nature catalysis

Review article

https://doi.org/10.1038/s41929-024-01138-z

Catalytic atroposelective synthesis

Received: 31 July 2023

Accepted: 29 February 2024

Published online: 30 April 2024

Check for updates

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Atropisomeric architectures are increasingly encountered in modern materials and medicinally important compounds. More importantly, they are now a characteristic of broadly useful chiral ligands and organocatalysts. Over the past decade, substantial advancements have been made in enhancing the accessibility of major classes of atropisomers through the refinement of existing strategies and the introduction of contemporary concepts for catalytic atroposelective synthesis. This synthetic capability enables the expansion of chemical space and facilitates the preparation of valuable atropisomeric scaffolds. Here we review the state of the art in the asymmetric synthesis of atropisomers with the help of selected examples. Focus will be placed on the strategies that have emerged rapidly in recent years, and that are characterized by high versatility and modularity. Additionally, the incorporation of emerging synthetic tools and representative scaffolds are discussed, alongside future directions in this research domain.

Axial chirality is a stereochemical phenomenon originating from restricted rotation around a stereogenic axis with four non-planar arranged *ortho*-substituents. According to this definition, atropisomers, spiranes, allenes and spiro structures could display this form of molecular chirality. The phenomenon of axial chirality was established in 1922, when Christie and Kenner successfully crystallized salts for two enantiomers of 6,6′-dinitro-2,2′-diphenic acid (Fig. 1a)[1]. At present, this chirality element is widely acknowledged in bioactive natural products and serves as a fundamental component in the functionality of materials, exerting a substantial influence on the design and advancement of contemporary drugs and functional materials. Latent atropisomers have been categorized into three groups (by LaPlante and colleagues[2]) based on the rotational energy (E_{rot}) barriers of the stereogenic axis. A molecule has the potential to exert atropisomerism when ΔE_{rot} > ~20 kcal mol^{-1}, and axial chirality is generally stable for values over ~30 kcal mol^{-1}. At elevated temperatures, rotational energy barriers decrease and give rise to a conformational stability issue. Accordingly, syntheses of atropisomers are usually implemented under mild reaction conditions. For some time, axial chirality was disregarded, whereas point chirality received fervent attention across a range of fields. This changed in 1980 when Noyori and colleagues pioneered the adoption of optically pure BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) as a ligand in asymmetric metal catalysis[3]. This report shed light on the stereo-controlling ability of atropisomeric scaffolds, providing a fresh perspective on axial chirality. Since then, a series of typically atropisomeric ligands, including QUINAPs (1-(2-diphenylphosphino-1-naphthyl)isoquinolines) and phosphoramidites, as well as their derivatives, have been introduced[4–6]. Meanwhile, intensive follow-up research has also uncovered diverse axial chirality-based organocatalysts, such as phase-transfer catalysts[7] and Brønsted acids[8,9]. These compounds have demonstrated competitive performance in addressing various challenges in asymmetric synthesis, leading to them holding a privileged position today (Fig. 1b).

Continuous evolution of the study of axial chirality has made it an indispensable part of modern organic synthesis and arguably a key discipline in asymmetric catalysis. The incorporation of axially chiral elements in catalytic species has become a routine and effective strategy to induce or enhance enantiocontrol capability. The design and catalytic enantioselective syntheses of atropisomers are at the core of these efforts, and the research output over the past decade reflects the intense activity in the field. However, there are several long-standing issues that are hindering realization of its full potential. One of the challenges is the high production costs associated with certain ligands and catalysts, which arise from their impractical synthetic routes. Early efforts primarily focused on method development, diverting attention from the discovery of core structures. Additionally, the configurational instability of axially chiral compounds presents a fundamental challenge, limiting their broad application. This Review aims to outline the contemporary advances in atroposelective synthesis under catalyst control. The content is organized under three main themes, beginning

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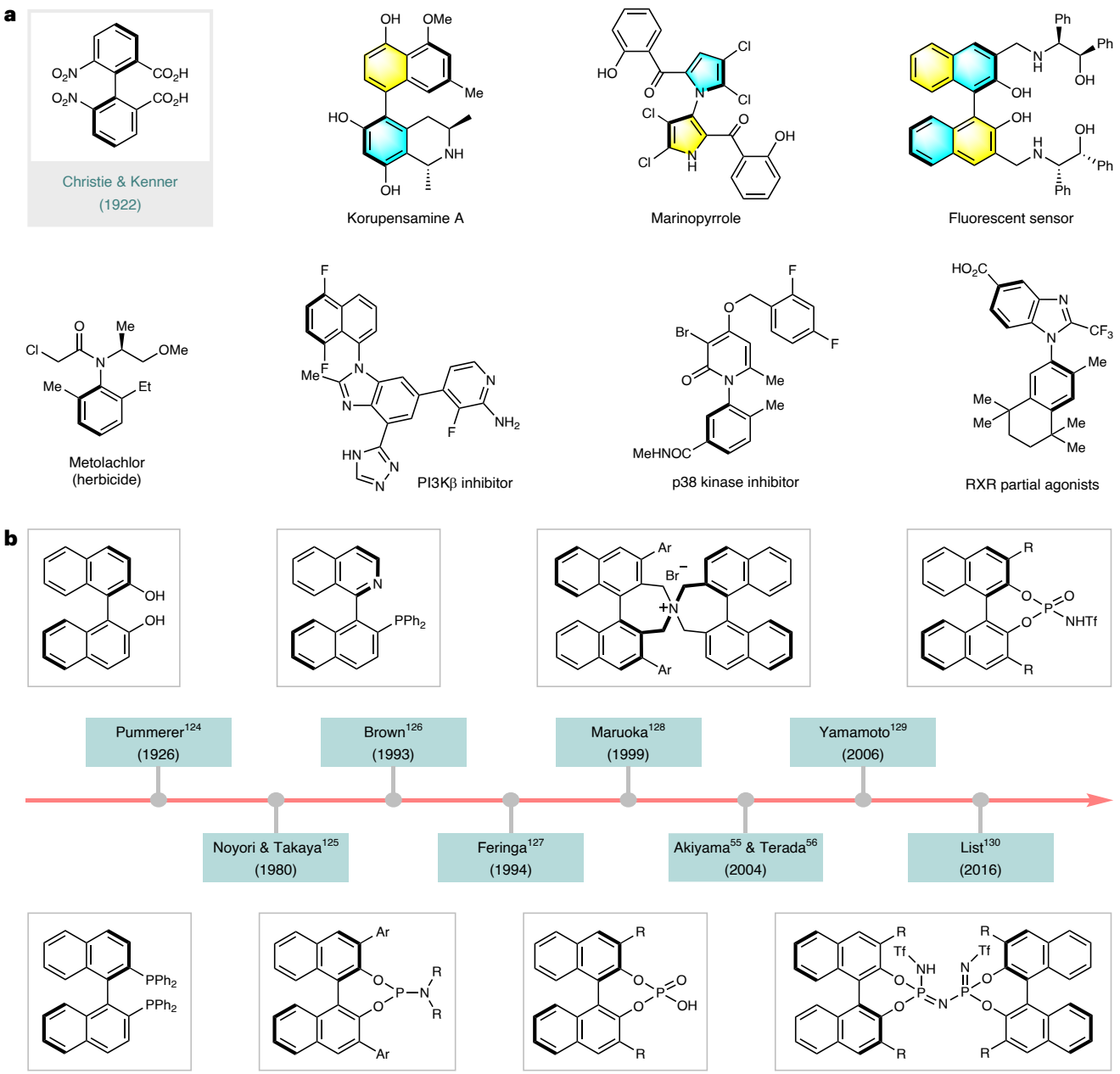

Fig. 1 | Discovery and importance of axial chirality. a, The first isolated molecule that established the axially chiral phenomenon, together with selected natural products and functional materials with a stereogenic axis. **b**, Time line of representative atropisomeric ligands and organocatalysts.

with a review of synthetic strategies. To provide focus, the discussion here is limited to contemporary and widely applied strategies with high versatility and modularity. Interested readers are directed to dedicated reviews[10–12] and books[13,14] that give comprehensive discussions on the various strategies available. The second section is devoted to an overview of how emerging synthetic tools have been used to construct atropisomeric scaffolds. Finally, several atropisomeric scaffolds that have rarely been reviewed elsewhere will be discussed to showcase the intriguing findings on the exploration of frameworks.

Strategies with high versatility and modularity

Diverse synthetic strategies have been established to forge atropisomeric skeletons that involve atroposelective functionalization of a pre-existing scaffold and formation of a stereogenic axis or a cyclic subunit. This section discusses selected catalytic asymmetric approaches that have far-reaching implications for the synthesis of atropisomers.

Atroposelective C–H functionalization

The *ortho*-aromatic C–H bond can be selectively converted into different functionalities via transition-metal-catalysed C–H activation, with the configuration of the neighbouring axis being set in the process. To this end, a series of prochiral heterobiaryl structures (**1**–**3**) with nitrogen as the directing group have been designed for metal-catalysed atroposelective C–H functionalization reactions by the groups of You[15,16] and Shi[17]. A pyrimidyl group enabling C–H activation and the functionalization of indoles (**4**) has been reported by Li and colleagues, affording pentatomic biindolyls in excellent enantiocontrol under rhodium catalysis[18]. Shi and colleagues employed a transient chiral auxiliary chemistry to achieve palladium-catalysed C–H functionalization of prochiral biaryl aldehydes (**5**) by including a sub-stoichiometric amount of amino acid for condensation with an aldehyde entity to act as a catalytic directing group and chiral ligand (Fig. 2a)[19,20]. The cooperation of electrosynthesis with palladium catalysis was used to

accomplish the dynamic kinetic asymmetric transformation (DYKAT) of prochiral biaryl aldehydes (**5**) or aryl-pyrroles by Ackermann and colleagues in 2020[21]. Subsequently, this was utilized in the kinetic resolution of racemic aryl-indoles[22]. Contributions have also been made by the groups of Cramer[23] and Lassaletta[24]. Recently, Akiyama developed an enantioselective synthesis of biaryl atropisomers through C(sp^3)–H activation, and mechanistic studies revealed that C–H activation played a crucial role as the rate- and enantio-determining step[25]. Notably, the more sustainable, cheaper and less toxic 3*d*-metal cobalt has been elegantly harnessed by Wencel–Delord[26,27], Shi[28] and colleagues to facilitate C–H activation and the ensuing atroposelective functionalization with a chiral ligand.

Multicomponent reactions have received massive interest due to their high versatility, modularity and convergent nature. Among the developed multicomponent reactions, the Catellani reaction offers a highly convergent approach that allows *ipso*- and *ortho*-C–H functionalization of aryl halides under palladium/norbornene cooperative catalysis[29]. This could circumvent the requirement for a circuitous and potentially challenging pre-functionalization step, delivering polyfunctionalized aromatic molecules selectively from alkyl or aryl halides with numerous terminating agents. Employment of this reaction in atropisomeric synthesis was developed by Gu and colleagues[30]. A phosphine ligand (**L1**) bearing a point chirality and an axial chirality effectively induced stereocontrol during the formation of an aryl–aryl axis on biaryls **10** (Fig. 2b). Subsequently, a breakthrough was achieved by the Zhou group by adopting a chiral norbornene ligand[31]. In this protocol, an atropisomeric Pd(II) biaryl complex is generated through the *ortho*-addition of 2,6-disubstituted aryl bromide **12** on aryl iodide **11** in the presence of a palladium catalyst and a chiral ligand NBE*-1. Upon the coupling of diverse terminating agents (olefins, alkyne, boronic acids, cyanide and ketone), axial chirality is transferred to the products. This method provides a highly modular access to biaryls **13** with an expanded range of *ortho*-substitution (Fig. 2c). Aiming to explore the axially chiral monophosphine ligand, the Song group developed an efficient approach to prepare atropisomeric biaryl-based monophosphine oxides (Fig. 2d, **14**,**15**), with good results and a similar strategy[32]. This chemistry was also designed to access atropisomers bearing a stereogenic C–N axis (Fig. 2e, **17**)[33] and 1,2-diaxes (Fig. 2f, **19**)[34].

Atroposelective ring-opening reactions

In 1992, Bringmann and co-workers introduced the lactone concept through atroposelective ring-opening of lactones **20** with a chiral hydride transfer agent to access enantioenriched biaryls **21**. Labilization of the C–C axis for atropisomerization is made possible by the bridged six-membered lactone ring (Fig. 3a,i)[35]. This concept was further popularized by various catalytic asymmetric reduction reactions[36,37]. Alcohols and phenols were also suitable reagents to promote ring-opening and gave transesterification products **22** through a chiral amine thiourea catalysis (Fig. 3a,ii)[38]. Biaryls **23** could be synthesized through reductive amination with racemic **24** or redox-neutral amination with racemic **21**. In these cases, the resulting imines interconvert through biaryl hemiaminal **25**, and reduction occurs selectively from one imine intermediate (Fig. 3a,iii)[39,40].

In another development, Gu's team realized a series of copper-catalysed atroposelective ring-opening reactions of five-membered-bridged diaryliodoniums **26** with different nucleophiles. The *o*,*o*′-disubstitution of cyclic biaryl substrates promotes ring-opening to release strain and stabilizes the stereogenic axis. Regioselectivity is conferred by steric bias for the less hindered site (Fig. 3b,i). A range of reagents worked well with this chemistry, including amines (**27**)[41], α,β-unsaturated carboxylic acids (**28**)[42], thiocarboxylates (**29**)[43], diarylphosphine oxides (**30**)[44] and trifluoromethanethiolates (**31**)[45]. More recently, alkoxygenation with weakly nucleophilic diols was established with borinic acid as co-catalyst, which activates 1,2- and 1,4-diols in the form of a boron-ate complex intermediate with enhanced nucleophilicity (**32**) (Fig. 3b,ii)[46].

Recently, the long elusive organocatalytic atroposelective ring-opening reaction was reported by our group, offering an important addition to this chemistry. Chiral Brønsted acid *N*-triflyl phosphoramide (**C1**) was identified to be effective in cleaving the Si–C bond of silafluorenes (**33**) through direct protonation of the aromatic ring. The addition of silanol was found to reduce dimer formation through silylation of biarylsilanol to afford **34**. The product could be readily converted to other valuable biaryl structures with high enantiopurities (**35**,**36**) (Fig. 3c)[47].

Organocatalytic arene umpolung for atroposelective direct arylation

An inspection of the chemical structures revealed the atroposelective cross-coupling of two aryl counterparts to be the most versatile and straightforward route. Among the established strategies, transition-metal-catalysed asymmetric Suzuki–Miyaura coupling of aryl halides (**37**) and aryl boronic acids (**38**) is one of the most well developed. Palladium-based chiral catalysts are conventionally involved in this type of transformation (Fig. 4a,i)[48–50]. To circumvent the uneconomic and tedious pre-functionalization of both aryl substrates, asymmetric dehydrogenative cross-couplings of arenes **39** and **40** were devised with miscellaneous transition-metal-centred chiral catalytic systems (Fig. 4a,ii)[51,52]. These coupling reactions have also recently been realized by 3*d*-metals such as iron[53] and cobalt[54]. Nevertheless, their organocatalytic variant has been an unmet synthetic challenge for a long time. Apparently, the inversion of intrinsic nucleophilicity of one aryl component to electrophilicity under a chiral organocatalyst is the biggest obstacle for this scenario. In this context, we envisioned that, by introducing an electron-withdrawing nitrogen functionality onto the aromatic ring (**42**), electrophilicity could be imparted to the tethered arene. Favourably, a hydrogen-bonding catalyst such as chiral phosphoric acid (CPA)[55,56] engages this entity for further activation and provides a suitable chiral environment for site- and enantioselective C–H functionalization. Additionally, cleavage of the N–X bond on **43** could liberate amine (**44**) (Fig. 4b,i). Potential candidates with azo (**42a**) or nitroso (**42b**) as the activating and directing group are displayed in Fig. 4b,ii.

This blueprint was realized in formal asymmetric nucleophilic aromatic substitution of C2-azo substituted naphthalenes **42a** with indoles under CPA catalysis[57]. Apart from the anticipated 3-arylindole atropisomers **45** formed following the 1,4-addition and rearomatization sequence, the smaller C2 substituent allows an intramolecular addition by hydrazine, which reveals 3-aniline-indoles **46** after ring-opening aromatization. When treated with aromatic alcohols in a CPA salt complex-based system and with 2-naphthylamines in a Ni/bis(oxazoline) system, cross-couplings proceeded smoothly to convert C2-azonaphthalenes into **47** and **48**, respectively[58]. The biaryl products gave rise to the highly sought-after privileged scaffolds, NOBIN (2-amino-2′-hydroxy-1,1′-binaphthyl) and BINAM (1,1′-binaphthyl-2,2′-diamine) after reduction. By means of CPA catalysis, carbazoles and hindered C3-substituted indoles coupled with azonaphthalenes at the nitrogen site (**49**,**50**) (Fig. 4c,i)[59]. Subsequently, *para*-C–H bond functionalization of azo-appendant benzenes with indoles was established asymmetrically by our group through subtle modulation of CPA catalysts[60]. More recently, C1-azonaphthalene compounds were applied in this transformation with acylimidazolinone as auxiliary and *N*-triflyl phosphoramide as chiral Brønsted-acid catalyst, furnishing C4-selective arylated **52** in high efficiency and enantiocontrol (Fig. 4c,ii)[61].

Guided by density functional theory (DFT) studies, C2-nitrosonaphthalenes **42b** were identified as another suitable set of electrophilic coupling partners[62]. Arylation with indole nucleophiles generates atropisomers **53** in the presence of an external oxidant. Otherwise, the nucleophilic hydroxylamine triggers an intramolecular

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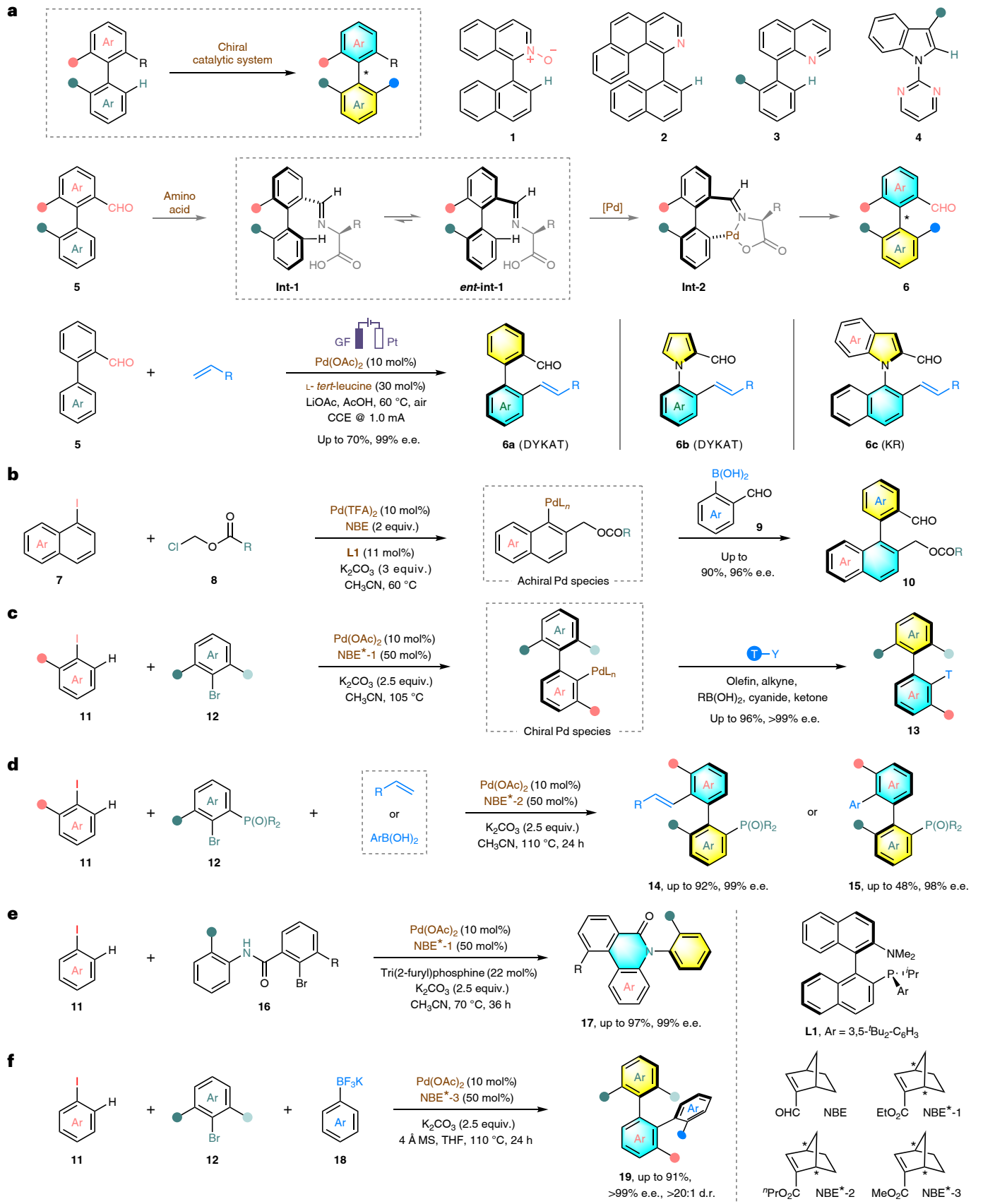

Fig. 2 | Catalytic asymmetric synthesis of atropisomers through C–H functionalization. a, Atroposelective C–H functionalization enabled by a directing group. GF, graphite felt; CCE, constant current electrolysis; KR, kinetic resolution. **b**, Atroposelective Catellani reaction by Gu and colleagues, involving achiral palladium species. **c**, Generation of axially chiral biaryl palladium species. **d**, Application in the synthesis of atropisomeric biaryl monophosphine oxides. **e**, Construction of C–N atropisomeric skeletons. **f**, Assembly of diaxial structures.

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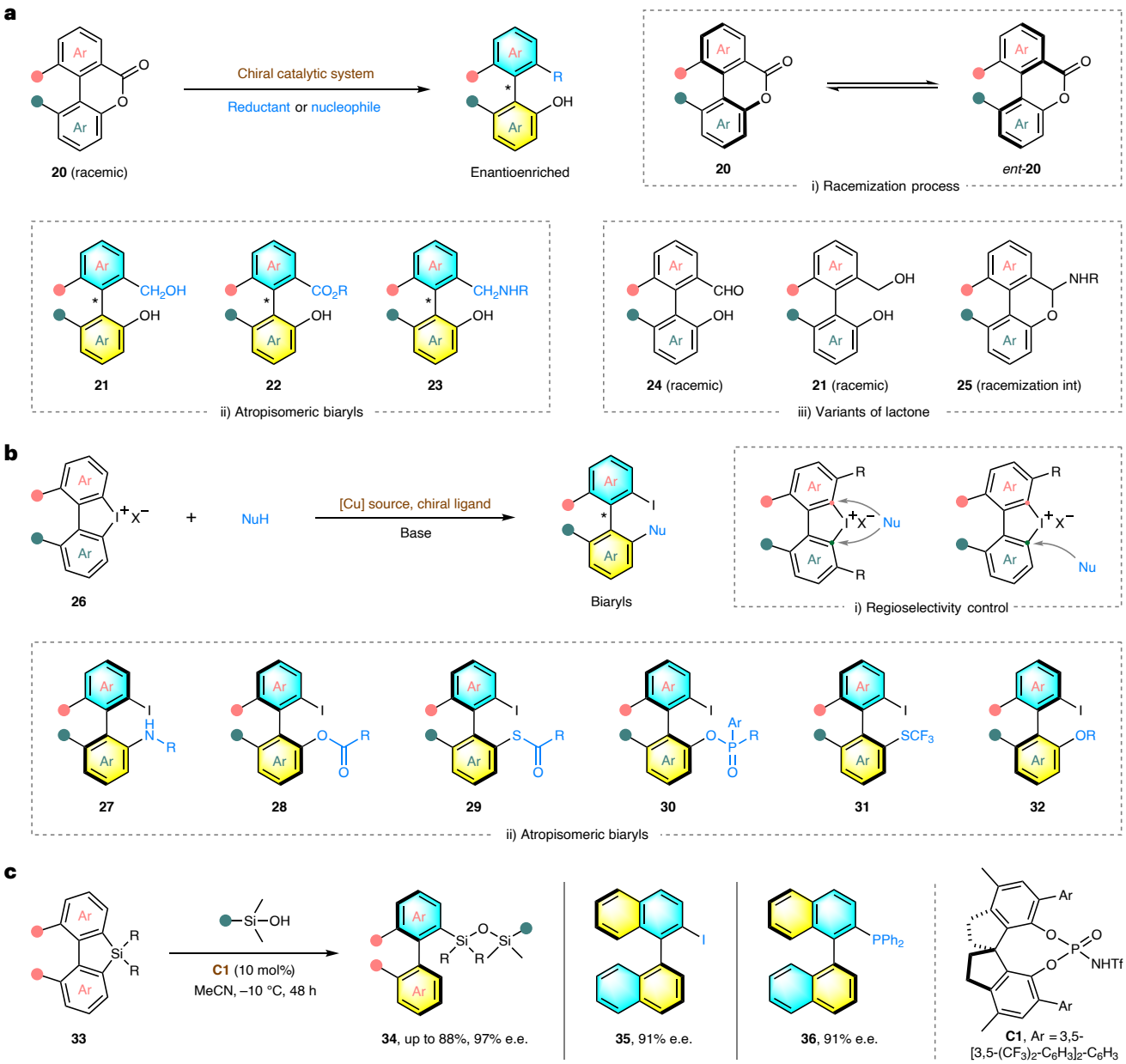

Fig. 3 | Synthesis of atropisomeric biaryls through atroposelective ring-opening reactions. a, Application of Bringmann lactones and their variants. **b**, Application of five-membered-bridged diaryliodoniums with ring strain through copper catalysis. **c**, Organocatalytic atroposelective ring-opening of silafluorenes.

cyclization to form indole-anilines **54**. Extension of this coupling paradigm to 2-naphthols furnished NOBINs **55** in a one-pot cross-coupling/reduction reaction (Fig. 4d).

Differently, Shi and colleagues used 2-indolylmethanols **56** that possess C3-electrophilicity after water elimination for CPA-catalysed arylation with 2-naphthols or phenols to generate 3-aryl-indoles **57**. The *gem*-diaryl groups stabilize the stereogenic axis and cation intermediate, while also imparting C3-regioselectivity by congesting the benzylic reactive site (Fig. 4e)[63]. They have also utilized the same strategy in the construction of axially chiral alkenes[64].

Chiral VQM intermediate for atroposelective synthesis

Vinylidene *ortho*-quinone methide (VQM) species generated from 2-ethynylnaphthol or aniline derivatives **58** (known as aza-VQM) via a 1,5-proton shift are highly electrophilic (Fig. 5a)[65]. The prospect of chiral catalyst control in this process allows the generation of axially chiral VQMs (**59**) in enantioenriched form. These species are susceptible to nucleophilic interception or can participate in a formal cycloaddition to form (hetero)aryl–aryl atropisomers (**60**) via axial-to-axial chirality transfer. In 2013, this protocol was utilized by Irie's team to access aryl-naphthopyrans **64** from alkynes **63**, which occurs through an intramolecular [4 + 2] cycloaddition of VQM with another tethering alkyne entity. However, moderate enantiomeric excess (e.e.) values were observed under cinchona alkaloids catalysis[66]. The subtle modification of chiral base catalyst to quinine-derived thiourea (**C2**) by the Yan team substantially improved the enantiocontrol and broadened the substrate range (Fig. 5b)[67]. Notably, for compounds **65**, which contain both 2-ethynylnaphthol and 2-ethynylaniline, an axially chiral VQM intermediate is selectively formed from the former unit. The stereoselective intramolecular annulation offered atropisomeric aryl-C2-indoles **66** in generally excellent enantiopurities[68]. In addition, naphthyl-benzocarbazoles **67** and napththyl-quinolines **68** harbouring an aryl–aryl axis have been delivered by Irie (cinchona alkaloids catalysis)[69] and our group (CPA catalysis)[70], respectively.

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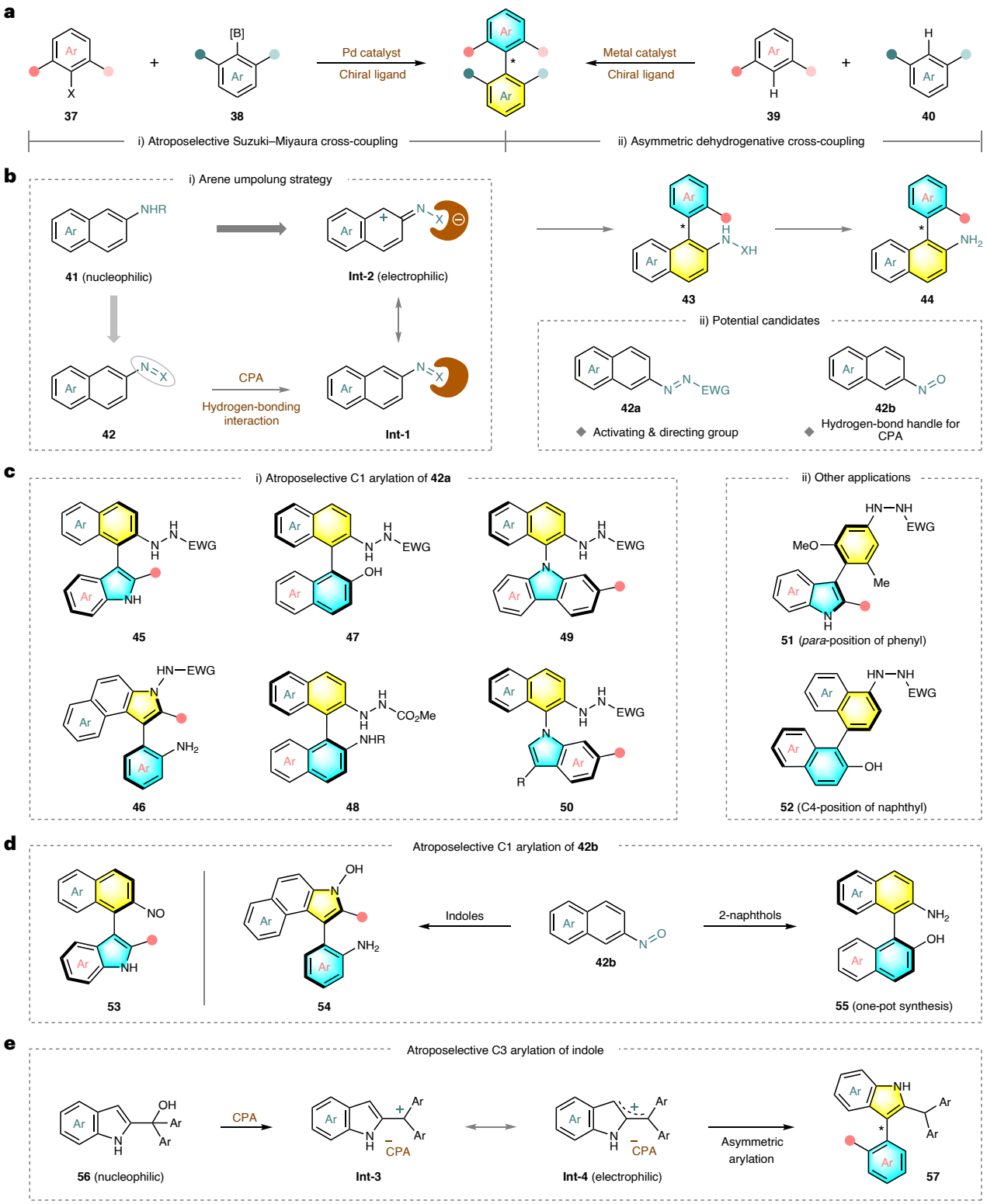

Fig. 4 | Atroposelective direct arylation enabled by organocatalytic arene umpolung. a, Typical transition-metal-catalysed asymmetric coupling of two aryl counterparts. **b**, Design of the organocatalytic arene umpolung strategy and potential aryl candidates with azo or nitroso as the activating and directing group. **c**, Atroposelective arylation with azo-group-substituted arenes. **d**, Atroposelective arylation with nitroso-group-substituted arenes. **e**, Further extension to 2-indolylmethanols. EWG, electron-withdrawing group.

On the other hand, the addition of alkynes through a VQM intermediate is a rapidly evolving method to construct alkene-type atropisomers without formation of another aromatic ring (Fig. 5c). For example, Yan and colleagues have assembled atropisomeric sulfone-containing alkenes **69** from 1-alkynyl-naphthalen-2-ols **58** with sodium sulfinates as nucleophiles[71]. Our group established the CPA-catalysed nucleophilic addition of VQM with aromatic alcohols to afford alkene analogues (**70**) of BINOL and NOBIN in high

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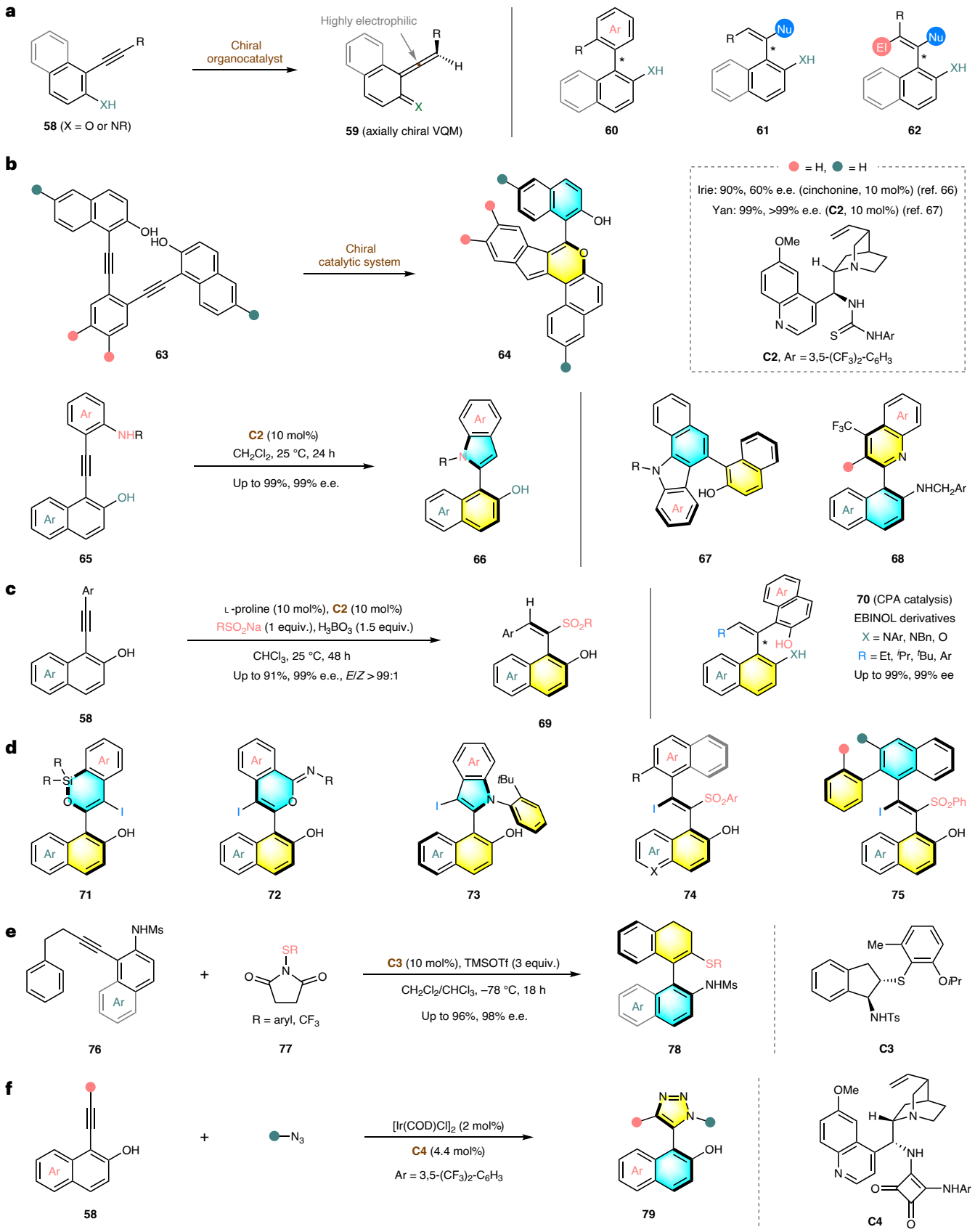

Fig. 5 | Catalytic asymmetric synthesis of atropisomers involving axially chiral VQM. a, Formation of VQM and streamlined conversions. El, electrophile; Nu, nucleophile. **b**, Construction of the (hetero)aryl–aryl stereogenic axis. **c**, Assembly of atropisomeric alkene structures. **d**, Difunctionalization of the alkyne. **e**, Bifunctional sulfide catalyst promoted generation of VQM. **f**, Application in atroposelective azide–alkyne cycloaddition.

enantiocontrol[72]. Since then, the scope of nucleophilic reactants has been intensively explored, and diverse atropisomeric alkene skeletons were readily constructed. This chemistry was also extensible to the organocatalytic difunctionalization of an internal alkyne with an electrophile and a nucleophile, which provides a practical approach to assemble alkenes bearing a vicinal diaxis (**73**,**74**) or multiaxis (**75**) (Fig. 5d)[73,74]. Notably, the isolation and characterization of transient axially chiral intermediates was recently accomplished by the Yan group, opening the door for the elucidation and further application of the VQM intermediate[75]. Additionally, the tetra-substituted aza-VQM intermediate could be generated by bifunctional sulfide (**C3**) catalytic thiolation of *ortho*-alkynylaryl amines **76**, as in Zhao's report, which offers an attractive approach to access atropisomeric alkenes **78** (Fig. 5e)[76].

Catalytic enantioselective azide–alkyne cycloaddition (E-AAC) offers an efficient way to forge structurally diverse centrally chiral triazoles, usually involving a copper catalyst. However, this type of click reaction was not used in producing heterobiaryl atropisomers until 2022. Based on VQM chemistry, success with atroposelective E-AAC was achieved by Xu and colleagues by using Ir(I) catalysis with chiral squaramide **C4** as the cooperative catalyst starting from **58** (Fig. 5f)[77]. Concurrently, a catalytic system comprising a rhodium source and a chiral phosphoramidite ligand was disclosed by Li, Qian, Deng and colleagues[78]. In contrast, the VQM intermediate is not involved in their mechanistic pathway, and a hydrogen bond between the free hydroxy group and Rh catalyst was proposed to account for the regioselectivity. Soon after, a similar catalytic system featuring higher practicality, much broader substrate scope, lower catalyst loading as well as a faster reaction rate was provided by the Cui group[79].

Strategies with emerging synthetic tools

Over the past decade, photocatalysis that exploits abundant visible light as a sustainable power source has become an indispensable synthetic tool in conquering challenging transformations via a radical course. The synergy of photocatalysis with asymmetric metal catalysis or organocatalysis provides an effective route to forge useful chiral molecules. Initial efforts by Katsuki and colleagues were used to accomplish the asymmetric aerobic oxidative coupling of 2-naphthol[80]. However, only moderate atroposelectivities were obtained with a (NO) Ru(II)–salen complex under irradiation with visible light. Success in the construction of axially chiral skeletons arrived in 2018[81]. In Bach's pioneering work, enantioenrichment of allenes was achieved by irradiation with visible light in the presence of bifunctional thioxanthone as an energy transfer-based photosensitizer and catalyst responsible for atroposelective induction. In 2022, Xiao, Lu and colleagues revealed a metallaphotoredox system that merges cobalt catalysis and chiral bisphosphine ligand **L2** for the dynamic kinetic asymmetric transformation of heterobiaryls **80**[82]. Reaction with 1,4-dihydropyridine derivatives **81** as coupling partners and 2,4,5,6-*tetra*-9*H*-carbazol-9-yl-1,3-benzenedicarbonitrile (4CzIPN) as photocatalyst delivered highly enantioenriched **82** in good to excellent yields. The formation of cobalt complex **Int-1** bearing a five-membered ring enabled the enantioenrichment process via axial rotation uniting chiral ligands (Fig. 6a,i). Recently, this strategy was applied in the dynamic kinetic reductive conjugate addition of acrylates[83] and desymmetrization of biaryl dialdehydes[84] to access atropisomeric structures **83**–**85** (Fig. 6a,ii). In addition, the involvement of organocatalysis in photocatalytic atroposelective synthesis was achieved by the same group (Fig. 6b)[85]. Utilizing redox-active ester **87** as a radical precursor and **C5** as a chiral source, compounds **88** containing both axially and centrally chiral elements were produced with excellent diastereo- and enantioselectivity through a Minisci reaction.

Electrosynthesis has been widely recognized as another green synthetic tool for molecular functionalization. The merging of electrosynthesis and asymmetric catalysis offers an alternative strategy to synthesize important chiral structures, including atropisomers[86]. In this realm, pioneering work was reported by Ackermann and colleagues that involved cooperation with palladium catalysis[21,22]. In 2023, application of electro-oxidative cobalt catalysis in aryl C–H functionalization and a N–H annulation cascade reaction between benzamides **89** and 4-hydroxyalkynoates **90** was realized by the same group to access *N*-aryl atropisomers **91**[87]. Additionally, allenes were found to be suitable candidates for this type of transformation (Fig. 6c)[88]. By incorporating cathodic reduction into nickel catalysis, Mei's group realized the asymmetric homocoupling of aryl bromides (**93**) with chiral oxazoline ligands (**L4** and **L5**). Notably, the use of electric current as a reducing agent gave the enantioenriched C_2-symmetric biaryls **94** in much higher yields than when using the conventional reductant manganese (Fig. 6d)[89].

Emerging atropisomeric scaffolds

Strategies for atroposelective synthesis have seen creative extension in various ways, enabling more efficient access to privileged biaryl-type scaffolds. Besides expansion in the diversity of peripheral substituents, increased knowledge and more powerful chemical tools are laying the groundwork for the exploration of core frameworks. This section illustrates advancements of the field towards tackling the synthesis of unconventional atropisomers that were previously intractable by catalytic chemical tools.

Axially chiral alkenes and stereogenic axis involving heteroatom(s)

Compared to biaryl-type structures, the development of axially chiral alkenes is more recent. This is largely attributed to the lower rigidity of the axis that connects an arene and a vinyl unit, posing issues for stereocontrol and the preservation of configurational stability. Unlike cyclic alkenes, which bear structural resemblance to biaryl cores, the tactical design of steric elements is crucial for the development of acyclic congeners. There is a general absence of methods that construct a stereogenic axis involving a heteroatom as efficiently, except the C–N analogues[90]. One limiting factor might be the inherently low configurational stability of such an axis, as can be gauged from the bond lengths (Fig. 7a). Undoubtedly, the past two decades have witnessed a surge in interest in the atropisomerism originating from the restricted rotation around a C–N bond. This intriguing theme has already been intensively discussed several times very recently, and readers are referred to other reviews for specialized perspectives[91–93].

Considering that an acyclic alkene could partially retain axial chirality, the Tan group embarked on pursuing a catalytic asymmetric strategy to access such atropisomeric alkene structures through nucleophilic addition to alkynals[94]. Their study commenced with evaluation of the configurational stabilities of several alkenes in terms of both rotation barriers and half-lives to identify a suitable starting point. The choice of nucleophile had a major effect on the rotational barrier, with the steric influence imposed at the α-position to alkene being most decisive. Based on these data, Michael addition of 1,3-dicarbonyls to alkynals (**95**) was successfully implemented to deliver atropisomeric alkenes **97** (Fig. 7b). Alkynal is activated by an amino catalyst as iminium ion, and Michael addition yields stereochemically defined allenamine **Int-1**. Isomerization to iminium ion **Int-2** and hydrolysis reveals axially chiral alkenes. Notably, cyclic atropisomeric alkenes were forged by Gu and colleagues through enantioselective palladium-catalysed cross-coupling of aryl bromides and hydrazones[95]. In the work by Smith and colleagues on the catalytic enantioselective synthesis of atropisomeric biaryls by a cation-directed *O*-alkylation, analogous structures were isolated as the key intermediates[96]. Since then, continuous efforts have been devoted to this sub-branch of the axial chirality realm[97].

Scaffolds featuring a chiral C–B bond represent a class of atropisomers for which catalytic asymmetric access has not been established.

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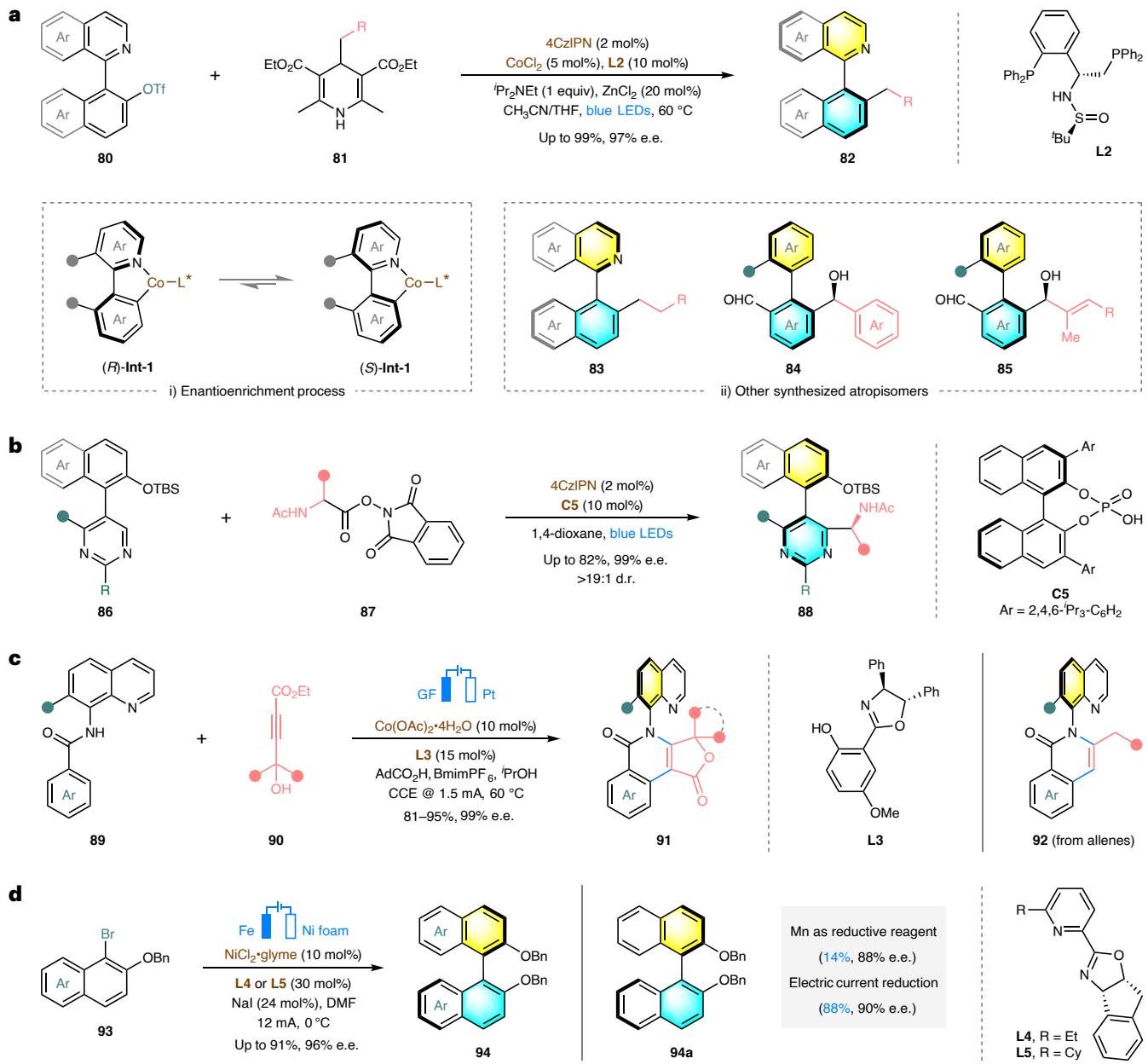

Fig. 6 | Catalytic asymmetric synthesis of atropisomers involving emerging synthetic tools. a, Merging of photocatalysis with metal catalysis. 4CzIPN, 2,4,5,6-*tetra*-9*H*-carbazol-9-yl-1,3-benzenedicarbonitrile. **b**, Incorporation of photocatalysis with organocatalysis. **c**, Electro-oxidative metal catalytic asymmetric transformations. Bmim, 1-butyl-3-methylimidazolium. **d**, Use of electric current in asymmetric reductive homocoupling. Glyme, ethylene glycol dimethyl ether; Et, ethyl; Cy, cyclohexyl.

This paucity was recently addressed by Song and colleagues, as well as our works. They detailed the atroposelective Suzuki–Miyaura borylation of aryl halides with unsymmetrical diboron reagents **98** to assemble arylborons **99**, which derive their optical activity from a C–B axis (Fig. 7c)[98]. *P*-chiral monophosphorus ligand **L6**, previously studied for this type of reaction, was utilized, and reductive elimination of the transmetallated intermediate was proposed to be stereodetermining. Very recently, two alternative strategies were developed by the same group through tetracoordinate boron-mediated dynamic kinetic asymmetric cross-coupling[99] and atroposelective kinetic C–H functionalization[100] under palladium catalysis. Our approach to the catalytic enantioselective construction of axially chiral B-aryl-1,2-azaborines **101** that contain a stereogenic C–B axis involved a CPA-promoted desymmetrization of 1,2-azaborine derivatives with diazodicarboxamides[101].

Construction of N–N axial chirality could be favoured by the shorter bond length and repulsive interaction between the lone pairs of the two nitrogen atoms. However, a low rotational barrier could emerge from deplanarization of the two N-containing planes upon rotation. A recent study by Houk, Lu and colleagues showed that stable N–N axial chirality could be present in 1-aminopyrroles (**103**) and 3-aminoquinazolinones, in their atroposelective synthesis of these compounds through a quinidine-catalysed *N*-allylic alkylation reaction (Fig. 7d)[102]. The axial disposition of the existing N–N axis is determined following introduction of an allyl group, which also hinders further rotation of the chiral axis. This hot topic has been well reviewed recently by the groups of Lu[103] and Bencivenni[104], so details of the advances will not be presented here.

Heteroatom tethered diaryls could display apparent axial chirality when sterically hindered substituents are installed at the

https://doi.org/10.1038/s41929-024-01138-z

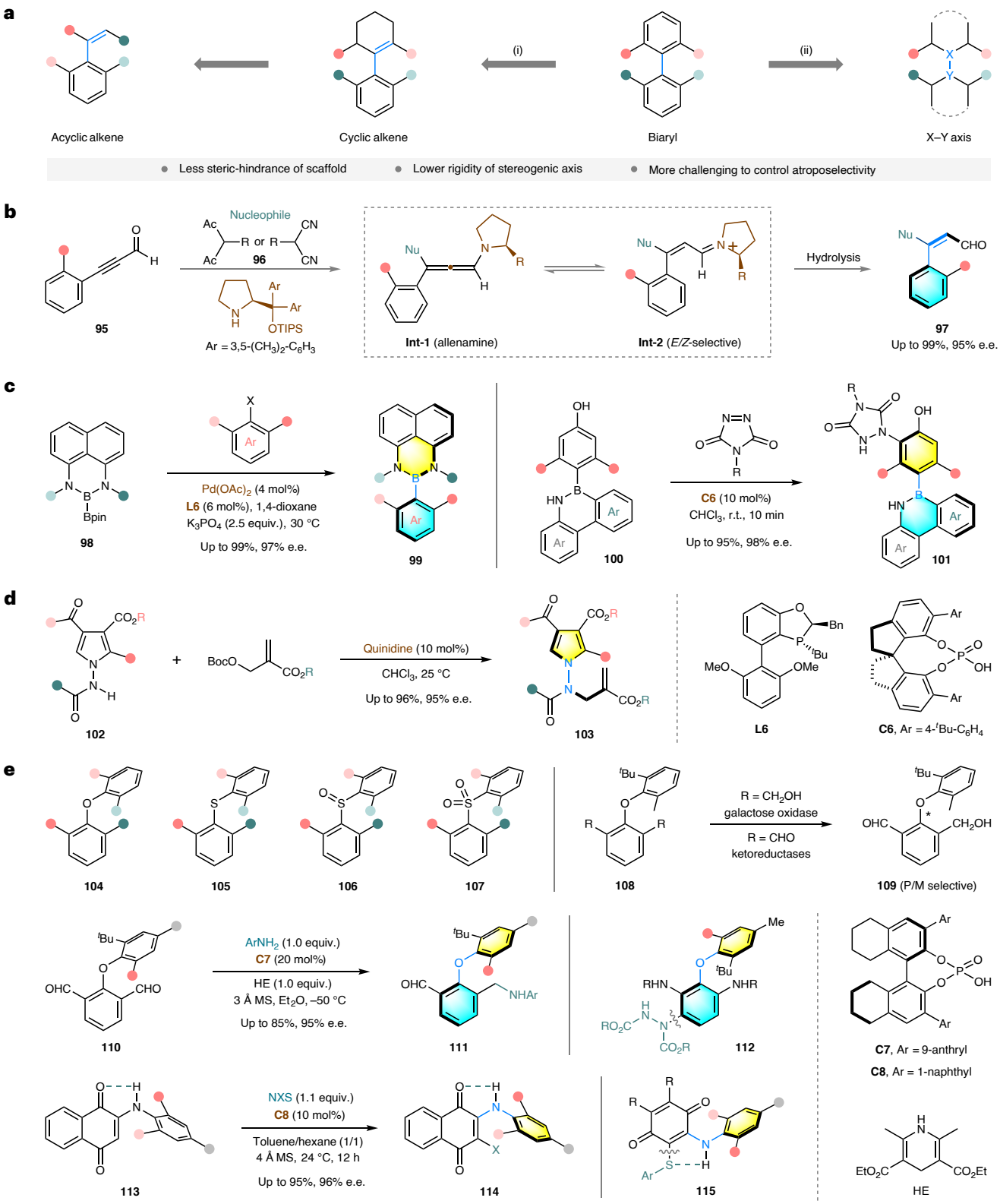

Fig. 7 | Axially chiral alkenes and stereogenic axis involving heteroatom(s). **a**, Challenges in the control of atroposelectivity in the modified structures of biaryls. **b**, Catalytic asymmetric synthesis of axially chiral acyclic alkenes. **c**, Asymmetric syntheses of atropisomers bearing a C–B stereogenic axis. **d**, Asymmetric synthesis of atropisomers with a N–N stereogenic axis. **e**, Catalytic atroposelective syntheses of axially chiral diaryl ethers and their derivatives. P/M, plus (+)/minus (−) configuration; HE, Hantzsch esters; NXS, *N*-halogenated succinimides.

ortho-positions of the C–X bond. A series of investigations have been carried out by the Clayden group to reveal the atropisomerism in diaryl ethers (**104**), sulfides (**105**), sulfoxide (**106**) and sulfones (**107**)[105,106]. They also realized the asymmetric synthesis of diaryl-ether-type atropisomers **109** by biocatalysis[107]. In 2023, Zeng, Zhong and colleagues described the atroposelective synthesis of diaryl ethers **111** bearing

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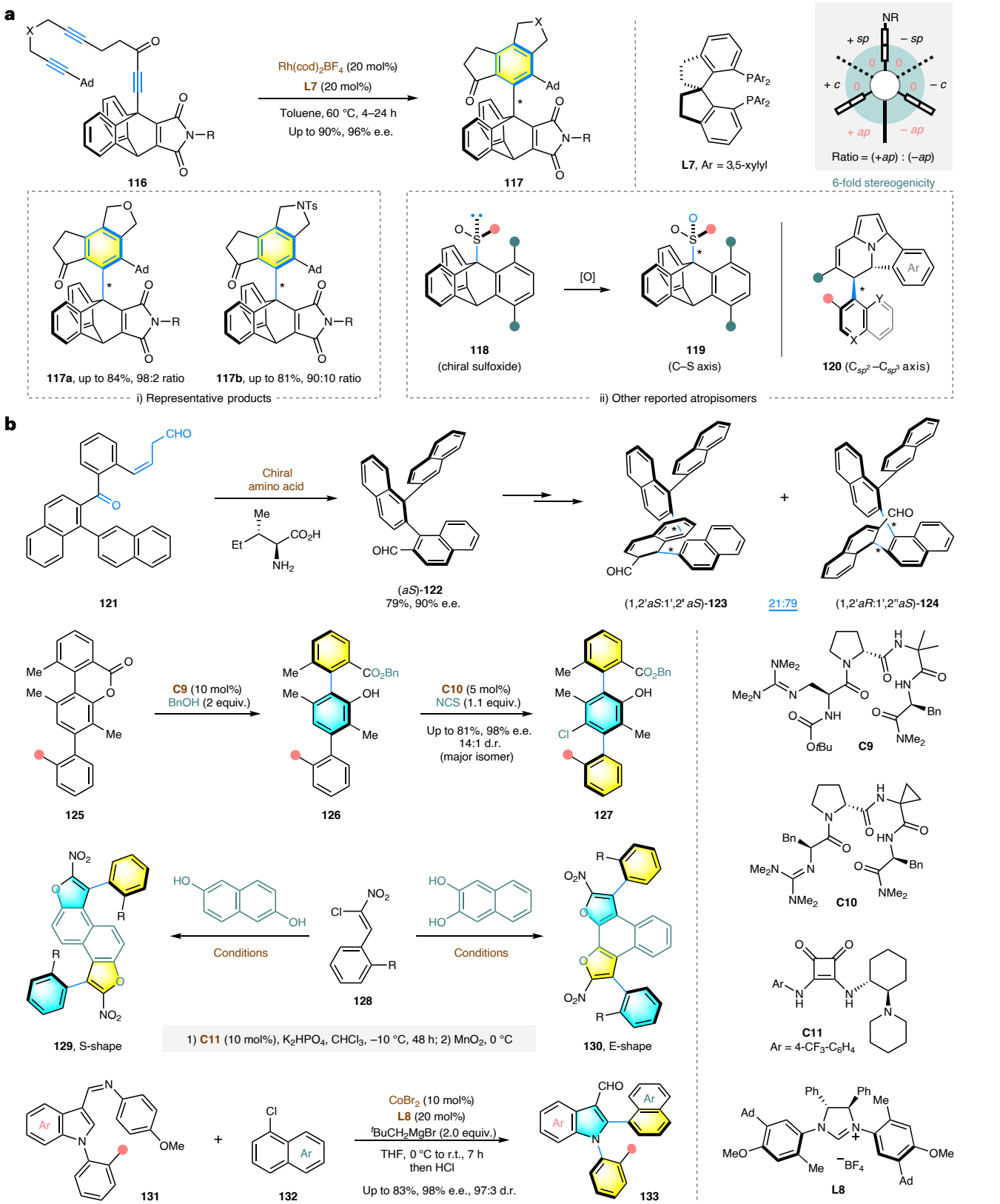

Fig. 8 | Atropisomers with a stereogenic C(sp^3)–X axis or multiple axes. a, Atroposelective syntheses of structures involving a C(sp^2)–C(sp^3) or C(sp^3)–S stereogenic axis with high-order stereogenicities. **b**, Catalytic asymmetric syntheses of atropisomers containing multiple axes. Ad, adamantyl.

a dual *O*-aryl axis through CPA-facilitated desymmetrization of Clayden's achiral dialdehydes[108] with a Hantzsch ester as hydride donor. Concurrently, diamine-substituted diaryl ethers were used to construct this type of atropisomer (**112**) via electrophilic amination with azodicarboxylates under CPA catalysis[109]. Moreover, *N*-aryl aminoquinones (**114**, **115**), as oxidative precursors of diaryl amines, have been

obtained atroposelectively by organocatalysis. Mechanistic studies have suggested that the intramolecular N–H···O/S hydrogen bond is crucial for the stability of the C–N axis (Fig. 7e)[110,111].

Atropisomers with a stereogenic C(sp^3)–X axis or multiple axes

Atropisomerism about C(sp^2)–C(sp^3) bonds has received extensive interest from the synthetic chemistry community[112]. However, the catalytic enantioselective synthesis of conformationally stable atropisomers bearing such a stereogenic axis remained in its infancy until Sparr's pioneering work, where interlocked **117** displaying an uncommon sterically congested C(sp^2)–C(sp^3) stereogenic axis with six pronounced rotational barriers (instead of two) was achieved through Rh-catalysed [2 + 2 + 2] cyclotrimerization (Fig. 8a,i)[113]. This reaction was realized by using trialkynyl ethenoanthracene substrates **116**, outfitted with a bulky adamantyl group and an interdigitating keto functionality. The replacement of substitution was possible at the C(sp^3) component. They also showed that, with distinct ligand systems, four of the six possible stereoisomers could be selectively assembled. Recently, the same team achieved the asymmetric synthesis of atropisomeric sulfones **119** with a stereogenic C(sp^3)–S axis under oxidation conditions from rotationally dynamic sulfoxide **118** with chirality on the sulfur atom, enriching the library of this type of structure[114]. Conformationally stable C(sp^2)–C(sp^3) atropisomers **120** were also synthesized by Jørgensen and colleagues via an organocatalytic enantioselective cyclization (Fig. 8a,ii)[115]. The prospect of controlling the resulting higher-order stereogenicities with a chiral catalyst uncovers an unexplored domain of atroposelective synthesis that will benefit the design of functional molecular systems.

The topology resulting from the existence of multiple stereogenic axes in a single architecture may establish a range of applications in asymmetric catalysis as well as functional materials. This is stimulating the evolvement of the field towards the construction of multiaxis systems[116]. Based on the established atroposelective aldol cyclization strategy, Sparr and colleagues prepared enantioenriched 1,2-ternaphthalene carbaldehyde (a*S*)-**122** with a stereogenic C–C axis from ketoaldehyde **121** (Fig. 8b)[117]. After synthetic elaboration to generate another aldol cyclization precursor and in situ oxidation, substrate-controlled atropo-diastereoselective aldol condensation yielded 1,2-diaxes compounds **123** and **124** with 21:79 d.r. A similar strategy was utilized by them to access all four stereoisomers of atropisomeric two-axis systems with cinchona alkaloid-based chiral ion-pairing catalysts in 2022[118]. Miller and colleagues inventively designed a two-fold dynamic kinetic resolution synthesis to fabricate 1,4-diaxis terphenyl atropisomers **127** with the signature peptide catalysts[119]. Ring-opening/transesterification of lactone **125** is catalysed by strongly basic guanidine peptide catalyst **C9** with the use of benzyl alcohol. The revealed phenol group facilitates **C10**-catalysed *para*-C–H chlorination to set the second stereogenic axis. Rodriguez, Bonne and co-workers ingeniously utilized two-fold central-to-axial chirality conversion for the synthesis of such types of compounds enabled by oxidative aromatization[120]. With chiral squaramide-tertiary amine **C11** as the bifunctional catalyst, bidirectional domino bisheterocyclization between chloronitroalkenes **128** and naphthalene-2,6-diol or naphthalene-2,3-diol proceeded smoothly twice to generate the *S*- (**129**) and *E*-shaped (**130**) bis-benzofuran atropisomeric oligoarenes featuring two distal C–C stereogenic axes in generally excellent enantiocontrol. Furthermore, simultaneous control of two atropisomeric elements could be realized by a one-reaction–double-stereoinduction strategy[121]. Organocatalytic atroposelective difunctionalizations of internal alkynes involving chiral VQM intermediates have been elegantly used in the assembly of multiaxial frameworks by Yan's team[73,74]. More recently, a one-step synthesis of atropisomeric indoles (**133**) bearing vicinal C–C and C–N diaxes was carried out by Wencel-Delord, Ackermann and colleagues through double cobalt-catalysed imine-directed C–H activation starting from *N*-arylated indoles **131**[122]. In a report by Shi and colleagues, this class of diaxial scaffolds was forged by cobalt-catalysed atroposelective C–H annulation reactions[123].

Conclusions and outlook

In line with progress regarding asymmetric catalysis, atroposelective synthesis has made substantial strides in the past decade. A variety of enabling strategies with broad applicability have emerged, offering efficient access to valuable scaffolds. This, in turn, could reduce the cost and resources needed to convert these scaffolds into ligands and catalysts. The increased availability of these chirality-inducing agents will further drive advancements in asymmetric synthesis. However, practical access to certain privileged scaffolds remains elusive, necessitating ongoing innovation. Despite the emergence of electro- and photochemical synthesis, their compatibility with chiral catalysts poses a major challenge.

Recent progress in catalytic atroposelective synthesis is also serving as a platform to broaden the chemical space of atropisomers, as evidenced by the thriving development of axially chiral alkenes and the unveiling of unconventional atropisomers.

Finally, future developments in this emerging field are primarily manifested in three directions. First, investigations into atropisomeric backbones with stereocontrol potential continue to be a major focus. This exploration may entail the creation of multiaxial scaffolds that display distinct and rigid chemical topologies, and the inclusion of heteroatoms on these scaffolds as interaction sites holds promise for the development of potent ligands or organocatalysts. Second, in the quest for the more practical construction of privileged atropisomeric skeletons, there is a growing interest in the exploration and development of innovative strategies and chemical methodologies. Leveraging the power of photocatalysis, electrochemical synthesis or a combination of both holds great promise as a practical and effective synthetic approach to overcome this long-standing challenge. Finally, to gain a deeper understanding of the underlying factors that influence rotational barriers and to explore broader applications in medicinal chemistry and materials science, computational calculations and the emerging field of artificial intelligence chemistry offer valuable tools for advancement.

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Acknowledgements

We are grateful for financial support from the National Natural Science Foundation of China (21825105, 22231004, 22271135 and 22301125), the National Key R&D Program of China (2022YFA1503703 and 2021YFF0701604), Guangdong Innovative Program (2019BT02Y335) and Shenzhen Science and Technology Program (KQTD20210811090112004, JCYJ20210324120205016 and JCYJ20210324105005015). We appreciate assistance from SUSTech Core Research Facilities.

Author contributions

B.T. and W.-Y.D. supervised the study. S.-H.X. and W.-Y.D. conducted the literature search. B.T., S.-H.X., W.-Y.D. and Y.-B.W. wrote the manuscript.

Competing interests

The authors declare no competing interests.

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Peer review information *Nature Catalysis* thanks the anonymous reviewers for their contribution to the peer review of this work.