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TUTORIAL REVIEW

Stereoselective Arene Formation

Achim Link and Christof Sparr*

While aromatic hydrocarbons are ubiquitous in organic chemistry, they are typically not associated with chirality and stereoisomerism. Due to the planarity and symmetry of simple arenes, methods to assemble aromatic rings are therefore not routinely considered for the stereoselective synthesis of chiral compounds. The aim of this tutorial review is to contrast this common perception with the counterintuitive circumstance that stereoselective arene formation offers a means to stereoselectively prepare an exceptional range of chiral aromatic structures. The versatility of these methods across various types of molecular scaffolds allows to control stereocentre configuration, helical chiral compounds, the configuration of rotationally restricted stereogenic axes, planar chiral molecules or curved polyaromatic systems. Furthermore, stereoselective arene formation holds great promise for the selective construction of extended- but structurally well-defined chiral structures.

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Key learning points: 1) Counterintuitively, arene formation offers a means to stereoselectively prepare a broad range of chiral structures.
2) Substrate desymmetrization by the de novo construction of an aromatic ring allows controlling stereocentre configuration
3) The non-planar shape of helicenes or curved aromatic systems can be controlled during arene assembly.
4) Rotationally restricted atropisomers and planar chiral compounds are readily accessible by stereoselective arene formation.

1. Introduction

Owing to the high symmetry of arene-archetypes such as benzene, naphthalene or anthracene, aromatic hydrocarbons are not intuitively associated with stereochemical considerations. However, stereoselective methods for the de novo construction of an aromatic ring represent exceptionally versatile strategies for various chiral structures. Moreover, given the importance of arenes as structural motif, arene-forming reactions offer unique opportunities to prepare various stereochemically complex compounds in isomerically enriched form, a concept that has recently gained momentum and emerged as an effective strategy also for the synthesis of extended structures.

The aim of this tutorial review is to feature conceptually unconventional arene-forming methods that provide stereoisomerically-enriched chiral aromatic compounds. However, chiral arene-metal complexes, conversion of redox derivatives (e.g. quinones) and heteroarene products are beyond the scope of this review. In a broader context, the stereocontrolled de novo construction of an aromatic ring is distinct from the stereoselective coupling or functionalization of existing arenes.

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Christof Sparr received his PhD from the ETH Zurich (Switzerland) working in the group of Prof. Ryan Gilmour. He then joined the groups of Prof. Dieter Seebach (ETH Zurich) and subsequently Prof. Steven V. Ley (University of Cambridge, UK). In 2013, Christof became habilitand mentored by Prof. Karl Gademann and was given the opportunity to start an independent research project. Since 2016, Christof works as Assistant Professor at the University of Basel with a research program focussing on synthetic organic chemistry. He is recipient of the ETH silver medal, an SNSF starting grant and the Werner Prize of the Swiss Chemical Society 2017.

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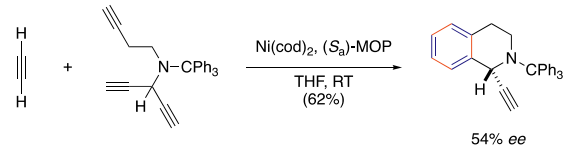
Achim Link, born in 1985, studied chemistry at the University of Freiburg i. Br. (Germany) and at the University of Basel (Switzerland). He joined the Sparr group first as a Master student investigating the stereoselective arene-forming aldol condensation and in 2014, he started his PhD studies focussing on bifunctional organometallic reagents for the direct transformation of esters into arenes. He received a fellowship from the Camille and Henry Dreyfus Foundation, an Early Postdoc.Mobility fellowship of the Swiss National Science Foundation and the Travel Award of the Swiss Chemical Society and the Swiss Academy of Sciences.

The departure from the prevailing notion of an aromatic ring system as a predetermined unit and the elaboration of new concepts for the stereocontrolled de novo construction of arenes, evolved to conceptually distinct synthetic strategies towards various preferred molecular topologies. Combined with means to address the configuration of different stereogenic units, the assembly of the aromatic ring thereby allows highly convergent synthetic approaches crucial for an increasingly complex molecular design. These virtues were impressively demonstrated in pioneering efforts on catalytic [2+2+2]-cycloadditions, by which a broad range of chiral structures is accessible and thus represents a seminal reaction manifold for stereoselective arene-formation.[1–3] Today, the capacity of [2+2+2]-cycloadditions is impressively complemented by various other versatile stereocontrolled methodologies, including benzannulation and cyclisation reactions that were widely applied in numerous substrate-, auxiliary-, reagent-, and catalyst-stereocontrolled processes. The breadth of strategies is also reflected by the variety of stereoinduction modes stemming from interactions with chiral catalysts, reagents or substrates with hitherto existing stereogenic units. The versatility of intra- and intermolecular arene-assembly methods allows the stereoselective construction of well-defined rigid aromatic compounds over a broad range of structural scaffolds and various molecular topologies. Therefore, the reviewed reactions not only complement stereoselective coupling and arene functionalization-methodology, but represent conceptually unique synthetic strategies to access novel molecular architecture. Versatile stereoselective arene-forming reactions hence allow to control stereocentres, the configuration of helicenes,[4,5] molecules with a chirality plane[6] or stereogenic axes.[7–10] They further enabled the enantioselective preparation of curved polyaromatics with inherent[11,12] chirality and hold great promise for the synthesis of chiral mechanically interlocked molecules.[13]

2. Controlling stereocentre configuration

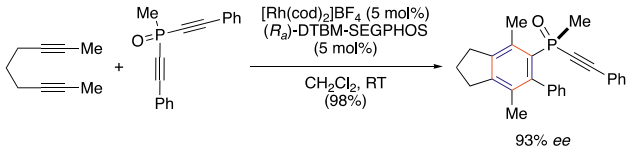
Aromatic compounds with adjacent or remote stereocentres are exceptionally common structural motifs. The configuration of these compounds is traditionally controlled in stereoselective reactions with enantioface discrimination. A conceptually different and perhaps counterintuitive approach is a reaction design, where stereoinduction occurs during arene formation. Particularly the desymmetrisation in the course of aromatic ring assembly offers a means to efficiently control stereocentre configuration. For instance, enantiotopic group selective [2+2+2]-cycloadditions culminate in stereoinduction during arene-formation from the use of chiral catalysts. Pioneered by Mori and co-workers in 1994, this strategy was based on a nickel-catalysed [2+2+2]-cycloaddition[14] of triynes with acetylene. The stereoselective desymmetrisation reaction provided alkyne-substituted isoindoline and isoquinoline derivatives by employment of a chiral binaphthyl phosphine ligand such as (S_a)-MOP at ambient temperature (Scheme 1). During the course of the reaction, one of the vicinal alkynes is selectively transformed to a nickelacyclopentadiene as controlled by the chiral ligand in the productive catalytic cycle. The bulky nitrogen protecting trityl group (CPh_3) was found to ameliorate the enantioselectivity.



Scheme 1 Nickel-catalysed [2+2+2]-arene forming cycloaddition to afford an isoquinoline with control over stereocentre configuration.

By functionalising the alkyne termini, various arene substitution patterns where readily accessible, which impressively illustrates the modularity of this prototypical stereoselective arene-forming reaction. Groups at specific positions are introduced by straightforward synthesis of acyclic precursors and then brought together while simultaneously controlling the stereochemical course of the reaction.

Intriguingly, the stereoselective arene formation strategy is not limited to the preparation of *C*-stereogenic compounds and can be employed for the synthesis of *P*-stereogenic products. Molecules with *P*-stereocentres are highly valuable products as exemplified by DIPAMP, a ligand utilized by W. S. Knowles and employed in the Monsanto synthesis of L-DOPA. Traditionally, *P*-stereogenic molecules are obtained by resolution methods employing chiral auxiliaries. Therefore, direct stereoselective strategies are highly desirable. Tanaka reported the enantioselective synthesis of *P*-stereogenic aryl-alkynylphosphine oxides by desymmetrisation of dialkynylphosphine oxides *via* a Rh-catalysed [2+2+2]-cycloaddition (Scheme 2).[15] The chiral phosphine oxides were directly obtained in excellent yields and with high enantioselectivity.



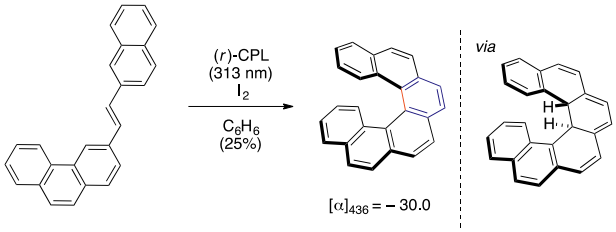
Scheme 2 Desymmetrisation of dialkynylphosphine oxides by a Rh-catalysed arene-forming [2+2+2]-cycloaddition.

Desymmetrisation reactions thus demonstrate the potential to expand on traditional arene modification methods and the feasibility to control stereocentre configuration by novel stereoselective arene-forming methodology. From readily accessible starting materials, enantioenriched products with *C*- and *P*-stereocentres at the benzylic position of the new aromatic rings became available in a single step. Since this strategy is not inherently limited to control the configuration of benzylic stereocentres, remote chirality centres would further expand the scope of stereoselective arene formation.

3. Helical chiral compounds

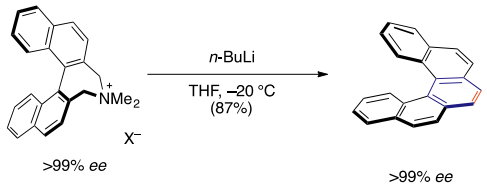
A characteristic of stereocontrolled aromatic ring assembly is that it embraces practically all different types of chirality units. Besides control over stereocenter configuration, it also allows to govern the shape of extended chiral molecules, a feature that is distinctively illustrated in the synthesis of helicenes. Helical structures are an often-encountered motif in nature, where the helical arrangement of biomolecules results from intra- and intermolecular interactions, such as in nucleic acid tertiary structure. Nevertheless, they are not only of importance in biological systems, but also for functional compounds that require a well-defined topology. As a π-conjugated *ortho*-fused, angularly arranged polycyclic aromatic hydrocarbons, helicenes are a particularly attractive class of conformationally restricted structures. The spatial arrangement of the *ortho*-annulated rings results in screw-shaped molecular entities with a sense of rotation and hence helical chirality. Furthermore, configurationally stable helicenes often show exceptionally large optical rotation values. As resolution or separation of stereoisomeric mixtures impacts the accessibility of the desired helicene enantiomer, their selective synthesis is highly anticipated.

The strategies to control the configuration of helical chiral compounds by arene-forming methods are usually distinct from the enantiotopic group selective methods that control stereocentre configuration. Instead, configurationally more dynamic starting materials are often converted into the rotationally restricted helicenes with catalyst-, reagent- or substrate enantioinduction. The stereochemical information of other chirality units is thereby transferred into the helix sense of the products. However, in preceding seminal studies by Kagan and Calvin on the photocyclisation of (*E*)-configured stilbene precursors with circularly polarised light that was followed by arene-forming oxidation, a measurable, but low stereoinduction was attained during the formation of helicenes (Scheme 3).[16,17] Irradiation of a racemic mixture of the helicene confirmed that enantioenrichment is originating from the photocyclisation/oxidation cascade and is not the result of photoresolution or selective photodestruction. While these results constitute a pioneering early contribution in the field of absolute stereoselective arene-forming synthesis, with many interesting possible implications,[18] the low levels of stereoenrichment with circularly polarised light does not provide a practical route to access isomerically enriched helicenes.



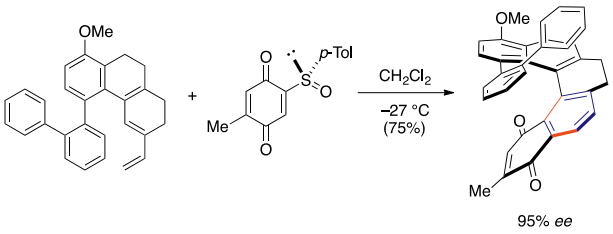
Scheme 3 Absolute stereoselective synthesis of [6]helicene with right circularly polarized light = (*r*)-CPL *via* arene-forming photocyclisation/oxidation sequence.

Contrariwise, high levels of stereocontrol are achieved in substrate-controlled diastereoselective arene-forming photocyclisation reactions using chiral auxiliaries or tethers. To prevent [2+2]-dimerisations in photocyclisations, typically high dilution techniques are employed. To enable scale-up, several research groups have therefore developed alternative methodologies to access large amounts of enantiomerically enriched helicenes. An expedient approach is to use enantiomerically enriched starting materials to perform stereospecific helicene forming arene formation. Axially chiral compounds are particularly suitable starting materials, since their accessibility in enantiomerically enriched form is well advanced. The axially chiral compounds are thus converted into helical chiral products in an arene forming reaction that results in an axial-to-helical chirality exchange. For instance, Stará and Starý synthesised (*P*)-pentahelicene in high yield and enantiospecificity by a *n*-BuLi induced Stevens-rearrangement-1,2-elimination sequence of axially chiral binaphthyl ammonium salts (Scheme 4).[19] Due to the low configurational stability of pentahelicenes, the reaction was performed at low temperature, which allowed to achieve a highly stereospecific formation of >99% enantiomerically enriched product.



Scheme 4 Stereospecific Stevens-rearrangement, followed by 1,2-elimination leading to >99% enantiomerically enriched pentahelicenes.

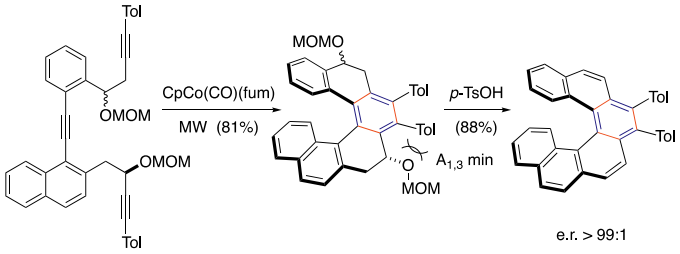
Helicenes that do not racemise over a broad temperature range are particularly desirable, since they can be employed in various areas of application, such as for optoelectronics, as helically chiral ligands or structurally well-defined organocatalysts. The configurational stability of helicenes can either be increased by terminal *peri*-substitution (towards the helix axis) or by the preparation of longer helical aromatic systems. The stereoselective construction of a rigid aromatic ring offers a means to combine both strategies. By inter- or intramolecular arene-fusion, a new conformationally restricted aromatic backbone with various substitution patterns can be created. For instance, a [5]helicene with a high level of configurational stability due to *peri*-substituents was prepared by Carreño and coworkers in a auxiliary-stereocontrolled Diels-Alder/elimination/oxidation sequence of chiral sulfinyl quinones[20] with vinyl tetrahydrophenanthrenes (Scheme 5).[21]



Scheme 5 Simultaneous control of helical and axial chirality in a chiral reagent controlled arene-forming Diels-Alder/elimination/oxidation sequence.

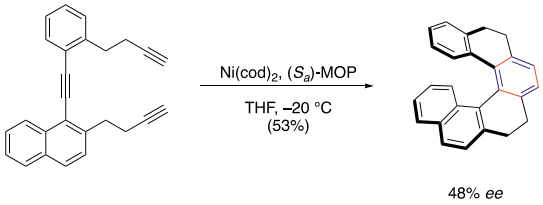
The stereodynamic diene substrate hence allowed a dynamic kinetic resolution to control simultaneously the helix sense and the configuration of the stereogenic axis of the product during arene-formation. Notably, only a single stereoisomer of the (2-biphenyl)-substituted tetrahydro[5]helicene quinone was obtained by this arene forming reaction with an excellent level of enantioselectivity.

An approach based on a point-to-helical chirality conversion governed by a 1,3-allylic strain during a [2+2+2]-cycloisomerisation was recently described by Stará, Starý and co-workers (Scheme 6).[22] Under thermodynamic control, two tetrahydrohelicene-diastereoisomers of uniform helicity are obtained exclusively. The peri-hydroxy group serves as a traceless selectivity-determining moiety and is eliminated together with a second stereochemically inconsequential hydroxy-group during the acid promoted arene formation, thus delivering exclusively one enantiomer of the rigid aromatic [6]helicenes. The synthesis of the precursors was based on a reliable lipase-catalysed resolution of different propargylic alcohols. This strategy thus permitted to accomplish various substitution patterns and even the incorporation of a heterocycle into the helicenes with high efficiency.



Scheme 6 Arene-forming [2+2+2]-cycloisomerisation-elimination sequence to give enantiomeric enriched, fully aromatic helicenes.

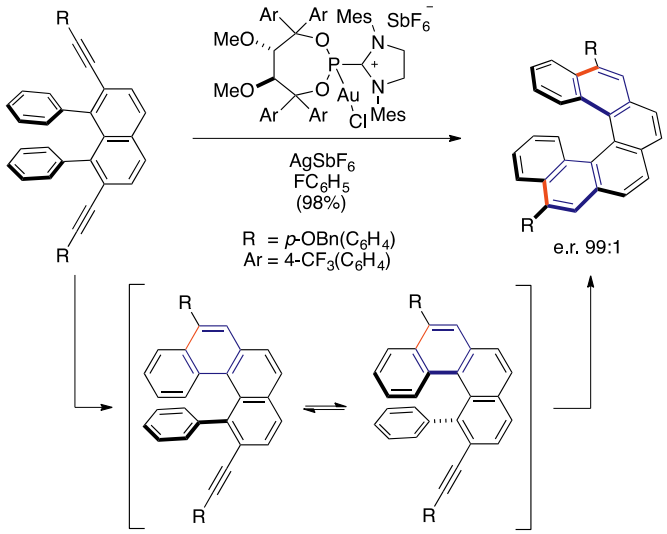
As stereospecific reactions require stereoisomerically enriched starting materials, the utility of a method is directly correlated to the accessibility of the chiral precursors in isomerically enriched form. The development of catalytic stereoselective methods is therefore highly desirable. In this respect, transition metal catalysed stereoselective cycloisomerisation of triynes proved to be a remarkably efficient to access enantiomerically enriched helicenes. In seminal studies by Stará and Starý, a nickel catalysed intramolecular stereoselective arene formation by a [2+2+2]-cycloaddition delivered tetrahydro-[6]helicenes in enantioenriched form (Scheme 7).[23] By recognizing the higher reactivity of $Ni(cod)_2$-catalysts compared to a $CpCo(CO)_2$-based system, the reaction could be carried out at low temperature. This allowed to employ the axially chiral (S_a)-MOP ligand to induce the stereoselection to give the tetrahydro-[6]helicene with 48% enantiomeric excess. In a subsequent step, the obtained tetra-hydrohelicenes were oxidised with DDQ to give the all-benzoid helicenes.



Scheme 7 Enantioselective arene-forming [2+2+2]-cycloaddition.

The capacity of this methodology was impressively demonstrated by the synthesis of various helicene-type molecules up to [11]helicene-like scaffolds.[24,25]

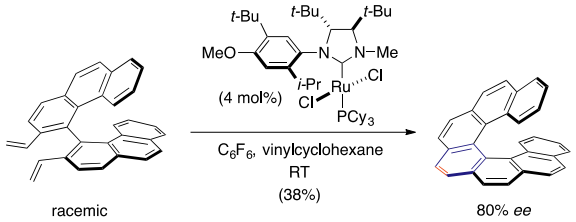
While [2+2+2]-cycloadditions have proven to be exquisite synthetic tools to stereoselectively prepare helical chiral molecules by arene formation, they require an additional oxidation or elimination step to access fully aromatic helicenes. A direct gold-catalysed intramolecular and enantioselective double hydroarylation of 1,8-diphenylnapthalene-diynes was recently described by Alcarazo and co-workers to obtain fully aromatic [6]helicenes (Scheme 8).[26] To address the challenge of stereocontrol with the linearly coordinated Au(I)-catalysts, a TADDOL-type cationic ancillary ligand was developed. Consequently, the two-fold arene-forming cyclisation proceeded in high yield and with excellent stereocontrol.



Scheme 8 Gold-catalysed two-fold hydroarylation *via* configurationally dynamic intermediary [4]helicenes.

With a half-life of five seconds at –20 °C, the dynamic processes of the intermediary [4]helicenes suggests that stereoselection takes place in the second hydroarylation step. Considering the overall reaction time, it was thus concluded that the chiral catalyst reacts preferentially with one of the rapidly interconverting intermediate stereoisomers. Enantio-enrichment would therefore take place by a dynamic kinetic resolution of the intermediary [4]helicenes.

Kinetic resolution, where the reaction rate for the conversion of one enantiomer over the other differs as consequence of the catalyst's chirality, enables to partially convert racemic substrates to isolate products and remaining substrate in enantioenriched form. A remarkable kinetic resolution based on a stereospecific arene-forming ring-closing metathesis was described by Collins and Grandbois for the preparation of fully aromatic helicenes starting from axially chiral divinyl precursors (Scheme 9).[27]



Scheme 9 Stereospecific kinetic resolution by an arene-forming ring closing metathesis to form all-carbo-[7]helicenes.

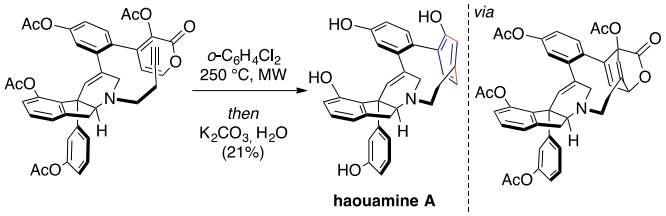
Due to the high catalytic activity of the chiral Ru-catalysts, the reactions to form [7]helicenes could be conducted at room temperature. With an advantageous solvent effect of hexafluorobenzene, vinylcyclohexane as an additive, a yield of 38% and optical purity of 80% enantiomeric excess was achieved.

Overall, the sense of rotation of helical chiral compounds can be efficiently controlled by stereoselective arene-forming reactions. The catalyst controlled enantioselective synthesis of all-benzoid helicenes is impressively accomplished by [2+2+2]-cycloaddition strategies. Furthermore, the intramolecular hydroarylation emerged as a novel approach to directly access all-benzoid helicenes by enantioselective arene formation. Besides the catalytic methods, substrate and reagent controlled strategies enabled to stereospecifically transfer axial- or point-chirality into the helix sense by the de novo construction of an aromatic ring.

4. Planar chiral compounds

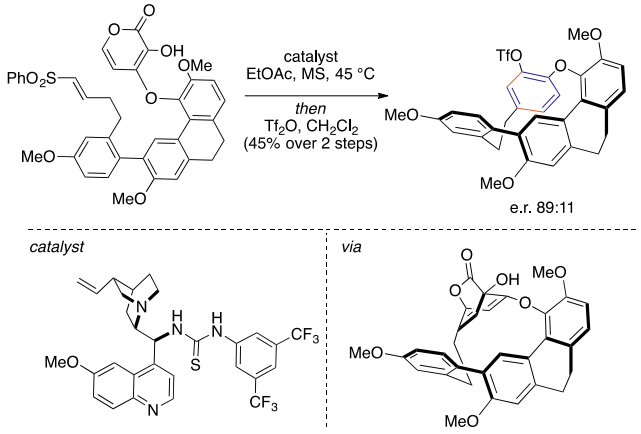
Planar chiral motifs are frequently encountered in natural products and are of increasing importance in synthetic chemistry. As structural entity, chirality planes result from confined adjacent groups that prevent the plane to lie in a symmetry plane. An exemplary class of planar chiral molecules are the cyclophanes, which consist of at least one aromatic moiety bridged by one or more alkyl-chains. These aromatic moieties are at well-defined spatial positions in relation to the other components of the molecular scaffold as a result of transannular interactions. Hence, the specific assembly of the aromatic rings in the skeleton allows to control their precise spatial orientation in stereoselective arene-forming reactions.

The de novo construction of aromatic rings that allows the stereoselective preparation of planar chiral systems is illustrated by the total synthesis haouamine A by Baran and co-workers (Scheme 10).[28] In a pyrone-alkyne Diels-Alder reaction, the desired cyclophane stereoisomer was obtained with a high level of substrate-control. With its boat like conformation, the intermediary cyclohexadiene serves as a prearranged precursor to give the desired curved aromatic structure upon decarboxylation. The arene formation strategy hence represents a novel approach to achieve a cyclisation and allowed the stereoselective synthesis of this strained congested cyclophane with a bent aromatic ring.



Scheme 10 Diastereoselective pyrone-alkyne Diels-Alder reaction in the synthesis of haouamine A.

For the total synthesis of the natural product (+)-cavicularin without other stereogenic units, Beaudry has impressively demonstrated a low temperature vinyl-sulfone-pyrone Diels-Alder reaction by means of a catalyst-controlled enantioselective formation of an aromatic ring (Scheme 11).[29] By employing a thiourea-substituted cinchona-alkaloid catalyst, a high level of enantioinduction was achieved. Also here, the strained macrocycle is formed *via* a cyclohexadiene derivative, which selectively forms an aromatic ring to give the desired product with an enantiomeric ratio of 89:11.

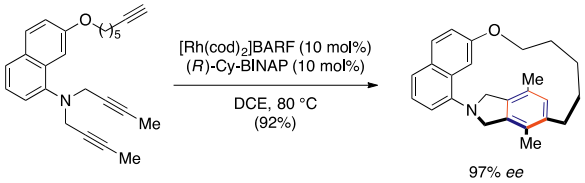


Scheme 11 Catalyst-controlled arene-forming enantioselective pyrone-olefin Diels-Alder reaction in the synthesis of (+)-cavicularin.

Natural product campaigns impressively illustrate the potential of the stereoselective arene formation methodology for target

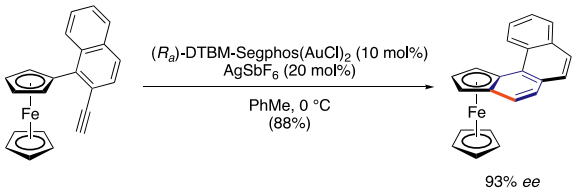
specific synthesis. Beyond naturally occurring compounds, a wide variety of cyclophanes and other structurally well-defined planar chiral molecules such as metallocenes have received considerable interest and were prepared by transition metal catalysed [2+2+2]-cycloaddition or cycloisomerisation reactions.

For instance, Shibata accomplished a remarkable intramolecular arene-forming cyclotrimerisation of various triynes to obtain cage-type macrocyclic molecules (Scheme 12).[30] The Rh-catalysed [2+2+2]-cycloaddition of a triyne branched by 8-amino-2-naphthol as a rigid tether thus gave the corresponding cyclophane with excellent yield and stereoselectivity.



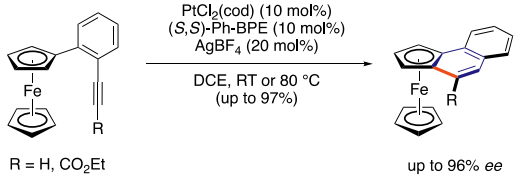
Scheme 12 De novo synthesis of an aromatic ring by a [2+2+2]-cycloaddition for the synthesis of a cage-type tripodal cyclophane.

Planar chiral molecules are also increasingly important for catalyst design. Especially chiral ferrocene derivatives are particularly privileged scaffolds, as exemplified by the pioneering Josiphos-ligand, which was successfully applied for most efficient catalyst systems in the large-scale hydrogenation in the synthesis of (*S*)-metolachlor. Such planar chiral ferrocenes have recently become directly accessible by stereoselective arene-forming reactions. Urbano and Carreño developed an Au(I)-catalysed cycloisomerisation to afford planar chiral ferrocene derivatives by a highly selective arene forming reaction (Scheme 13).[31] The stereoselective de novo construction of an aromatic ring hence provides a means for the desymmetrisation of the starting material. The required substrate was obtained by a Suzuki-cross-coupling of ferrocene boronic acid with 1-bromo-2-naphthaldehyde, followed by a Seyferth-Gilbert homologation with the Ohira-Bestmann reagent. After initial cycloisomerisation attempts by Pt-catalysis, a chiral cationic Au(I)-catalysis was employed. With a bulky bidentate phosphine ligand, excellent yields and selectivities were accomplished due to the mild reaction conditions.



Scheme 13 Planar chiral ferrocene prepared selectivity by a Au(I)-catalysed arene-forming cycloisomerisation.

Similar naphthalene and anthracene-merged ferrocene products were obtained by a related desymmetrising aromatization method reported by Shibata (Scheme 14).[32] In a cationic Pt-catalyzed cycloisomerisation using a chiral BPE ligand, excellent yields and enantioselectivities were achieved. Preliminary mechanistic studies suggest activation of the alkyne moiety followed by an arene-forming 6-endo-dig cyclisation giving the fully aromatic planar chiral ferrocenes.



Scheme 14 Pt-catalysed arene-forming cyclotrimerisation to give an enantioenriched planar chiral ferrocene.

Even substitution at the terminal alkyne was tolerated. The direct functionalisation in close proximity to the metallocene is ideal for the design of new ligands, rendering this versatile strategy particularly promising.

In summary, strained chiral cyclophane macrocycles are accessible by the pyrone-Diels-Alder strategy as illustrated in elegant total syntheses of planar chiral natural products. Furthermore, [2+2+2]-cycloadditions allow the preparation of cage-like tripodal cyclophanes by the de novo construction of an aromatic ring. These methods were complemented by various methods, including the recently developed hydroarylations that are effective to stereoselectively obtain planar chiral ferrocenes by arene formation.

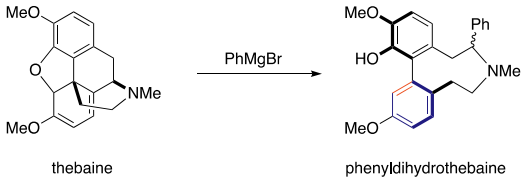
5. Axially chiral compounds

Similar to structurally well-defined planar chiral ligands, axially chiral compounds also allow for a precise spatial positioning of groups and are hence of particular significance in current catalyst design. Compared to the frequent use of axially chiral molecules, their stereoselective preparation remains challenging considering the structural diversity of atropisomers. In this respect, the enantioselective de novo construction of aromatic rings offers wide-ranging strategies to prepare a broad variety of axially chiral compounds. Direct access to diverse stereoisomerically enriched atropisomers is also essential to provide novel scaffolds for the development of new stereoselective reactions and functional molecular systems. Nevertheless, the majority of the contemporary stereoselectively prepared atropisomers are axially chiral biaryls with a high degree of *ortho*-substitution that prevent rotation and allow the isolation of the individual conformers. Beyond catalyst design, axially chiral scaffolds are also of particular importance in various areas of application such as natural product synthesis, medicinal chemistry or material science. For natural products and active pharmaceutical ingredients, atropisomerism is remarkably well-represented. Besides biaryls, axially chiral amides are increasingly encountered and utilized, specially in the area of medicinal chemistry.

It is pertinent to note that next to stereoselective arene-forming reactions, various sophisticated methods for the

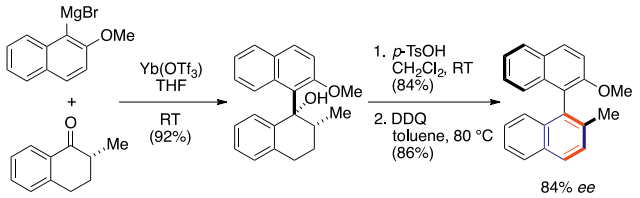
atroposelective synthesis of diverse axially chiral compounds have been developed. For instance, desymmetrization reactions, kinetic resolution, the direct formation of the stereogenic axis by cross coupling, or the atroposelective conversion of stereodynamic compounds allow to access a broad range of enantioenriched and configurationally stable axially chiral products. Nevertheless, stereoselective arene-formation evolved to a remarkably versatile strategy to synthetize diverse axially chiral molecules, but are often not intuitively considered at first.

In seminal investigations, Berson recognized that the selective formation of a rotationally restricted biaryl bond is feasible by a central-to-axial chirality conversion upon treatment of the opiate alkaloid thebaine with phenylmagnesium bromide (Scheme 15).[33] This remarkable stereospecific transformation benefits from arene-formation as a driving force, delivering the product as a mixture of two diastereoisomers that differ in the configuration of the stereocentre. Berson assigned the absolute configuration of the axially chiral product and suggested to use this compound as a standard to determine the configuration of other optically active biarylic systems using polarimetry.[34] However, since small changes in the substitution pattern of biaryls can influence the sense of optical rotation, X-ray crystallography has become the most frequently utilized method for the determination of the absolute configuration.



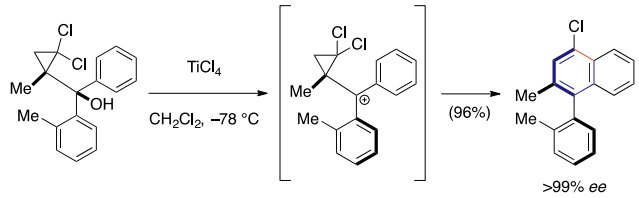
Scheme 15 PhMgBr induced arene formation of thebaine leading to the axially chiral biaryl phenyldihydrothebaine.

The approach to convert central chiral compounds into axially chiral molecules has evolved to a well-established strategy. The enantiospecific transformations are thereby either directly taking place during arene formation or in an sequence of steps, as exemplified by Miyano's elegant synthesis of tetra-*ortho*-substituted binaphthalenes (Scheme 16).[35] Enantiomerically enriched (*R*)-2-methyl-1-tetratalones were employed as electrophiles in combination with organometallic nucleophiles. The stereochemical outcome is thereby controlled by the ketone substrate bearing a stereocenter in α-position. The addition of Grignard reagents thus provided the desired carbinols, however with initial competing α-deprotonation. This side reaction was prevented by pre-formation of the corresponding ytterbium reagents that allow a high yielding 1,2-addition. Subsequent acidic dehydration and arene formation with DDQ gave enantioenriched tetra-*ortho*-substituted binaphthalenes. The point-to-axial exchange strategy provided the binaphthalenes in good yields and with an enantiomeric excess of up to 84%.



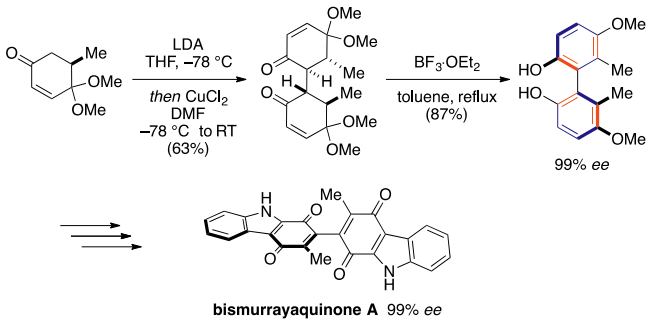
Scheme 16 Point-to-axial chirality conversion in an acid induced elimination followed by oxidative arene formation providing enantioenriched axially chiral binaphthalenes.

A conceptually different strategy that encompasses the intramolecular arene-forming cyclopropane-opening was developed by Nishii and Tanabe, directly giving access to atropisomerrically enriched biaryls without succeeding dehydration and oxidation steps (Scheme 17).[36] With chiral *gem*-dihalocyclopropanes employed as substrates, Lewis acid addition promotes arene forming reaction with efficient chirality conversion. A mechanistic rational was proposed that involves steric repulsion of the cyclopropyl methyl-group with the *ortho*-methyl phenyl substituent. Therefore, subsequent carbocation formation proceeds stereospecifically, while planarization and shortening of the C–C-bonds leads to higher configurational stability of the stereogenic axis. Cyclopropane ring opening, Friedel-Crafts-type cyclization and arene formation by a $TiCl_4$-promoted elimination provides the axially chiral arylnaphthalenes in excellent yields and enantioselectivities within a single step.



Scheme 17 Direct transformation of optically active dihalocyclo-propanes into chiral biaryls by a Lewis-acid induced arene formation.

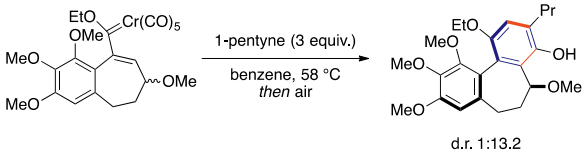
The strategy to transfer point-to-axial chirality in arene-forming reactions is not limited to specific starting materials and was also successfully applied in various natural product syntheses. In the elegant total synthesis of bismurrayaquinone A, Thomson applied a gram-scale oxidative dimerisation of an enantiomerically enriched enone to give the corresponding dione with excellent stereospecificity (Scheme 18).[37] An axially chiral biaryl was thus obtained after Lewis acid induced arene formation with efficient transfer of the stereochemical information. Subsequent bromination, Buchwald-Hartwig amination and carbazole formation was followed by oxidation giving the natural product bismurrayaquinone A in high enantiomeric purity.



Scheme 18 Substrate-controlled enantioselective Lewis-acid induced arene formation in the total synthesis of bismurrayaquinone A.

Furthermore this strategy embraced a broad scope with enones bearing aryl-groups in β-position that were coupled and efficiently transformed into an aromatic ring to give sterically congested enantiomerically enriched biaryls through traceless central-to-axial chirality conversion.[38]

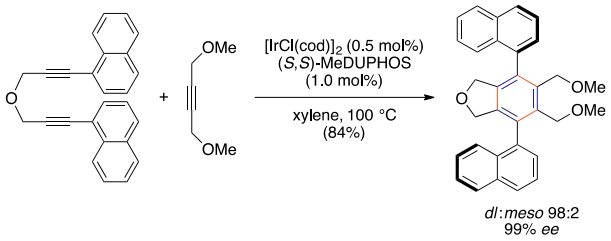
An approach to differentiate the two aromatic rings by a de novo aromatic ring construction strategy was reported by Wulff, describing a stereospecific benzannulation of chiral Fischer carbene complexes with 1-pentyne (Scheme 19).[39] While racemic starting material was employed in this study, a high level of diastereoselectivity for the axially chiral products was obtained after oxidative demetalation.



Scheme 19 Stereospecific synthesis of biaryls from chiral chromium carbene complexes by the de novo construction of an aromatic ring.

While diastereoselectivity can be controlled by the inherent substrate-bias for one diastereoisomer, substrate-stereocontrolled methods towards non-racemic atropisomers by a central-to-axially chirality conversion require an efficient synthesis of enantioenriched substrates. Therefore, catalyst stereoinduction is highly desirable and several conceptually intriguing catalytic arene-forming atroposelective reactions have been developed.

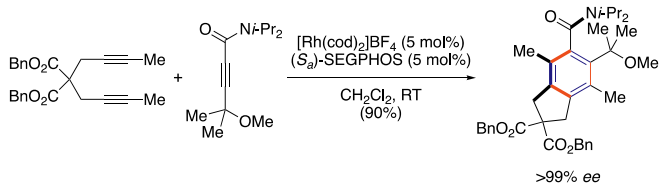
As for the previous stereogenic units, the catalyst-stereocontrolled [2+2+2]-cycloaddition is again an outstanding strategy for the synthesis of axially chiral molecules. This was impressively demonstrated by Shibata with the simultaneous atroposelective formation of two rotationally restricted bonds giving axially chiral teraryls in one step (Scheme 20).[40] With MeDUPHOS as chiral ligand and an Ir-catalyst loading decreased to 0.5 mol%, the desired teraryls were obtained in high yields and with excellent enantioselectivity. The prospect of employing symmetric molecules as starting materials and to break the symmetry during the final arene-forming step, allows to take advantage of bidirectional precursor synthesis. Hence, the capability of the [2+2+2]-arene-forming strategies is seamlessly illustrated by the straightforward stereoselective synthesis of these axially chiral linearly arranged *p*-teraryls directly from readily accessible symmetric substrates.



Scheme 20 Arene-forming [2+2+2]-cycloaddition of a central aromatic ring to enantioselectively give axially chiral teraryls.

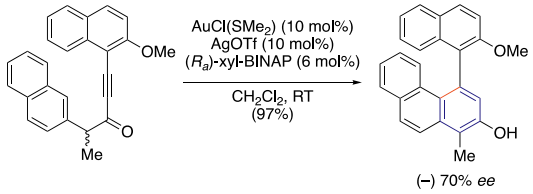
Remarkably, this approach was expanded by employing tetraynes and octaynes as starting materials giving axially chiral polyaryls with four and eight consecutive rotationally hindered bonds in high enantiomeric purity.[41] The asset of this method is that exclusively one diastereoisomer out of multiple possibilities is formed. An enthralling challenge to be tackled is hence the individual addressability of each stereogenic axis to control the structurally well-defined topology of individual atropodiastereoisomers.

Besides the frequently encountered and utilized axially chiral biaryl motif, the ability of the stereoselective de novo construction of an aromatic ring allows to synthesise other sterically congested scaffolds, such as rotationally hindered and hence configurationally stable aromatic amides. Since these compounds can be restricted in rotation not only about the Ar–CO, but also about the N–CO and R–N bonds, the prediction and study of their interplay during conformational changes is fascinating by itself. Despite their increasing importance in medicinal chemistry,[43] the accessibility of enantiomerically enriched axially chiral amides have mostly relied on kinetic resolutions, conglomerate crystallisations or the stoichiometric use of chiral reagents or substrates. Expedient catalyst controlled stereoselective methods therefore pave the way also for a better understanding of the individual rotational behaviour of partially stereodynamic or configurationally stable atropisomeric multi-axis systems. Due to the aromatic ring as a rigid backbone together with its firmly oriented *ortho*-substituents, stereoselective arene formation often allows unified strategies across the different classes of atropisomers. In a pioneering effort, Tanaka extended the scope of the atroposelective arene-forming [2+2+2]-cycloadditions to synthesise axially chiral amides by fusing symmetric *N*,*N*-dialkylalkynylamides with 1,6-diynes under Rh-catalysis (Scheme 21).[42] This selectively afforded benzamides with a rotationally hindered aryl-carbonyl bond and remarkable enantioselectivities and high yields were achieved by the catalyst-controlled assembly of the highly substituted aromatic backbone.



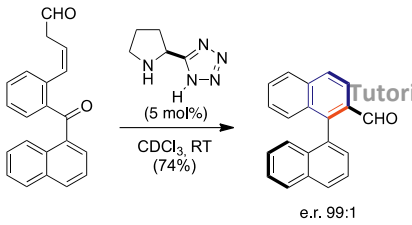
Scheme 21 Direct access to axially chiral amides by a Rh-catalysed arene-forming [2+2+2]-cycloaddition.

To assert chemoselectivity in the [2+2+2]-cycloadditions, the alkynes are tethered and result in the formation of a ring vicinally connected to the new aromatic system. In contrast, in the Au(I)-catalysed intramolecular cycloisomerisations, the alkyne reacts directly with the arene to form a new aromatic ring. This approach was elegantly utilized by Tanaka for the atroposelective synthesis of phenanthrenes *via* a stereoselective arene-forming hydroarylation of racemic propargylic ketones (Scheme 22).[44] Unsymmetrically substituted biaryls were obtained in exquisite yields and enantioselectivities of up to 70% enantiomeric excess were achieved.



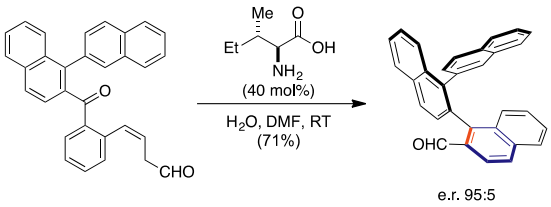
Scheme 22 Au-catalysed intramolecular arene-forming hydroarylation to give enantioenriched axially chiral phenanthrenes.

Typically, catalyst-controlled atroposelective arene-assembly methods rely on transition metals. The requirement for rare elements can be detrimental in developing chemical processes and particularly in the synthesis of active pharmaceutical ingredients, the removal of the transition metals to the required levels is often laborious. Catalysis using small organic molecules therefore holds great promise, not only from a conceptual, but also from an economic and ecological perspective. Considering the reliability of aldol methodology, our group developed an organocatalysed arene-forming aldol condensation to obtain axially chiral binaphthalene carbaldehydes under mild conditions and with a high level of stereocontrol (Scheme 24).[45] With a secondary amine catalyst, the unsaturated ketoaldehydes are activated by enamine formation, which react stereoselectively in an intramolecular aldol addition. Ensuing *in situ* dehydration directly leads to arene formation, providing enantiomerically enriched binaphthalenes with an atroposelectivity of up to 99:1 and a yield of up to 89%.



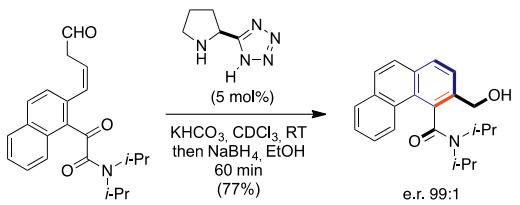
Scheme 24 Secondary amine catalysed stereoselective arene-forming aldol condensation to give 1,1'-binaphthalene-2-carbaldehydes.

The aptitude to construct a well-defined molecular architecture is of notable importance for the design of functional synthetic systems. It is hence essential to further improve systematic bottom-up approaches to access materials with unique topologies and properties. However, precise stereocontrol of individual stereogenic axes in atropisomeric oligomer synthesis remains challenging. In this context, our group studied a strategy to access individual stereoisomers of 1,2-naphthylene oligomers (Scheme 25).[46] Iterative addition of an organometallic building block and consecutive catalyst- or respectively substrate-controlled stereoselective arene-forming aldol condensation gave access to structurally well-defined oligo-1,2-naphthylene stereoisomers. Intriguingly, for the configurationally stable stereoisomer with a secondary helical structure, a racemisation barrier of 154 kJ mol^{-1} was measured. Hence, the stereoselective de novo construction of aromatic rings is a viable strategy to control the configuration of stereogenic axes of atropisomeric, *ortho*-trisubstituted arylenes.



Scheme 25 Synthesis of an atropisomeric 1,2-ternaphthalene carbaldehyde by the stereoselective arene-forming aldol condensation.

Besides the axially chiral oligo-1,2-naphthylenes, the secondary amine catalysed arene-forming aldol condensation enabled the synthesis of axially chiral amides. By employing *ortho*-substituted arylglyoxylic amides as substrates, the amine catalysed atroposelective arene-forming aldol condensation expediently delivered axially chiral amides (Scheme 26).[47] The stereoselective arene formation was coupled with an *in situ* reduction of the intermediary carbaldehydes using $NaBH_4$, which increased the barriers of rotation about the Ar–CO bond, thus allowing to expand the scope of the reaction.



Scheme 26 Secondary amine catalysed stereoselective arene-forming aldol condensation yielding axially chiral aromatic amides.

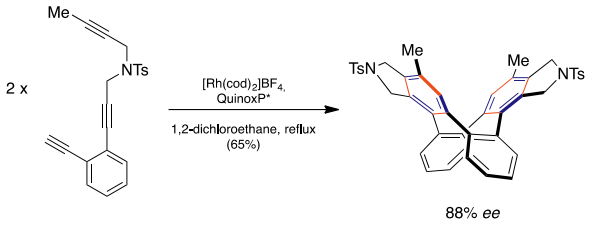
Organocatalytic methods thus complement the established transition-metal catalysed stereoselective arene-forming reactions for the synthesis of axially chiral molecules. Besides the catalytic methods, the substrate controlled stereospecific reactions remain as a viable strategy in case the chiral starting materials are readily available in enantioenriched form. In context of the stereoselective arene-forming strategies, the synthesis of axially chiral molecules constitutes the scaffold that was addressed by a majority of synthetic studies, reflecting the importance of these compounds. The structural diversity of axially chiral compounds and the prospects of controlling multi-axis systems stimulate the development of conceptually unconventional synthetic strategies that nourish this vibrant field.

6. Curved polyaromatics

Recently, the ability of arene-forming methods to control point, helical, planar, and axial chirality was extended to control the chirality of curved polyaromatics. This underlines the potential of arene-forming reactions to control the entire shape of a molecule in order to escape the aromatic flatland, with which arenes are often associated. Curved polyaromatics constitute an exciting emerging class of graphene-like structures and have already attracted considerable interest. The field of stereoselective synthesis of curved chiral structures, showing so called inherent chirality, is however still in its infancy and the specific virtues of these structures were just recently recognized. The stereoselective arene-forming methodology is successfully applied to access inherent chiral molecules and allows progressing this intriguing novel area of research. By formally introducing one or several smaller or larger ring fragments into a graphene framework, curved molecules are accessible. The insertion of smaller rings (<six-membered) provides bowl shaped structures, while the introduction of larger rings (>six-membered) lead to saddle-shaped structures. By the definition of Schiaffino and Szumna,[11] inherent chirality can be ascribed to curved structures that are free of any vertical symmetry planes in their hypothetic planar 2D-representations. Inherent chiral compounds show the known properties of other chiral structures i.e. optical activity, circular dichroism and specific interaction in a chiral environment. Racemisation of inherent chiral molecules can take place through inversion of the curvature. Fascinatingly, the configurational stability of these molecular scaffolds can be exceedingly high and therefore offers a unique spatial arrangement even at elevated temperatures. The control over the curvature and thus the spatial arrangement of polyaromatics was therefore successfully achieved by stereoselective arene-forming methods.

Saddle-shaped tetraphenylenes consist of four *ortho*-annulated aromatic rings, which form a central eight-membered ring. While unsubstituted tetraphenylene is not chiral (D_{2d}-symmetry), substitution can give molecules displaying inherent chirality. Their synthesis is commonly accomplished by oxidative dimerisation of di-*ortho*-metalated biphenylenes. However, direct stereoselective synthesis by this strategy led so far only to moderate enantioinduction. Therefore, tedious resolution techniques are usually required to obtain enantiomerically enriched samples of this interesting class of chiral molecules.

A novel stereoselective arene-forming strategy by Shibata enables to prepare chiral substituted tetraphenylenes in high enantiopurity from readily available starting materials (Scheme 27).[48] The formation of a metallacyclopentadiene and a consecutive intermolecular dimerisation with the terminal alkyne of the second molecule leads to an initial arene-formation. This sets the stage for a subsequent intramolecular [2+2+2]-cycloaddition, stereoselectively creating another new aromatic ring and simultaneously closing the non-planar eight-membered ring responsible for the curvature of the resulting chiral tetraphenylene. Various substituted tetraphenylenes were obtained in excellent enantioselectivities with of up to 99% *ee*.



Scheme 27 Enantioselective rhodium-catalysed consecutive double [2+2+2]-cycloaddition to give saddle-shaped tetraphenylene by arene formation.

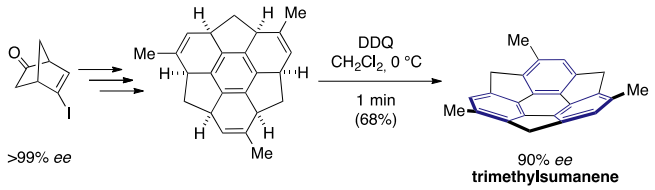
The enantioselective synthesis of a different type of inherent chiral molecules, the tribenzothiepins, was recently accomplished by Shibata in an arene-forming [2+2+2]-cycloaddition (Scheme 28).[49] Tribenzothiepins consist of a central, unsaturated, sulfur containing seven-membered non-planar heterocycle, which is fused with three benzene rings. Together with other analogous heteroatom containing tricyclic structures, the corresponding dibenzothiepins constitute an important class of active pharmaceutical ingredients mainly used as antidepressants. In contrast, the synthesis and properties of corresponding inherent chiral tribenzothiepins have only recently been examined in more detail. Shibata accomplished their first direct catalytic stereoselective synthesis by a Rh-catalysed intermolecular [2+2+2]-arene formation of unsymmetrical substituted diphenyl-sulfide

tethered diynes with dimethyl acetylenedicarboxylate. The products were obtained in good to excellent yields and in selectivities of up to 93% enantiomeric excess.

Scheme 28 Synthesis of tribenzothiepins by an intermolecular arene-forming [2+2+2]-cycloaddition.

In case of the tribenzothiepin, the energy of the saddle inversion barrier was measured at 80 °C in xylene and calculated to be 29.1 kcal mol^{-1}, which corresponds to an estimated half-life for racemisation of 9 years at 20 °C. With the same cycloaddition strategy, the scope was expanded to the first reported synthesis of corresponding tribenzoselenepins.

The synthesis of trimethylsumanene, which represents a member of another class of inherent chiral compounds, the chiral buckybowls, was accomplished by the group of Sakurai (Scheme 29).[50] The precursor for the stereospecific oxidative arene formation was prepared in four steps from an enantiomerically enriched halonorbornene. A regioselective cyclotrimerisation and conversion of the carbonyl groups to methyl-substituted olefins was followed by a ring-opening/closing metathesis sequence. Oxidation at 0 °C with DDQ gave the configurationally labile, enantioenriched buckybowl trimethylsumanene within one minute and an efficient direct point-to-inherent chirality conversion. Furthermore, a low racemisation barrier of the methyl-substituted buckybowl was estimated (21.6 kcal mol^{-1}) by following the signal-decay in circular dichroism spectra of a solution of the enantioenriched polyaromatic in CH_3CN at 10 °C. Selective *exo*-substitution at the dibenzylic positions with TMS increased the bowl-to-bowl inversion barrier and the enantiomeric excess could indirectly be determined (90% *ee*) by ^{1}H-NMR diastereomeric ratio analysis.



Scheme 29 Stereospecific arene formation by a central-to-inherent-chirality conversion to give an enantioenriched C_3-symmetric buckybowl.

The enantioselective preparation of curved polyaromatic structures is an emerging field with a prospect for inventive synthetic concepts. Due to their generality across different stereochemically complex scaffolds, stereoselective arene-forming methodology hold great promise for the preparation of novel chiral structures to engineer novel functional organic molecules.

7. Conclusions

While often counterintuitive, the stereoselective arene-forming reactions offer numerous possibilities to synthesise structurally diverse molecules with different chirality units and often with high stereoselectivity. With reliable stereoselective arene formation strategies, various opportunities to design and construct novel aromatic entities with a high degree of structural diversity have become viable. These strategies perfectly expand and complement arene chemistry that enables transformations around the aromatic system. The construction of the aromatic core synthesis itself from readily available fragments allows an unconventional retrosynthetic perspective to tackle complex molecular systems. It enables the convergent stereoselective synthesis of often sterically congested and stereochemically complex scaffolds with helical, planar, axial or inherent chirality. Moreover, it allows to stereoselectively control stereocentre-configuration by enantiotopic group selective processes. A prospective field to apply the stereoselective arene formation strategy is the synthesis of chiral mechanical interlocked molecules. These molecular scaffolds constitute the basic components of a rapidly expanding research area. It can be expected, that the stereoselective arene-formation methodology will continue to fascinate and to contribute to the synthesis of well-defined molecular architectures.

Conflicts of Interest

There are no conflicts to declare.

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Notes and references

1 K. Tanaka, *Chem. Asian J.*, 2009, **4**, 508–518.
2 S. Li, L. Zhou, K.-I. Kanno and T. Takahashi, *J. Heterocyclic Chem.*, 2011, **48**, 517–528.
3 M. Amatore and C. Aubert, *Eur. J. Org. Chem*., 2015, 265–286, and references cited therein.
4 M. Gingras, G. Félix and R. Peresutti, *Chem. Soc. Rev.*, 2013, **42**, 968–1006, 1007–1050, and references cited therein.
5 M. Rickhaus, M. Mayor and M. Juríček, *Chem. Soc. Rev*., 2016, **45**, 1542–1556.
6 P. G. Ghasemabadi, T. Yao and G. J. Bodwell, *Chem. Soc. Rev.*, 2015, **44**, 6494–6518.
7 G. Bringmann, A. J. P. Mortimer, P. A. Keller, M. J. Gresser, J. Garner and M. Breuning *Angew. Chem. Int. Ed.*, 2005, **44**, 5384–5427, and references cited therein.
8 M. C. Kozlowski, B. J. Morgan and E. C. Linton, *Chem. Soc. Rev*., 2009, **38**, 3193–3207.
9 G. Bringmann, T. Gulder, T. A. M. Gulder and M. Breuning, *Chem. Rev*., 2011, **111**, 563–639.

10 J. Wencel-Delord, A. Panossian, F. R. Leroux and F. Colobert, *Chem. Soc. Rev*. 2015, **44**, 3418–3430, and references cited therein.
11 A. Szumna, *Chem. Soc. Rev.*, 2010, **39**, 4274–4285.
12 M. Rickhaus, M. Mayor and M. Juríček, *Chem. Soc. Rev.,* 2017, **46**, 1643–1660.
13 N. H. Evans, *Chem. Eur. J.,* DOI: 10.1002/chem.201704149.
14 Y. Sato, T. Nishimata and M. Mori, *J. Org. Chem*., 1994, **59**, 6133–6135.
15 G. Nishida, K. Noguchi, M. Hirano and K. Tanaka, *Angew. Chem. Int. Ed.*, 2008, **47**, 3410–3413.
16 H. Kagan, A. Moradpour, J. F. Nicaud, G. Balavoine and G. Tsoucaris, *J. Am. Chem. Soc.*, 1971, **93**, 2353–2354
17 W. J. Bernstein, M. Calvin and O. Buchardt, *J. Am. Chem. Soc*., 1972, **94**, 494–497.
18 B. L. Feringa and R. A. van Delden, *Angew. Chem. Int. Ed.*, 1999, **38**, 3418–3438, and references cited therein.
19 I. G. Stará, I. Starý, M. Tichý, J. Závada and V. Hanuš, *J. Am. Chem. Soc.*, 1994, **116**, 5084–5088.
20 M. C. Carreño, S. García-Cerrada and A. Urbano, *J. Am. Chem. Soc.*, 2001, **123**, 7929–7930.
21 A. Latorre, A. Urbano and M. C. Carreño, *Chem. Commun*., 2009, 6652–6654.
22 M. Šámal, S. Chercheja, J. Rybáček, J. Vacek Chcholoušová, J. Vasek, L. Bednárová, I. G. Stará and I. Starý, *J. Am. Chem. Soc.*, 2015, **137**, 8469–8474.
23 I. G. Stará, I. Starý, A. Kollárovič, F. Teplý, Š. Vyskočil and D. Šaman*, Tetrahedron Lett.*, 1999, **40**, 1993–1996.
24 Y. Kimura, N. Fukawa, Y. Miyauchi, K. Noguchi, K. Tanaka, *Angew. Chem. Int. Ed.*, 2014, **53**, 8480–8483.
25 T. Shibata, T. Uchiyama, Y. Yoshinami, S. Takayasu, K. Tsuchikama and K. Endo, *Chem. Commun.*, 2012, **48**, 1311–1313.
26 E. González-Fernández, L. D. M. Nicholls, L. D. Schaaf, C. Farès, C. W. Lehmann and M. Alcarazo, *J. Am. Chem. Soc.*, 2017, **139**, 1428–1431, and references cited therein.
27 A. Grandbois and S. K. Collins, *Chem. Eur. J*., 2008, **14**, 9323–9329.
28 P. S. Baran and N. Z. Burns, *J. Am. Chem. Soc.*, 2006, **128**, 3908–3909.
29 P. Zhao and C. M. Beaudry, *Angew. Chem. Int. Ed.*, 2014, **53**, 10500–10503.
30 T. Shibata, M. Miyoshi, T. Uchiyama, K. Endo, N. Miura and K. Monde, *Tetrahedron*, 2012, **68**, 2679–2686.
31 A. Urbano, G. Hernández-Torres, A. M. del Hoyo, A. Martínez-Carrióna and M. C. Carreño, *Chem. Commun*., 2016, **52**, 6419–6422.
32 T. Shibata, N. Uno, T. Sasaki and K. S. Kanyiva, *J. Org. Chem.*, 2016, **81**, 6266–6272.
33 J. A. Berson and E. Brown, *J. Am. Chem. Soc.*, 1955, **77**, 450–453.
34 J. A. Berson, *J. Am. Chem. Soc.*, 1956, **78**, 4170.
35 T. Hattori, M. Date, K. Sakurai, N. Morohashi, H. Kosugi and S. Miyano, *Tetrahedron Lett.*, 2001, **42**, 8035–8038.
36 Y. Nishii, K. Wakasugi, K. Koga and Y. Tanabe, *J. Am. Chem. Soc.*, 2004, **126**, 5358–5359.
37 L. C. Konkol, F. Guo, A. A. Sarjeant, and R. J. Thomson, *Angew. Chem. Int. Ed.*, 2011, **50**, 9931–9934.
38 F. Guo, L. C. Konkol and R. J. Thomson, *J. Am. Chem. Soc.*, 2011, **133**, 18–20.
39 A. V. Vorogushin, W. D. Wulff and H.-J. Hansen, *J. Am. Chem. Soc.*, 2002, **124**, 6512–6513.
40 T. Shibata, T. Fujimoto, K. Yokota and K. Takagi, *J. Am. Chem. Soc.*, 2004, **126**, 8382–8383.
41 T. Shibata and T. Tsuchikama, Chem. Commun., 2005, 6017–6019.
42 T. Suda, K. Noguchi, M. Hirano and K. Tanaka, *Chem. Eur. J.* 2008, **14**, 6593–6596.
43 S. R. LaPlante, P. J. Edwards, L. D. Fader, A. Jakalian and O. Hucke, *Chem. Med. Chem.*, 2011, **6**, 505–513.
44 M. Satho, Y. Shibata, Y. Kimura and K. Tanaka, *Eur. J. Org. Chem.,* 2016, 4465–4469.
45 A. Link and C. Sparr, *Angew. Chem., Int. Ed.*, 2014, **53**, 5458–5461.
46 D. Lotter, M. Neuburger, M. Rickhaus, D. Häussinger and C. Sparr, *Angew. Chem., Int. Ed.*, 2016, **55**, 2920–2923
47 V. C. Fäseke and C. Sparr, *Angew. Chem., Int. Ed.*, 2016, **55**, 7261–7264.
48 T. Shibata, T. Chiba, H. Hirashima, Y. Ueno and K. Endo, *Angew. Chem. Int. Ed.*, 2009, **48**, 8066–8069.
49 Y.-k. Tahara, R. Matsubara, A. Mitake, T. Sato, K. S. Kanyiva and T. Shibata, *Angew. Chem. Int. Ed.*, 2016, **55**, 4552–4556.
50 S. Higashibayashi and H. Sakurai, *J. Am. Chem. Soc.*, 2008, **130**, 8592–8593.

Table of Contents:

Tutorial Review

Stereoselective Arene Formation

Achim Link and Christof Sparr

The common perception of arenes as flat and symmetrical entities is juxtaposed to the counterintuitive circumstance that stereoselective arene formation offers a means to prepare an exceptional range of chiral aromatic structures in isomerically enriched form.