Scheme 5).[20] After surveying a series of enzymes, they chose a lipase-catalyzed transesterification for the resolution of helicenediol **13**. An optimized protocol was developed that consisted of treating compound **13** with *Pseudomonas cepacia* in dichloromethane in the presence of 4 Å molecular sieves and vinyl acetate at room temperature for 25 h. On scales of 100 mg or 1 gram of compound **13**, the resolution afforded the unchanged diol (*P*)-**14** in 98% ee and 45% yield. A similar protocol was developed using the enzyme *Candida antarctica*, which reversed the selectivity in the resolution and afforded the (*M*)-enantiomer as the diol **15** in high enantiomeric purity (92% ee) and yield (42%). Importantly, Tanaka and co-workers then prepared the diamines (*P*)-**16** and (*M*)-**17** from the corresponding diols and investigated their binding with various DNA polymorphs.[21] Although small carbohelicenes had been investigated for their specific binding to the right-handed *B*-DNA structure,[22] (*P*)-**16** was found to be the first enantioselective small molecule capable of converting *B*-DNA to the *Z*-DNA form. The selectivity displayed by (*P*)-**16** for *Z*-DNA is a significant observation as *Z*-DNA has been implicated in a number of biologically relevant activities.[23] The unique chirality

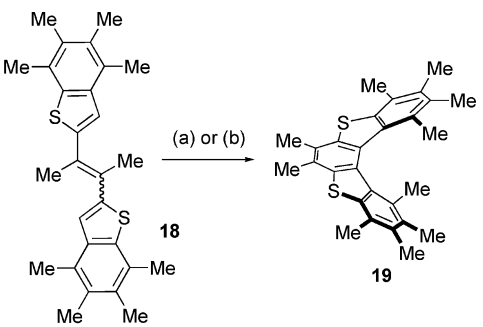


(a) *Pseudomonas cepacia*, CH_2Cl_2, molecular sieves 4 A, vinyl acetate, RT, 25 h **(*P*)-14** 98 % *ee*, 48 % yield, (b) *Candida antarctica*, CH_2Cl_2, vinyl acetate, 28 -29 °C, 9.5 h, **(*M*)-15** 92 % *ee*, 42 % yield, (c) NaOH (aq.), MeOH, **(*M*)-15**, 94 % ee, 13 % yield

Scheme 5 Enzymatic resolution of thiaheterohelicenes.

inherent to the helicene motif offers a new skeleton for the rational design of inhibitors of biological functions that may depend on *Z*-DNA.

In addition to difficulties in obtaining single enantiomers, the photocyclization method also suffers from several other disadvantages, including the dilute reaction conditions necessary, incompatibility with acid-sensitive groups and problems with nitro and amino functional groups due to their quenching of the singlet photo-induced state involved in ring closure. Not surprisingly, these drawbacks have provoked study of alternatives for ring closure. For example, Larsen and co-workers have investigated the cyclization of stilbenes *via* direct electrochemical oxidation (Scheme 6).[24] It was found that stilbene **18** could be cyclized in a nearly quantitative conversion. However, significant product was lost during purification and product **19** was isolated in 50% yield. Another attractive alternative is the use of anhydrous $FeCl_3$ in CH_2Cl_2. This non-photochemical method is experimentally

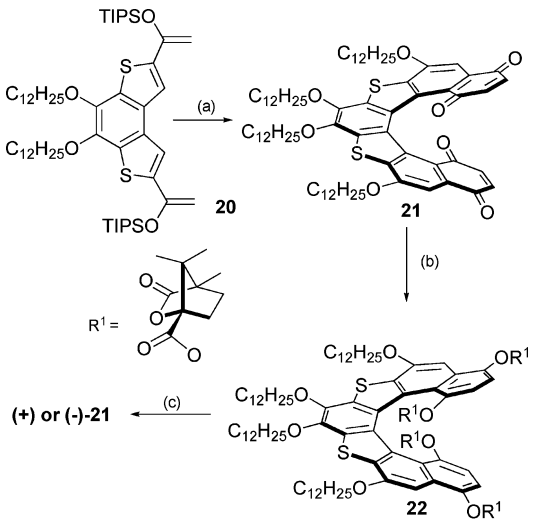


(a) Electrochemical oxidation, 100 % conversion, 50 % yield. (b) $FeCl_3$ (4 eq.), CH_2Cl_2, 2 h, 85 % conversion, 65 % yield.

Scheme 6 Direct oxidative or chemical ring closure.

simple, leading to a slightly higher yield of product **19** (65% yield). Despite the ease of the above approach, it is rarely used in thiaheterohelicene synthesis.

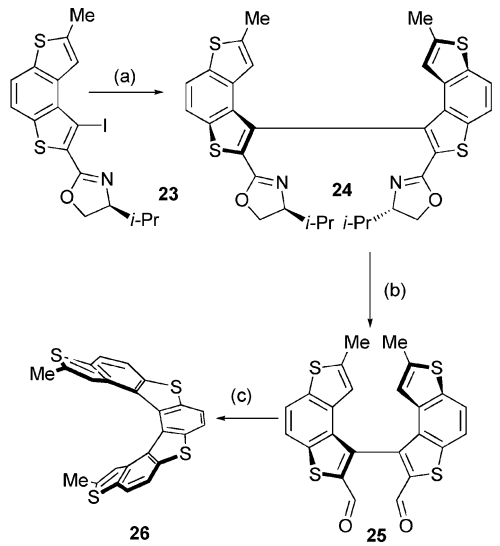
In 2001, Katz and co-workers investigated a different chemical approach in the course of studying whether thiaheterohelicenes would exhibit similar nonlinear optical properties as previously prepared analogous carbohelicenes (Scheme 7).[25] Katz and co-workers demonstrated that the electron-rich dienophile **20** facilitated a Diels–Alder (D–A) reaction, producing the D–A adduct in quantitative yield and requiring only trituration for purification. Subsequent oxidations of the D–A adduct also occurred more efficiently than in analogous carbohelicenes, due to the presence of the thiophene groups. Although assemblies of enantiopure thiaheterohelicene **21** display significant nonlinear optical properties, it is important to note that these properties depend on the enantiopurity of **21**. Synthetically, compound **21** is resolved *via* reduction, installation of a chiral auxiliary, separation *via* column chromatography, removal of the auxiliary and re-oxidation. All of these steps, although high yielding and affording large quantities of material, highlight the need for an efficient chemical resolution to form the helicene skeleton, which is still absent from the repertoire of synthetic chemists. It should be noted that Carreño and co-workers have reported that *p*-benzoquinones bearing chiral sulfones can effect moderate levels of enantioexcess in the preparation of carbohelicenes.[26] Although it has yet to be demonstrated for thiaheterohelicenes, it is assumed that this method would function equally well.



(a) 1. *p*-benzoquinone, heptanes, Δ 95 %; 2. CsF, $C_{12}H_{25}I$, DMF 91 % yield; (b) Zn, Et_3N, DMAP, DCE 90 % (-)-diastereomer, 70 % (+)-diastereomer; (c) *n*-BuLi, Et_2O then chloranil, 88 % yield (-)-enantiomer 85 % yield (+)-enantiomer

Scheme 7 Preparation of thiaheterohelicene bisquinones *via* Diels–Alder cycloadditions.

The need for additional asymmetric non-photochemical routes to thiaheterohelicenes was also recognized by Osuga and co-workers, who have reported a strategy that utilizes metal-mediated coupling reactions as the key steps (Scheme 8).[27] They demonstrated that iodo-precursor **23**, appropriately substituted with a chiral oxazoline moiety derived from (*S*)-valinol, could be treated

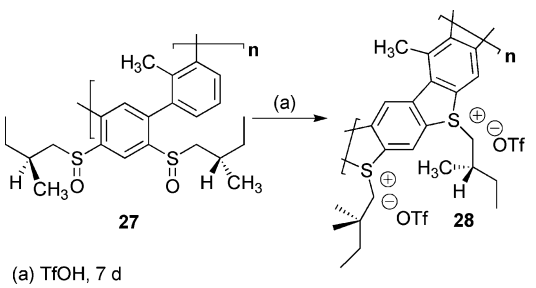


(a) Cu, DMF, 1 h, 100 °C, 99 % yield, 2: 1 ratio of diastereomers; (b) 1. TFA, Na_2SO_4 2. Ac_2O, pyr. 3. $LiAlH_4$, 86 % yield; (c) 1. PCC, CH_2Cl_2, 2. $TiCl_3$-$DME_{1.5}$, Zn-Cu, 52 % yield.

Scheme 8 Metal-mediated biaryl coupling as an asymmetric route to thiaheterohelicenes.

with activated Cu in DMF to afford the coupled product **24** in nearly quantitative yield as a 2 : 1 mixture of diastereomers. The diastereomers could be separated by chromatography and the chiral auxiliary transformed into an aldehyde group. Subsequent McMurry coupling gave the enantiopure thiaheterohelicene **26** in acceptable yield (52%).

Recently, Nishide and co-workers prepared a poly(thiaheterohelicene) as a stiff helical polymer (Scheme 9).[28] Their method for inducing asymmetry reveals another method for exploiting the presence of sulfur atoms about the periphery of the helical skeleton. An aromatic polymer **27** was prepared in which the sulfur atoms were oxidized after alkylation with an (*S*)-(+)-2-methylbutyl group. Treatment of the polymer with TfOH for one week effected ring closure with the sense of asymmetry controlled *via* the auxiliary sidechain. Although Nishide *et al.* did not remove the sidechains during their study, the researchers confirmed that a solenoid-like magnetism occurs upon electronic transmittance about the helical π-conjugated structure, suggesting the potential of poly(thiaheterohelicenes) for constructing nanoscale devices.

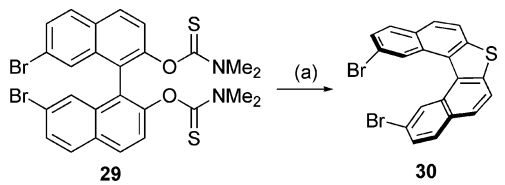


(a) TfOH, 7 d

Scheme 9 Asymmetric synthesis of a poly(thiaheterohelicene).

(2) Racemic and enantiopure routes to thiaheterohelicenes involving construction of a thiophene ring

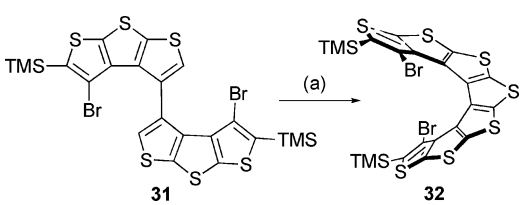
Recently, more attention has been focused on how to form a thiaheterohelicene where the final ring installed is a thiophene ring. A popular method is *via* the Newman–Kwart rearrangement.[29] Dötz and co-workers, in developing a chromium-templated benzannulation reaction at the termini of helicene skeletons,[30] investigated the reaction of the carbamoyl derivative **29** *via* the rearrangement (Scheme 10).[31] Heating precursor **29** at 285 °C for 45 min resulted in a 36% isolated yield of thiaheterohelicene **30**. Although the yields of the rearrangement are modest, this route represents a facile route to substituted thiaheterohelicenes using BINOLs as precursors. It is noteworthy that Nozaki and co-workers have recently disclosed a palladium-catalyzed coupling strategy for making aza- or oxahelicenes.[32] The authors have not reported using this method to construct thiaheterohelicenes.



Scheme 10 Newman–Kwart rearrangement to form thiaheterohelicenes.

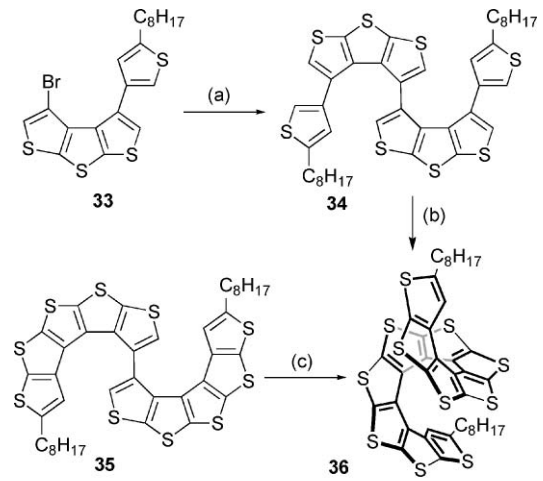
Carbon–sulfur [*n*]helicenes are unique derivatives of β-oligothiophenes. The helical curvature and cross-conjugation of their carbon–carbon framework may provide extraordinary chiral properties and transparency in the optical region. In contrast to the thiaheterohelicenes discussed previously, there is no alternation of thiophene and benzene rings. The carbon–sulfur [*n*]helicenes are solely twisted thiophene units with all the sulfur atoms located along the periphery. To make such compounds, both racemic and asymmetric methodologies for constructing a thiophene ring are necessary.

Rajca and co-workers have developed a unique strategy for making enantiopure carbon–sulfur [*n*]helicenes (Scheme 11).[33] The synthetic approach is an annelation mediated by (−)-sparteine. When the racemic precursor **31**[34] is treated with LDA and (−)-sparteine, a diastereomeric complex of a dilithiated species and (−)-sparteine is formed. Upon quenching with $(PhSO_2)_2S$, the carbon–sulfur [7]helicene **32** is formed in 20–37% yield. Despite the fact the ee's are low (19–47%), this represents a creative strategy for making a thiophene unit in an enantioselective manner.



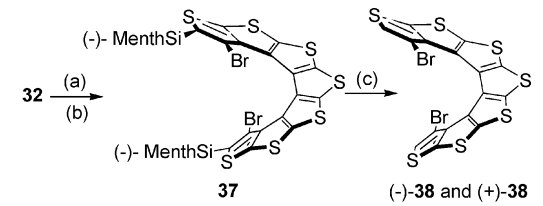
Scheme 11 (−)-Sparteine mediated annelation to form carbon–sulfur [*n*]helicenes.

The authors attempted to further demonstrate the potential of the method by attempting a tri-annelation to form a carbon–sulfur [11]helicene (Scheme 12).[35] In this case, the tetrathiophene **33** was dimerized *via* a Pd-catalyzed homocoupling to yield product **34** in 60–70% yield. Subsequent treatment of intermediate **34** with an excess of LDA and (−)-sparteine yielded an approximate 1% yield of helicene **36** in 11–17% ee. However, compound **36** can be formed in higher yields when octathiophene **35** is subjected to the annelation protocol, affording **36** in 47–59% yield and identical ee (12–19%).



Scheme 12 Tri-annelation to form carbon–sulfur [11]helicenes.

The same authors have disclosed a route to these structures in higher enantiomeric excess *via* a resolution using (−)-menthylSiCl (Scheme 13). [7]Helicene **32** could be desilylated with TFA in $CHCl_3$ affording the product in 82% yield. Following deprotonation with LDA and quenching with (−)-menthylSiCl, the diastereomers were separated using preparative TLC or flash column chromatography. The final desilylation and removal of the chiral auxiliary were effected with TFA in $CHCl_3$ to give either enantiomer of compound **38** in high yield (for (−) : 96%, 97% ee, (+): 93%, 93% ee).



Scheme 13 Resolution of carbon–sulfur [*n*]helicenes.

Conclusions

The possibility of combining the electronic properties of oligothiophenes with potential chiroptical properties has fueled research in the area of thiaheterohelicenes. The presence of sulfur atoms embedded in the helicene skeleton allows for S–S molecular contacts in the solid state, and it also has a significant impact on the way the compounds can be synthesized. Perhaps the most exciting property of thiaheterohelicenes revealed to date is their interaction with biologically important macromolecules.[36,37] The studies involving interactions with DNA and other macromolecules suggest that these molecules may act as a new scaffold for drug design.

The advances described in this review represent a large body of work directed towards developing new methods to build thiaheterohelicenes in a more streamlined and efficient manner (Fig. 2). These efforts include attempts to improve the popular photocyclization protocol and to develop new non-photochemical routes. Among the various known routes to carbohelicenes,[38] those such as carbenoid couplings,[39] radical cyclizations,[40] and ring-closing olefin metathesis[41] have yet to be investigated for making the benzenoid rings of thiaheterohelicenes. Most importantly, although resolution remains a viable option for both thiaheterohelicenes and carbon–sulfur [*n*]helicenes, there is a need for catalytic and enantioselective routes. Again, it is likely that asymmetric methods of carbohelicene synthesis can be applied to thiaheterohelicenes. In particular, the elegant [2 + 2 + 2] cyclotrimerization of acetylenes developed by Stary and co-workers could be a powerful method for the preparation of thiaheterohelicenes, as it affords carbohelicenes in good yields with moderate levels of ee.[42] The annelation procedure developed by Rajca and co-workers is an imaginative and potentially powerful route. However, despite the advances described within this review, it is clear that a general, catalytic and highly enantioselective route to thiaheterohelicenes remains a synthetic challenge and a hurdle that must be overcome to allow the full potential of chiral helical frameworks to be exploited in both materials science and medicinal chemistry.

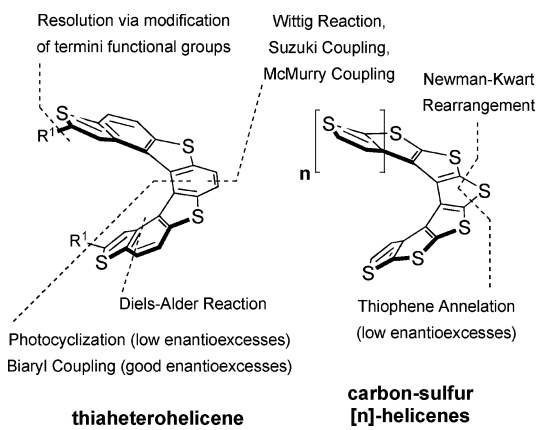


Fig. 2 Existing methods for the formation of thiaheterohelicenes and carbon–sulfur [*n*]helicenes in both racemic and enantioenriched manners.

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