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Review article

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Atroposelective catalysis

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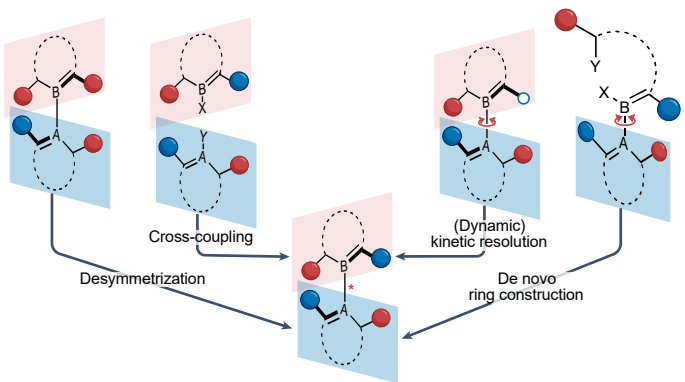
Abstract

Atropisomeric compounds—stereoisomers that arise from the restricted rotation about a single bond—have attracted widespread attention in recent years due to their immense potential for applications in a variety of fields, including medicinal chemistry, catalysis and molecular nanoscience. This increased interest led to the invention of new molecular motors, the incorporation of atropisomers into drug discovery programmes and a wide range of novel atroposelective reactions, including those that simultaneously control multiple stereogenic axes. A diverse set of synthetic methodologies, which can be grouped into desymmetrizations, (dynamic) kinetic resolutions, cross-coupling reactions and de novo ring formations, is available for the catalyst-controlled stereoselective synthesis of various atropisomer classes. In this Review, we generalize the concepts for the catalyst-controlled stereoselective synthesis of atropisomers within these categories with an emphasis on recent advancements and underdeveloped atropisomeric scaffolds beyond stereogenic C(sp^2)–C(sp^2) axes. We also discuss more complex systems with multiple stereogenic axes or higher-order stereogenicity.



Sections

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Introduction

Compounds with distinguishable stereoisomers arising from the restricted rotation about a single bond are termed atropisomers, with their name being derived from the Greek word atropos (ἄτροπος, 'without turn'). According to an approximate rule formulated by Michinori Ōki, mostly for synthetic chemistry, a compound is an atropisomer if its racemization half-life is ≥1000 s, corresponding to a rotational barrier of at least 93 kJ/mol at 27 °C[1]. In medicinal chemistry, a similar classification is utilized, and rotationally restricted single bonds are divided into three groups on the basis of their rotational barriers under physiological conditions[4]: class 1 (<20 kcal/mol; <84 kJ/mol), class 2 (20–30 kcal/mol; 84–126 kJ/mol) and class 3 (>30 kcal/mol; >126 kJ/mol), with the last class corresponding to a racemization half-life of years. However, as the rates of the bond rotations are temperature-dependent and conditions can be varied gradually, a fundamental differentiation of conformers and atropisomers is not possible, as the feasibility to separate atropisomers depends on the method used. However, in the field of atroposelective synthesis, a configurational stability with rotational barriers >110 kJ/mol is usually ideal to avoid undesired isomerizations.

Owing to their defined topology, atropisomeric compounds have proven to be valuable building blocks for nanomaterials, and atropisomeric scaffolds are now indispensable in stereoselective synthesis as catalyst and ligand scaffolds (Fig. 1a). Although biaryl atropisomers with extended aromatic systems such as in BINOL (1,1′-bi-2-naphthol) or BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) provide a well-defined shielding environment for efficient stereoinduction, they possess sufficient conformational flexibility to allow structural changes within the catalytic cycle. Following the discovery of atropisomeric natural products[2], atropisomerism has become of high interest in drug discovery programmes, as a result of the different biological activities and pharmacokinetic profiles of atropisomers[3–5], and several small molecules possessing stereogenic axes have been approved by the FDA or are currently in clinical trials. The presence of a rotationally restricted axis in a bioactive compound typically reduces the number of accessible conformations and increases its preorganization, leading to lower entropic costs upon binding to the biological target[6]. Additionally, off-target effects are reduced when a different conformation is preferred for binding to other proteins, so that a configurationally defined stereogenic axis adds an enthalpic cost to this undesired binding. Furthermore, the inclusion of stereogenic axes can inhibit degradation pathways by attenuating or suppressing an undesired metabolism.

As the number of applications has grown, so too have approaches for the stereocontrolled synthesis of atropisomers and the range of accessible scaffolds (Fig. 1b). Although initial strategies relied on chiral auxiliary-based couplings and resolutions, often leading only to atropisomeric biaryls and suffering from poor atom economy, efficient and more general catalytic methods were developed more recently. Additionally, the application of these methods was extended to more complex systems, enabling control over multiple stereogenic axes[7], stereogenic axes combined with stereocentres within the same molecule[8] and compounds with higher-order stereogenicity, necessitating not only enantiocontrol but also diastereocontrol[9,10] (Fig. 1c). Notably diastereodivergent methods allow access to all conceivable stereoisomers of a molecule[11].

Despite the diversity of reaction manifolds and product classes, the utilized strategies can be generalized to belong to four classes (Fig. 1d): a stereogenic axis can be directly forged, connected rings constructed de novo, substrates desymmetrized and (dynamic) kinetic resolutions utilized. Although desymmetrizations, (dynamic) kinetic resolutions and de novo ring constructions[12] have been extensively applied to all kinds of stereogenic elements, the stereocontrolled formation of rotationally restricted single bonds is peculiar to atropisomers.

Several reviews have appeared over the past years compiling recent advances[13–16], particular strategies[12,17–24] and product classes[25–28]. In this Review, we aim to provide a conceptual overview of the field of atroposelective catalysis and generalize the developed synthetic strategies on the basis of these classifications. Therefore, recent key developments are presented along with pioneering research in atroposelective synthesis while identifying persisting challenges and possibilities for novel approaches.

In order to provide a concise overview, particular advantages or disadvantages, areas of application and limitations of the individual methodologies and catalysts are only discussed in specific cases. However, we explore the similarities of the synthetic methodologies suitable for the construction of stereotypical C–C atropisomers and the less explored scaffolds bearing stereogenic C–X axes (X ≠ C, for example, X = N, S, B…). Furthermore, we show how applications of atropisomers in medicinal chemistry, catalysis and molecular nanoscience (Box 1) have influenced the development of new methodologies.

Desymmetrization

Selectively transforming a molecule or a molecular fragment with an improper rotation element into a system with a chiral point group is a versatile strategy for the stereoselective construction of stereocentres, which has been extrapolated to atropisomers. Here, a chiral catalyst differentiates a substrate's enantiotopic sites adjacent to or remote from the emerging stereogenic axis and introduces either a new substituent or transforms a pre-existing one to yield the enantioenriched atropisomer. The preferential reaction of the catalyst with the minor enantiomer of the desymmetrized product often leads to an increased enantioenrichment of the desired product through a kinetic resolution in a second derivatization to a symmetrical product[18] (Fig. 2a).

A wide range of reactions enable access to enantioenriched biaryl atropisomers by derivatizing *ortho*-substituents. Particular interest was received by mono-*O*-protected 2-arylbenzene-1,3-diols, and enantioenriched atropisomers were obtained by the stereoselective protection of the symmetrical diol or by the deprotection of *O*,*O*′-diprotected starting materials (Fig. 2b). Lipases were established as highly efficient biocatalysts for stereoselective acylation[29] and deacylation[30–33] reactions. For instance, diacetate hydrolysis by *Rhizopus oryzae* lipase (ROL) yielded the key atropisomeric intermediate in the total synthesis of dermocanarin 2[32], and the stereogenic axis was used as stereochemical primer for a substrate-controlled aldol addition. Although biocatalytic desymmetrizations often proceed with high stereoselectivity and efficiency, enantiodivergence can be hard to achieve, given that the truly enantiomeric catalyst is usually unavailable. However, a range of lipases have been identified as equally effective biocatalysts that furnish the opposite enantiomer[31,33]. The combination of computational tools with directed evolution has the potential to enable the design of enzymes that grant enantiodivergent access to a wide range of atropisomers through desymmetrizations. Overcoming the limitations in enantiodivergence, small-molecule chemocatalysis facilitated the *O*-protection of symmetrical 2-arylbenzene-1,3-diols with various groups. The enantioface-selective acylation of *N*-protected 2′-amino-[1,1′-biphenyl]-2,6-diols was realized by means of oxidative *N*-heterocyclic carbene catalysis, utilizing aldehydes as acyl precursors[34,35], and the scope of accessible products was expanded by the chiral Lewis base-catalysed

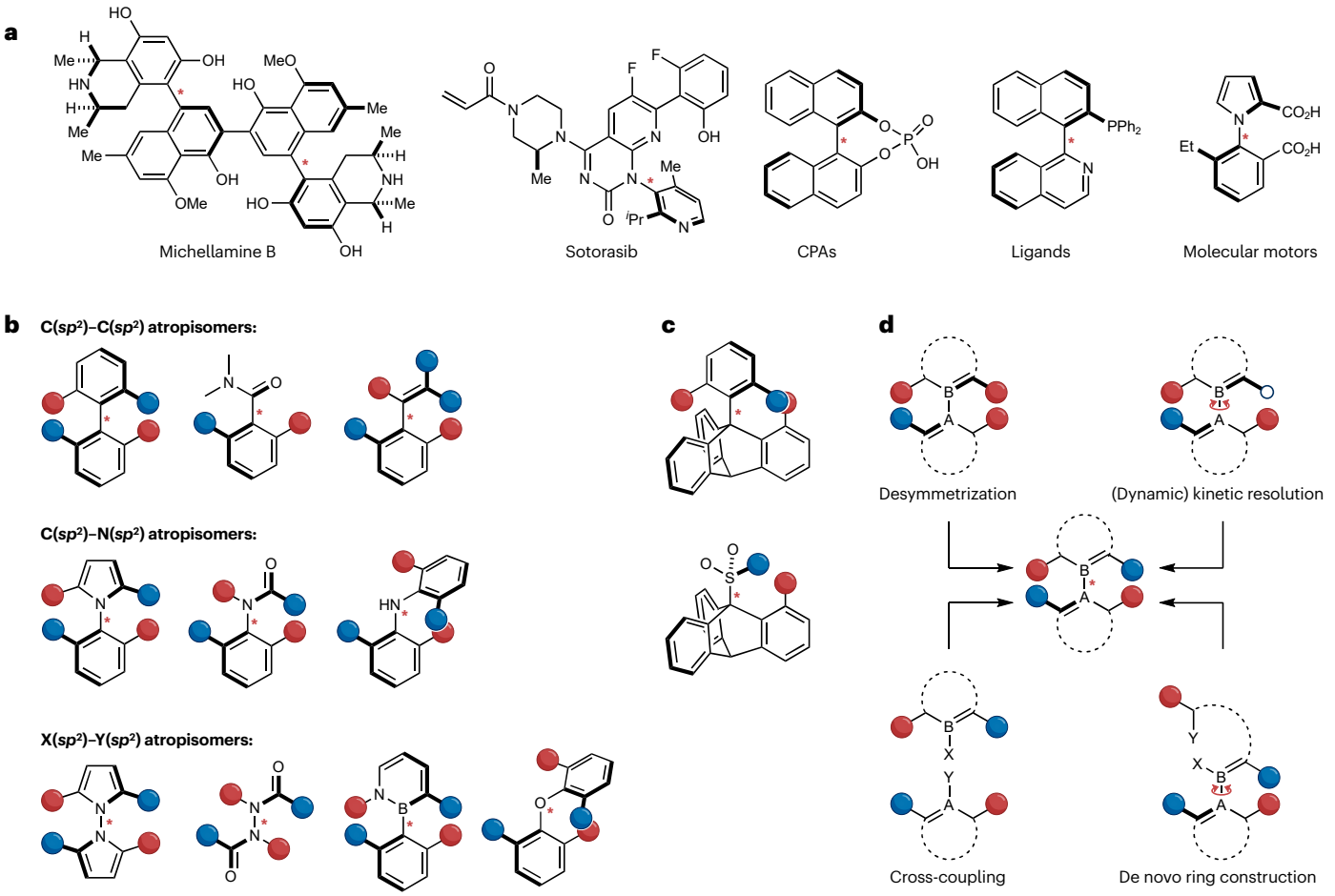


Fig. 1 | Relevance of atroposelective transformations. a, Examples of atropisomers in various fields of application. **b**, Atropisomeric frameworks for which a stereoselective synthesis was reported. **c**, Ōki atropisomers with higher-order stereogenicity. **d**, Approaches for the stereoselective synthesis of atropisomeric scaffolds under catalyst control. The red asterisks mark stereogenic axes arising from rotationally restricted single bonds. CPAs, chiral phosphoric acids.

acylation with carboxylic acid anhydrides[36]. Furthermore, orthogonal protecting groups were introduced in a desymmetrizing silylation using an imidodiphosphorimidate catalyst[37] and in a Pd-catalysed allylation[38]. Notably, in all of these reactions, the kinetic resolution of the mono-protected product resulted in enantiomeric amplification, contributing to the high enantiomeric purities obtained.

Lipases are not the only biocatalysts that have been used in atroposelective desymmetrizations[22], as galactose oxidase (GOase) and ketoreductases (KREDs) converted symmetrical dimethanols and dialdehydes to atropisomeric products by enantioselective oxidations and reductions, respectively[39,40]. Chemocatalytic counterparts to these reactions have also been explored[41]. This biocatalytic strategy was transferred from biaryl atropisomers[39] to an atropisomeric diaryl ether[40] (Fig. 2c). Structural motifs of the Ar–X–Ar′ kind (X = O, NH, S or SO_2) exist in two discrete enantiomeric forms arising from the two proximal rotationally restricted Ar–X axes, which give rise to two enantiomeric pairs of diastereomers. As the coupled conrotatory motion about these axes, which interconverts the pairs of diastereomers, has a low barrier and takes place under ambient conditions, the molecular systems exist in two distinguishable enantiomeric forms. Although GOase yielded the (*P*)-enantiomer by enantioselective oxidation of the diol with a remarkable 94% e.e., enantiodivergent access to the (*M*)-enantiomer was achieved by using the dialdehyde as the substrate of a KRED-catalysed reduction[40]. Besides the enzymatic oxidations and reductions, aldehydes were also found to be suitable linchpins for photocatalytic reductive arylation and alkynylation reactions[42]. Moreover, a copper-catalysed azide–alkyne cycloaddition desymmetrized dialkynes[43], and less activated benzylic *ortho*-methyl groups were arylated by a chiral Pd-phosphate catalyst, while a picolinamide group directed the C–H activation to the methyl group[44].

Aside from the derivatization of *ortho*-substituents, methods for their desymmetrizing *ipso*-substitution were established (Fig. 2d). For example, the Pd-catalysed Kumada coupling between Grignard reagents and bis(trifluoromethanesulfonate)s provided contiguous teraryls in up to 95% e.e.[45,46]. The versatility of Pd-catalysed desymmetrization reactions to provide enantioenriched atropisomers was demonstrated by the enantioselective Sonogashira coupling to provide C–N stereogenic anilides[47] and by the protodebromination of 3-(2,6-dibromophenyl)-2-methylquinazolin-4(3*H*)-ones[48] to deliver the intermediate for the synthesis of the GABA acceptor antagonist

Box 1 | Atropisomer-based molecular motors

The transient, dynamic behaviour of rotationally restricted compounds was utilized in the design of molecular motors and rotors[356,357]. These compounds enable the conversion of chemical or photonic energy into (directed) molecular motion. The controlled rotational directionality of molecular motors, in other words, the feasibility to induce 360° clockwise or anticlockwise motion, makes them stand out from molecular switches and rotors. As the directional motion is entropically disfavoured, energy needs to be supplied, for example, by light irradiation or by an exergonic chemical reaction, whereas the directionality is induced by chiral auxiliaries, reagents or catalysts, leading to a diastereomeric relationship between the clockwise and anticlockwise rotation. Besides the established scaffolds, several molecular motors serve as proof-of-principle systems, although there is still a great need for further advancements and fundamental research. In particular, molecular motors completing a full rotation in even fewer steps compared to the reported systems would be highly desirable.

methaquanolone, although a kinetic resolution contributed largely to the e.e. obtained. The construction of heterobiaryl atropisomers under organocatalytic stereocontrol was realized by desymmetrizing electron-poor 4,6-dichloro-5-(naphthalen-1-yl)pyrimidines[49]. Here, an *N*-benzylquininium catalyst governed the enantioface-selective nucleophilic aromatic substitution of an *ortho*-chlorine substituent with thiophenol. The products were suitable for downstream transformations, and the remaining chlorine substituent could be substituted in an enantiospecific fashion by various nucleophiles.

Not requiring the installation of a linchpin for *ipso*-substitution, *ortho*-C–H activation reactions grant streamlined access to single atropisomers, although they necessitate a directing group that guides the catalyst to the sterically encumbered *ortho*-position. C–C, C–N and N–N atropisomers were stereoselectively prepared by Pd-catalysed alkynylations and alkenylations using carbaldehyde substrates that form a transient imine directing group with α-amino acids[50–52] (Fig. 2e). Additionally, permanent directing groups were used in atroposelective desymmetrizations[53]. Conversely, the Minisci reaction of photochemically generated α-aminoalkyl radicals with pyrimidines provided a range of C–C atropisomers without the need for a directing group[54] (Fig. 2f). The reaction was promoted by a dual catalyst system comprising an organophotocatalyst for generating the radicals and a chiral phosphoric acid for stereoinduction.

The development of new methodologies for the stereocontrolled construction of novel classes of atropisomers is frequently hampered by the need for specific structural features that ensure the configurational stability of the products. Because the rotationally restricted axis can be pre-installed in the substrate, desymmetrizations remote from the stereogenic axis allow access to even challenging classes of atropisomers, without changing the immediate environment of the said axis. However, the absence of direct interactions between the chiral catalyst across the forming stereogenic axis requires advanced catalytic concepts for efficient stereoinduction, for example, the formation of an H-bond network that connects substrate, reagent and catalyst. This was realized in the desymmetrization of various activated arenes by chiral phosphoric acid-catalysed electrophilic aromatic substitutions remote from the rotationally restricted single bond (Fig. 3a). In order to form an H-bond network that spans the two halves of the rotationally restricted substrate, the 2-arylbenzene-1,3-diol substrates for a desymmetrizing atroposelective bromination were designed to contain two free hydroxy groups and a methoxymethyl group at opposing ends of the rotationally restricted C–C bond[55]. The bulkiness of the methoxymethyl group was found to be advantageous for efficient stereoinduction via steric repulsion. Similarly, C–B[56] and diaryl ether atropisomers[57] were made accessible from rotationally confined symmetrical phenols and anilines by electrophilic aminations with diazodicarboxamides conducted while leaving the substituents near the stereogenic axis unchanged.

Furthermore, remote desymmetrizations were effectively used in the atroposelective synthesis of C–N and N–N atropisomeric pyrroles (Fig. 3b). Using substrates that included both an activated and an unactivated aromatic system, 2,5-disubstituted pyrroles were selectively alkylated with 2-oxomalonates under the guidance of a chiral phosphoric acid catalyst to afford C–N atropisomeric products[58]. In the case of N–N atropisomeric 1,1′-bipyrroles, a Cu/BOX (BOX, bisoxazoline) catalyst alkylated the more electron-rich heteroaromatic system[59]. Copper catalysis was also found to be a suitable method for the atroposelective arylation with diaryliodonium salts[60], whereas the C–H insertion of di-acceptor-substituted diazo compounds via electrophilic Rh-carbene complexes produced a series of enantioenriched *N*,*N*′-bipyrroles[61].

The manipulation of the 3-position of five-membered heterocycles is the underlying design concept in various other atroposelective syntheses of C–N atropisomeric systems, and a range of nucleophilic addition reactions to 1-aryl-1*H*-pyrrole-2,5-diones and 4-aryl-3*H*-1,2,4-triazole-3,5(4*H*)-diones have been realized (Fig. 3c). Reported reaction manifolds include the organocatalytic Michael additions of enols or their equivalents[62–65] and activated aromatics such as 2-naphthols and indoles[66], and *N*-heterocyclic carbene-catalysed oxidative spirocyclizations with phthalaldehyde[67]. Aside from these, transition metal-catalysed additions of boronic acids under Rh/diene ligand catalysis[68], Rh/Cp^x-catalysed (Cp^x, chiral cyclopentadienyl) amide-directed C–H activation[69] and Pd/phosphoramidite-catalysed silylations with tertiary silanes[70] increase the accessible structural variety. As these reactions form at least one new stereocentre beside the stereogenic axis, both enantiocontrol and diastereocontrol are required. For instance, a vinylogous Michael addition in which two stereocentres were constructed generated products with high stereochemical complexity from simple starting materials[62]. Although high levels of diastereoselectivity were achieved, the implementation of diastereodivergence remains a hurdle. Notably, no kinetic resolutions can take place from the atropisomeric products during these desymmetrizations, given that defunctionalization prevents a repeated reaction. Starting from a saturated backbone, 4-aryl-1,2,4-triazolidine-3,5-diones acted as nucleophiles in their *N*-heterocyclic carbene-catalysed oxidative annulation with propiolaldehydes[71].

Atropisomeric styrenes were prepared by addition reactions to alkynes (Fig. 3d). To produce the atropisomeric alkene, activated alkynes were reacted in Michael additions with various C-nucleophiles under the control of secondary amine[72] and bifunctional thiourea[72] catalysts. Achieving a high *E*/*Z*-selectivity from the intermediate allenyl amine or alcohol is crucial to selectively obtain the configurationally stable products. Under an inverted order of electrophilic and nucleophilic addition, electrophile addition to 1-alkynylnaphthalen-2-ols or 2-aminonaphthalenes generates vinylidene *ortho*-quinone methides[24] (VQMs), which were established as versatile intermediates in chiral

phosphoric acid-catalysed[73,74], bifunctional squaramide-catalysed[75–77] and thiourea-catalysed reactions[78,79]. Attack of a nucleophile to the VQM, which can also be a radical species[77], subsequently provides the atropisomeric product. Computational studies enabled the rationalization of the enantioselectivity determining step, and they showed that the chiral catalyst promotes the enantioselective formation of the chiral VQM intermediate and that atroposelectivity is the result of an enantiospecific addition of the nucleophile to the VQM[73,77]. The concept was expanded to 3-alkynylindoles proceeding through a vinylidene iminium ion[80,81]. Moreover, intramolecular nucleophilic attack on the VQM provides access to a range of (hetero)biaryl atropisomers by stereoselective de novo ring construction[24,82–84]. Besides these reactions, a sequence of organocatalytic electrophilic bromination and nucleophilic chlorination was implemented for substrates containing an urea directing group[85], and also transition metal-catalysed hydrofunctionalizations[86–88] and difunctionalizations[89–91] efficiently produced enantioenriched C–C and C–N atropisomeric alkenes.

Kinetic resolution and dynamic kinetic resolution

In many desymmetrizations, the kinetic resolution of the atropisomeric product, in other words, the preferential reaction of the chiral catalyst with one of the product enantiomers, results in an enantiomeric amplification through a second derivatization. Conversely, the kinetic resolution of racemates is a well-established route to access atropisomers in enantioenriched form, and many catalytic methods that have been used in desymmetrizations have also been used for

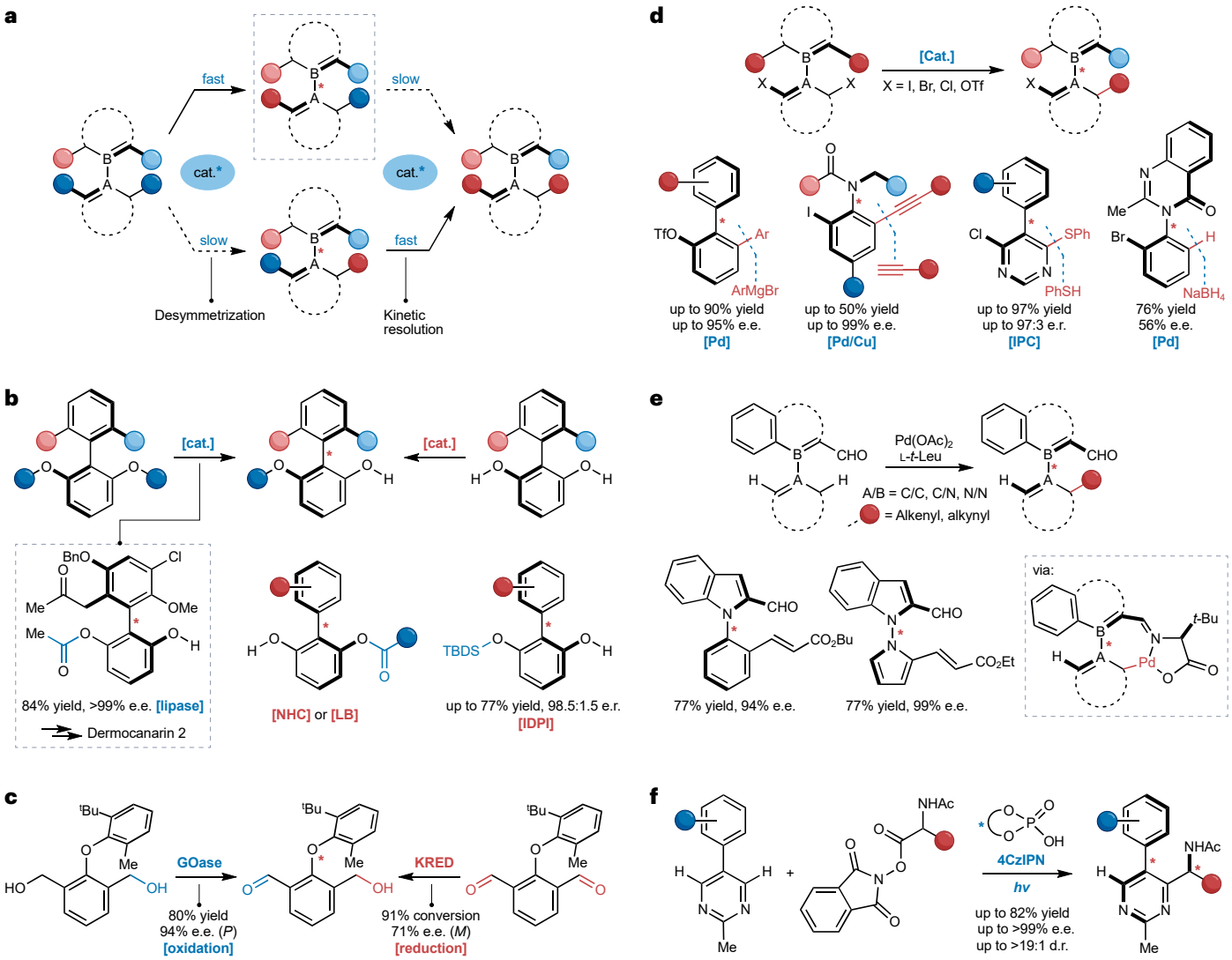


Fig. 2 | Desymmetrization adjacent to the emerging stereogenic axis. **a**, Kinetic resolution of the desymmetrized atropisomer. **b**, Enantioselective protection and deprotection of diols. **c**, Enzymatic reduction and oxidation. **d**, *ipso*-Substitution of aryl halides and triflates. **e**, Pd-catalysed C–H bond activation with a transient imine directing group. **f**, Dual catalytic Minisci reaction. The red asterisks mark stereogenic axes arising from rotationally restricted single bonds. The blue asterisks indicate the presence of a stereogenic element with defined configuration in the catalyst. 4CzIPN, 2,4,5,6-tetrakis(9*H*-carbazol-9-yl) isophthalonitrile; cat., catalyst; e.r., enantiomeric ratio; IDPI, imidodiphosphorimidate; IPC, ion-pairing catalyst; LB, Lewis base; NHC, *N*-heterocyclic carbene; Tf, trifluoromethylsulfonyl.

kinetic resolutions, for example, the enantioselective reduction of biaryl-2-carbaldehydes to the respective alcohols[92], and the lipase-catalysed hydrolysis[93–97] and formation[98–101] of esters. Additionally, the scope of these enzymatic resolutions includes the hydrolysis of atropisomeric thioesters[102] and the formation of amides[103,104]. Furthermore, using small-molecule catalysis, aromatic amines were allylated in the presence of an ion-pairing catalyst[105], and atropisomeric alcohols were kinetically resolved by organocatalytic acylations[106–110], utilizing similar catalytic concepts as in the related desymmetrization reactions. Other transformations like the kinetic resolution of C–C atropisomeric vinyl ethers[111] by Pd-catalysed devinylation might also be utilized in desymmetrizations in the future.

Although kinetic resolutions can be used for virtually all stereogenic elements, as long as a functional group for the selective derivatization of one enantiomer is present, they are limited to a theoretical yield of 50%, as they provide mixtures of the enantioenriched starting material and the product, which must then be separated after the reaction. Conversely, dynamic kinetic resolutions, in which a kinetic resolution is coupled with the racemization of the starting material, enable the stereoconvergent synthesis[112] of enantioenriched products in 100% theoretical yield (Box 2, Fig. 4a). In the case of atropisomers, the racemization can for instance be affected chemically, for example, by a catalyst, as is also established for stereocentres, or thermally. In the case of a catalytically triggered racemization, the racemization catalyst needs to exhibit a high substrate chemoselectivity in order not to deteriorate the e.e. of the product. The enzymatic resolution of BINOLs by atroposelective acetylation was successfully coupled with the entropy-driven racemization by a Ru-catalyst[113] (Fig. 4b, left). Crucially, the Ru complex was only chelated by the starting material containing two hydroxy groups, which provided the required chemoselectivity for the substrate, and afforded the acetylated product in 83% yield and 93% e.e. Additional combinations of compatible racemization and kinetic resolution protocols may be identified in the future.

In contrast to many stereocentres, the configurational stability of atropisomers can be varied gradually. By utilizing stereodynamic starting materials, dynamic kinetic resolutions were realized under thermal racemization conditions. The barrier to rotation for the substrate is low enough to enable racemization, but the atroposelective reaction introduces sufficient additional rotational hinderance in the product that atropisomers can be isolated in enantioenriched form. The

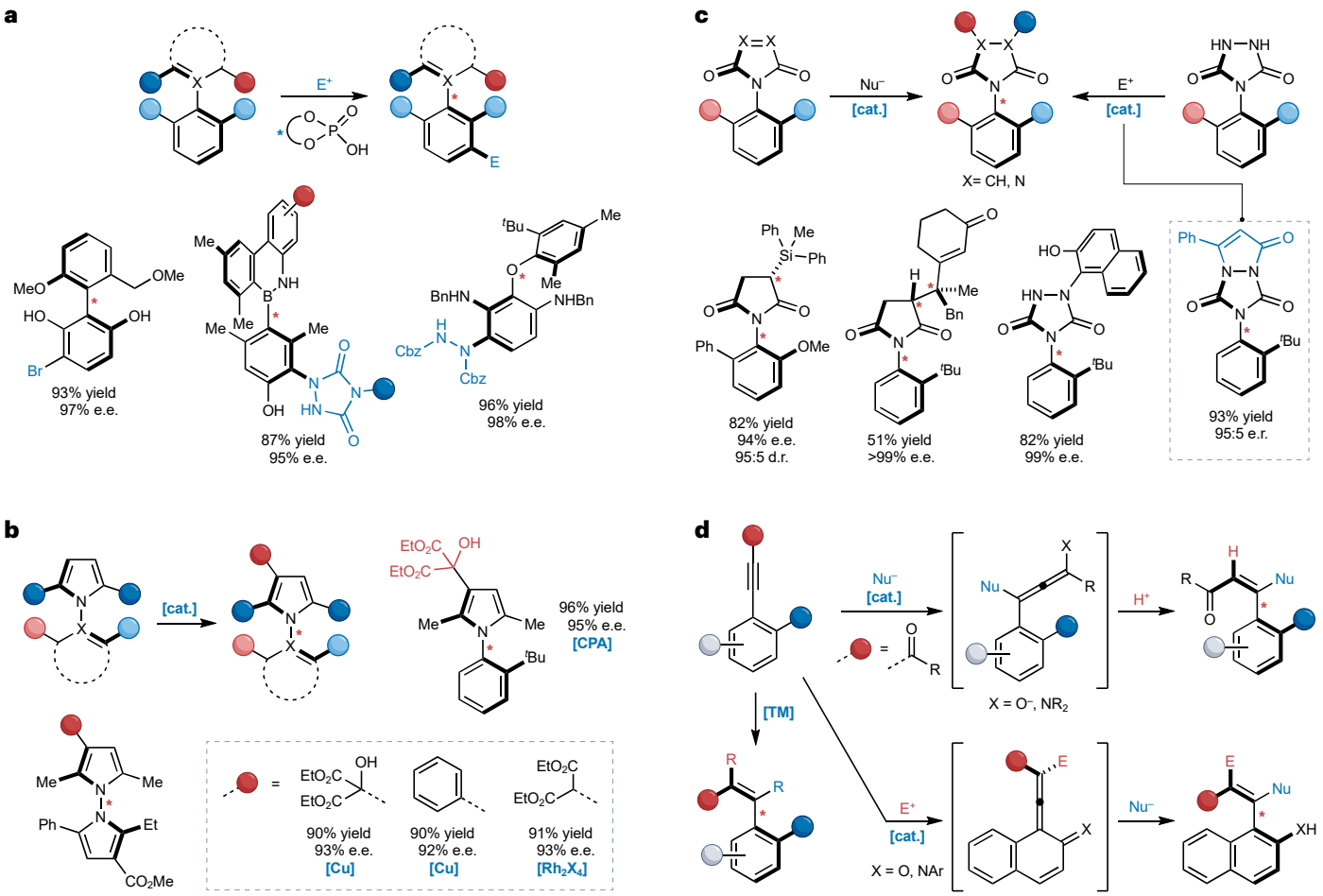


Fig. 3 | Remote desymmetrization approaches. a, Electrophilic aromatic substitution. **b**, C3-derivatization of pyrroles. **c**, Desymmetrization to C–N atropisomeric imides. **d**, Enantioselective synthesis of styrene atropisomers from alkynes. The red asterisks mark stereogenic axes arising from rotationally restricted single bonds. The blue asterisks indicate the presence of a stereogenic element with defined configuration in the catalyst. cat., catalyst; CPA, chiral phosphoric acid; e.r., enantiomeric ratio; TM, transition metal.

enhancement of the configurational stability is often realized by introducing a stabilizing substituent near the stereogenic axis. Acylation of the hydroxy group in rotationally dynamic 2-(2-methoxynaphthalen-1-yl)phenol with a pyridine-based chiral acyl transfer catalyst sufficiently increased the steric bulk in the *ortho*-position to produce the configurationally stable atropisomer in 90:10 enantiomeric ratio and 81% yield[114] (Fig. 4b, right). Following the same concept, the enantioselective oxidation of (1-(pyridin-2-yl)naphthalen-2-yl)phosphine oxide by a chiral ketone catalyst provided the atropisomeric *N*-oxide through a dynamic kinetic resolution[115] (Fig. 4c). Notably, the configurationally stable isoquinoline analogues underwent a kinetic resolution, and the *N*-oxides were isolated beside the enantioenriched starting material in similar enantiomeric ratios, showing the close relationship between the configurational stability and the (dynamic) kinetic resolution of atropisomers. Consequently, some of the stereoselective reactions that have thus far only been reported as kinetic resolutions[116–118] might be turned into dynamic kinetic resolutions by tuning the rotational barriers of the starting materials.

Methods that afford the replacement of an *ortho*-H-atom with a bulkier group are predestined for the dynamic kinetic resolution of rotationally dynamic substrates. Mono-*ortho*-bromination of 3-arylquinazolin-4(3*H*)-ones is sufficient to obtain configurationally stable C–N atropisomers (Fig. 4d). Peptide-catalysed bromination provided the tribrominated atropisomer, from which monobrominated material was obtained after twofold debromination[119]. Direct access to monobrominated quinazoline atropisomers was provided by a halogenase[120] that had been optimized by directed evolution to reach a 25-fold increase in conversion and a 91-fold enhancement in selectivity, showcasing the promising potential of biochemical engineering in atroposelective synthesis. The same reaction concept was also applied to the atroposelective synthesis of C–C atropisomers[121,122], in which the introduction of two *ortho*-substituents was required to obtain configurationally stable products[122]. Various other dynamic kinetic resolutions based on the introduction of sterically demanding groups were utilized to enantioselectively access diarylethers[123], diarylamines[124,125], and various C–C[126,127] and C–N atropisomers[127]. Here, the development of an atroposelective organocatalytic iodination was supported by chemoinformatics-guided catalyst design[126]. Moreover, a stereogenic-only-at-ruthenium Lewis acid catalyst was competent in the atroposelective Michael addition of *N*-arylpyrroles to form configurationally stable C–N atropisomers[128].

The generation of sterically interlocked structures through the replacement of a H-substituent *ortho* to the stereogenic axis has been effected using C–H bond activation reactions. For example, the transient carboxylate-imine-directed Pd-catalysed C–H bond activation was utilized not only in desymmetrizations (Fig. 2e) but also in dynamic kinetic resolutions for the introduction of vinyl, allyl, alkynyl and naphthyl groups into (hetero)biaryl[50,129–136], *N*-arylindole[51,137,138] and styrene substrates[139,140]. Here, the atom economy of oxidative alkenylations was increased by an electrochemical oxidation[133,138]. Besides, various permanent directing groups, such as amides[141], primary amines[142–144], tosyl amides[145], carboxylic acids[146,147], imines[148], oximes[149], phosphine oxides[150–153] and thioethers[154–156], were used to enantioselectively access an array of atropisomers (Fig. 4e). For this purpose, pyridines are particularly interesting, as they can be part of the atropisomeric system, for example, in 1-arylisoquinolines, and various Ru-catalysed[157,158], Rh-catalysed[159–165] and Ir-catalysed transformations[166–168] have been developed for the atroposelective synthesis of 2-arylpyridines. Aside from aromatic C–H bonds, the more challenging olefinic C(sp^2)–H bonds were activated by a Pd-catalyst to enantioselectively access atropisomeric conjugated dienes[154]. Although for most of these reactions the C–H bond activation step is directed by a group across the stereogenic axis, the Ir-catalysed alkylation of 1-(pyrrol-1-yl)-indole-3-carboxamides was directed by an amide function on the same aromatic ring, providing N–N atropisomers in excellent enantioselectivities and yields[141].

For the stereoselective synthesis of C–N atropisomeric anilides, a picolinamide directing group was strategically included in the substrate, and Pd-catalysed C–H bond activation and subsequent alkenylation, alkynylation and allylation provided configurationally stable compounds by introducing *ortho*-substituents in the aromatic system[169–171] (Fig. 4f, left). Moreover, the stereocontrolled synthesis of these systems was realized through dynamic kinetic resolutions by *N*-alkylations[172–182], acylations[183–185] and arylations[186,187], utilizing various catalyst classes (Fig. 4f, right). Similar transformations were established for the stereoselective synthesis of N–N atropisomeric 3-aminoquinazolinones[188–191] and hydrazides[192], and C–C atropisomeric enamides[193].

In the directed C–H bond activations, a metallacycle intermediate is generated upon C–H bond cleavage (Fig. 4g). Similar catalytic intermediates are also obtained by the oxidative addition of a transition metal catalyst into a C–X (X = Br, Cl, OTf and other groups; OTf, trifluoromethanesulfonate) bond. Although the starting materials are configurationally stable, the products arising from these catalytic intermediates can be obtained in stereoconvergent fashion in high yields and enantiomeric purities. In these dynamic kinetic atroposelective transformations (DYKATs)[112], configurational equilibration of the stereogenic axis is possible in the five-membered metallacycle, as the chelating coordination widens the angle between the aromatic systems and lowers the rotational barrier. Release from the metal complex upon introduction of a new substituent gives rise to the

Box 2 | Stereoconvergent transformations in atroposelective catalysis

Kinetic resolutions are limited to a theoretical yield of 50% as the catalyst (or reagent) discriminates between the enantiomers of the substrate that do not interconvert. By coupling a kinetic resolution with a catalytic racemization reaction, which is ideally much faster than the resolution, a theoretical yield of 100% is achieved. Alternatively, in atroposelective synthesis, conformationally dynamic substrates can be used, allowing for the transformation of stereodynamic starting materials into configurationally stable atropisomers (dynamic kinetic resolution). Whereas in kinetic resolutions, starting material with an enantiomeric purity enhanced beyond the stereoselectivity of the resolution reaction can be isolated by driving the reaction to over 50% conversion, the enantioenrichment of the product of a dynamic kinetic resolution is solely determined by the selectivity of the stereoselective reaction. In dynamic kinetic asymmetric transformations, configurationally stable starting materials form stereodynamic intermediates, for example, upon binding to a chiral catalyst, which then controls the configuration of the dynamic axis. The catalytic cycle is terminated by a stereoselective reaction that discriminates the rotameric states of the intermediate, giving rise to configurationally stable atropisomers in enantioenriched form.

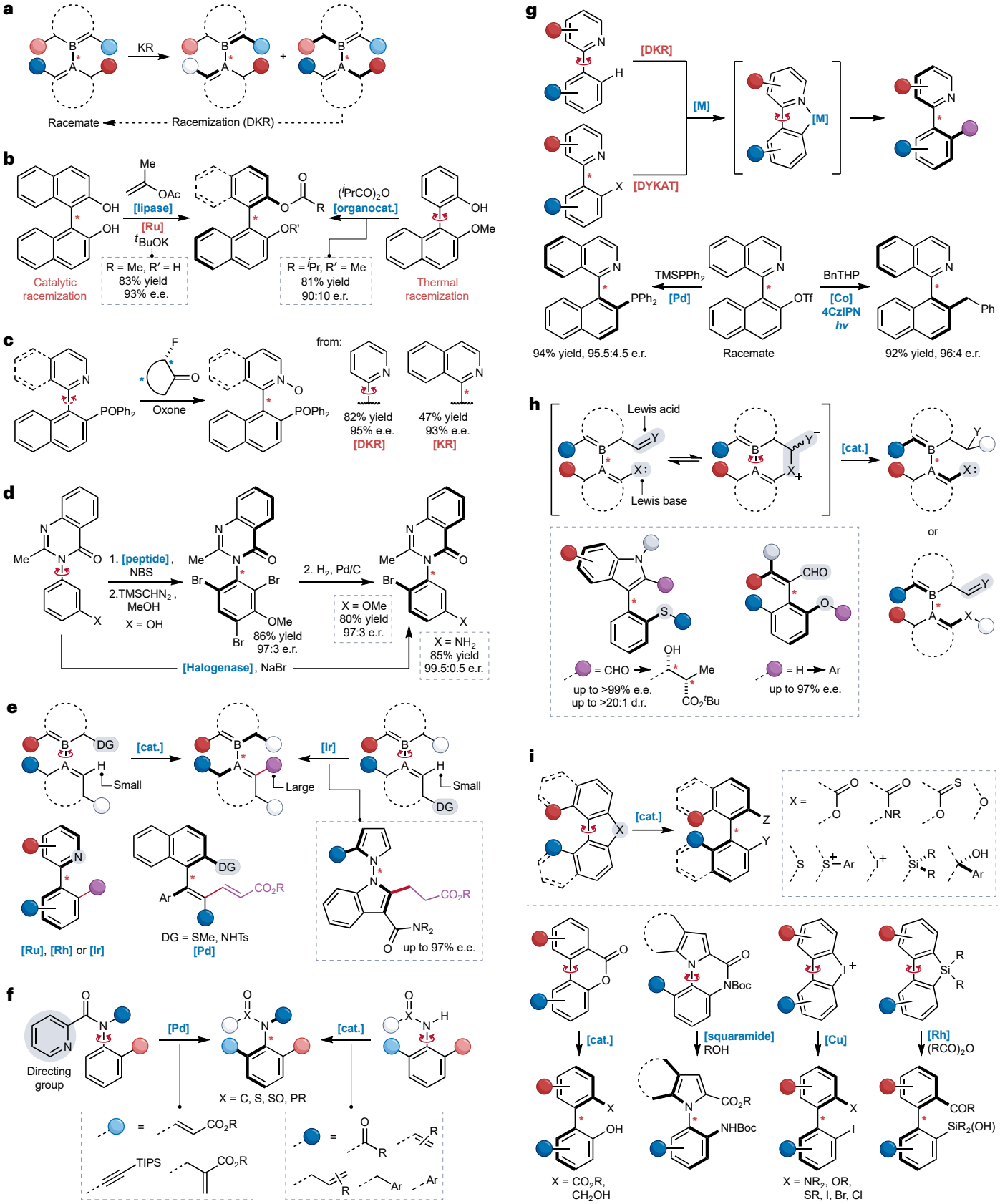

a
KR
Racemate
Racemization (DKR)
b
[lipase]
[Ru]
tBuOK
R = Me, R′ = H
83% yield
93% e.e.
Catalytic racemization
(iPrCO)2O
[organocat.]
R = iPr, R′ = Me
81% yield
90:10 e.r.
Thermal racemization
c
Oxone
from:
82% yield
95% e.e.
[DKR]
47% yield
93% e.e.
[KR]
d
1. [peptide], NBS
2.TMSCHN2, MeOH
X = OH
2. H2, Pd/C
X = OMe
80% yield
97:3 e.r.
86% yield
97:3 e.r.
X = NH2
85% yield
99.5:0.5 e.r.
[Halogenase], NaBr
e
[cat.]
[Ir]
Small
Large
DG
[Ru], [Rh] or [Ir]
DG = SMe, NHTs
[Pd]
up to 97% e.e.
f
Directing group
[Pd]
[cat.]
X = C, S, SO, PR
TIPS
g
[DKR]
[M]
[DYKAT]
94% yield, 95.5:4.5 e.r.
TMSPPh2
[Pd]
Racemate
BnTHP
[Co]
4CzIPN
hv
92% yield, 96:4 e.r.
h
Lewis acid
Lewis base
[cat.]
or
up to >99% e.e.
up to >20:1 d.r.
up to 97% e.e.
i
[cat.]
X =
[cat.]
[squaramide]
ROH
[Cu]
[Rh]
(RCO)2O
X = CO2R, CH2OH
X = NR2, OR, SR, I, Br, Cl

Fig. 4 | Kinetic resolutions and stereoconvergent transformations. **a**, (Dynamic) kinetic resolutions ((D)KRs) of atropisomers. **b**, DKR by hydroxy group acylation coupled with catalytic or thermal racemization of the starting material. **c**, (D)KR by enantioselective *N*-oxidation. **d**, DKR by *ortho*-bromination. **e**, DKR by C–H bond activation with permanent directing groups (DGs). **f**, DKR of C–N atropisomeric anilides. **g**, Dynamic kinetic atroposelective transformations (DYKATs). **h**, DKR making use of intramolecular Lewis acid–base interactions across the stereogenic axis. **i**, DKR by the enantioselective opening of rotationally dynamic cyclic structures. The red asterisks mark stereogenic axes arising from rotationally restricted single bonds. The blue asterisks indicate the presence of a stereogenic element with defined configuration in the catalyst. 4CzIPN, 2,4,5,6-tetrakis(9*H*-carbazol-9-yl) isophthalonitrile; cat., catalyst; e.r., enantiomeric ratio; M, metal; NBS, *N*-bromosuccinimide; Ts, tosyl group; organocat., organocatalyst.

enantioenriched atropisomers with stereoinduction resulting from different rates between the rotameric states in the subsequent functionalization. The generation of the cyclic catalytic intermediates from 1-(naphthalen-1-yl)isoquinolines and related systems is well established with Pd-based catalysts, which open up various options for downstream reactivities, including Suzuki couplings[194], alkynylations[195], Heck reactions[196], vinylations via a carbene complex[197], Buchwald–Hartwig aminations[198] and phosphinylations[199,200]. The Buchwald–Hartwig aminations and the phosphinylations provided streamlined access to N,N-type and P,N-type chiral ligands. In recent reports, the use of first-row transition metal catalysts was achieved in a Ni-catalysed activation of a C–OMe bond for arylations[201] with Grignard reagents, in photoredox/Co-catalysed alkylations of aryl triflates[202,203] and a Co-catalysed cross-electrophile coupling[204]. A conceptionally distinct DYKAT process was reported for C–B atropisomers that made use of the Lewis acidity of boron to form a rotationally dynamic four-membered palladacyclic borate in the presence of hydroxide[205].

As is highlighted by the DYKATs, incorporation of the stereogenic axis into a normal-sized ring can lower the rotational barrier of the axis. Although the DYKATs include the rotameric equilibration as part of the catalytic cycle, the configurational stability of a starting material can be lowered by intramolecular Lewis acid–base interactions across the stereogenic axis, which stabilize the transition state of the internal rotation (Fig. 4h). By interconverting the donor or acceptor group, so that the transient cyclization is intercepted, stereodynamic starting materials can be transformed in dynamic kinetic resolutions into configurationally stable products. For example, the carbonyl group of a thioether/aldehyde donor/acceptor couple was interconverted into an alcohol by a Rh-catalysed reductive aldol addition[206], and the configuration of atropisomers with various other donor/acceptor pairs, such as *N*-oxide/aldehyde[207], alcohol/imine[208–210], amine/ketone[211], alcohol/aldehyde[212], amine/aldehyde[213,214] and amide/aldehyde[215], was locked by transforming the acceptor group. On the contrary, *O*-arylation of 2-(2-hydroxyphenyl)cinnamaldehydes by a peptide-phosphonium-salt-catalysed nucleophilic aromatic substitution blocked the donor group and provided atropisomeric styrenes in high yields and stereoselectivities[216].

Like the Lewis acid–base-substituted systems, cyclic biaryls represent suitable stereodynamic starting materials for dynamic kinetic resolutions (Fig. 4i). Following the seminal examples for the reagent-controlled stereoselective opening of the Bringmann lactones[217], catalytic methods such as transition metal-catalysed reductions to the alcohol[218–220] and organocatalytic and Lewis acid-catalysed transesterifications[221–223] were realized more recently. This rotationally dynamic behaviour of substrates has been induced in a variety of five-membered and six-membered cyclic amides[224], thionoesters[225], thioethers[226,227], ethers[228–230], silanes[231–233], benzylic alcohols[234–236], and iodonium[237–253] or sulfonium salts[254]. Moreover, the opening of a lactam to an ester was used to access C–N atropisomeric systems under organocatalytic stereocontrol[224]. Cyclic iodonium salts are of particular value as stereodynamic precursors, because their Cu-catalysed stereoselective opening allows the reaction with various heteroatom nucleophiles including halides[247,250], and the resulting iodoarenes are desired substrates for further functionalizations.

Because the ring-opening reactions that lead to tetra-*ortho*-substituted atropisomers occur under the release of steric strain, they are particularly energetically favoured and can be performed under remarkably mild conditions. Additionally, the torsional strain of the substrate can enable the catalytic activation of otherwise less reactive bonds, and torsional strain drove the Rh-catalysed opening of silafluorenes and the subsequent transformation with acid anhydrides into silanols[231]. Here, the strain was also responsible for the chemoselective activation of the inner-cyclic C–Si bond.

Direct construction of stereogenic axes

Intermolecular formation of the rotationally restricted single bond grants efficient and readily diversifiable access to various atropisomeric compound classes. C(sp^2)–C(sp^2) single bonds are conveniently forged by transition metal-catalysed redox-neutral cross-couplings between aryl halides and organometallic compounds (Fig. 5a). Therefore, reactions like the Suzuki–Miyaura coupling[255] are predestined for the construction of (hetero)biaryl atropisomers, and stereoselective versions of these efficient Pd-catalysed and Ni-catalysed transformations have been known for a long time[256–259], but the presence of a minimum of three *ortho*-substituents in the final biaryl systems remained a constraining hurdle for their applicability. Consequently, numerous efforts have been devoted to developing catalytic systems that could be efficient with these sterically encumbered systems[19,20].

With the increasing interest in atropisomers in medicinal chemistry, chemical development groups in industry began searching for efficient and diversity-oriented routes towards pharmaceutically active atropisomers. Although many routes still rely on the resolution of enantiomers, the use of crystallization with a chiral counterion or crystallization of diastereomers, catalytic processes such as dynamic kinetic resolutions or atroposelective cross-coupling reactions are highly desirable. For instance, the stereogenic axis in the KRAS G12C covalent inhibitor GDC-6036 was constructed using a Negishi coupling between a di-*ortho*-substituted arylzinc chloride and a 2-bromopyridine[260,261] (Fig. 5b). The configurationally defined stereocentre in the organozinc reagent did not impact the atroposelectivity of this transformation when [$PdCl_2(PPh_3)_2$] was used as catalyst, providing the desired GDC-6036 precursor in 50:50 d.r. Conversely, optimized Walphos ligand W057-2, which was identified by combining high-throughput experimentation with statistical modelling, provided the target compound in 92:8 d.r., which was further enriched to 98:2 by crystallization. With the demand for larger quantities of the atropisomeric key intermediate, the reduction of the catalyst loading and the identification of a chiral ligand available on large scale was required. After re-optimization, Chiraphite provided the (R_a)-isomer in 95:5 d.r. at a Pd-loading of 0.5 mol%, enabling isolation of the said isomer by crystallization in

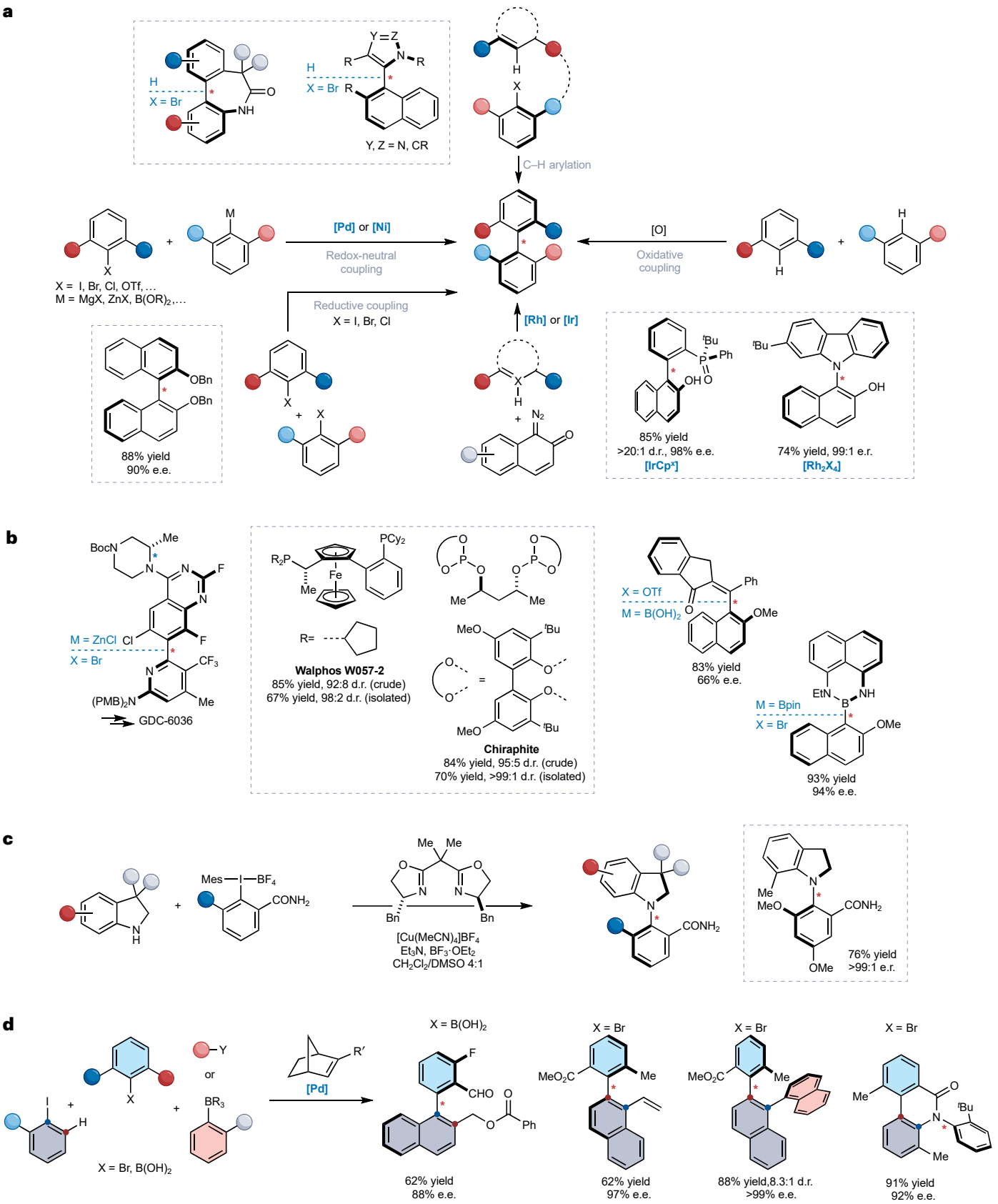

a
H
X = Br
NH
Y=Z
R
N
R
H
X = Br
R
Y, Z = N, CR
C–H arylation
X = I, Br, Cl, OTf, …
M = MgX, ZnX, B(OR)2,…
[Pd] or [Ni]
Redox-neutral coupling
[O]
Oxidative coupling
Reductive coupling
X = I, Br, Cl
[Rh] or [Ir]
OBn
OBn
88% yield
90% e.e.
tBu
P
Ph
OH
O
85% yield
>20:1 d.r., 98% e.e.
[IrCp*]
tBu
N
OH
74% yield, 99:1 e.r.
[Rh2X4]
b
BocN
Me
N
N
F
N
F
M = ZnCl
Cl
X = Br
CF3
N
(PMB)2N
Me
GDC-6036
R2P
PCy2
Fe
Me
R=
Walphos W057-2
85% yield, 92:8 d.r. (crude)
67% yield, 98:2 d.r. (isolated)
O
P
O
O
P
O
Me
Me
MeO
tBu
O
O
=
O
O
MeO
tBu
Chiraphite
84% yield, 95:5 d.r. (crude)
70% yield, >99:1 d.r. (isolated)
X = OTf
M = B(OH)2
Ph
O
OMe
83% yield
66% e.e.
EtN
NH
B
M = Bpin
X = Br
OMe
93% yield
94% e.e.
c
N
H
Mes
I
BF4
CONH2
Me
Me
O
O
N
N
Bn
Bn
[Cu(MeCN)4]BF4
Et3N, BF3·OEt2
CH2Cl2/DMSO 4:1
N
CONH2
Me
MeO
N
CONH2
OMe
76% yield
>99:1 e.r.
d
I
H
X
Y
or
BR3
X = Br, B(OH)2
R′
[Pd]
X = B(OH)2
F
CHO
O
O
Ph
62% yield
88% e.e.
X = Br
MeO2C
Me
62% yield
97% e.e.
X = Br
MeO2C
Me
88% yield,8.3:1 d.r.
>99% e.e.
X = Br
Me
O
N
tBu
Me
91% yield
92% e.e.

Fig. 5 | Atroposelective formation of stereogenic axes. a, General overview of available cross-coupling transformations. **b**, Examples of diverse atropisomeric scaffolds prepared by Pd-catalysed cross-couplings. **c**, Application of hypervalent iodine(III) reagents for the direct formation of atropisomeric C–N axes. **d**, Atroposelective Catellani-type reactions. The red asterisks mark stereogenic axes arising from rotationally restricted single bonds. Bpin, pinacol boronic ester; Cp^x, chiral cyclopentadienyl; e.r., enantiomeric ratio; Tf, trifluoromethylsulfonyl; PMB, *p*-methoxybenzyl.

70% yield with >99:1 d.r. Underlining the versatility of atroposelective cross-coupling reactions, stereoselective Suzuki couplings have been utilized in total syntheses, for example, that of gossypol[262]. Atroposelective Suzuki couplings have also been realized in aqueous media using a water-soluble chiral SPhos ligand[263] and using artificial metalloenzymes for stereoinduction[264].

Given that the scope of transition metal-catalysed cross-coupling reactions goes beyond the C–C bond formation between (hetero)biaryls, they were successfully utilized in the synthesis of less-established atropisomeric scaffolds as well. The enantioselective Suzuki coupling between vinyl triflates, which were expeditiously accessed from the respective diketones, and 1-naphthalene boronic acids afforded atropisomeric alkenes in excellent enantioselectivities and yields (Fig. 5b). Showing the versatility and diversity of this reaction class, the enantioselective synthesis of a C–B atropisomer was accomplished by a Pd-catalysed Miyaura borylation to furnish a variety of arylboron derivatives from unsymmetrical diboron reagents[265].

Compared with these classical redox-neutral cross-coupling reactions, the direct atroposelective reductive coupling of two aryl halides would give rise to an increased efficiency as the result of an improved step economy, as no transformation of aryl halides into aryl metal reagents is required (Fig. 5a). This approach was realized in Ni/diamine-catalysed homocouplings of iodoarenes, bromoarenes and chloroarenes using either chemical reductants[266,267] or electrochemistry for an increased atom economy[268]. Although these methodologies grant streamlined access to various BINOL and BINAP ligand scaffolds in few steps, the methodology is still limited to homocouplings, and general conditions for atroposelective cross-electrophile couplings of different aryl halides are still elusive[269].

Not requiring the pre-activation of a coupling partner, C–H bond activation-based transition metal-catalysed coupling reactions have been used to forge the stereogenic axes of (hetero)biaryls. Following reports on the coupling of thiophenes with arylboronic acids[270,271], the C–H bonds of arenes were activated by a Pd/phosphoramidite catalyst to facilitate the intramolecular coupling with a bromoarene to dibenzazepinones. Related to the atroposelective desymmetrization reactions, an enantioface-differentiation in the concerted metalation–deprotonation step is proposed to provide a palladacycle from which the stereogenic axis is formed upon fast reductive elimination[272] (Fig. 5a, top). Intermolecularly, Pd/H_8-BINAPO (BINAPO, [1,1′-binaphthalene]-2,2′-diylbis(diphenylphosphine oxide)) catalysed the C–H arylation to atropisomeric triazoles, imidazoles and pyrazoles, making drug-like scaffolds accessible under catalyst stereocontrol[273]. Recently, the substrate scope of this transformation was expanded to include *ortho*-nitro/formyl-substituted heterobiaryls using a deuterated *P*-stereogenic phosphine ligand[274].

Other stereoselective aryl–aryl couplings involving a C–H activation step were based on *ortho*-quinone diazides as common arylating agents to furnish a variety of atropisomeric 2-arylphenols[275] (Fig. 5a, bottom). For instance, an iridium(III) complex containing a Cp^x ligand and phthaloyl *tert*-leucine as co-catalyst promoted the stereoselective desymmetrizing C–H arylation of phosphine oxides via a migratory insertion of an intermediate carbene into an Ir–C bond to provide products with a stereogenic axis and a *P*-stereogenic centre[276]. Alternative directing groups were used in Rh/Cp^x-catalysed couplings enabling the stereoselective synthesis of atropisomeric biaryls[277,278] and atropisomers bearing different five-membered heterocycles such as 2-arylindoles[279], 3-arylindoles[280] and 7-arylindoles[281]. No directing group, in turn, is required with dirhodium tetracarboxylates. This class of privileged catalysts enabled the atroposelective coupling of electron-rich aromatic systems via intermolecular attack on electrophilic Rh-carbene complexes[282,283]. Aside from the C–C bond formation, the Rh-carbenoids were successfully deployed in the atroposelective N–H activation of indoles and carbazoles to produce the C–N atropisomeric scaffolds[284–286]. Besides these N–H arylations, only few transition metal-catalysed reactions for the direct formation of atropisomeric C–N axes have been reported. *N*-arylindoline atropisomers were accessed by the Cu/BOX-catalysed coupling of hypervalent iodine(III) reagents with indolines under mild conditions. Here, the amide functionality in the λ^3-iodane was crucial for an efficient and selective reaction. Remarkably, the reaction showed a strong positive nonlinear effect as a result of the formation of catalytically less active heterochiral $(CuL)_n$ oligomers[287] (Fig. 5c).

Another approach towards the preparation of biaryl systems relying on transition metal-based C–H bond activation is the Catellani domino reaction, in which a Pd/norbornene (NBE) catalytic system enables the simultaneous *ipso*-functionalization and *ortho*-functionalization of aryl halides (Fig. 5d). This approach offers various advantages, such as a high step economy and the application of readily accessible *ortho*-substituted aryl iodides instead of trisubstituted aryl halides. Stereoselective versions of this multi-component coupling were successfully applied in atroposelective synthesis using chiral phosphine and NBE ligands. In particular, an atroposelective Catellani reaction was achieved by Suzuki-type termination to form the atropisomeric C–C bond, using a P,C-type ligand that displays axial and *P*-centred stereogenicity for stereoinduction[288]. An alternative approach takes advantage of the Pd/NBE-synergistic nature of the Catellani reaction by using chiral NBE ligands. Here, an initial aryl–aryl coupling between a iodoarene and a 2,6-disubstituted aryl bromide leads to the atroposelective construction of the stereogenic axis and sets the stage for the diversity-oriented termination with various reagents, including alkenes, alkynes, cyanides and ketones[289].

Termination by Suzuki coupling with an aryl-trifluoroborate enabled the rapid construction of dual-axis systems with high e.e.'s and excellent diastereoselectivities[290]. However, access to the other diastereomer was not realized. Furthermore, Pd/chiral NBE cooperative catalysis is not limited to the creation of C–C stereogenic axes, as was shown by the atroposelective synthesis of C–N stereogenic phenanthridinones[291] (Fig. 5d).

In addition to the transition metal-catalysed C–H arylations, redox-neutral organocatalytic couplings enable enantioselective access to biaryl atropisomers. These transformations generally rely on the organocatalyst-controlled addition of nucleophilic aromatic systems like phenols, anilines and indoles to electrophiles such as quinones.

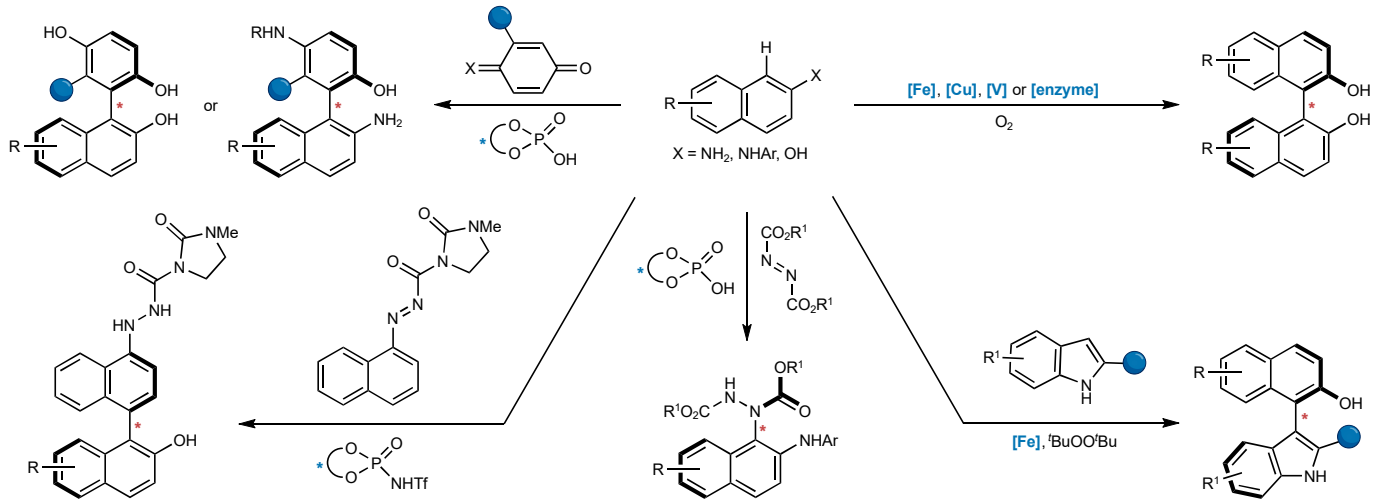


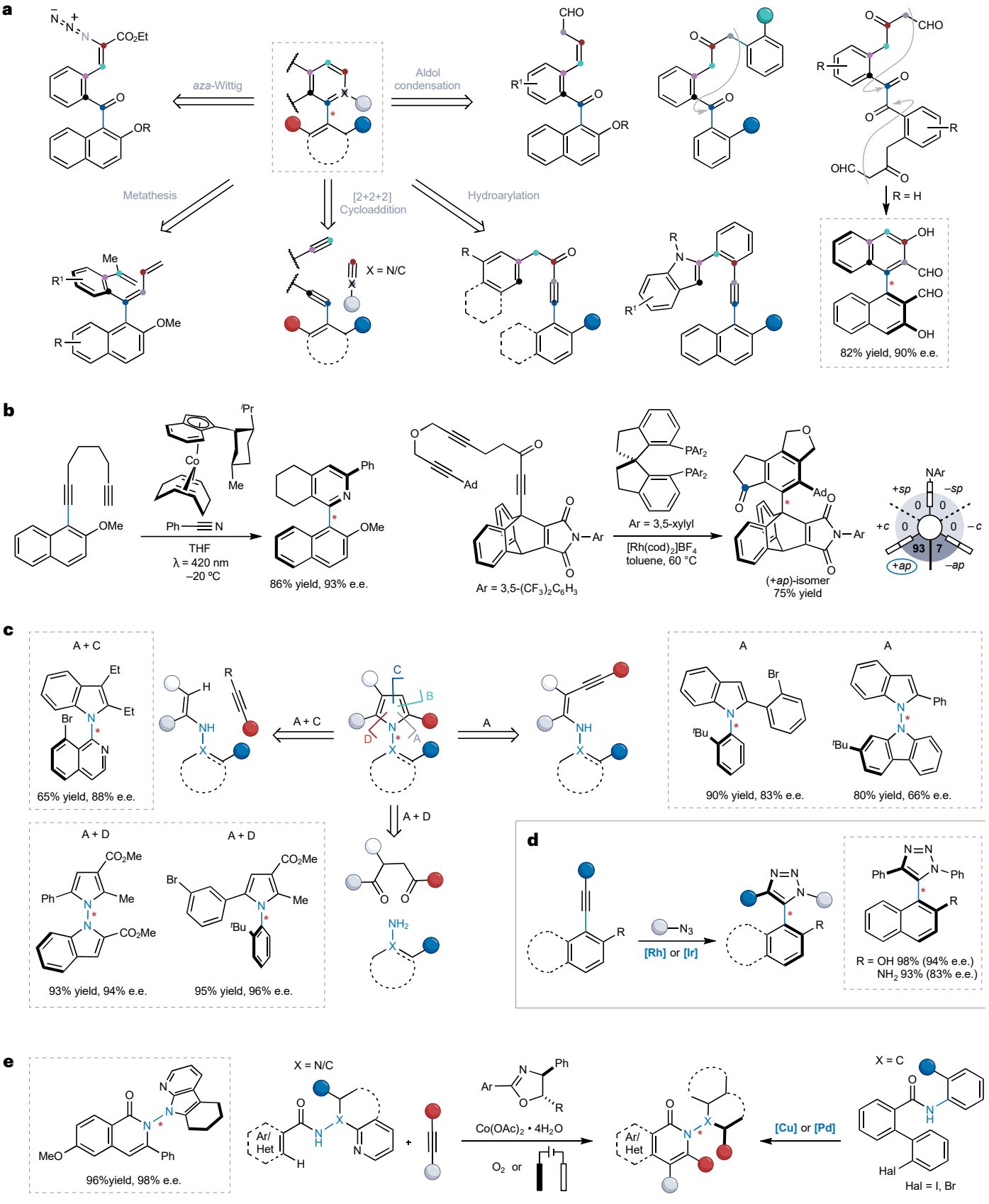
Fig. 6 | Organocatalytic redox-neutral and oxidative atroposelective cross-couplings. Organocatalytic arylation to produce enantioenriched phenol, naphthol, naphthylamine or indole atropisomers and the addition to diazodicarboxylates to control stereogenic C–N axes. Oxidative couplings offer high atom economy and are most effective for homocouplings. Alternatively, a combination of nucleophilic and electrophilic coupling partners facilitates selective cross couplings. The red asterisks mark stereogenic axes arising from rotationally restricted single bonds. The blue asterisks indicate the presence of a stereogenic element with defined configuration in the catalyst. Ar, aryl.

Following the stereoselective addition, the resulting intermediate, which contains a stereocentre, is converted to an atropisomeric product upon aromatization (Fig. 6). A representative example is the direct chiral phosphoric acid-catalysed arylation of 2-naphthols with ester quinones[292] (Fig. 6). Similarly, 2-naphthylamines could be subjected to reaction with iminoquinones yielding C–C atropisomeric biaryl alcohols with high stereoselectivities[293]. Another class of suitable electrophiles for the redox-neutral coupling of electron-rich arenes are azonaphthalenes. Depending on the substitution pattern of the said azonaphthalenes, various regioselective addition reactions leading to products with a C–C stereogenic axes have been realized[294–297]. Remarkably, 1-azonaphtalenes bearing a directing auxiliary on the diazo group even enabled the atroposelective 1,6-addition of 2-naphthols catalysed by a chiral *N*-triflylphosphoramide[297]. In addition, C–N atropisomerism was controlled by cinchona alkaloids[298] and chiral phosphoric acids[299,300] in the enantioselective addition to diazocarboxylates.

The intramolecular formation of stereogenic axes by a [3,3]-rearrangement represents an additional redox-neutral approach towards the stereoselective construction of atropisomers, and BINAM (2,2′-diamino-1,1′-binaphthalene) derivatives were synthesized via the asymmetric benzidine rearrangement of *N*,*N*′-dinapthylhydrazines under the control of a chiral phosphoric acid catalyst[301,302].

Another strategy towards the creation of a stereogenic axis in biaryl systems is oxidative cross-coupling[23], which resembles the biosynthesis of biaryl atropisomers by oxidative phenolic couplings[303]. The use of oxidative couplings offers benefits such as a high atom economy and readily accessible starting materials. Numerous oxidative conditions, including iron-based[304], vanadium-based[305–307] and copper-based catalysis[308–311], besides enzymatic methods, proved to be efficient for the enantioselective homocoupling of phenols and naphthols (Fig. 6), but cross-couplings remain challenging owing to competing homocoupling. However, combining an electron-poor and an electron-rich coupling partner has facilitated various oxidative cross-couplings. For instance, the aerobic oxidative homocoupling of naphthols catalysed by Fe(salan) complexes turned to be especially suitable for 3-substituted naphthols, due to the high atroposelectivities achieved[304]. The application of this oxidative system was then extended to the cross-coupling of 3-substituted 2-naphthols with less electron-rich 2-naphthols[312]. A further broadening of the limited substrate scope of the oxidative cross-coupling was realized using a chiral phosphoric acid-derived iron complex as catalyst and di-*tert*-butylperoxide as oxidant, and under improved conditions, this system facilitated the oxidative cross-coupling of 3-unsubstituted 2-naphthols[313]. Mechanistic studies revealed that the reaction proceeds through a radical–anion coupling step, whereas the observed product racemization could be explained by a metal-promoted reversible single electron transfer leading to delocalized binaphthoxyl radicals. A remarkable example of further application of an abundant iron-based catalyst for direct cross-oxidation is the atroposelective preparation of heterobiaryl compounds starting from naphthols and indoles[314] (Fig. 6). No homocoupling was observed, giving rise to the desired products in good-to-excellent yields and high atroposelectivity. Other established metal-based oxidative systems include a Cu^{II}/1,5-diaza-*cis*-decalin catalyst with

Fig. 7 | Atroposelective de novo ring constructions. a, General overview of possible retrosynthetic disconnections. **b**, Selected examples of atroposelective [2 + 2 + 2] cycloadditions. **c**, Representative strategies towards the atroposelective formation of five-membered heterocyclic rings. **d**, Atroposelective click reaction. **e**, Diverse stereoselective approaches towards the formation of six-membered rings to access the same scaffold bearing a C–N stereogenic axis. The red asterisks mark stereogenic axes arising from rotationally restricted single bonds. *ap*, antiperiplanar; *c*, clinal; *sp*, synperiplanar; Het, heteroaryl.


a
aza-Wittig
Aldol condensation
Metathesis
[2+2+2] Cycloaddition
Hydroarylation
X = N/C
R = H
82% yield, 90% e.e.
b
THF
λ = 420 nm
–20 °C
86% yield, 93% e.e.
Ar = 3,5-xylyl
[Rh(cod)2]BF4
toluene, 60 °C
(+ap)-isomer
75% yield
Ar = 3,5-(CF3)2C6H3
c
A + C
65% yield, 88% e.e.
A + D
93% yield, 94% e.e.
95% yield, 96% e.e.
90% yield, 83% e.e.
80% yield, 66% e.e.
d
[Rh] or [Ir]
R = OH 98% (94% e.e.)
NH2 93% (83% e.e.)
e
96%yield, 98% e.e.
Co(OAc)2 • 4H2O
[Cu] or [Pd]
Hal = I, Br

Box 3 | Higher-order stereogenicity

Molecules with more than two stereoisomeric states arising from a single stereogenic element have been known for a long time, with the first examples dating back to hexacoordinate cobalt complexes investigated as early as 1911 by Alfred Werner. Pioneering work on rigid and conformationally well-defined iptycene-based and triptycene-based C(sp^3)–C(sp^2) and C(sp^3)–X(sp^3) atropisomers (X = heteroatom) with three-fold to six-fold stereogenicity was reported by Michinori Ōki and co-workers[358,359]. Following an extended Le Bel–van 't Hoff rule $m = x_1^{n1} * x_2^{n2} * \ldots$ (m, number of stereoisomers; x, stereogenicity; n, number of stereogenic units with specific stereogenicity), systems with higher-order stereogenicity expand stereochemical space substantially, but their catalyst-controlled stereoselective synthesis remained elusive until recently.

dioxygen as the oxidant[311] and the recently developed Cu/spirocyclic pyrrolidine-oxazoline complexes that were successfully utilized for oxidative cross-couplings with small amounts of homocoupling byproducts[315,316]. Here, the reaction efficiency was also correlated to the differences in redox potentials between the coupling partners. In addition to 2-naphthols, which are frequently used as substrates for oxidative cross-couplings, phenols can also undergo this transformation, albeit with additional difficulties associated with their lower oxidation potential and a higher number of potential reactive sites for coupling. A chiral mononuclear vanadium(V) catalyst was designed to perform the homocoupling of phenols with good and moderate selectivities[317]. However, the limitation of the scope is governed by the need for a methyl or other groups of similar size at the *ortho*-position to control the enantioselectivity.

De novo ring formation

De novo ring construction is a versatile strategy for the stereoselective synthesis of atropisomers that relies on the simultaneous control over the configuration of the stereogenic axis along with the formation of one or two aromatic rings. Numerous possible retrosynthetic disconnections of the assembled aromatic ring allow diverse synthetic transformations to be used in this approach. For instance, the formal retrosynthetic cleavage of three bonds within the aromatic core indicates the transition-metal-catalysed [2 + 2 + 2] cycloaddition as the tool to realize this disconnection. This extensively developed method offers several advantages, including high atom economy and a broad substrate scope for compounds bearing unsaturated bonds, such as alkynes and nitriles[318–320] (Fig. 7a). Following the application of enantioselective [2 + 2 + 2] cycloadditions for the construction of stereocentres by desymmetrization[321,322], this strategy was also used for atroposelective de novo ring formations. For instance, the use of a cobalt-catalysed [2 + 2 + 2] cycloaddition for the enantioselective preparation of 2-arylpyridines starting from alkynes and nitriles was reported[323] (Fig. 7b). Meanwhile, highly active catalytic systems were developed for atroposelective [2 + 2 + 2] cycloadditions. For example, 1,4-teraryls were prepared that afforded outstanding atroposelectivities using an Ir^{I}/bisphosphine complex[324], whereas a Rh^{I}/(*S*)-H_8-BINAP complex was shown to be efficient for the [2 + 2 + 2] cycloaddition of electron-deficient 1,6-diynes with propargyl alcohols or acetates to yield biaryls with high enantioselectivities[325]. This rhodium(I) complex was also applied for the atroposelective [2 + 2 + 2] cycloaddition of dialkynes with nitriles[326]. The large driving force of the [2 + 2 + 2] cyclotrimerization resulting from the arene formation enables its application for the synthesis of atropisomers with high steric demand. Recently, it was demonstrated that catalyst control over higher-order stereogenicity (Box 3) is feasible by a Rh-catalysed [2 + 2 + 2] cycloaddition leading to the selective formation of one out of six stereoisomers arising from a single stereogenic C(sp^2)–C(sp^3) axis in *ortho*-substituted aryl ethenoanthracenes[9] (Fig. 7b). Furthermore, stereodivergent catalyst control was realized by using different ligand systems, opening selective access to four of the six stereoisomers. Another example of the catalytic stereoselective construction of a configurationally stable C(sp^2)–C(sp^3) stereogenic axis comprised the preparation of partially saturated two-fold stereogenic cycl[3.2.2.]azines via the enantioselective aminocatalytic cycloaddition of 5*H*-benzo[*a*]pyrrolizie-3-carbaldehydes to electron-deficient olefins[327]. This transformation also showcases the application of the de novo ring construction strategy beyond the formation of the aromatic rings.

Retrosynthetic disconnection of one bond adjacent to the stereogenic axis gives the opportunity to apply hydroarylations for the stereoselective de novo ring construction (Fig. 7a). A remarkable example of this approach is the Au^{I}/(*R*)-xyl-BINAP-catalysed atroposelective hydroarylation of alkynones to yield enantioenriched 4-aryl-2-naphthol derivatives[328] (Fig. 7a). Similarly, atroposelective hydroarylation of alkynes to yield 4-aryl-2-quinolinones was achieved with a Pd^{II}/(*S*)-xyl-H_8-BINAP complex[329]. An approach representing the retrosynthetic disconnection of the arene C=C bond neighbouring the emerging stereogenic axis is the aldol condensation. In contrast to the aforementioned methodologies, this strategy uses small organic molecules as catalysts, rather than transition metals. The atroposelective synthesis of binaphthylenes was reported starting from the corresponding unsaturated ketoaldehydes via an intramolecular aldol condensation to yield the desired arene[330] (Fig. 7a). The application of the method was extended to C–C atropisomeric amides[331] and a cascade of two arene ring formations by the intramolecular aldol cyclization of noncanonical polyketide hexacarbonyl substrates to tetra-*ortho*-substituted binaphthalenes controlled by a small secondary amine catalyst[332]. As with stereocentres, several stereogenic axes can be combined within one molecule to give rise to an exponentially increasing number of stereoisomers, as it is predicted by the Le Bel–van 't Hoff rule. In their stereoselective synthesis, control not only over enantioselectivity but also over diastereoselectivity is required, ideally achieving diastereodivergence to access all conceivable stereoisomers from the same starting materials[11]. Therefore, the stereoselective arene-forming aldol condensation strategy was investigated for the preparation of atropisomeric multiaxis systems. The synthesis of individual stereoisomers of 1,2-naphthylene oligomers was thus investigated by implementing an iterative organometallic building block addition followed by a catalyst-controlled or substrate-controlled stereoselective arene-forming aldol condensation[333]. Another example comprises the synthesis of diverse *ortho*-disubstituted β-naphthols through the construction of the central arene ring by an aldol condensation with cinchona-based ion-pairing catalysts. In this case, simultaneous control over two stereogenic axes generated in a single reaction is feasible[334]. Full stereodivergence with organocatalytic stereocontrol allowed access to all four stereoisomers as major product starting from the same substrate.

Another retrosynthetic disconnection of the bond next to the stereogenic axis was recently considered for the synthesis of atropisomeric isoquinolines based on a Staudinger–aza-Wittig reaction.

Azido cinnamates thereby rapidly converted to the corresponding isoquinoline heterocycles with high atroposelectivities using a chiral phosphine catalyst that was regenerated by a silane reductant under Brønsted acid co-catalysis[335]. Alternative disconnections of the arene ring for its de novo construction entail C–C bonds that are more remote from the stereogenic axis. This strategy was explored for stereoselective arene-forming metathesis utilizing a chiral molybdenum complex as the catalyst. In particular, stereodynamic trienes were selectively transformed into the corresponding binaphthalene atropisomers[336] (Fig. 7a).

All the aforementioned examples of de novo ring constructions yield products with C–C stereogenic axes. Beyond atropisomeric biaryls, several methods for the atroposelective de novo ring construction of heterocyclic systems have been developed[17]. The shift to C–N axes opens access to numerous appealing heterocyclic systems that could be also prepared in atroposelective fashion. Interestingly, previously underdeveloped N–N stereogenic axes have gained substantial attention over the past few years, expanding the range of rotationally restricted bonds of possible heterocyclic atropisomers. One of the most investigated systems for both C–N and N–N atropisomers are scaffolds containing five-membered rings (indole and pyrrole derivatives) due to the numerous available synthetic strategies for the construction of these rings. As a result, a conventional approach to the de novo assembly of pyrrole/indole heterocycles could be transformed to the atroposelective methodology via the selection of a suitable catalytic system. Retrosynthetic disconnection of two bonds leads to [3 + 2] annulation that could be realized by a Rh^{III}-catalysed C–H bond activation of anilines possessing an *N*-isoquinolyl directing group[337] (Fig. 7c). The alkyne moiety could also be applied for the atroposelective construction of indole derivatives via transition metal-catalysed 5-*endo*-hydroaminocyclizations. The approach is applicable for the construction of both C–N and N–N stereogenic axes with Pd^{II}/SEGPHOS (SEGPHOS, 5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole) complexes as suitable catalysts[338–340]. Pyrrole rings were prepared with high atroposelectivities by conducting modified Paal–Knorr reactions. Notably, this approach is efficient for both C–N and N–N atropisomers with chiral phosphoric acids serving as catalysts in both cases[341–343]. Interestingly, an enantiodivergent synthesis could be achieved for N–N atropisomeric systems by adding $Fe(OTf)_3$ to the reaction mixture[342]. Other notable examples of the de novo assembly of five-membered rings with high atroposelectivity are click reactions. Both Rh^{I} and Ir^{I} catalytic systems proved to be efficient for these transformations with phosphoramidites and squaramides as the ligands of choice[344–347] (Fig. 7d).

The shift to more sustainable methodologies has also motivated advancements in the field of atroposelective catalysis. Therefore, the atroposelective electrochemical cobalt-catalysed aryl C–H and N–H bond annulations of carboxylic amides with dihydrogen as the only by-product was developed[348,349] (Fig. 7e). Recently, this approach was extended to the stereoselective synthesis of systems bearing N–N stereogenic axes[350]. Notably, a similar cobalt-catalysed C–H activation/annulation was reported earlier with oxygen as the oxidant[351]. It was also shown that these strategies are suitable for allene substrates[352], whereas 3-iminoisoindolinone products with a five-membered N-heterocycle could be obtained using isonitriles instead[353]. It was also proven that pyridine-*N*-oxides serve as an efficient directing group for the C–H activation/annulation[354]. Another investigated atroposelective de novo construction of this scaffold involves copper-catalysed C–N bond coupling with cyclohexane-1,2-diamine picolinic amide as a ligand[355] (Fig. 7e).

Conclusions and outlook

Atroposelective synthesis underwent a remarkable development over the past two decades to become a particularly active field of chemical research. Methods evolved from auxiliary-based and reagent-based approaches that require stoichiometric amounts of chiral reagents to efficient catalytic protocols, streamlining the access to a variety of structural motifs and stereogenic axes, including C–N, N–N and C–B atropisomers. These developments have fuelled new discoveries in medicinal chemistry, nanochemistry and chemical synthesis. The development of new drug candidates bearing configurationally stable stereogenic axes will thus require new efficient methodologies that can also be implemented on an industrial scale. Here, atroposelective methodologies that allow for the stereoselective formation of heterocyclic atropisomers can play a key role in making the manifold ring systems tractable in a stereoselective fashion. Given the large number of heterocycle syntheses, the atroposelective de novo ring construction bears high potential as suitable tool for this purpose. Moreover, considering the increased demand for scalable atroposelective reactions under catalyst control, a shift towards improved sustainability by replacing the methods using precious metal-based catalysts with organocatalytic or base metal-catalysed transformations is highly appealing. Furthermore, stoichiometric oxidants and reductants could be substituted for electrochemical oxidations and reductions respectively. The development of efficient methods has been supported by chemoinformatics, and the common use of computational and statistical tools in atroposelective reaction development is expected. Besides, considering that a major part of the developed methodologies is focused on the construction of (hetero)biaryl scaffolds, it is anticipated that the atroposelective synthesis of so far under-represented frameworks will undergo substantial advancements. In particular, C–X stereogenic axes (X ≠ C) and atropisomerism between two nonplanar fragments, such as in $C(sp^2)$–$C(sp^3)$ atropisomers, might become of particular interest, given that the development of stereoselective methods for many of these systems is at the time still severely limited.

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T.A.S. and V.H. contributed equally. T.A.S. wrote the original draft, reviewed and edited; V.H. wrote the original draft, reviewed and edited. All authors contributed to the discussion of content and to the reviewing and editing of the article.

Competing interests

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