THE SYNTHESIS OF AZAHELICENES

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Abstract. *Azahelicenes as heteroanalogues of iconic helically chiral helicenes consist of all-ortho-fused carbocycles (mostly benzene core units) and various nitrogen heterocycles. They have recently attracted increasing attention owing to their remarkable shape and unique chemical and physical properties. The first astonishing applications of azahelicenes to chemistry, physics and biology ranging from enantioselective organocatalysis to circularly polarised light detection have appeared. The present review surveys the recent progress in the synthesis of neutral or cationic azahelicenes and their congeners employing a rich portfolio of synthetic methods. The manifold ways to receive nonracemic azahelicenes are also reviewed.*

Contents

1. Introduction

Remarkable progress in the synthesis of inherently chiral aromatics such as helicenes, heterohelicenes, heterohelicenium dyes, helquats and helicene-like molecules has been accomplished recently.[1] Accordingly, various helicene derivatives are now accessible at a reasonable cost and synthetic effort and, in particular, most of them can be obtained in a nonracemic form by racemate resolution or asymmetric synthesis. Moreover, significant applications of these compounds have already been demonstrated in different areas of science and others have been envisioned.[2]

A specific attention has been paid to azahelicenes that represent helical *N*-heteroaromatics. Actually, the first helicene molecules ever synthesised were 7*H*-dibenzo[*c,g*]carbazole **1** and benzo[*f*]naphtho[2,1-*c*]cinnoline **2** pioneered by Meisenheimer and Witte[3] in 1903 (Figure 1). Azahelicenes are composed of all-*ortho* (or mostly *ortho*) condensed benzene, pyridine, pyrrole, pyridazine, pyrazine or other *N*-heterocyclic rings to form a helical backbone. They are usually chemically stable and soluble in common organic solvents, which makes a difference to many other large π-conjugated heterosystems. The most abundant are aza[5]- and aza[6]helicenes (such as **3** and **4**; they are alternatively called pyridohelicenes) with a various location of the nitrogen atom(s). The number in square brackets in their generic name expresses the number of fused (hetero)cycles. As azahelicenes can exist in two enantiomeric forms regardless of their configurational stability, the handedness of the helix is specified by adding the (*M*) (minus) or (*P*) (plus) prefix.

Chemistry of azahelicenes has already been reviewed in dedicated articles.[4] Since 2010, when the last comprehensive overview was published,[4a] a significant progress in their synthesis and utilisation was recorded. Accordingly, this chapter is focused on important achievements in azahelicene chemistry

published after 2010 and synthetic methodologies explored recently rather than providing a comprehensive review looking back to the history. The subject of this review is limited mostly to aza[5]helicenes and higher homologues that exhibit reasonable configurational stability as the chirality issue plays an important role in the realm of helically chiral azahelicenes. Finally yet importantly, the review does not cover the rich chemistry of metalloazahelicenes (*i.e.* azahelicenes with an incorporated metal atom in their helical backbone) as this specific topics was reviewed separately.[2a]
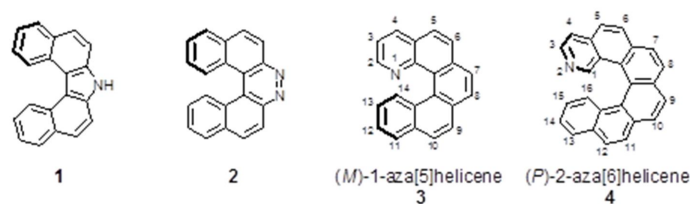

Figure 1. Examples of a structural variability of azahelicenes.

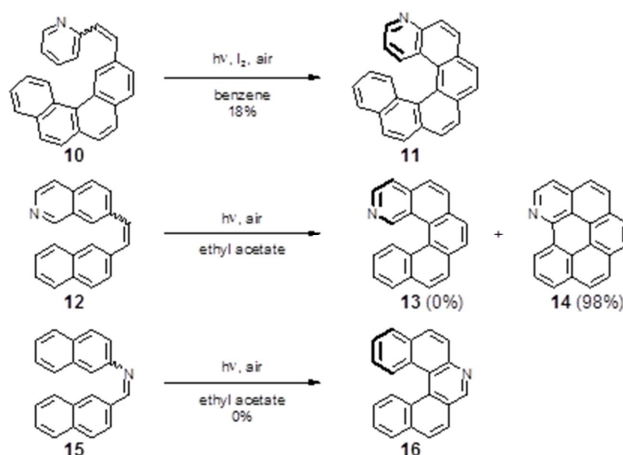## 2. Synthesis of pyridohelicenes
2.1. Photochemical methodology

A remarkable step forwards in the synthesis of helicenes came in the late sixties when photodehydrocyclisation of stilbene-type precursors was introduced as a preparative method.[5] It is based on UV-light induced *cis/trans* isomerisation of 1,2-diarylethylenes followed by conrotatory electrocyclisation of the *cis* isomer to generate a primary dihydroaromatic product with *trans* configuration. In the presence of air and a catalytic amount of iodine as an oxidising agent, it is immediately converted to fully aromatic helicene. This methodology has remained popular in the helicene community over decades as it benefits from an easy access to the key stilbene-type precursors (via the Wittig olefination reaction) without a need to control the *cis/trans* configuration of the alkene unit. Photodehydrocyclisation can successfully be applied also to the synthesis of pyridohelicenes but discouraging results might occasionally be obtained. While 3-aza[5]helicene **6** can be prepared from **5** in almost quantitative yield as reported by Caronna *et al.*,[6] the higher homologue 3-aza[6]helicene **8** is received from **7** in moderate yield being accompanied by a minor regioisomer 1-aza[6]helicene **9** as described by Ben Hassine *et al.*[7] (Scheme 1). Following this synthetic approach, a series of different azahelicenes such as 4-, 5-, 6-aza[5]helicene and 4,11-, 5,10-, 6,9-, 4,9-, 4,10- or 5,9-diaza[5]helicene could successfully be synthesised.[8] It is worth noting that propylene oxide or tetrahydrofuran is occasionally added as instantaneous scavenger of HI since its high concentration generated would lead to photoreduction of double bonds.[9]
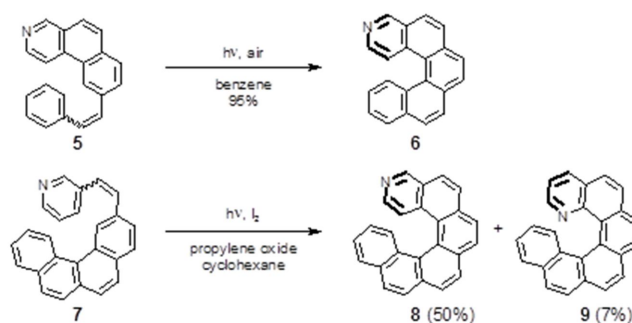
Scheme 1. Photochemical synthesis of racemic pyridohelicenes by Caronna *et al.*[6] and Ben Hassine *et al.*[7]

However, the position of the nitrogen atom in the stilbene-type precursor and the presence of additional substituent(s) might be critical with respect to the yield of photodehydrocyclisation and

occurrence of unwanted side/subsequent reactions. Such difficulties can be illustrated by the formation of 4-aza[6]helicene **11** from **10** in low yield as observed by Martin *et al.*[10] (and followed by Crassous *et al.*[11]) and complete failure to get 2-aza[5]helicene **13** from **12** (receiving 7-azabenzo[*ghi*]perylene **14** instead) or 7-aza[5]helicene **16** from **15** as found by Caronna *et al.*[8] (Scheme 2). Also Bedekar *et al.* experienced non-regioselective photodehydrocyclisation of a bis-stilbene-type precursor to receive a carbazole-derived aza[9]helicene along with its angular-linear, linear-linear and linear-fused angular counterparts in moderate overall yield.[12]


Scheme 2. Attempts at a photochemical synthesis of racemic pyridohelicenes by Martin *et al.*[10] and Caronna *et al.*[8]

The synthesis of functionalised azahelicenes by photodehydrocyclisation of stilbene-type precursors points to the strength and versatility of this methodology even though not many examples of that have been published. Branda *et al.* prepared the oxygenated 4,15-diaza[7]helicenes **19** and **20** utilising double photodehydrocyclisation (Scheme 3).[13] His study perfectly illustrates the directing role of the bromine auxiliary in the regioselective photosynthesis of helicenes (introduced by Katz *et al.*[14]). While the non-brominated bis-stilbene precursor **17** affords the undesired S-shaped double aza[4]helicene molecule **21** along with minor 4,15-diaza[7]helicene derivative **19**, the presence of the bromine atom in **18** directs photocyclisation away from its *ortho* positions to furnish exclusively the azahelicene **20**. Autschbach, Crassous, Réau *et al.*[15] demonstrated the tolerance of an alkyne substituent in **23**, whose presence led to the increased yield of the functionalised 4-aza[6]helicene **24** in comparison to the native 4-aza[6]helicene **11** (*cf.* Scheme 2). Employing the photocyclisation strategy, Dehaen *et al.* developed a straightforward synthesis of the highly complex pyrido-pyrrolo[6]helicene **26** from **25** with respect to the presence of manifold substituents.[16] Finally, the thiophene moieties and alkylsulfanyl groups can also be tolerated in the photochemical synthesis of diazadithia[7]helicenes by Dehaen *et al.*[17]

2.2. Non-photochemical methodologies

The transition metal catalysed [2+2+2] cycloisomerisation of aromatic triynes represents a new paradigm for the highly versatile nonphotochemical synthesis of helicenes.[18] It relies on a facile, convergent and modular assembly of aromatic triynes that can easily be cyclised to helicenes. Utilising this methodology, Stará, Starý *et al.* reported the practical syntheses of 1-aza[6]helicene **9** and 2-aza[6]helicene **4** (Scheme 4).[19] The Co[I]-catalysed [2+2+2] cyclotrimerisation of aromatic pyridotriynes allowed building the helical scaffolds. Moreover, they succeeded in resolving racemates of **9** and **4** into enantiomers, assigning their absolute configuration, determining the energy barriers to racemisation and obtaining X-ray structures of their corresponding silver complexes.
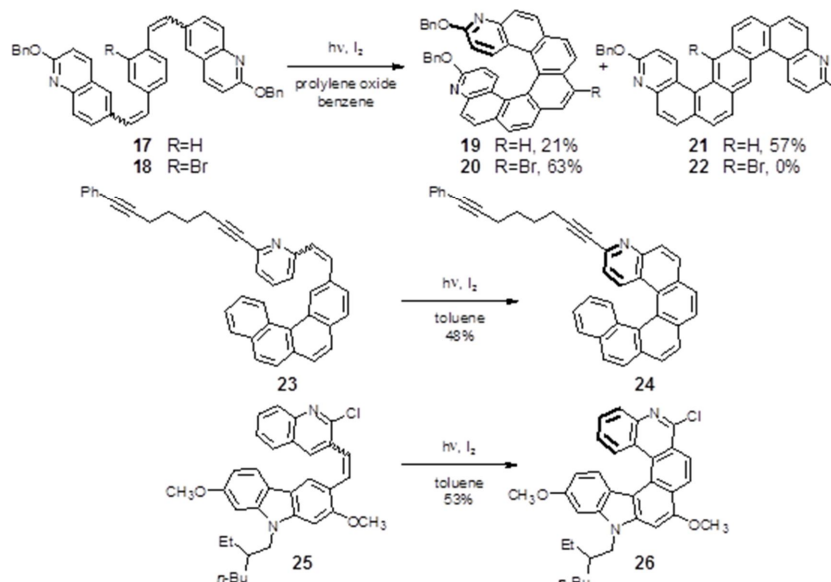
Scheme 3. Photochemical synthesis of functionalised racemic pyridohelicenes by Branda *et al*.,[13] Crassous *et al*.[15] and Dehaen *et al*.[16]
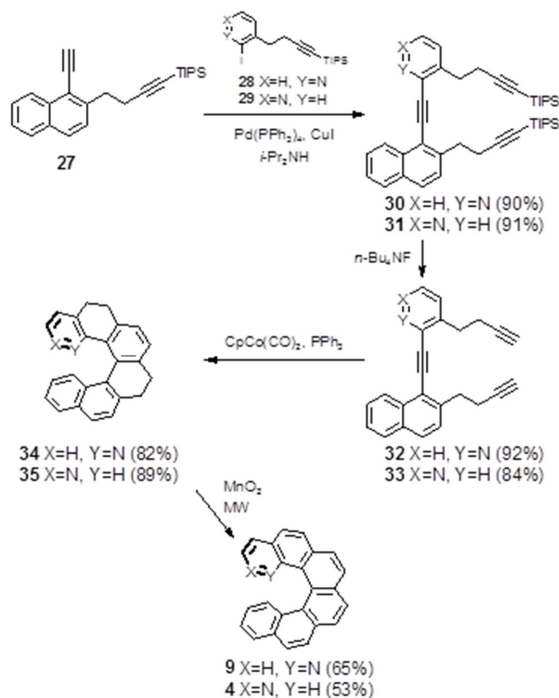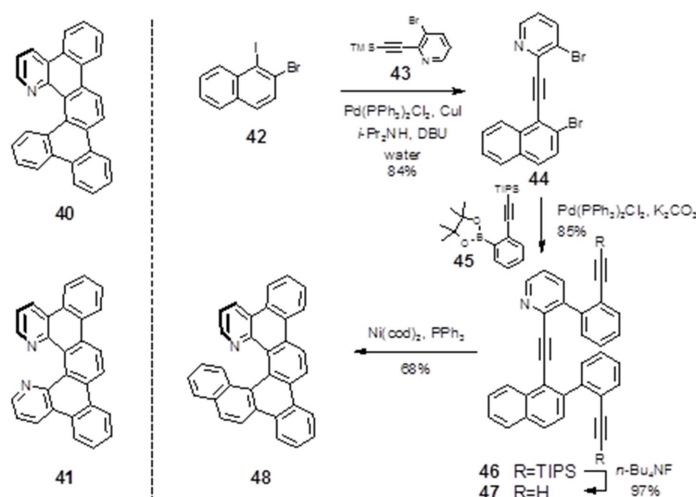

Scheme 4. Synthesis of racemic pyridohelicenes by Stará, Starý *et al*.[19] based on alkyne [2+2+2] cycloisomerisation.

A similar synthetic methodology for the preparation of 1,14-diaza[5]helicene **39** was developed by Stará, Starý *et al*. (Scheme 5).[20] It employs the sequence of a double propargyl magnesium bromide addition to a tolan-2,2'-dialdehyde-type intermediate **36**, a cobalt-mediated [2+2+2] cycloisomerisation of a triyne intermediate **37** and a double silica gel-assisted acetic acid elimination from **38** to receive **39**.
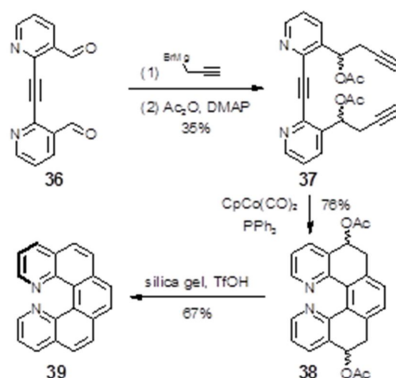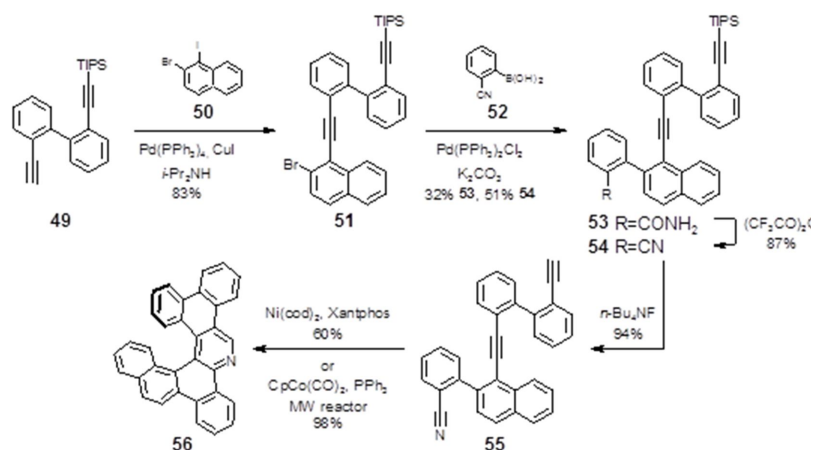

Scheme 5. Synthesis of racemic pyridohelicenes by Stará, Starý *et al*.[20] based on alkyne [2+2+2] cycloisomerisation.

Moreover, the transition metal catalysed [2+2+2] cycloisomerisation of aromatic triynes could be employed in a simple and versatile synthesis of 1-azadibenzo[5]helicene **40**, 1,14-diazadibenzo[5]helicene **41** and 1-azadibenzo[6]helicene **48** by Stará, Starý *et al*. (Scheme 6).[18a] These helically chiral heteroaromatics can be synthesised within four to five operations in overall yields ranging from 35% to 53% by employing a short sequence of reliable processes such as Sonogashira coupling (**42**→**44**), Suzuki–Miyaura coupling (**44**→**46**), desilylation (**46**→**47**) and [2+2+2] alkyne cycloisomerisation (**47**→**48**). Azadibenzohelicenes have an advantage over the parent azahelicenes because of the simplicity of their non-photochemical preparation and, therefore, they have the potential to mimic or even substitute parent azahelicenes in envisaged applications.
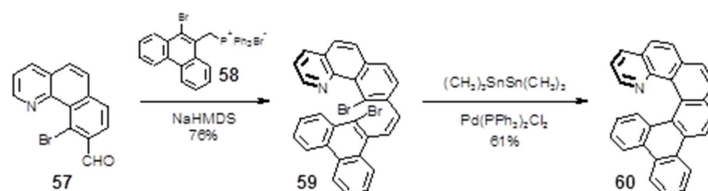

Scheme 6. Synthesis of racemic pyridodibenzohelicenes by Stará, Starý *et al*.[18a] based on alkyne [2+2+2] cycloisomerisation.

The transition metal catalysed [2+2+2] cycloisomerisation of aromatic triynes has recently passed the scrutiny of synthetic challenges in azahelicene chemistry to become a useful alternative to the photochemical methodology. It allows for the embedding of *N*-heterocyclic subunit(s) (pyridine or pyridinium) in the helicene scaffold if these heterocyclic parts are already present in linear heterohelicene precursors that undergo a helical folding during the [2+2+2] cyclisation step. However, the pyridine unit can also be formed by [2+2+2] cycloisomerisation of two alkynes and one nitrile.[21] Surprisingly, this well-established synthetic methodology for the *de novo* construction of the pyridine derivatives was not used in the synthesis of pyridohelicenes until Stará, Starý *et al.* published the preparation of [5]-, [6]- and [7]pyridohelicenes based on [2+2+2] cycloisomerisation of aromatic cyanodiynes (Scheme 7).[22] The preparation of pyridodibenzo[6]helicene **56** illustrates well this methodology: a sequence of the chemoselective Sonogashira coupling (**49**→**51**) followed by Suzuki-Miyaura coupling results in the formation of the desired nitrile **54** that is accompanied by the minor amide **53**. This product of hydrolysis of the cyano moiety can be recycled back to nitrile **54** on reaction with trifluoroacetic anhydride. After desilylation (**54**→**55**), cyanodiyne **55** is cyclised to the target pyridohelicene **56** under Ni[0] or Co[I] catalysis in good to high yield.
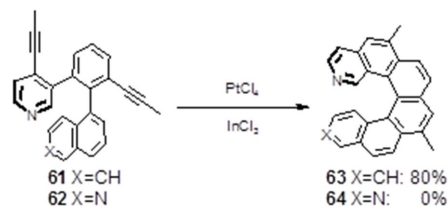

Scheme 7. Synthesis of racemic pyridohelicenes by Stará, Starý *et al.*[22] based on cyanodiyne [2+2+2] cycloisomerisation.

Takenaka *et al.* devised a modular synthetic route to a series of 1-aza[5]- and [6]helicenes that is based on the key Stille-Kelly reaction[23] to form an internal benzene ring of the helical backbone (Scheme 8).[24] Combining the benzo[*h*]quinoline-derived aldehyde **57** with the complementary benzyl-type phosphonium salt **58** allowed performing a highly Z-selective Wittig olefination to receive the aromatic dibromide **59**. Its reaction with hexamethylditin under Pd-catalysis led first to a monostannylated intermediate that underwent a spontaneous intramolecular Stille cross-coupling (the overall Stille-Kelly reaction) resulting in a benzo derivative of 1-aza[6]helicene **60**. The authors proved a scalability of this synthetic approach to prepare some 1-azahelicenes on a multigram scale.
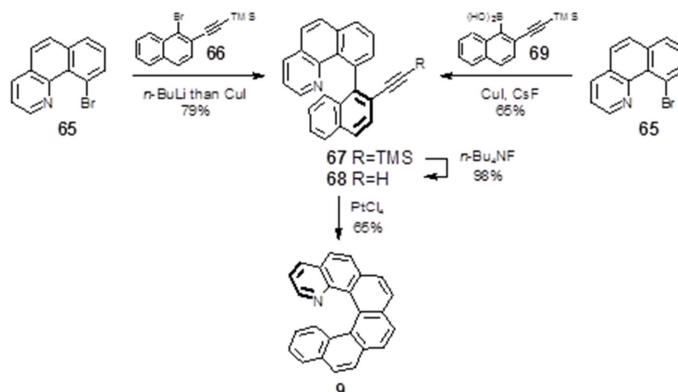

Scheme 8. Synthesis of racemic pyridohelicenes by Takenaka *et al.*[24] employing the Stille-Kelly reaction.

Storch *et al.* pioneered the use of alkyne-arene cycloisomerisation in the synthesis of azahelicenes to build their aromatic scaffold (Scheme 9).[25] Using a series of cross-coupling steps in the mostly linear synthetic sequences, the authors prepared azabiphenylylnaphthalene **61** and azabiphenylylisoquinoline **62** as suitable substrates for the following double alkyne-arene cycloisomerisation. After screening a diverse portfolio of well-established π-electrophilic Lewis acids (Pt[II], Pt[IV], In[III], Hg[II], Au[I], Au[III]) or ICl (to perform electrophilic cyclisation), they succeeded in cyclising **61** to 2-aza[6]helicene derivative **63** in good yield when employing simultaneously $PtCl_4$ and $InCl_3$ catalysts at elevated temperature. Identical results were achieved in alkyne-arene cycloisomerisation of **61** mediated by ICl. However, all attempts at cyclising the precursor **62** to the diaza[6]helicene derivative **64** failed.
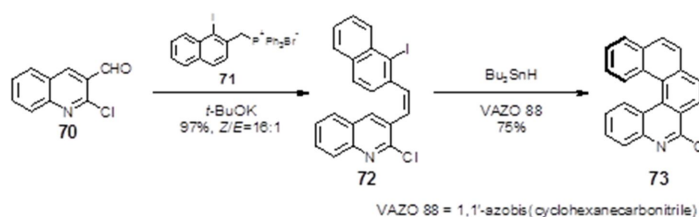

Scheme 9. Synthesis of racemic pyridohelicenes by Storch *et al.*[25] using alkyne-arene cycloisomerisation.

Stemming from the aforementioned study by Storch *et al.*, Fuchter *et al.* developed a scalable and expedient route to 1-aza[6]helicene derivatives employing a Pt-catalysed alkyne-arene cycloisomerisation to form an internal benzene ring of the azahelicene skeleton (Scheme 10).[26] It represents both the shortest and most practical synthesis of 1-aza[6]helicene **9** so far. Starting from 10-bromobenzo[*h*]quinoline **65**, it was cross-coupled with organocuprate generated *in situ* from the bromonaphthalene derivative **66** as either C-H arylation chemistry or conventional metal-catalysed cross-coupling methodologies failed (except of Suzuki-Miyaura cross coupling of bromide **65** with boronic acid **69**, which provided a mixture of **67** and desilylated **68** in moderate yield). Actually, the construction of such a hindered biaryl bond in **67** was the first challenge in the synthesis of 1-aza[6]helicene **9** faced by the authors. Another one was to pursue a metal-catalysed alkyne-arene cycloisomerisation on the system bearing a π-deficient pyridine moiety (only electron-rich systems were so far reported as suitable substrates[27]). Indeed, the conversion of alkyne-arene **68** to 1-aza[6]helicene **9** was found difficult but a successful protocol was finally developed employing $PtCl_4$ at elevated temperature (120 °C) to receive **9** in good yield. The TMS derivative **67** was also possible to convert directly to **9** in a comparable yield as desilylation took place first under these conditions.

Scheme 10. Synthesis of racemic pyridohelicenes by Fuchter *et al.*[26] using alkyne-arene cycloisomerisation.

Harrowven *et al.* reported the use of the radical chemistry to form the helicene backbone.[28] The strategy developed was exemplified by a short and efficient synthesis of the 5-aza[5]helicene derivative **73** (Scheme 11) in which the chloro substituent controls both the stereochemical course of Wittig olefination (**70→72**) and regioselectivity of the homolytic aromatic substitution reaction (**72→73**). However, this methodology for the azahelicene synthesis has not been widely exploited so far.
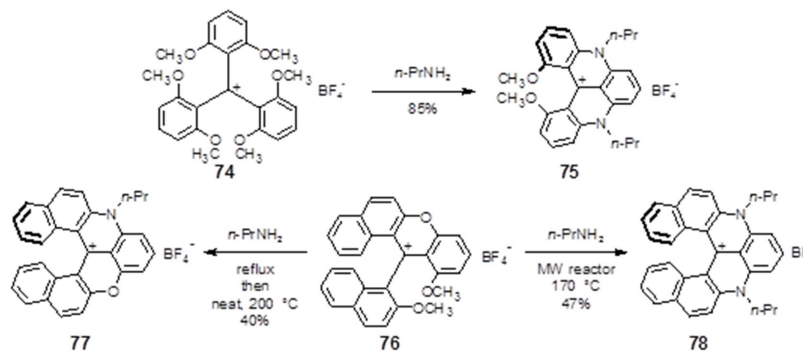

Scheme 11. Synthesis of racemic pyridohelicenes by Harrowven *et al.*[28] employing radical cyclisation.

3. Synthesis of other azahelicenes

Azahelicenes may encompass not only the pyridine subunit(s) but also other nitrogen heterocycle(s) such as neutral pyrrole, imidazole, triazole, pyridazine, piperazine, 2-pyridone, dihydropyridine, dihydroazepine or cationic pyridinium, dihydropyridinylium or imidazolium. Their combinations were also reported. In this regard, the attention was paid mostly to the synthesis of cationic aza[4]- or aza[6]helicenes (with the dihydropyridinylium unit(s) in their backbone) and helquats (with the pyridinium units). Although the dominance of pyridohelicenes is so far considerable, the number of azahelicenes containing other fused nitrogen heterocycles is gradually increasing.

3.1. Cationic azahelicenes

Lacour *et al.* explored the synthesis of cationic diaza[4]helicene **75**, azaoxa[6]helicene **77** and diaza[6]helicene **78** that are accessible from simple building blocks on a multigram scale (Scheme 12).[2c] The synthesis of azaoxahelicene **77** and diazahelicenes **75** or **78** took advantage of susceptibility of the respective key CH_3O-substituted triaryl carbocations **74** and **76** to undergo facile nucleophilic aromatic substitution reactions with proper nucleophiles. The progress of the consecutive *ortho* S_NAr reactions proceeding via an addition-elimination mechanism can be governed by the properly chosen reaction conditions. A readily available salt of the cation **74** reacted with primary amines giving rise to the dimethoxyquinacridinium system **75** in high yield.[29,58] This cationic diaza[4]helicene **75** is conformationally locked owing to the presence of *ortho*-methoxy substituents and exhibits a very high configurational stability ($\Delta G^{\neq}$ of racemisation is *ca* 42 kcal mol^{-1}, higher than that of [6]helicene).
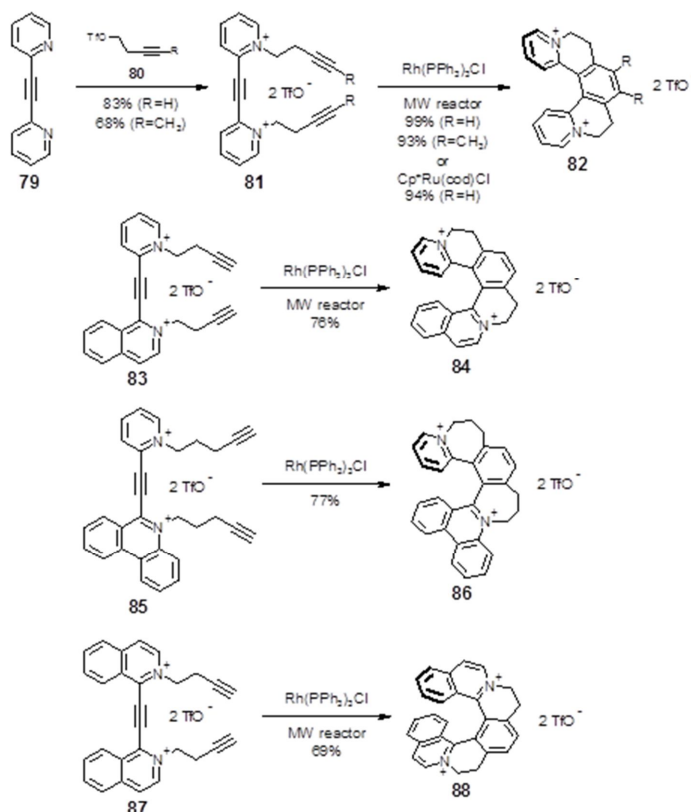

Scheme 12. Synthesis of racemic cationic azahelicenes by Lacour *et al.*[2c] employing S_NAr substitution reactions.

Similarly, the cationic azaoxo- and diaza[6]helicene **77** and **78** were prepared in one step from a single common intermediate **76**, which is accessible by a short synthetic sequence.[30] Straightforward, yet orthogonal, aromatic electrophilic and vicarious nucleophilic substitution reactions afforded a series of mono-, di- and trisubstituted diazahelicenes which were additionally derivatised through cross-coupling, reduction, or condensation processes (see Chapter 5.). These helical carbocations are exceptionally stable even in basic media as expressed by their very large and positive pK_{R+} values.[2c]

Teplý *et al.* developed an original approach to a large collection of dicationic azahelicenes (diazoniahelicenes) that he coined helquats as they encompass structural features of both helicenes and viologens (*e.g.*, paraquat).[31,32,33,34,54] Their synthesis is straightforward: it capitalises on a facile quaternisation of symmetrical or unsymmetrical diazaarylacetylene precursors to form a dicationic triyne precursor (**79**→**81**) that can smoothly undergo [2+2+2] cycloisomerisation in the presence of a Wilkinson's catalyst or Cp*Ru(cod)Cl to form the helical backbone (**81**→**82**, Scheme 13). This methodology can be employed for the synthesis of a variety of helquats in a racemic form such as **84**, **86** and **88**, some of them were prepared within a few steps on a multigram scale. Asymmetric synthesis of helquats was not yet reported but there are ways how to resolve their racemates into enantiomers on a preparative scale (see Chapter 4.1.).

Scheme 13. Synthesis of racemic cationic azahelicenes by Teplý *et al.*[31,32,33,34,54] based on alkyne [2+2+2] cycloisomerisation.

Helquats were uniformly synthesised as partially hydrogenated cationic heteroaromatics and there is so far no example of their conversion to the fully aromatic entities. Furthermore, diverse [5]-, [6]- and

[7]helquats were prepared from diazaarylacetylene precursors by two successive distinct pyridine-type nitrogen quaternisations followed by rhodium-catalysed [2+2+2] cycloaddition.[32] This route allowed for straightforward molecular editing of cationic helical skeletons varying the size of embedded partially saturated cationic heterocycles. The methodology was also applied to the synthesis of the helical tricationic helicene-like system with an imidazolium core unit (Scheme 14).[35] The synthetic route was based on Sonogashira coupling, *N*-alkylation and double [2+2+2] cycloaddition reaction to yield the tricationic imidazolium tetraaza[9]helicene **90** from **89**. It represents the highest order helical nitrogen-based cationic system reported to date as it features nine contiguous *ortho*-annulated rings.
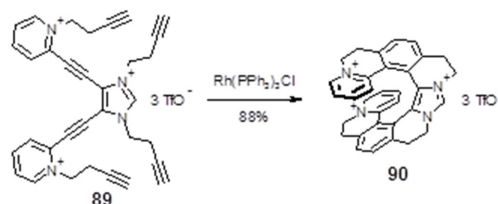

Scheme 14. Synthesis of racemic imidazolium-based cationic azahelicenes by Teplý *et al.*[35] employing alkyne [2+2+2] cycloisomerisation.

Recently, a breakthrough in the step-economy of the preparation of azahelicenes was published by Otani, Shibata *et al.* (Scheme 15).[36] They succeeded in minimising the number of steps necessary to build up the azahelicene backbone developing a facile two-step synthesis of polyaza[7]helicenes from a commercially available 2,9-dichloro-1,10-phenanthroline precursor **91**. By employing a double amination with the various aniline derivatives (*e.g.*, **91**→**93**) followed by a hypervalent iodine reagent-mediated intramolecular double C-N oxidative coupling (**93**→**94**), various tetraaza- and hexaaza[7]helicenes were prepared in moderate to good yields.
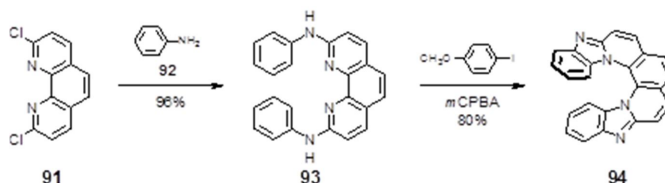
Scheme 15. Synthesis of racemic polyazahelicenes by Otani, Shibata *et al.*[36] using C-N oxidative coupling.

An original approach to a new type of azahelicene-like molecules was described by Huang, Shi *et al.* (Scheme 16).[37]
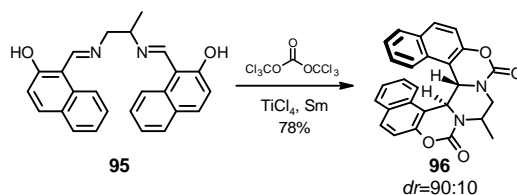
Scheme 16. Synthesis of racemic azahelicene congeners by Huang, Shi *et al.*[37] employing reductive coupling of imines.

They synthesised a series of diaza[5]-, tetraaza[5]- and diaza[7]helicene-like compounds such as **96** from the corresponding aromatic diimines such as **95** and triphosgene employing a cascade of reductive coupling of imines mediated by TiCl$_4$ and samarium that was followed by a closure of two six-membered heterocycles embedded into the heterohelicene scaffold. If the linker between the imine moieties contained a stereogenic centre, the high diastereoselectivity of the double cyclisation was observed.
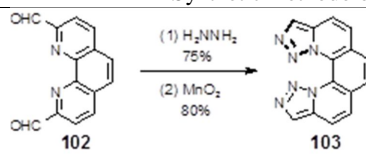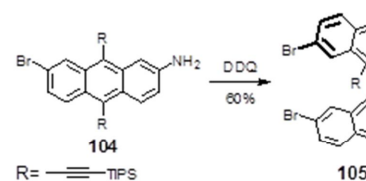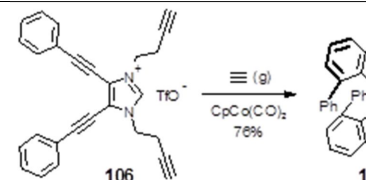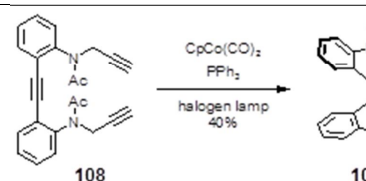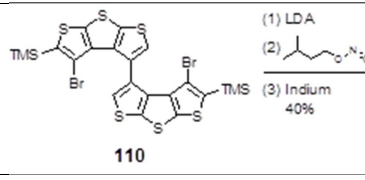
Stará, Starý *et al.* developed recently a cobalt-mediated [2+2+2] cycloisomerisation of ynedinitriles to pyridazine helicenes in moderate to high yields (Scheme 17).[38] The de novo construction of pyridazine heterocycle, which combines one alkyne unit with two nitrile groups in such a way that two nitrogen atoms become connected under otherwise neutral reaction conditions, is proposed to obey either the conventional mechanism of alkyne/nitrile [2+2+2] (co-)cycloisomerisation or the single electron transfer-triggered radical cyclisation of ynedinitrile mediated by a CpCo^{II}L$_n$ species might also operate in cyclisation. This synthetic methodology was applied to the preparation of a series of helical pyridazines including [5]-, [6]- and [7]helicene derivatives such as **2**, **99** and **101**. It was shown by DFT calculations that [2+2+2] cycloisomerisation of ynedinitriles to the pyridazinohelicenes is an exergonic reaction although being less downhill in energy than that of the analogous triynes (to provide helicenes) or cyanodiynes (to provide pyridohelicenes). This new cyclisation reaction described independently also by Snyder *et al.*[39] might develop into a useful tool for the preparation of other complex pyridazines by cyclisation of ynedinitriles.
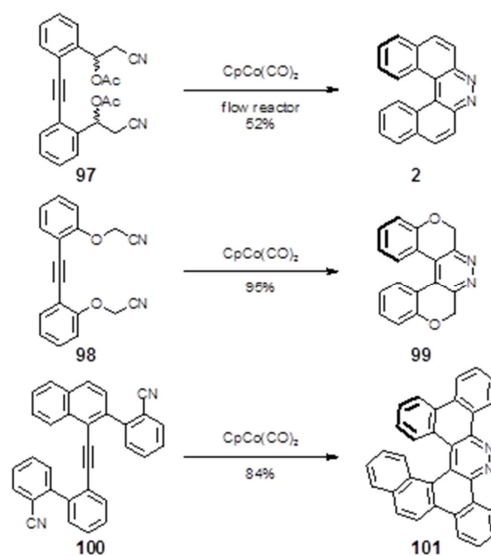
Scheme 17. Synthesis of racemic pyridazinohelicenes by Stará, Starý *et al.*[38]
based on ynedinitrile [2+2+2] cycloisomerisation.

The interest in azahelicenes is steadily growing as they attract nowadays a considerable attention also beyond the frontiers of helicene chemistry. Accordingly, alternative attempts at the effective synthesis of original azahelicenes and their congeners were undertaken. Although these new concepts are promising and may complement the established methodologies, *vide supra*, the further synthetic effort is needed to explore their scope and limitation. A brief overview of these new synthetic methods for the preparation of azahelicenes such as **103**, **105**, **107**, **109** or **111** is presented in Table 1. Other methodologies for the synthesis of azahelicenes are described in Chapter 4.2. in the context of asymmetric synthesis of nonracemic azahelicenes.

Table 1. Additional methods for the synthesis of racemic azahelicenes and their congeners.
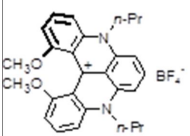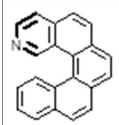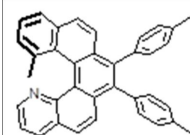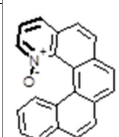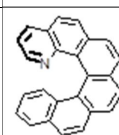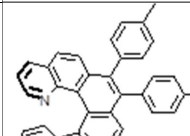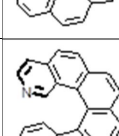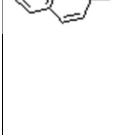
Entry	Synthetic methodology	Key reaction(s)	Authors	Ref.
1		N-N oxidative coupling	Abarca, Ballesteros, Rius *et al*.	40
2		C-C and C-N oxidative coupling	Hiroto, Shinokubo *et al*.	41
3		[2+2+2] cycloisomerisation	Teplý *et al*.	35
4		[2+2+2] cycloisomerisation	Stará, Starý *et al*.	42
5		double carbanion amination	Rajca *et al*.	43
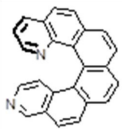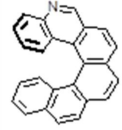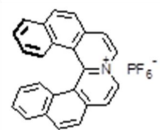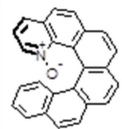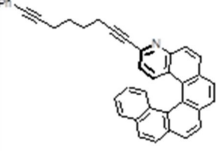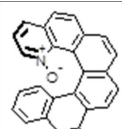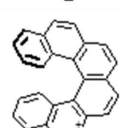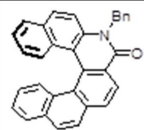
4. Nonracemic pyridohelicenes and other azahelicenes
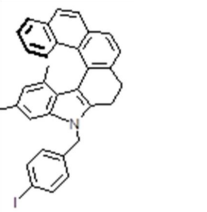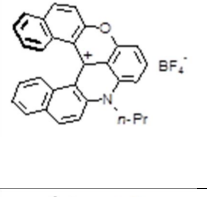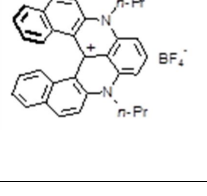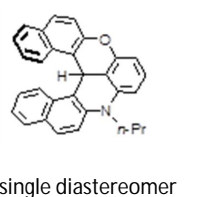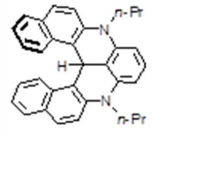
4.1. Resolution of racemates
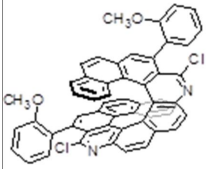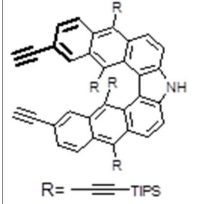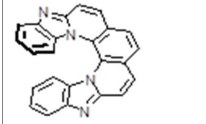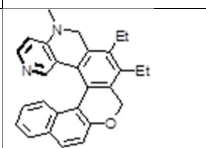
Regardless of the synthetic methodology used, diverse azahelicenes were mostly prepared as racemates. Owing to the remarkable progress in the development and commercialisation of chiral stationary phases for high-performance liquid chromatography, racemic azahelicenes can easily be resolved into enantiomers by HPLC on chiral columns. Although it is a simple, general and straightforward approach to enantiopure (or highly enantioenriched) azahelicenes, some problems might be met. First, semipreparative and namely preparative chiral columns are still expensive. Moreover, azahelicenes exhibit basic character and, therefore, even chiral stationary phases with chemically bound chiral selector might be unstable if, in particular, numerous automated separations are performed. Nevertheless, if small amounts of nonracemic azahelicenes from a few milligrams to tens of them (exceptionally hundreds of milligrams) are required then resolution of racemate by HPLC on a chiral column is a method of choice (even an analytical chiral column might do the job if enantiomers are well resolved and soluble enough but multiple injections are needed). Some representative examples are shown in Table 2. For instance, racemic 1-azahelicenes, after oxidation to the corresponding *N*-oxides in 32–49% yields, were resolved into enantiomers by HPLC on a chiral column.[24]

Table 2. Resolution of racemic azahelicenes into enantiomers by HPLC on a chiral column.

Entry	Azahelicene[a]		Chiral column	Amount of racemate resolved[b]	Eluent	Ref.
1	(structure)	**75**	Chiralcel OD-RH (4.6 × 150 mm) Chirobiotic-TAG (4.6 × 250 mm)		acetonitrile-water, KPF_6 ethanol-water, KPF_6	50
2	(structure)	**13**	Chiralpak IB (5 μm, 4.6 × 250 mm)		heptane-chloroform-diethylamine (50:50:0.1)	68
3	(structure)	**112**	Chiralpak IA (5 μm, 4.6 × 250 mm)		heptane-chloroform-diethylamine (70:30:0.1)	65
4	(structure)	**113**	Chiralcel OD-H (10 × 250 mm)	4.5 mg	hexanes-isopropanol (60:40)	24
5	(structure)	**9**	Chiralcel OD (20 × 250 mm)	13 mg	*n*-hexane-isopropanol (95:5)	44
6	(structure)	**114**	Chiralpak IA (5 μm, 4.6 × 250 mm)		heptane-chloroform-diethylamine (70:30:0.1)	65
7	(structure)	**4**	Chiralcel OD (4.6 × 250 mm) Chiralcel OD-H (4.6 × 250 mm)	0.3 mg (injected in 5 portions) 55 mg (injected in 37 portions)	hexane–isopropanol (75:25) heptane–isopropanol (75:25)	45 19
8	(structure)	**11**	Chiralpak IA (10 × 250 mm)	180 mg (injected in 100 portions)	CO_2-ethanol (80:20)	11

#	Structure	Compound	Column	Amount	Mobile phase	Ref
9		**115**	Daicel Chiralpak IB (20 × 250 mm)	10 mg	*n*-hexane-ethanol-CH$_2$Cl$_2$-diethylamine (90:8:2:0.1)	44
10		**116**	Chiralpak IE (10 × 250 mm)	72 mg (injected in 20 portions)	hexane-EtOH-chloroform (80:10:10)	46
			Chiralpak IC (10 × 250 mm)	≤59 mg (injected in 60 portions)	hexane-ethanol-chloroform-triethylamine (80:10:10:0.1)	
			Chiralpak-IA (10 × 250 mm)		*n*-hexane-isopropanol (97:3)	47
11		**117**	Chiralpak OD-R (20 × 250 mm)		aqueous 0.1 M KPF$_6$-acetonitrile (50:50)	44
12		**118**	Chiralcel OD-H (10 × 250 mm)	30 mg	hexanes-isopropanol (60:40)	24a
13		**24**	Chiralcel OD (10 × 250 mm)	240 mg (injected in 750 portions)	hexane-ethanol (50:50)	15
			Chiralcel OD-H (4.6 × 250 mm)		hexane-ethanol (50:50)	
14		**119**	Chiralcel OD-H (10 × 250 mm)	40 mg	hexanes-isopropanol (60:40)	24a
15		**120**	Chiralcel OD-H		hexane-isopropanol (90:10)	61
16		**121**	Chiralpak AD-H		hexane-isopropanol (80:20)	64

17		122	Chiralcel OD-RH		acetonitrile-water (95:5)	63
18		77	Chiralpak IA (5 μm, 4.6 × 250 mm)		methanol-water, AcONH$_4$ (90:10)	51
			LARIHC CF6-P (5 μm, 4.6 × 250 mm)		heptane-ethanol-TFA-triethylamine (60:40:0.6:0.4)	
19		78	Chiralpak IA (5 μm, 4.6 × 250 mm)		methanol-water, AcONH$_4$ (90:10)	51
			LARIHC CF6-P (5 μm, 4.6 × 250 mm)		heptane-ethanol-TFA-triethylamine (60:40:0.6:0.4)	
20	single diastereomer	123	Chiralpak ID (5 μm, 4.6 × 250 mm)		*n*-heptane-dichloromethane (85:15)	51
			Chiralpak ID (5 μm, 20 × 250 mm)	396 mg (injected in *ca* 10 portions)	*n*-heptane-dichloromethane (88:12)	
			LARIHC CF7-DMP (5 μm, 4.6 × 250 mm)		heptane-ethanol (99.9:0.1)	
21		124	Chiralcel OD-I (20 μm, 4.6 × 250 mm)		*n*-heptane-dichloromethane (90:10)	51
			Chiralpak IB (5 μm, 4.6 × 250 mm)		*n*-heptane-dichloromethane (90:10)	
			Chiralcel OD-I (20 μm, 50 × 200 mm)	577 mg (injected in *ca* 55 portions)	*n*-heptane-dichloromethane (90:10)	
			LARIHC CF7-DMP (5 μm, 4.6 × 250 mm)		heptane-ethanol (99.9:0.1)	

22		**125**	Chiralpak IA		hexane-isopropanol (85:15)	48
23		**126**	Chiralpak IA			41
24		**94**	Chiralcel OD (10 × 250 mm) Chiralpak IC Chiralflash IC (30 × 100 mm)	Injected in 1 mg portions injected in *ca* 34 mg portions	*n*-hexane-isopropanol (70:30) choloform-ethanol (95:5) chloroform-ethanol-diethylamine (95:5:0.1)	36
25		**127**	Chiralpak IC (5 μm, 4.6 × 250 mm)		hexane-ethanol-isopropylamine (90:10:0.4)	49

[a)]Only (*P*)-enantiomer shown. [b)] For the sake of a semipreparative racemate resolution, the sample injected in multiple portions.

Intriguingly, conformationally locked cationic [4]heterohelicenium dyes were effectively resolved by HPLC on chiral cellulose derivative-based stationary phases (Chiralcel OD-RH and Chirobiotic TAG columns) using reversed-phase eluents as reported by Villani, Lacour *et al.*[50] In a broader study, Francotte, Villani, Armstrong, Lacour *et al.*[51] described HPLC resolution of neutral and cationic azaoxa- and diaza[6]helicenes such as *rac*-**78** by using Chiralcel OD-I or Chiralpak ID CSP columns when neutral adducts *rac*-**124** were resolved on a preparative scale (Scheme 18). Racemic helical carbenium ions *rac*-**77** and **78** were separated on the regular Chiralpak IA CSP column using water-containing eluents. Resolution of cationic helicenes *rac*-**77** and **78** and their neutral forms *rac*-**123** and **124** and was also achieved on more recently developed LARIHC columns underlying a versatility of the cyclofructan phases that allowed for the baseline separations for both cases.

Alternatively, Teplý, Kašička *et al.* reported on chiral analysis of helquats (helical *N*-heteroaromatic dications, Chapter 3.1.) by capillary electrophoresis (CE).[52,53] These highly polar systems with embedded quaternary nitrogen atoms are decently soluble in water that makes them suitable analytes for CE. Indeed, using acidic sodium/phosphate background electrolyte and randomly sulfated α-, β- and γ-cyclodextrins as chiral selectors, enantioresolution of a wide series of racemic helquats comprising 5, 6 or 7 fused rings in the helical backbone was achieved to reach mostly baseline separation. Advantageously, the CE analysis of chiral helquats is very fast as migration times of both resolved enantiomers are usually well below 10

minutes. The CE methodology allowed also to monitor a complex pathway of racemisation of nonracemic [6]helquat via an isolable saddle-shaped intermediate [6]saddlequat.[54]
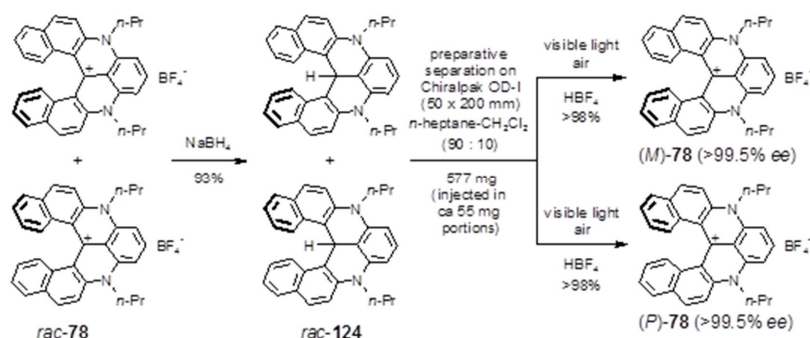
Scheme 18. Resolution of racemic non-cationic diaza[6]helicenes by chiral HPLC by Francotte, Villani, Armstrong, Lacour *et al.*[51]

Some racemic azahelicenes and their congeners were resolved into enantiomers by using chiral resolving agents. The noncovalent or covalent diastereomeric pairs formed were separated by crystallisation or by means of liquid chromatography, respectively. As reported by Stará, Starý *et al.*,[19] racemic 1-aza[6]helicene **9** was separated into enantiomers by crystallisation with (+)-*O,O'*-dibenzoyl-D-tartaric acid in a large excess followed by a solvent trituration of the formed yellow crystalline diastereomeric complex. Upon basification, enantiopure (+)-**9** was received. The optical antipode, enantiopure (−)-**9** was separated from the mother liquor by an analogous way employing (-)-*O,O'*-dibenzoyl-L-tartaric acid. Similarly, Takenaka *et al.* reported the optically pure (*P*)-11,12-benzo-1-aza[6]helicene **60** was obtained from racemate by fractional crystallisation of the corresponding diastereomeric salts with (+)-*O,O'*-dibenzoyl-D-tartaric acid and subsequent recrystallisation of the free base.[55]

Diastereomeric dibenzoyltartrate salts derived from racemic dicationic helquats were separated by crystallisation as reported by Teplý *et al.*[53,56,57] This procedure led to the enantiopure helquats in milligram quantities or enantioenriched materials on a (sub)multigram scale. Taking advantage of that, the racemic bistriflate salt of [5]helquat *rac*-**128** or bis(trifluoroacetate) salt of [7]helquat *rac*-**129** crystallising as conglomerates could effectively be resolved into enantiomers by preferential crystallisation (Figure 2). For example, starting with 5 g of the slightly enantioenriched (*P*)-[7]helquat **129** (5% *ee*) and seeds of enantiopure (*P*)- and (*M*)-[7]helquat **129** (3.7 mg each), nine repetitions of the two-step cycle, supplementing the systems after each crystallisation with racemate to 5 g, led to 5 g samples of each pure enantiomer of [7]helquat **129** (after double recrystallisation).[57]
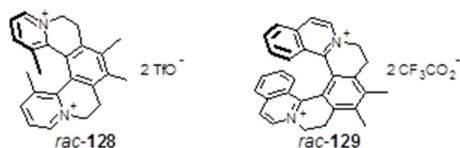
Figure 2. Racemic helquats resolved by preferential crystallisation by Teplý *et al.*[56,57]

Laursen, Lacour *et al.* succeeded in resolving racemic dimethoxyquinacridinium cation *rac*-**75** by combining it with chiral hexacoordinated phosphorus-centered binphat anions **130** (Scheme 19).[29] A mixture of the racemic configurationally locked diaza[4]helicenium ion *rac*-**75** and enantiopure (Δ,*S*)-binphat salt **130** (or (Λ,*R*) one) was chromatographed on alumina (CH₂Cl₂ as eluent) to obtain a pair of diastereomers [*rac*-**75**][(Δ,*S*)-**130**] (or [*rac*-**75**][(Λ,*R*)-**130**]). A single diastereomer was separated by crystallisation and

converted into the hexafluorophosphate salt (+)-(*P*)-**131** (*er* = >98:2) (or (-)-(*M*)-**131**, *er* = >98:2, when using (Λ,*R*)-**130** as a resolving agent).

Scheme 19. Resolution of racemic cationic diaza[4]helicene by Laursen, Lacour *et al.*[29]
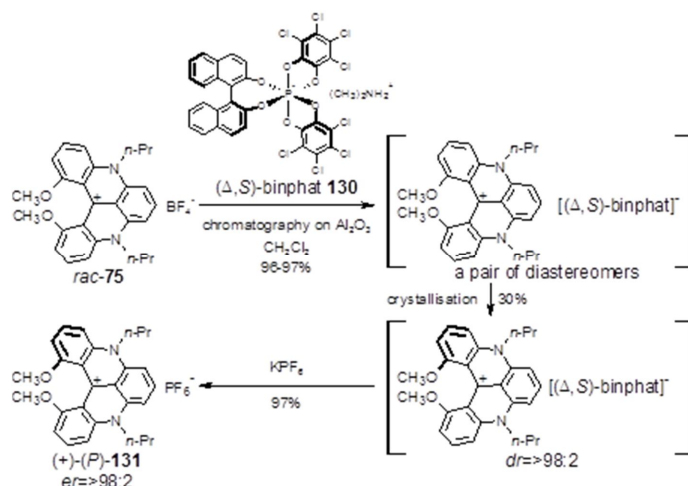
Racemic azahelicenes and their congeners were alternatively resolved into enantiomers through the separation of the respective covalent diastereomers. Accordingly, Lacour *et al*. resolved [4]heterohelicenium cations *rac*-**75** through diastereomeric neutral adducts (*R*,*M*)-**133** and (*R*,*P*)-**133** that were formed by reaction of *rac*-**75** with carbanion derived from the optically pure sulfoxide (*R*)-**132** (Scheme 20).[58] After chromatographic separation of these diastereomerically pure adducts, they were converted to the enantiopure 1,13-dimethoxyquinacridinium cations (*M*)-**131** and (*P*)-**131** employing an unprecedented Pummerer-like C-C bond-fragmentation reaction.

Scheme 20. Resolution of racemic cationic diaza[4]helicene through diastereomeric neutral adducts by Lacour *et al.*[58]
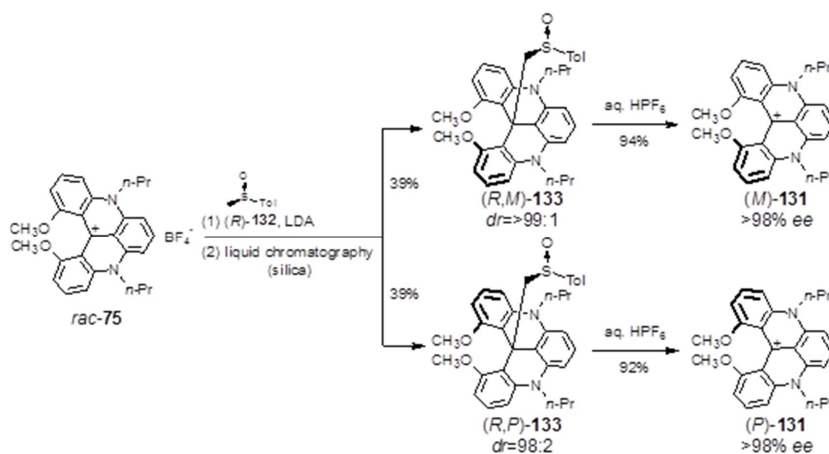
Dehaen *et al*. derivatised the highly functionalised racemic diaza[6]helicene **26** with optically pure (*S*)-1-phenylethan-1-amine **194** under Buchwald-Hartwig amination conditions[59] to receive a mixture of the

(*M,S*)- and (*P,S*)-diastereomer **195** (see Scheme 34, Chapter 5). They were then easily separated by column chromatography on silica gel.

4.2. Asymmetric synthesis

Asymmetric synthesis of azahelicenes is so far rare but the first significant achievements in this respect were already accomplished. Nozaki *et al*. took advantage of availability of enantiopure 4,4'-biphenanthryl-3,3'-diol whose nonaflyl derivative (*S*)-**134** was used in the stereospecific synthesis of the enantiopure carbazol-derived aza[7]helicene (*P*)-**135** (Scheme 21).[60] Employing the Buchwald-Hartwig amination methodology, Pd-catalysed double arylation proceeded in a stereoconservative way.
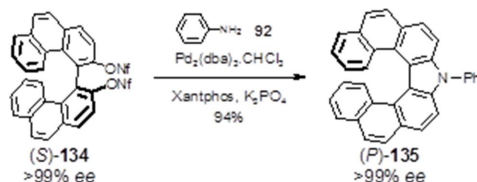

Scheme 21. Asymmetric synthesis of enantiopure pyrrolo[7]helicene by Nozaki *et al*.[60] employing Buchwald-Hartwig amination.

Using an analogous concept, Kamikawa *et al*. converted an enatiopure biaryl building block (*R*)-**136** (obtained by resolution of the corresponding racemate by liquid chromatography on a chiral column) into enantiopure 6-aza[6]helicene (*P*)-**138** in good yield by utilising a palladium-catalysed C-H annulation reaction (Scheme 22).[61] It is worth noting that annulation of the pendant bromovinyl side chain in (*R*)-**136** required first an activation of the respective C-H bond and, therefore, the original pyridine unit in (*R*)-**136** was converted into the pyridine *N*-oxide one being encompassed in (*R*)-**137**. This annulation methodology was studied in detail in the synthesis of the homologous 6-aza[5]helicene **139**).
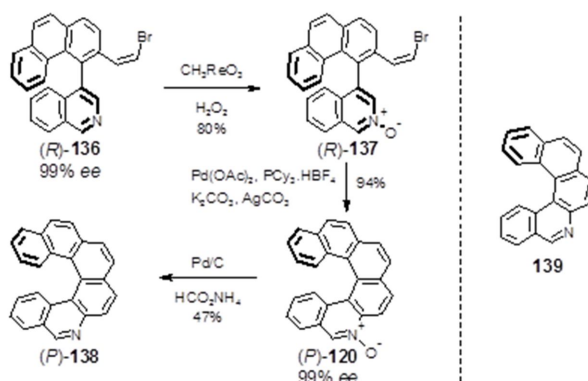
Scheme 22. Asymmetric synthesis of enantiopure pyrido[6]helicene by Kamikawa *et al*.[61] using the Pd-catalysed C-H annulation reaction developed in the synthesis of racemic pyrido[5]helicene.

Srebro-Hooper, Crassous, Guy *et al*. built the enantiopure backbone of the diazahelicene-like dibenzo[*c*]acridine compound (–)-**142** from the optically pure axially chiral bis-tetralone (+)-**140**, which was obtained from racemate by preferential crystallisation (it formed conglomerate) (Scheme 23).[62] After the enlargement of a chromophore unit by Friedlaender reaction without losing optical purity and the following demethoxylation ((+)-**140**→(–)-**141**), the axially chiral intermediate (–)-**141** was converted into the methylene-bridged heterohelicene (–)-**142** by forming the central 2*H*-1,3-dioxepine ring on reaction with chloroiodomethane. It represents a straightforward pathway for the preparation of azahelicene-like

molecules on a gram scale in an enantiopure form. The optical purity of (–)-**142** was checked by an ^{1}H NMR shift reagent as all attempts to resolve the racemate by liquid chromatography on a chiral column failed.
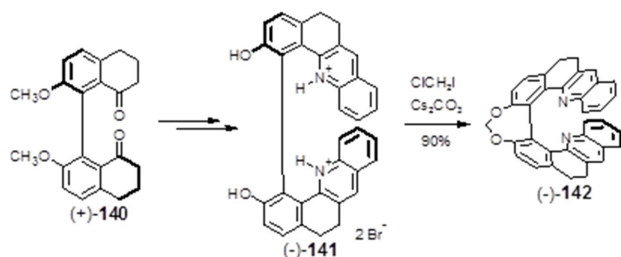
Scheme 23. Asymmetric synthesis of the enantiopure diazahelicene-like dibenzo[*c*]acridine derivative by Srebro-Hooper, Crassous, Guy *et al.*[62] utilising a methylene-bridge formation by the double S_N reaction.

The highly efficient synthetic route to racemic 1-aza[6]helicene **9** by Fuchter *et al.* (see Scheme 10) could be conducted asymmetrically.[26] Benefitting also from the separation of atropoisomers of the axially chiral biaryl **67** by semipreparative HPLC on a chiral column (OD-H, 250 × 4.6 mm, 5 μm, *n*-hexane-isopropanol 95:5) and their high configurational stability, alkyne-arene cycloisomerisation allowed for the transformation of axial chirality into helicity with an excellent relay of stereochemical information. Accordingly, the helicene products (*M*)-**9** and (*P*)-**9** were isolated in 90% and 92% *ee*, respectively.

A pioneering study published List *et al.* reported on the asymmetric organocatalytic approach to indole/carbazole-derived azahelicenes (Scheme 24).[63] It employed enantioselective Fischer indolisation reaction catalysed by a chiral SPINOL-derived phosphoric acid (*S*)-**145** to form the helical backbone in good yield.
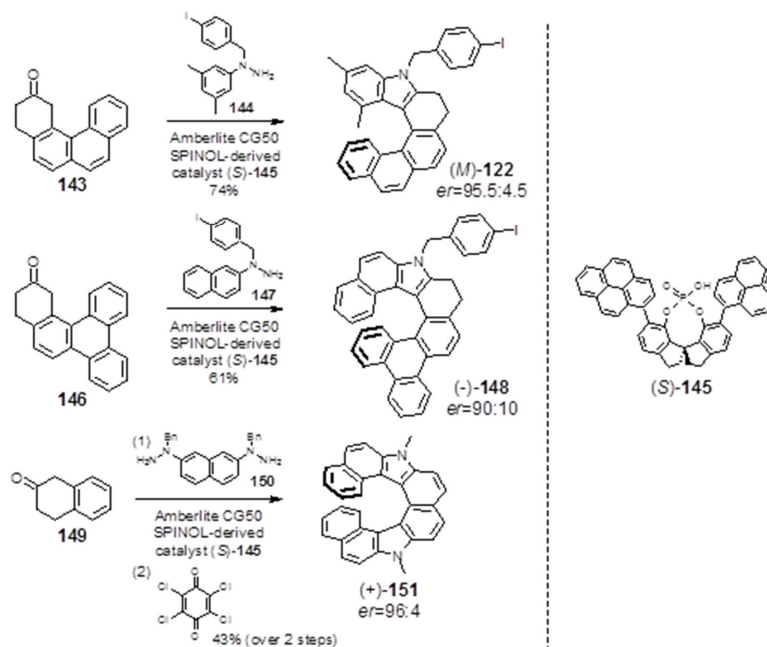
Scheme 24. Enantioselective organocatalysis in the synthesis of nonracemic pyrrolohelicenes by List *et al.*[63] employing a Fischer indolisation reaction.

The high level of stereocontrol in the synthesis of a series of aza[5]-, aza[6]-, aza[7]- and diaza[8]helicene derivatives such as (*M*)-**122**, (–)-**148** or (+)-**151** (receiving them in up to 92% *ee*) originated in a cleverly designed organocatalyst forming a deep chiral pocket to stabilise intermediates by π-π interactions. Furthermore, this original approach gives access to enantioenriched azahelicenes starting from simple achiral materials, which allow for broadening the substrate diversity.

A promising approach to nonracemic azahelicenes and S-shaped double azahelicenes was developed by Tanaka *et al.* utilising the Au-catalysed sequential intramolecular hydroarylation of aromatic diynes (Scheme 25).[64] In the presence of an excess of the Ag$^+$ salt with respect to the Au$^+$ complex and chiral BINAP ligand, diyne **152** was cyclised to (–)-**153** in excellent yield and with good *ee*. The following removal of the protecting 4-methoxybenzyl group that was accompanied by chlorination of the backbone afforded the enantioenriched 7-aza[6]helicene (–)-**154** in good yield. This methodology allowed preparing the enantiopure S-shaped double aza[6]helicene (+)-**157**. It was separated from a mixture of the corresponding racemate and *meso* form by preparative TLC on silica gel as the excess enantiopure (+)-**157** moved slower owing to its lower solubility.
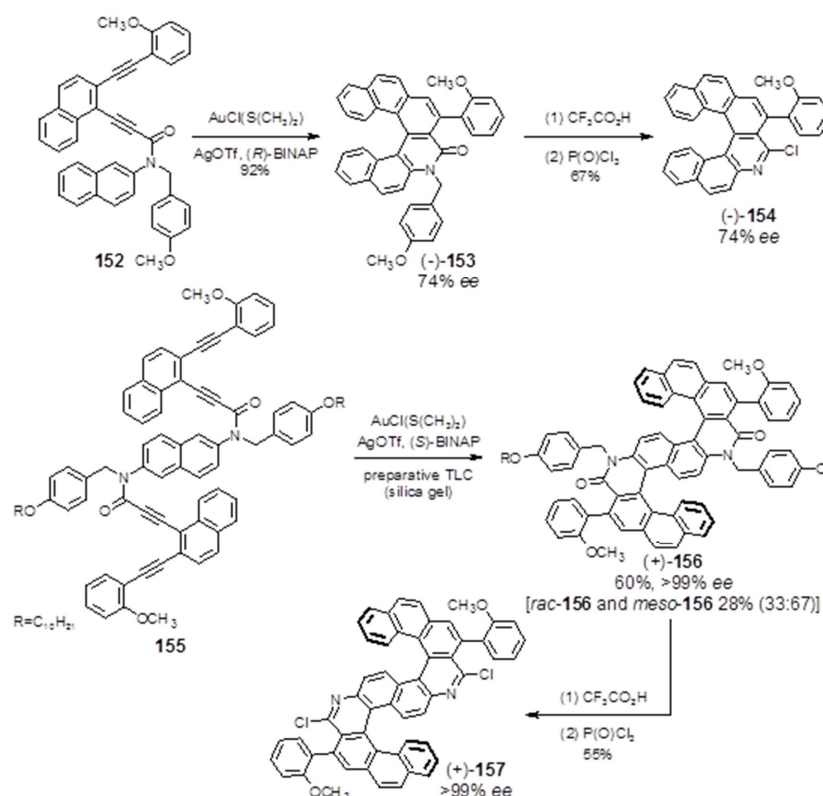
Scheme 25. Enantioselective Au catalysis in the synthesis of nonracemic pyridohelicenes by Tanaka *et al.*[64]

Stará, Starý *et al.* reported on an ultimate stereocontrol through the 1,3-allylic-type strain in an asymmetric synthesis of archetypal fully aromatic aza[5]- and aza[6]helicene such as (*M*)-**114** to be uniformly obtained in enantiomer ratios of >99:<1 (Scheme 26).[65] As the absolute configuration of the stereogenic centre determines helicity, it can reliably be predicted. This study, which utilised a biocatalytic approach to enantiopure building blocks to synthesise chiral triynes such as (*RS,S*)-**158** (a 1:1 mixture of enantiopure diastereomers), diastereoselective alkyne [2+2+2] cycloisomerisation ((*RS,S*)-**158**→(*M,RS,S*)-

159) and traceless chiral auxiliary strategy ((*M*,*RS*,*S*)-**159**→(*M*)-**114**) in asymmetric synthesis, provided a solution to a problem of (hetero)helicene chemistry present since its birth in 1956 (M. S. Newman and D. Lednicer)[66] that was the lack of a general synthetic methodology for the preparation of diverse enantiopure (hetero)helicenes. The same principle of stereocontrol was applied to the asymmetric synthesis of optically pure azahelicenes such as (*M*,*R*,*R*)-**161** from enantiopure (*R*,*R*)-**160** with embedded 2*H*-pyran rings.[67] The presence of stereogenic centres guaranteed the diastereomeric purity of the respective azahelicenes that exist in the form of a single helix even at higher temperature (in contrast to the parent 1,14-diaza[5]helicene **39**, see Scheme 5, that racemises at room temperature).[68] This principle of stereocontrol was successfully applied to the asymmetric synthesis of long pyridohelicenes through the multiple [2+2+2] cycloisomerisation as exemplified by the preparation of the diaza[17]helicene congener (*M*,*R*,*R*)-**163** (the longest azahelicene prepared to date) from (*R*,*R*)-**162**.[69] The 2*H*-pyran-modified aza[6]helicene derivative was synthesised by Carbery *et al.* in an enantiopure and highly diastereomerically enriched form using also a point-to-helical triyne [2+2+2] cycloisomerisation.[70]
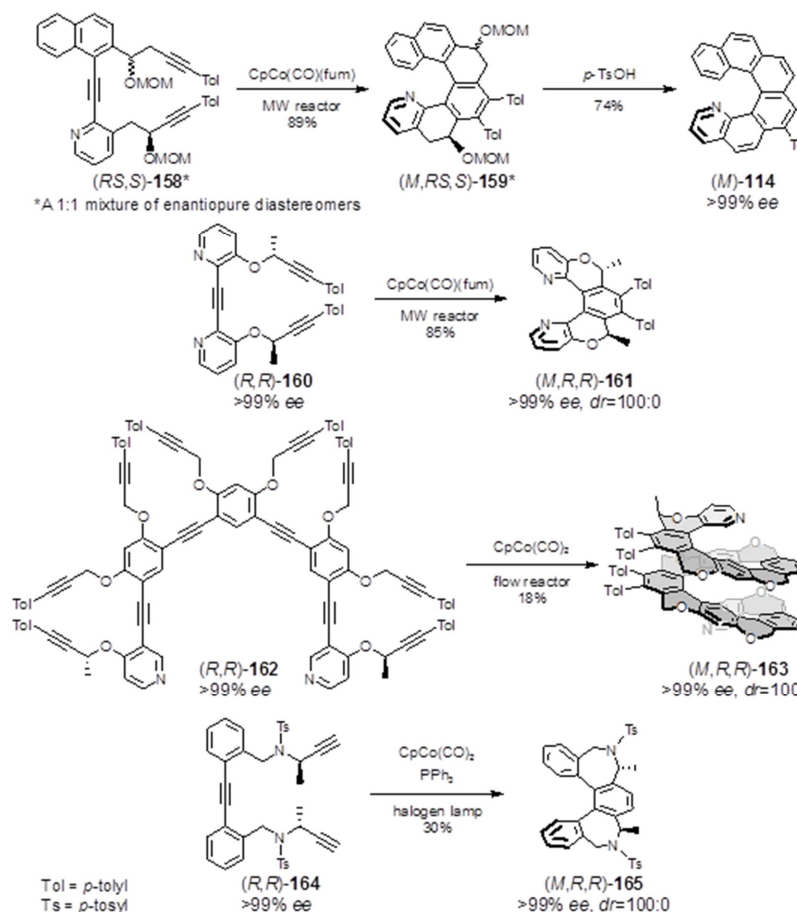
Scheme 26. Synthesis of enantiopure azahelicenes and their congeners by Stará, Starý *et al.*[42,65,67,69] based on diastereoselective alkyne [2+2+2] cycloisomerisation.

Interestingly, the [2+2+2] cycloisomerisation of (R,R)-**164** led to the enantio- and diastereomerically pure product even though no strong 1,3-allylic-type strain between two carbon substituents operated in the molecule.

The intramolecular [2+2+2] co-cycloisomerisation of enantiopure cyanodiyne (R)-**168** (accessible from the commercially available (2R)- or (2S)-but-3-yn-2-ol being easily transformed to (R)-**166**) mediated by CpCo(CO)$_2$/PPh$_3$ under microwave irradiation led to the enantio- and diastereomerically pure pyrido[6]helicene-like (M,R)-**169** in good yield (Scheme 27).[22] This chiral substrate-controlled diastereoselective cyclisation capitalises also on the fact that the pyridohelicene-like products are forced to adopt such a helicity that prevents the disfavoured 1,3-allylic-type strain between the methyl substituent at the stereogenic centre and adjacent tolyl group, *vide supra*.[65,67]
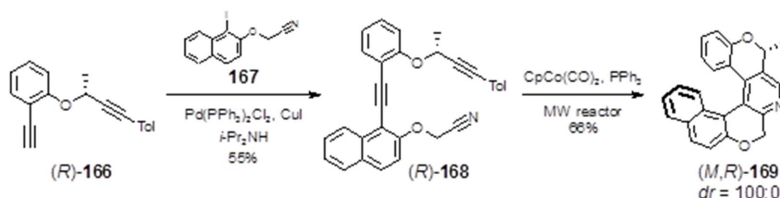
Scheme 27. Synthesis of enantiopure pyridohelicenes by Stará, Starý *et al.*[22] based on diastereoselective cyanodiyne [2+2+2] cycloisomerisation.

5. Functionalisation of existing pyridohelicenes and other azahelicenes

Functionalisation of already synthesised azahelicenes was rare in the past. However, there has been an increasing activity recently witnessed in this regard. There are several challenges that have to be faced: a problem of regioselectivity of the functionalisation, diminished reactivity in innermost positions of the heterohelicene backbone and fact that some reactions at (hetero)helicenes as electron rich substrates are slowed down (for example oxidative addition in cross-coupling chemistry). Nevertheless, the portfolio of reactions allowing the functionalisation of existing azahelicenes is steadily growing.

Takenaka *et al.* oxidised 1-azahelicenes **3**, **9** and **60** with *m*-chloroperbenzoic acid to furnish the corresponding pyridine *N*-oxides **113**, **118** and **119** in moderate yields (Scheme 28, not optimised), the enantiomers of which were readily resolved by HPLC on a chiral column (Daicel CHIRALCEL OD-H).[24] Later on, the preparation of 11,12-benzo-1-aza[6]helicene *N*-oxide **119** was optimised.[71]

Takenaka *et al.* presented a facile conversion of enantiopure 1-aza[6]helicene *N*-oxides (M)-**118** and (P)-**119** to the corresponding 2-amino and 2-alkylamino derivatives (M)-**171** and (P)-**172**, respectively (Scheme 29).[72,73] They were further protonated by HCl and isolated as TFPB salts (TFPB = tetrakis(3,5-bis(trifluoromethy)phenyl)borate) of stable 2-(amino)-1-aza[6]helicenium or 2-(alkylamino)-1-aza[6]helicenium species. On reaction with the lithiated pyridine **173**, the enantiopure 1-aza[6]helicene *N*-oxide (P)-**119** was also transformed to the helical 2,2'-bipyridine *N*-monoxide (P)-**174** in high yield.[72]

Kamikawa *et al.* developed intermolecular Pd-catalysed C-H arylation of 6-aza[5]- and 6-aza[6]helicene *N*-oxides such as enantiopure (P)-**120** (Scheme 30).[61] Various aryl substituents were regioselectively introduced into the *ortho* position to the nitrogen atom as exemplified by enantiopure (P)-**176**.

Fuchter *et al.* demonstrated the first successful Suzuki-Miyaura cross-coupling, Buchwald–Hartwig amination and Heck reaction performed on (trifluoromethanesulfonyl)oxy derivatives of 1-aza[6]helicene **177** or **182** (Scheme 31).[26] While the cross-coupling reaction of triflate **177** with boronic acid **178** proceeded without issue to give the functionalised 1-aza[6]helicene **179** in high yield, amination with pyrrolidine **180** delivered the product **181** in good yield and reaction of **182** with *n*-butylvinylether **183** gave the acetylderivative **184** in moderate yield.

Teplý *et al.* demonstrated a widely applicable one-step conversion of [5]- and [6]helquats equipped with the active methyl group(s) to cationic heterohelicene styryl-type dyes by utilising Knoevenagel

condensation with a plethora of aromatic aldehydes and their congeners as exemplified by the synthesis of the highly enantioenriched (*P*)-**187** from the nearly enantiopure (*P*)-**185** and aldehyde **186** (Scheme 32).[33,74,75] These studies introduced an original class of dicationic helical dyes with prominent optical, chiroptical and other physicochemical properties.
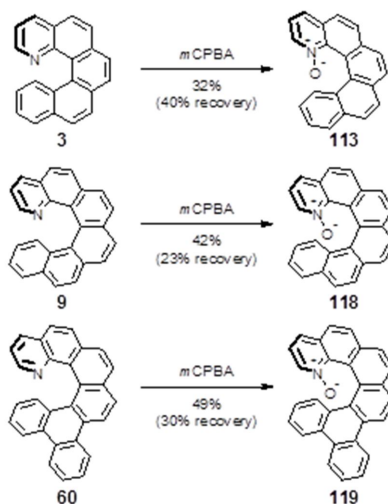
Scheme 28. Racemic pyridohelicene-derived *N*-oxides by Takenaka *et al.*[24,71]
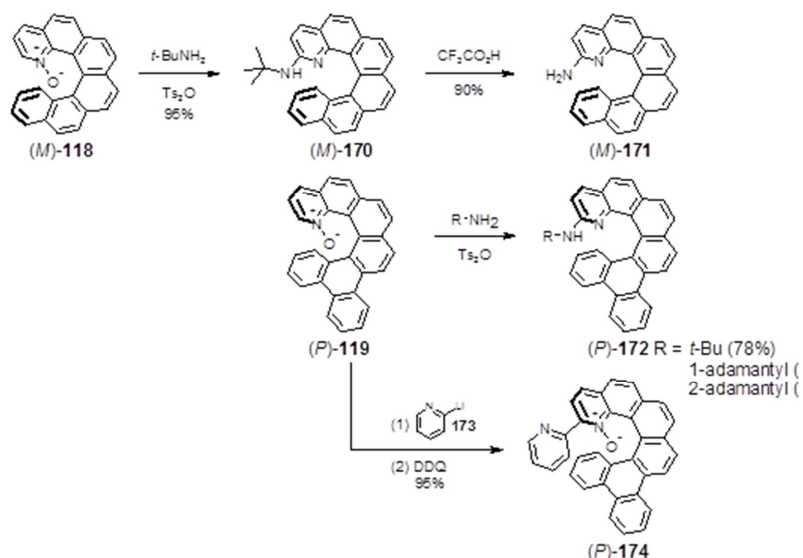
Scheme 29. Synthesis of enantiopure amino, alkylamino and bipyridine *N*-monoxide derivatives of pyridohelicene by Takenaka *et al.*[72,73]

Lacour *et al.* examined systematically orthogonal post-functionalisation of cationic aza[6]helicenes **78** and **188** (Scheme 33).[30] The median benzene ring, which is electronically richer than the terminal naphthalene ones, was found to smoothly undergo electrophilic aromatic substitution under nitration or

halogenation reaction conditions to deliver the dinitro **189**, dichloro **190**, dibromo **188** or iodo **191** derivatives in high yields. Regioselectivity of the reactions was perfectly controlled by the present nitrogen atoms. On reaction with nucleophiles, however, the terminal naphthalene units in **78** and **188** exhibited a higher propensity towards vicarious nucleophilic substitution that was further tuned up by the cationic character of the molecules to deliver the dicyano derivative **192** or amino derivative **193**.
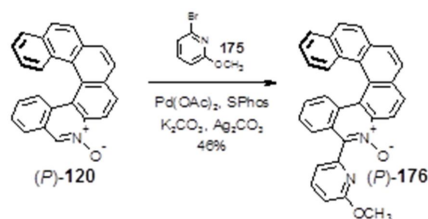
Scheme 30. Pd-catalysed C-H arylation of enantiopure pyridohelicene *N*-oxides by Kamikawa *et al.*[61]
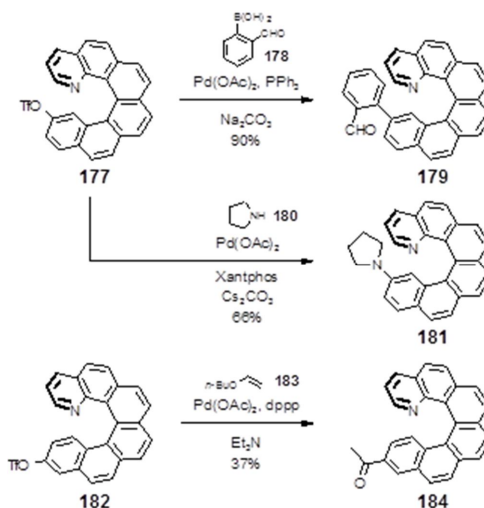
Scheme 31. Pd-catalysed Suzuki-Miyaura cross-coupling, Buchwald–Hartwig amination
and Heck reaction on racemic pyridohelicene derivatives by Fuchter *et al.*[26]
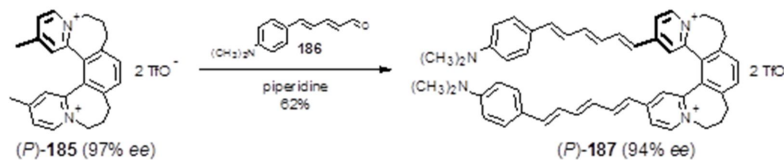
Scheme 32. Knoevenagel-type chemistry on nonracemic helquats with the active methyl group(s)
by Teplý *et al.*[74]

Dehaen *et al.* demonstrated that the electronically distinguished dimethoxycarbazole part and chloroquinoline one of the complex diaza[6]helicene **26** can undergo a sequence of substitution reactions (Scheme 34).[16] The chloro group was substituted under Buchwald-Hartwig amination conditions with the chiral benzyl amine (*S*)-**194**, allowing diastereomeric separation of (*M*,*S*)-**195** and (*P*,*S*)-**195** and the chiral forms were monofunctionalised via electrophilic substitution on the carbazole unit to provide the bromo

derivative (*P*,*S*)-**196** (on reaction with *N*-bromosuccinimide) or carbonyl derivative (*P*,*S*)-**197** (under the conditions of the Vilsmeier–Haack reaction). In addition, the S_NAr reaction, Buchwald-Hartwig amination or Suzuki coupling was also performed at a dichloro derivative of diazadithia[7]helicene by Dehaen *et al*. in good yields.[17]
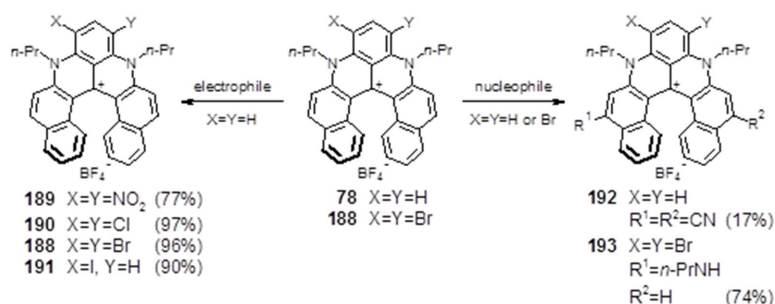
Scheme 33. Orthogonal post-functionalisation of racemic cationic diaza[6]helicenes on reaction with electrophiles or nucleophiles by Lacour *et al*.[30]
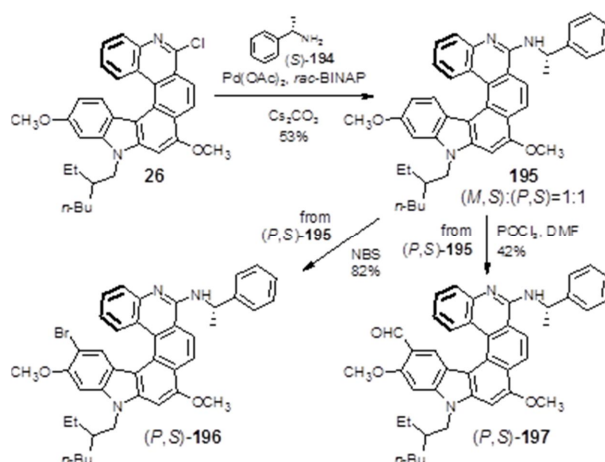
Scheme 34. Buchwald-Hartwig amination of racemic pyrido-pyrrolo[6]helicene and electrophilic substitution on the resolved diastereomerically pure products by Dehaen *et al*.[16]

The carbazole-derived aza[7]helicene **135** can be transformed into its dibromo or tetrabromo derivative **198** or **199**, respectively, simply by dosing the amount of *N*-bromosuccinimide as reported by Nozaki *et al*. (Scheme 35).[60] This electrophilic substitution exhibited high regioselectivity. On lithiation and subsequent reaction with methyl chloroformate, the tetrabromide **199** was converted into tetraester **200** in moderate yield.

Hiroto, Shinokubo *et al*. performed double Sonogashira reaction of dibromo azahelicene **105** with trimethylsilylacetylene where the use of the *t*-Bu₃P ligand for palladium was essential to receive high yield of the cross-coupling product (Scheme 36).[41]After desilylation and resolution of racemate into enantiomers by HPLC on a chiral column, the enantiopure diyne (*P*)-**126** was subjected to Eglinton oxidative coupling of terminal alkynes to undergo macrocyclisation delivering the bisbutadiyne bridged azahelicene dimer (*P*,*P*)-**201** with a figure-eight shape in good yield.
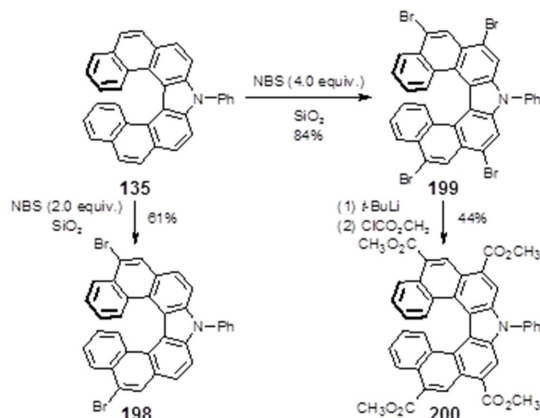
Scheme 35. Regioselective functionalisation of racemic pyrrolo[7]helicenes by Nozaki *et al.*[60]
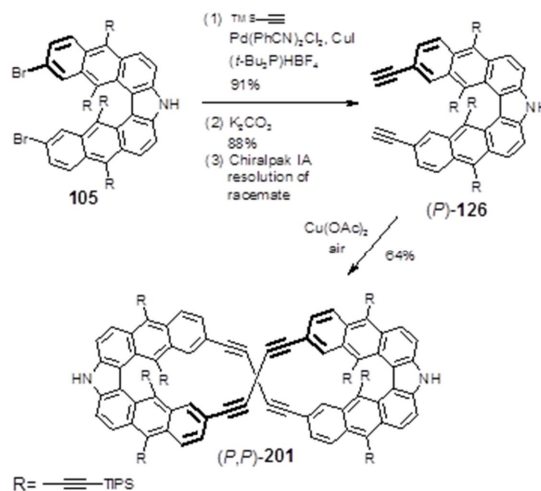
Scheme 36. Ethynylation of a racemic bromo azahelicene derivative and macrocyclisation of the corresponding enantiopure bisethynyl derivative by Hiroto, Shinokubo *et al.*[41]

6. Conclusions

In summary, a remarkable progress in the synthesis of azahelicenes and their congeners was achieved within the last decade. Nowadays, a plethora of synthetic methods is available to prepare manifold azahelicene structures on demand. Along with the traditional photodehydrocyclisation methodology, modern synthetic tools relying on transition metal catalysis such as alkyne [2+2+2] cycloisomerisation, cross-coupling chemistry or alkyne-arene cycloisomerisation are getting more popular to form azahelicene backbones. Moreover, numerous functionalised azahelicenes are now available through installing proper substituents at the beginning of the synthetic pathway or certain azahelicenes can be regioselectively functionalised. A significant effort has been made to obtain inherently chiral nonracemic azahelicenes by exploring diverse ways of asymmetric synthesis or employing various separation techniques among them racemate resolution by HPLC on commercially available chiral columns is central to this endeavour. In view of the future development, the application-driven step-economic synthesis of functionalised tailor-made

azahelicenes delivering them enantiopure and on a multigram scale is still challenging and will attract steadily growing attention.

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