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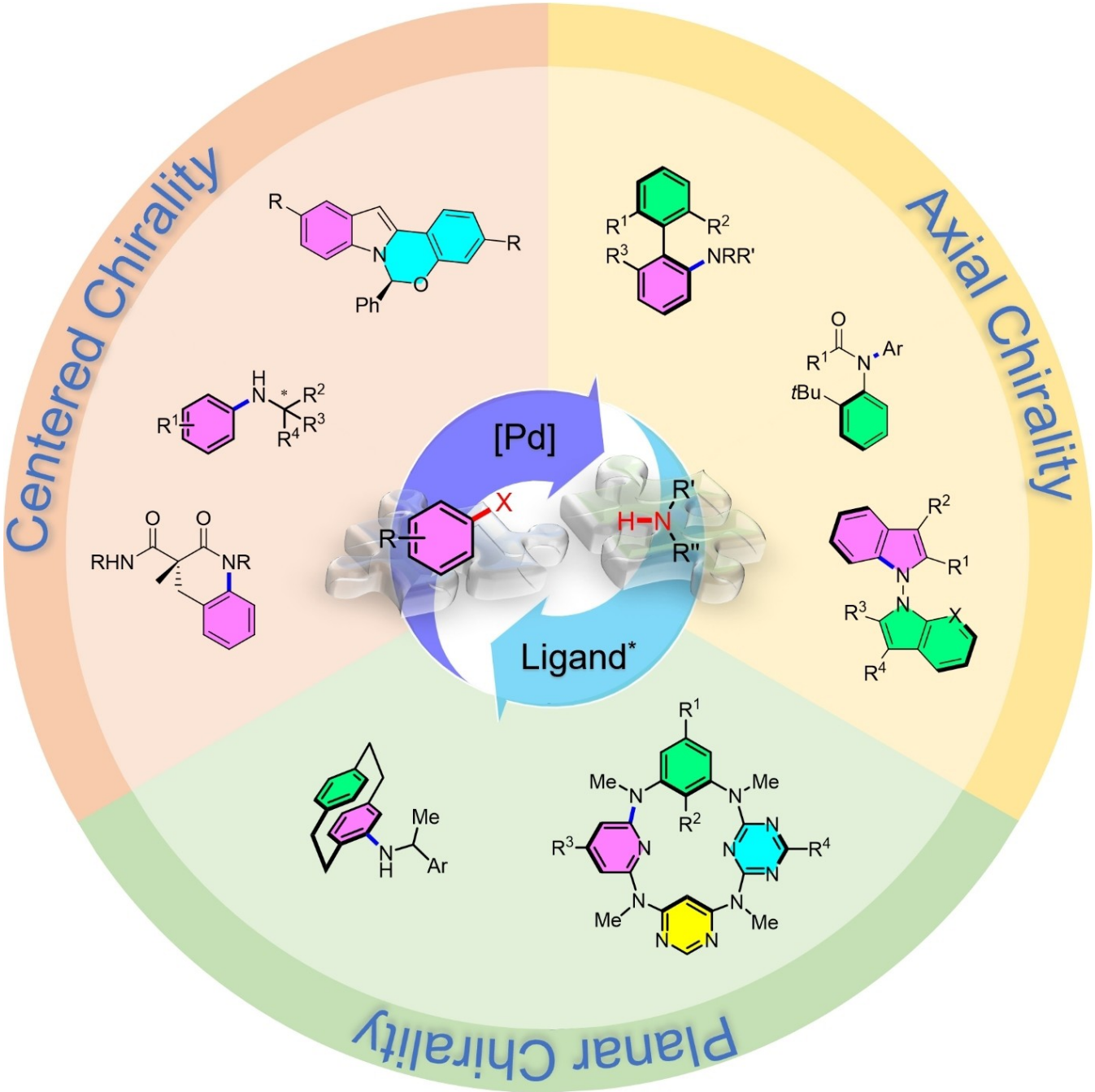
Asymmetric Synthesis

The Asymmetric Buchwald–Hartwig Amination Reaction

Chuan-Jun Lu[+], *Qi Xu*[+], *Jia Feng,* and Ren-Rong Liu**



Abstract: Over the past few decades, the Buchwald–Hartwig reaction has emerged as a powerful tool for forging C–N bonds, and has been vital to the pharmaceuticals, materials, and catalysis fields. However, asymmetric Buchwald–Hartwig amination reactions for constructing centered chirality, planar chirality, and axial chirality remain in their infancy owing to limited substrate scope and laggard ligand design. The recent surge in interest in the synthesis of C–N/N–N atropisomers, has witnessed a renaissance in asymmetric Buchwald–Hartwig amination chemistry as the first practical protocol for the preparation of C–N atropisomers. This review highlights reported asymmetric Buchwald–Hartwig amination protocols and provides a brief overview of their chemical practicality.

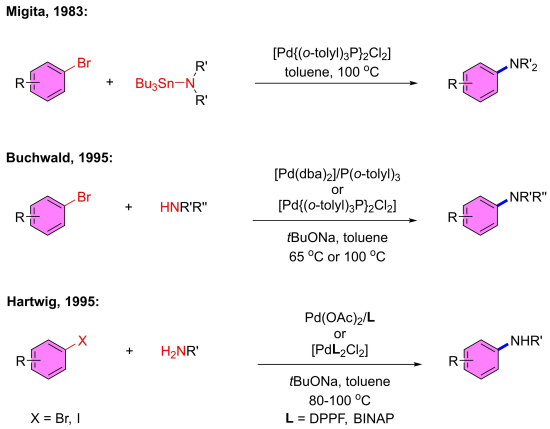
1. Introduction

The palladium-catalyzed amination of (pseudo) aryl halides with free amines, which is the Buchwald–Hartwig amination reaction, has developed into a powerful and robust tool for constructing arylamines, which has an extremely important application in pharmaceuticals, materials, and catalysis.[1–4] The Buchwald–Hartwig amination reaction is substantially advantageous for constructing aryl C–N bonds over other traditional methods, such as the S_NAr and Ullmann–Goldberg reactions,[5–8] owing to its broad substrate scope and mild reaction conditions. Readily available starting materials, efficient transformations, and fine-tunable catalyst systems render the Buchwald–Hartwig reaction an appealing approach to valuable arylamines.

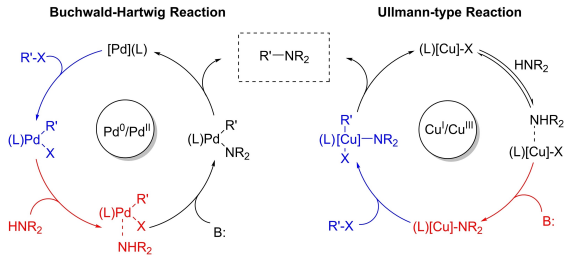
The first palladium-catalyzed aryl amination reaction involving a tin amide and an aryl halide was reported by Migita in 1983 (Scheme 1),[9] which was followed by breakthroughs that use free amines instead of toxic aminostannanes; this palladium-mediated amination chemistry was independently reported by Buchwald and Hartwig in 1995 (Scheme 1).[10,11] Buchwald reported chemistry that uses secondary amines catalyzed by palladium- and electron-donating P(*o*-tolyl)$_3$ ligands. On the other hand, as Hartwig's coupling partners were primary amines, he chose to coordinate aromatic bisphosphines, such as 1,1′-bis-(diphenylphosphino)ferrocene (DPPF) or 1.1′-binaphthyl-2.2′-diphemyl phosphine (BINAP), to palladium to facilitate to aryl amination.

When it comes to C–N coupling chemistry, a comparison of the Buchwald–Hartwig reaction and Ullmann-type reactions is instructive because they exhibit similar efficiencies and operate through similar catalytic cycles. Scheme 2 shows that halides undergo amination with palladium or copper and auxiliary ligands in the presence of a base to afford coupling products,[12–17] with similarities including oxidative addition, ligand exchange, and reductive elimination. During Cu catalysis, N-nucleophiles coordinate to copper prior to oxidative addition, which is a key step in the catalytic cycle. It should be noted that the entire catalytic system involves the activity of the N-nucleophile, copper source, base, and solvent, among others, which are responsible for ensuring that a given protocol is successful. With the abovementioned factors in mind, there is no doubt that this Cu-based chemistry is of limited generality.

In contrast, oxidative addition proceeds first during Pd catalysis, followed by combination with the N-nucleophile. Ligands play dominant roles in palladium-mediated amination processes; therefore, developing efficient ligands that contribute to broadening the applications scope is a critical objective. Starting with P(*o*-tolyl)$_3$ as the first-generation ligand, the Buchwald–Hartwig reaction has evolved to use aromatic phosphines,[18–21] hindered alkylphosphines,[22–25] carbene ligands,[26] and finally hindered alkyl bisphosphines[27–29] as fourth-generation ligands. Ligand evolution has extensively expanded substrate scope and greatly improved the efficiency of the Buchwald–Hartwig reaction.



Scheme 1. Palladium-catalyzed C–N coupling reactions.



Scheme 2. Typical catalytic cycles involved in Pd- and Cu-mediated C–N coupling chemistry.

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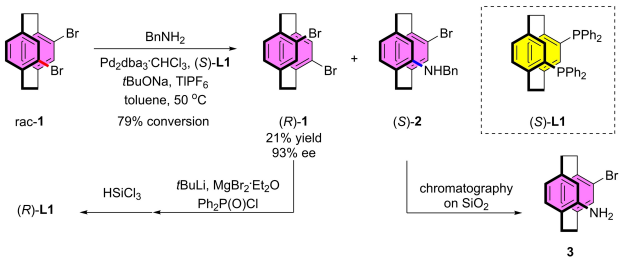
The regular catalytic cycle that operates in the Buchwald–Hartwig reaction includes three key steps: oxidative addition, ligand exchange, and reductive elimination, with palladium and amine complexes formed during ligand-exchange. Steric hindrance associated with the amine significantly affects the reaction rate. Differences in reaction rates and the steric sensitivity of the palladium-ligand complex provides opportunities for controlling the enantioselectivity of the Buchwald–Hartwig reaction.

In 1997, Pye and Rossen conducted the first asymmetric Buchwald–Hartwig reaction en route to enantiomeric [2.2]phanephos (**L1**) through kinetic resolution (Scheme 3).[30] Typically, stereogenic **L1** was obtained using chiral dibenzoyltartaric acid in a final resolution step, which limited further ligand modification. Dibromide rac-**1** underwent smooth asymmetric amination to give arylamine (*S*)-**2** using palladium and bisphosphine ligand (*S*)-**L1** as the catalyst, leaving behind enantioenriched (*R*)-**1** in 21 % yield with up to 93 % ee. The kinetic-resolution approach offers a toolbox for preparing various substituted planar bisphosphines that are broadly used in asymmetric catalysis.

Over the past few decades, centered chirality, axial chirality, planar chirality, and dual stereogenic centers have been constructed by harnessing the Buchwald–Hartwig amination reaction. This review covers the following four aspects, namely the construction of centered chirality, axial chirality, planar chirality, and dual stereogenic centers.

2. Constructing Centered Chirality

Aryl halides undergo asymmetric amination with a racemic or prochiral amine in the presence of an appropriate chiral ligand to form a stereogenic center through (dynamic) kinetic resolution or desymmetrization (Scheme 4). Intermolecular or intramolecular reactions are used to build chiral acyclic or cyclic amines during (dynamic) kinetic resolution, while prochiral amines are only intramolecularly aminated in desymmetrization-type reactions.



Scheme 3. Asymmetric amination chemistry using the kinetic resolution strategy.

2.1. (Dynamic) Kinetic Resolution

In 2015, Ohta disclosed that chiral aryl amines can be prepared by kinetically resolving secondary amines using asymmetric Buchwald–Hartwig chemistry (Scheme 5).[31] Arylbromides or aryliodides **4** undergo enantioselective amination with racemic amines **5** to afford arylamines **6** with ees of up to 80 % using $Pd_2(dba)_3$ and (*R*)-2,2′-bis(di-p-tolylphosphino)-1,1′-binaphthyl ((*R*)-Tol-BINAP) as the catalyst system. Control experiments using optically pure (*R*)-**5a** and (*S*)-**5a** under standard conditions revealed that (*R*)-**5a** reacts faster than its enantiomer (90 % conversion after 5 h vs.

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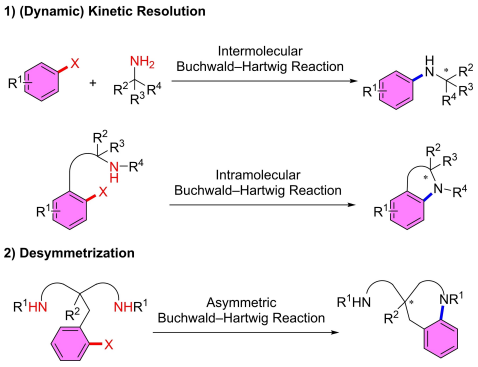
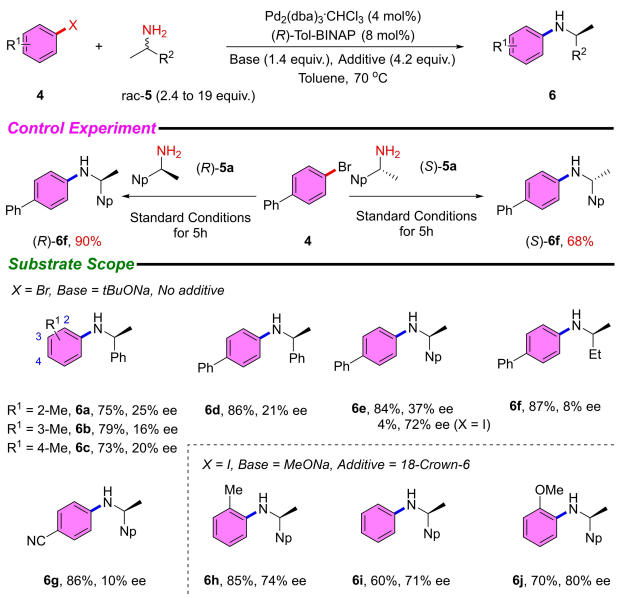


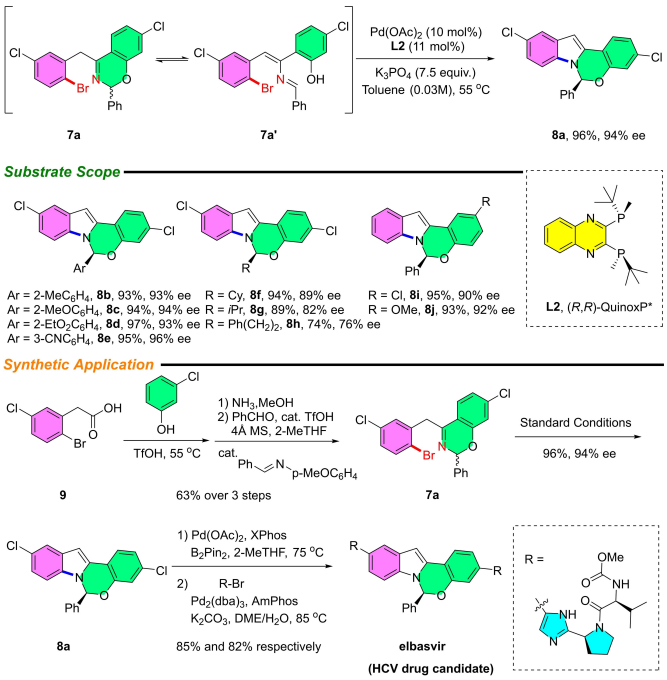
Scheme 4. Asymmetric Buchwald–Hartwig reactions for constructing centered chirality.



Scheme 5. Kinetically resolving alkyl amines using the Buchwald–Hartwig reaction.

68 %). Steric hindrance adjacent to the nitrogen atom appears to significantly impact the enantioselectivities of **6d**–**6f**. While a higher enantioselectivity (72 %) was obtained when the aryl iodide was used, the reaction delivered a very low yield of **6e** (4 %). On the other hand, much higher enantioselectivities were obtained using MeONa as the base in the presence of 18-crown-6.

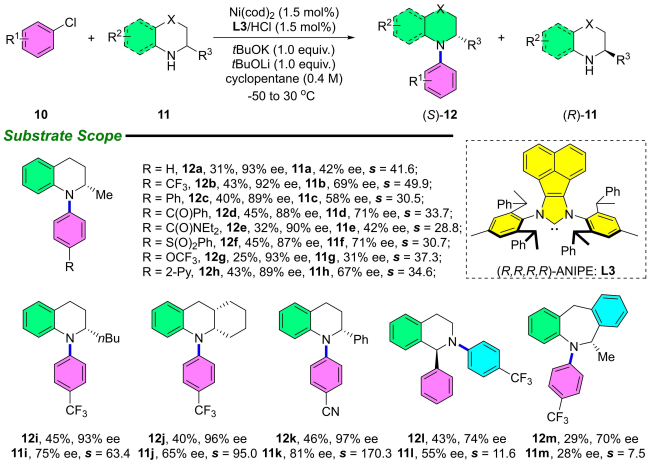
Compared to kinetic resolution, dynamic kinetic resolution offers the significant advantages of atom economy and enantioselectivity fine-tuning, rendering it more appealing despite being challenging.[32–34] In 2015, Belyk and Li enantioselectively synthesized hemiaminals using asymmetric Buchwald–Hartwig amination chemistry (Scheme 6).[35] The starting benzoxazine **7a** is racemic due to a rapid equilibration involving ene-imine **7a′**. However, **7a** underwent smooth asymmetric amination to give cyclic product **8a** in 96 % yield and 94 % ee in the presence of palladium and bisphosphine ligand **L2**. The generality of the protocol was examined using various aryl and alkyl substituents at the α-



Scheme 6. Dynamic kinetic resolution strategy for the synthesis of chiral hemiaminals.

position relative to the nitrogen atom (**8b**–**8h**) and backbone substituents (**8i**–**8j**). The applicability of this chemistry was demonstrated through the asymmetric synthesis of elbasvir, a potential hepatitis C virus (HCV) drug candidate. Starting with commercially available acid **9**, the synthetic protocol highlighted asymmetric amination as the key step that provided excellent enantioselectivity control. Finally, elbasvir was accessed in an overall yield of 42 % within six steps.

In 2021, Shi and Hong reported Ni-catalyzed amination chemistry involving aryl chlorides and kinetic resolution (Scheme 7).[36] The protocol used bulky and flexible chiral *N*-heterocyclic carbene (NHC) ligand **L3** to achieve enantio-



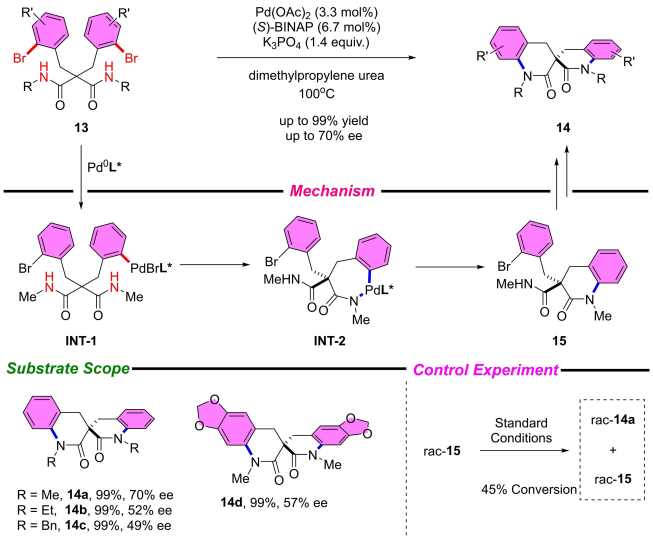
Scheme 7. Ni-catalyzed Buchwald–Hartwig-type amination reactions.

selective C–N coupling at low temperatures (as low as −50 °C). Aryl chloride **10** coupled smoothly with racemic amine **11** aided by Ni and **L3** to deliver the chiral amination product **12**, with enantioenriched **11** remaining behind. A broad range of amines has been successfully used in Buchwald–Hartwig-type coupling reactions with excellent enantioselectivities and high *s* factors reported.

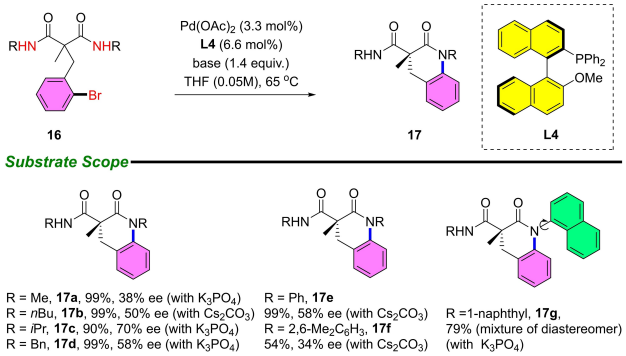
2.2. Desymmetrization

Desymmetrization is a useful asymmetric synthesis tool.[37,38] In 2009, Sasai used this strategy to synthesize chiral spiro skeleton **14** starting from symmetric substrate **13** (Scheme 8).[39] One-pot, two-step Buchwald–Hartwig amination chemistry with palladium and (*S*)-BINAP was used to construct C_2-symmetric spiro compounds **14** with ees of up to 70 %. Based on the proposed mechanism, a control experiment with semi-cyclic intermediate **15** was carried out under standard conditions, which revealed that both **14a** and the remaining **15** were racemic. These results show that the first amination step is stereo-determining, thereby ruling out a kinetic resolution process in the second amination step. Substrates with various substituents were found to be compatible with this methodology, with divergent spiro products that exhibited moderate enantioselectivities produced.

Meanwhile, Viirre disclosed that prochiral diamides **16** can be asymmetrically aminated to yield chiral quinolinones **17** by employing a desymmetrization strategy (Scheme 9).[40] In this process, monophosphine ligand **L4** delivered superior stereogenic control than other bisphosphine ligands, such as BINAP. In addition, the base and steric hindrance associated with substituent on the nitrogen atom appeared to significantly influence both enantioselectivity and efficiency. Excellent yields and moderate stereoselectivities were obtained for variously substituted systems. An inseparable mixture of diastereomers was obtained for **17g** (R = 1-naphthyl) owing to the restricted rotation of one C–N bond.



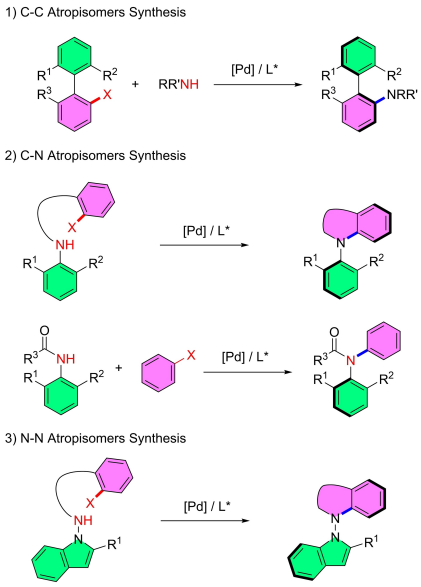
Scheme 8. Synthesizing chiral spiro compounds using asymmetric amination chemistry.



Scheme 9. Desymmetrization strategy for constructing centered chirality.

3. Constructing Axial Chirality

Axial chirality has been arising wide range of interests in recent years due to its important application in natural products, materials and asymmetric catalysis.[41,42] Transition metal mediated asymmetric synthesis is one of the important approaches to construct axial chirality.[43–49] The asymmetric Buchwald–Hartwig reaction was successfully used to synthesize atropisomers with excellent stereogenic control (Scheme 10). C–C and C–N atropisomers can be prepared using palladium and an appropriate chiral phosphine ligand, with the reactive site *ortho* to the existing axis when a chiral C–C axis is constructed. Asymmetric amination helps to forge the chiral axis through cyclization when synthesizing C–N/N–N atropisomers.

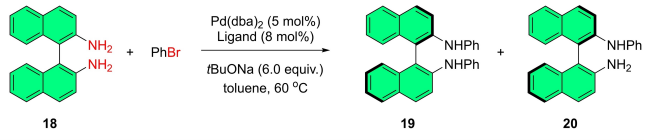


Scheme 10. Asymmetric Buchwald–Hartwig amination chemistry for constructing axial chirality.

3.1. C–C Atropisomers Synthesis

In 1998, Kočovský and Vyskočil reported the use of an atroposelective Buchwald–Hartwig amination process to kinetically resolve diamines **18** (Scheme 11).[50] Treating **18** with phenylbromide in the presence of $Pd(dba)_2$ and BINAP gave monoarylated product **20** and diarylated product **19**. High amination reactivity resulted in a lower enantiomeric excess when the reaction time was extended by 2 h. While resolution was further improved in terms of enantioselectivity, **18** was so poorly soluble in toluene that lower catalyst reactivity was observed.

Lassaletta and Fernández used a dynamic kinetic resolution strategy to synthesize isoquinoline-amino naphthalene derivatives using asymmetric Buchwald–Hartwig amination chemistry and rac-**21** as the starting material (Scheme 12).[51]

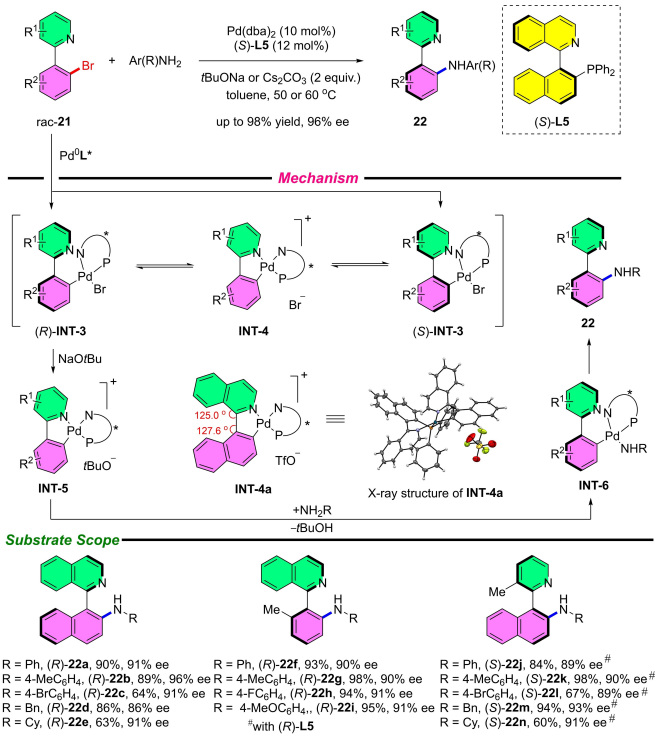


18 19 20

Entry	Substrate	Ligand	Reaction Time	Conversion (%)	Product
1	(*R*)-**18**	rac-BINAP	4 h	100	(*R*)-**19** + (*R*)-**20**
2	rac-**18**	(*S*)-BINAP	1 h	45	(*R*)-**19** (17% ee) + (*R*)-**20**[a]
3	rac-**18**	(*S*)-BINAP	2 h	70	(*R*)-**19** (10% ee) + (*R*)-**20**[a]
4	rac-**18**	(*S*)-BINAP	3 h	85	(*R*)-**19** (5% ee) + (*R*)-**20**[a]

[a] ee value was not analyzed

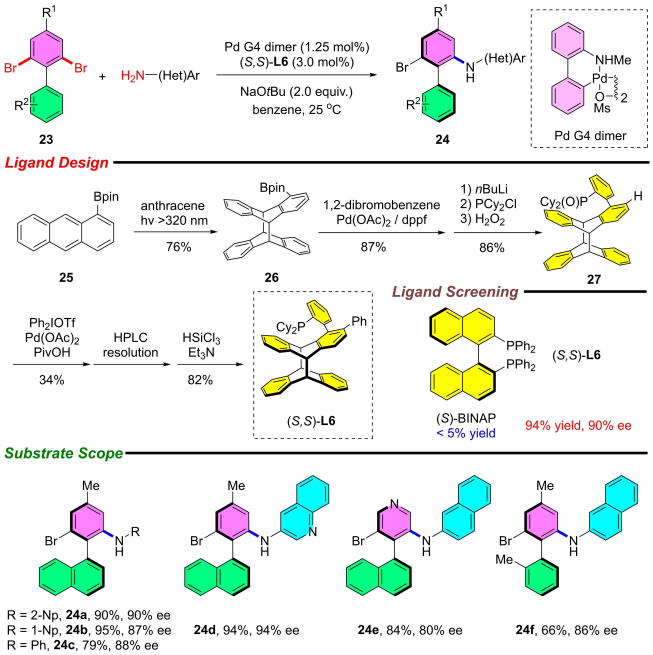
Scheme 11. Kinetic resolution strategy for constructing axial chirality.



Scheme 12. Dynamic kinetic resolution strategy for constructing axial chirality.

The enantioselective amination procedure was catalyzed by palladium and a chiral BINAP ligand to give aminated product **19** with stereoselectivities of up to 96 %. A plausible mechanism for stereogenic induction was proposed following control experiments. Oxidative addition involving bromide **21** and palladium generates palladium complexes (*R*)-**INT-3** and (*S*)-**INT-3**, which exist in equilibrium through key intermediate **INT-4**. Single crystals of **INT-4a** were cultivated and analyzed by X-ray diffractometry to determine its absolute configuration, which revealed that the two planar aromatic rings adopt a twisted structure, with angles of 125.0° and 127.6° between them and the C–C axis, leading to racemization of the axial chirality. Further amination releases axial chirality aided by the chiral ligand to form final product **22**. A broad range of arylamines and other structures were examined, with excellent yields and enantioselectivities obtained. It is worth noting that enantiomers were not obtained using (*R*)-**L5** under the standard conditions.

Recently, Cong reported an asymmetric Buchwald–Hartwig desymmetrization protocol for aminating dibromides during the construction of axially chiral bi(hetero)aryls (Scheme 13).[52] This procedure revealed that monophosphine **L6** derived from the anthracene photodimer is more reactive than BINAP, which is an excellent frequently used ligand in Buchwald–Hartwig chemistry. The synthesis of **L6** involved seven steps from borylated anthracene **25**, with the enantiomers separated by chiral high performance liquid chromatography (HPLC). The methodology was used to couple divergent arylamines and other biarylbromides using the Pd G4 dimer and **L6** as the catalyst.



Scheme 13. Synthesizing biaryl atropisomers by desymmetrizing dibromides.

3.2. C–N Atropisomer Synthesis

Given the vital application in natutal products[53] and drug design,[54–56] C–N atropisomers synthesis has became a hot topic in asymmetric synthesis recently.[57–59] Since its successful application in asymmetric synthesis in 1997,[30] Buchwald–Hartwig reaction has developed into a practical protocol to the synthesis of atropisomers bearing a C–N axis.

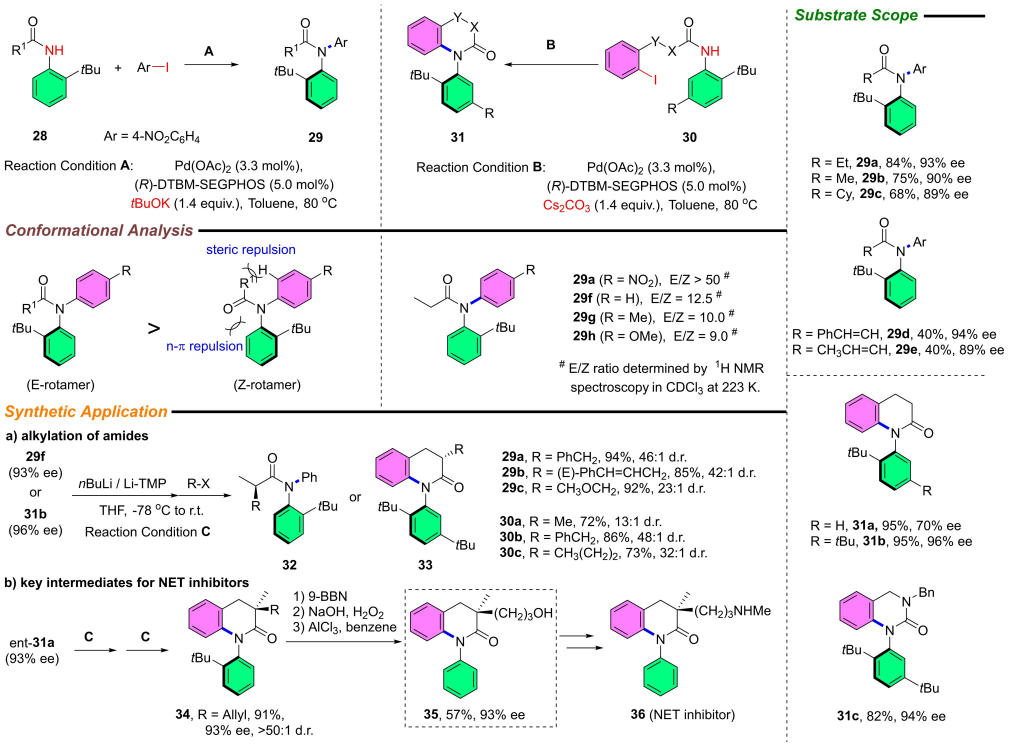
In 2005, Kitagawa and Taguchi disclosed the first atroposelective Buchwald–Hartwig amination protocol for preparing C–N atropisomers with $Pd(OAc)_2$ and (*R*)-5,5′-bis[di(3,5-di-t-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole ((*R*)-DTBM-SEGPHOS) as the catalyst system (Scheme 14).[60] Arylamides **28** reacted with aryliodides in the presence of *t*BuOK to deliver arylated amides **29** in an highly enantioselective manner. However, **30** cyclized to give **31** with up to 96 % ee when Cs_2CO_3 was used as the base. No erosion of enantioselectivity was observed when **29a** (93 % ee) was heated at 60 °C for 8 h, which indicates that these atropisomers have high rotational barriers. Substrates with various substituents were successfully asymmetrically aminated with excellent stereoselectivities.

A detailed study into conformational stability and the diastereoselective additions of chiral enolates was subsequently conducted.[61] An ^1H NMR experiment in $CDCl_3$ at 223 K revealed a sharp decrease in the *E*/*Z* ratio (from >50:1 to 9:1) with increasing electron density (**29a**, **29f**–**29h**). Compared with the *E*-rotamer, the *Z*-rotamer exhibited steric repulsion between its H and R^1 groups, as well as n-π repulsion between the carbonyl group and a phenyl group, and was the minor product as a consequence. Amides **29f** and **30b** α-alkylated smoothly and with excellent diastereoselectivities owing to the lack of conformation-locking chelation to the carbonyl group.

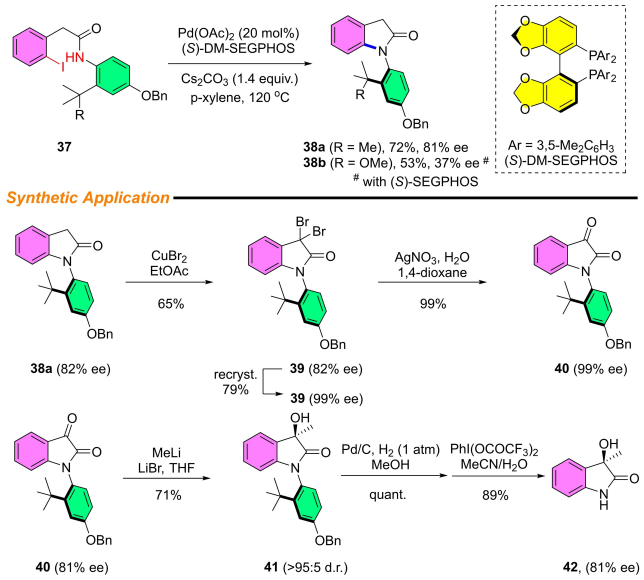
Furthermore, Kitagawa used the abovementioned protocol to synthesize key intermediate **35**, which is used to prepare norepinephrine transporter (NET) inhibitor **36**, a promising drug candidate for the treatment of attention-deficit/hyperactivity disorder (ADHD).[62,63] The two-step α-alkylation of enantioenriched *ent*-**31** (93 % ee) furnished α-tertiary amide **34** in greater than 50:1 diastereoselectivity. Subsequent borylation, oxidative hydroxylation, and removal of the *tert*-butyl group afforded **35** with excellent enantioselectivity; **35** can be converted into **36** following a reported procedure.

In 2015, Nakazaki reported an intramolecular Buchwald–Hartwig amination protocol for synthesizing axially chiral oxindoles (Scheme 15).[64] Aryl amide **37** underwent asymmetric amination to afford **38a** in 72 % yield with 81 % ee aided by the $Pd(OAc)_2$/(*S*)-DM-SEGPHOS catalyst. Oxindole **38a** was then converted into isatin **40** in a two-step bromination and hydrolysis procedure without any loss of enantioselectivity. Stereogenic information was transferred from **40** to center-chiral **42** during alkyl-group addition and removal of the aryl group. This protocol highlighted the asymmetric synthesis of an oxindole with a C–N chiral axis, which is applicable to drug-candidate design.

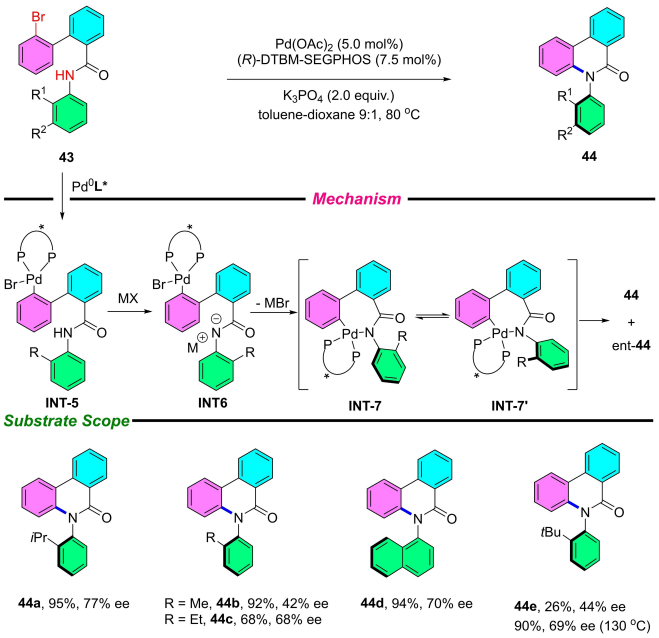
In 2016, Kitagawa reported the atropisomeric synthesis of phenanthridin-6-one using asymmetric Buchwald–Hartwig chemistry (Scheme 16).[65] Amides **43** cyclized to give



Scheme 14. Asymmetric Buchwald–Hartwig chemistry for synthesizing C–N atropisomers.



Scheme 15. Asymmetric Buchwald–Hartwig chemistry for the synthesis of axially chiral oxindoles.

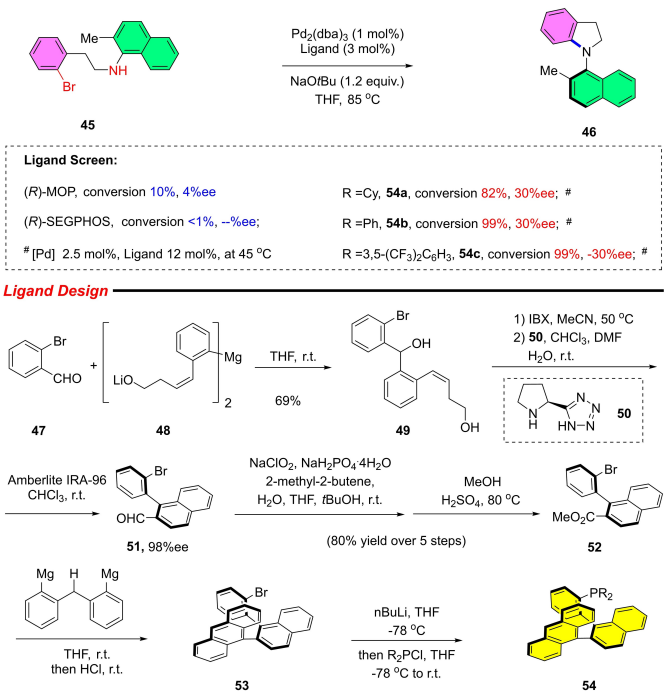


Scheme 16. Asymmetric Buchwald–Hartwig chemistry for constructing axial chirality.

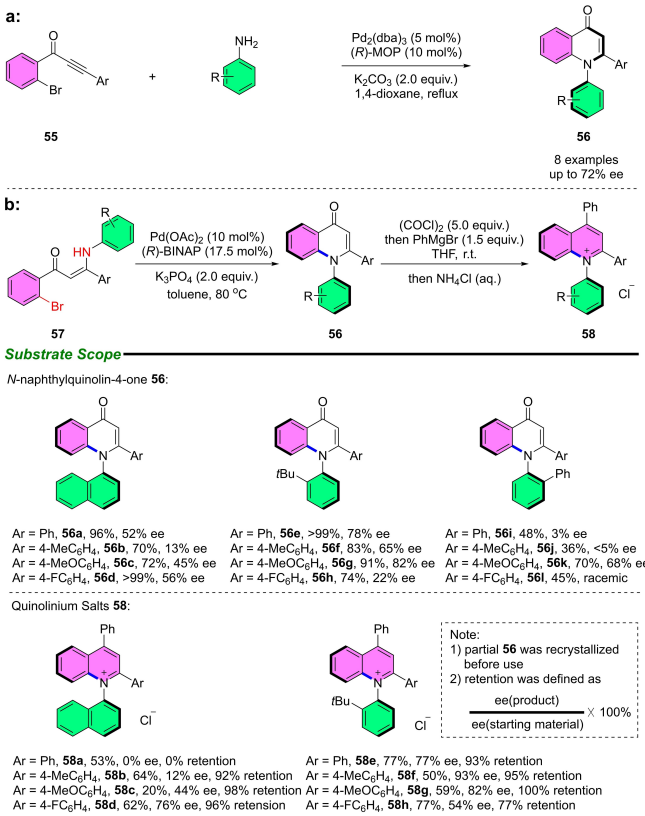
axially chiral compounds **44** bearing C–N axes with ees of up to 77 %. Pd^0 underwent oxidative addition with **43** to give **INT-5** under these reaction conditions, which was subsequently converted into **INT-6** by the action of a base. Subsequent removal of MBr afforded **INT-7**, which was transformed to **INT-7′** through an inversion equilibrium. Final reductive elimination afforded **44** in enantiomeric form. As for the generality of the protocol, substrates with various substituents delivered moderate (42–77 %) enantioselectivities. However, a higher enantioselectivity was obtained when *ortho-tert*-butyl-substituted amides were reacted at 130 °C (69 % *vs.* 44 % ee at 80 °C). The results reveal that **INT-7** or **INT-7′** reductively eliminate at different reaction rates, and that the bulky *tert*-butyl group restricts rotation around the C–N axis.

In 2020, Sparr reported an asymmetric amination/cyclization protocol for preparing *N*-aryl indolines (Scheme 17).[66] The procedure proceeded with palladium and a newly developed monophosphine ligand. The synthesis commenced with the addition of a diaryl magnesium to 2-bromobenzaldehyde **47**, which afforded diol **49**. Subsequent oxidation, asymmetric aldol addition, and aromatization afforded biaryl **51** with excellent enantioselectivity (98 % ee). Bromide **51** was then subjected to oxidation/esterification to give **52**, which was converted into the final ligand **54** through further anthracylation and phosphine-group introduction. Notably, **54** behaved as a privileged ligand in asymmetric Buchwald–Hartwig amination/cyclization reactions. Optimizing the reaction conditions of cyclic amination to deliver axially chiral **46** with **54** led to dramatically improved enantioselectivity and efficiency compared to those obtained with the frequently used [(*R*)-2′-methoxy[1,1′-binaphthalen]-2-yl]diphenylphosphine ((*R*)-MOP) and (*R*)-SEGPHOS ligands.

In 2012, Kitagawa reported palladium-mediated cyclic amination chemistry involving aryl bromides **55** and aryl amines to furnish atropisomeric *N*-arylquinolin-4-ones **56** bearing C–N axes (Scheme 18a).[67] This transformation involves the formation of a vinyl amine intermediate and a subsequent intramolecular Buchwald–Hartwig amination reaction to deliver the final product **56**. Later, Knipe reported the use of asymmetric Buchwald–Hartwig reactions



Scheme 17. Asymmetric cyclization chemistry for constructing axial chirality.



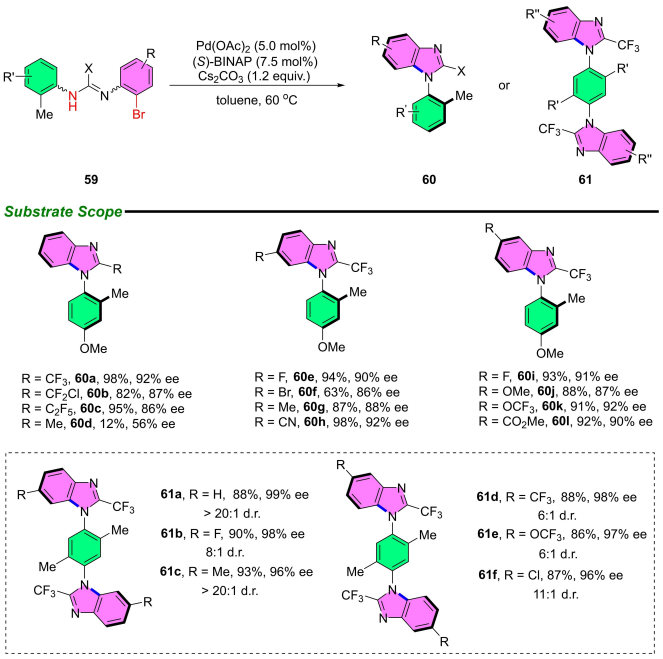
Scheme 18. Asymmetric Buchwald–Hartwig chemistry for the synthesis of axially chiral quinolinium salts.

en route to axially chiral *N*-arylquinolinium salts (Scheme 18b).[68] Enaminones **57** were treated with a palladium/(*R*)-BINAP catalyst to deliver enantioenriched *N*-arylquinolin-4-ones **56** with ees of up to 82%. Both efficiency and enantioselectivity depended on the electronic and steric nature of the substituent. *N*-Aryl quinolinium salts **58** were obtained from chiral **56** through phenyl addition and elimination, with most cases exhibiting little loss in enantioselectivity. Specifically, solvatochromic salts **58** are potential colorimetric sensors.

In 2021, Liu and Lu reported the formation of benzimidazole atropisomers using intramolecular cyclization chemistry involving amidines (Scheme 19).[69,70] Amidines **59** derived from commercially available anilines were treated with palladium and the chiral (*S*)-BINAP ligand to afford annulation products **60** or **61** bearing one or two chiral axes. The protocol exhibited broad substrate scope and included a diverse set of substituents at various positions of the benzimidazole and aryl ring. Benzimidazole atropisomers **61** exhibited diastereoselectivity that ranged between 6:1 and >20:1, along with excellent enantioselectivities.

In 2021, Zhou reported a palladium/norbornene co-catalyzed cyclic amination of amide and aryl iodide to the synthesis of C–N atropisomers, during which palladium mediated C–N coupling was involved as the final step.[71]

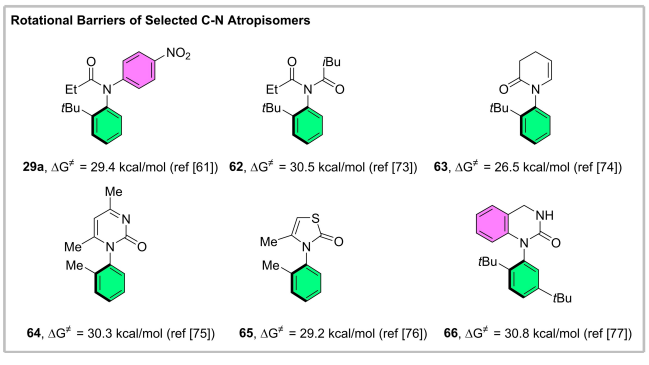
As the asymmetric Buchwald–Hartwig amination reaction is a practical protocol for the catalytic enantioselective syntheses of C–N atropisomers, it is essential to give a brief



Scheme 19. Asymmetric Buchwald–Hartwig chemistry for the synthesis of benzimidazoles atropisomers.

introduction to the stability of the chiral C–N axis.[72] As depicted in Scheme 20, bulky *ortho* substituents, such as methyl or tert-butyl, are associated with relatively high rotational barriers, irrespective of whether or not they are *N*-hetero-cyclized atropisomers. Compound **63** was determined to exist as a stable conformer with a 26.5 kcal mol^{-1} rotational barrier energy, even when only two *ortho* groups are present. A six-membered *N*-heterocycle exhibits a somewhat higher rotational barrier than a five-membered *N*-heterocycle. We conclude that steric hindrance associated with the *ortho* substituent around the C–N axis plays a dominant role in determining atropoisomeric stability.

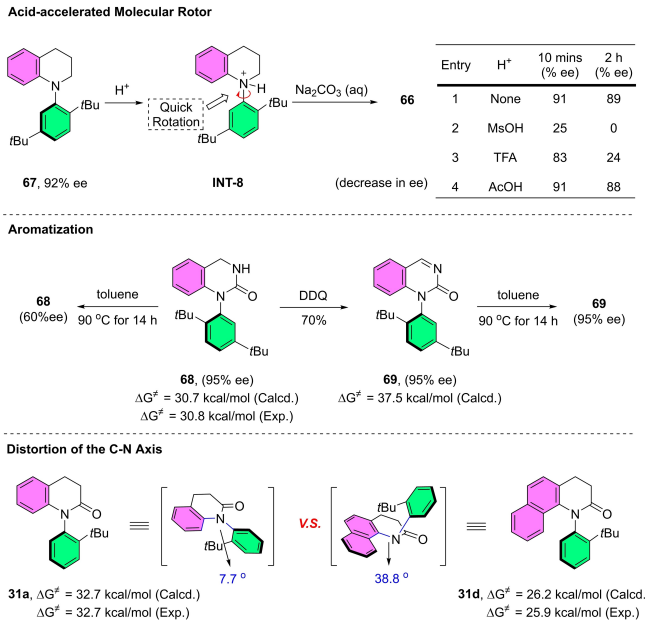
Several factors dominate atropisomeric stability owing to the intrinsic characteristics of axial chirality that arise through restricted free rotation of the axis. A C–N-axis-containing aryl amine can act as a base and react with an acid to form a quaternary ammonium salt, which may



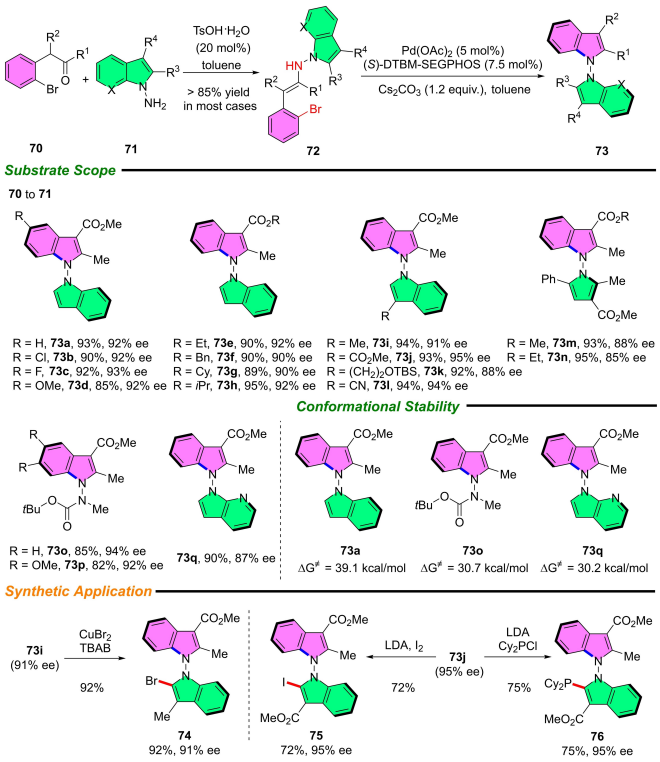
Scheme 20. Rotational barriers of some selected C–N atropisomers.

contribute to the rapid rotation of the chiral axis (Scheme 21).[77] Stereoenriched atropisomer **67** (92 % ee) was treated with acid for a period of time prior to being basified with Na_2CO_3, which led to an ee that sharply declined with increasing acidity, consistent with poor chiral C–N axis stability under acidic conditions.

Aromatization is another factor that needs to be considered when determining the stability of a C–N atropisomer.[78] The ee (95 %) of C–N atropisomer **68** (experimental rotational barrier: 30.8 kcal mol^{-1}; calculated: 30.7 kcal mol^{-1}) was observed to decrease by 60 % when heated at 90 °C in toluene for 14 h, highlighting its relatively low stability. Aromatic product **69** was obtained without any enantioselectivity erosion when **68** was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), even when heated at 110 °C for 14 h, which is most likely ascribable to the higher rigidity of the aromatic heterocycle with aromatization calculated to contribute an additional 6.8 kcal mol^{-1} to the rotational barrier. Steric hindrance may distort the C–N axis when the nitrogen atom becomes sp^3 hybridized, which destabilizes atropisomerism.[79] C–N atropisomer **31a** exhibits a rotational energy barrier of 32.7 kcal mol^{-1}; however, **31d**, which is more significantly sterically hindered, only has a rotational barrier of 25.9 kcal mol^{-1}. Insight provided by the single crystal structures of the two compounds reveals distortion angles between the aromatic rings and the C–N axis of up to 38.8°, which contributes to the relatively free rotation of the axis.



Scheme 21. Some factors affecting axial chirality stability.



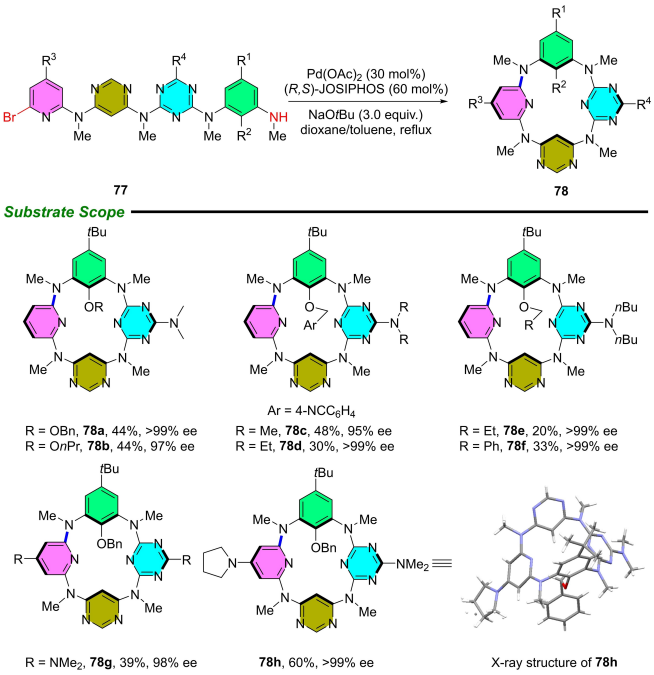
Scheme 22. Asymmetric Buchwald–Hartwig amination chemistry for the synthesis of N–N atropisomers.

3.3. N–N Atropisomer Synthesis

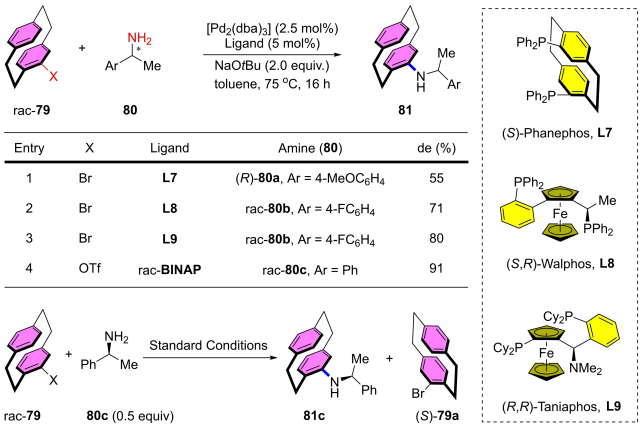
Recently, Liu and Li reported intramolecular Buchwald–Hartwig amination chemistry for constructing *N*,*N*-bisindole atropisomers (Scheme 22).[80] Firstly, enamines **72** were prepared in mostly excellent yields by condensing aryl bromides **70** with amino indoles **71**. Subsequent asymmetric amination was carried out with the assistance of $Pd(OAc)_2$ and (*S*)-DTBM-SEGPHOS to afford *N*,*N*-bisindole atropisomers **73** with excellent selectivities. The protocol was applied to a variety of substituted indoles, with other N-substituted heterocycles, such as pyrroles, delivering comparable stereoselectivities (**73a**–**73n**). Acyclic *N*-indoles were accessed with ees exceeding 90 % (**73o**–**73p**), and substituted 1*H*-pyrrolo[2,3-*b*]pyridine **73q** was obtained in 90 % yield and 87 % ee. The rotational barriers associated with these N–N atropisomers were experimentally shown to provide somewhat more stable chiral axes compared to their C–C analogs. Furthermore, the bisindoles were readily converted into bromides or iodides without any erosion of enantioselectivity, and the potential chiral ligand **76** was synthesized through the installation of a phosphorus group.

4. Constructing Planar Chirality

In 2020, Wang and Tong reported an elegant intramolecular asymmetric amination reaction for constructing ABCD-type tetraazacalix[4]aromatics that exhibit planar chirality (Scheme 23).[81] Palladium-mediated amination reactions proceeded smoothly to give cyclized products **78** with excellent enantioselectivities using (*R*, *S*)-2-(1-(dicyclohexylphosphino)ethyl)-1-(diphenylphosphino)ferrocene ((*R*,*S*)-JOSIPHOS) as the stereogenic source. The single crystal



Scheme 23. Asymmetric Buchwald–Hartwig amination chemistry for constructing planar chirality.



Scheme 24. Diastereoselective Buchwald–Hartwig chemistry for kinetic resolution.

structure of **78h** clearly reveals that these ABCD-type tetraazacalix[4]aromatics show planar chirality owing to restricted rotation associated with the -OBn substituents. The developed methodology can be used to synthesize a series of ABCD-type chiral molecules with excellent stereogenic control, albeit in yields of approximately 40 %. The prepared molecules displayed unique pH-triggered chiroptical switching and are potentially useful as guest-responsive chiroptical systems.

5. Diastereoselective Buchwald–Hartwig Amination

In 2005, Bräse reported the diastereoselective syntheses of [2.2]paracyclophane amines using Buchwald–Hartwig amination chemistry involving *rac*-4-bromo-[2.2]paracyclophane and chiral amines (Scheme 24).[82] Reacting racemic **79** with chiral or racemic primary amine **80** afforded amino [2.2]-paracyclophane **81** with good diastereoselectivities of up to 91 % achieved using various chiral biphosphines. Optically pure 4-bromo-[2.2]paracyclophane **81c** was obtained in only one step when *rac*-**79** was subjected to kinetic resolution using 0.5 equiv of chiral amine **80c**.

6. Summary and Outlook

Over the past few decades, the Buchwald–Hartwig reaction has emerged as a powerful tool for constructing aryl amines, and is widely applicable to the pharmaceutical and chemical industries. However, asymmetric Buchwald–Hartwig amination chemistry remains in its infancy, with efficiency and generality requiring improvement. Three pathways for advancing this chemistry appear suggested: a) the development of novel ligands that contribute to highly efficient amination chemistry in terms of both conversion and enantioselectivity; b) the development of efficient intermolecular Buchwald–Hartwig amination chemistry, which is highly desired because the asymmetric Buchwald–Hartwig paradigm is still largely limited to intramolecular aminations, with few intermolecular versions reported; and c) broadening the substrate scope to include new structures that are highly desirable to academia and industry. Having witnessed the great successes of the Buchwald–Hartwig reaction since its birth in 1995, we fully expect that the asymmetric version will broaden its applicability, thereby contributing to significantly expanding its applications scope.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Amination · Asymmetric Catalysis · C–N Coupling · Enantioselectivity · Palladium

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