Angewandte Chemie International Edition

Angewandte International Edition Chemie

GDCh German Chemical Society

How to cite: *Angew. Chem. Int. Ed.* **2026**, e6839352
doi.org/10.1002/anie.6839352

REVIEW OPEN ACCESS

Strategies Toward Accessing Enantioenriched (Hetero)Benzo-Fused 5- and 6- Membered Rings via Intermolecular Carbometalation

Clara Jans | Armaan Grewal | Xavier Abel-Snape | Mark Lautens

Department of Chemistry, Davenport Research Laboratories, University of Toronto, Toronto, Ontario, Canada

Correspondence: Mark Lautens (mark.lautens@utoronto.ca)

Received: 9 March 2026 | **Revised:** 2 April 2026 | **Accepted:** 8 April 2026

Keywords: catalysis | enantioselectivity | carbometalation | transition metals

ABSTRACT

Enantioenriched benzofused 5- and 6- membered rings continue to be found as notable motifs in important molecules such as pharmaceuticals and natural products. A key synthetic strategy towards accessing these structures is via a metal-catalyzed intermolecular carbometalation step across a substituted olefin or alkyne. This review emphasizes recent advances towards accessing enantioenriched benzofused 5- and 6- membered rings *via* intermolecular carbometalation strategy, catalyzed by late and early transition metals. Through covering the key mechanistic investigations and computed conformational analyses, this review hopes to allow for a more unified understanding of how asymmetric control is attained across a diverse array of metals and ligands, and to highlight significant advances made in the past decade.

1 | Introduction

Metal catalyzed asymmetric transformations remain a central strategy in synthesis, as complex transformations can be achieved in a one pot process, improving efficiency [1]. The design of new chiral ligands and catalysts have helped advance the development of asymmetric reactions. Specifically, carbometalations, where a metal-carbon bond adds across carbon-carbon π-systems, such as alkynes or alkenes, have been a privileged strategy to construct new C—C bonds. Products arising from methodologies involving a carbometalation step can be obtained in both high regio- and enantioselectivity. The enantiodetermining step is often the carbometalation across the π-system, as the migratory insertion allows for chiral induction (Figure 1). Furthermore, the added challenge in developing intermolecular reactions has pushed chemists to develop cost- and energy-efficient catalytic systems to achieve such transformations.

Convergent synthesis strategies, where two or more partners react, allow chemists to build a wide and diverse library of products from combination of simple substrates. Intermolecular carbometalations allow for greater structural diversity, and often easier access to starting materials. Established reactions like the Larock indole synthesis [2] allow chemists to access structurally diverse indole products using simple starting materials. Disubstituted alkynes are easily accessible substrates via Sonogashira coupling [3] or electrophilic additions to alkynyl anions [4, 5]. Retrosynthetically, they also provide easy access to acetylene-like synthons, particularly for the synthesis of indenes, indenols and indoles.

This review will focus specifically on transition-metal-catalyzed, asymmetric syntheses of (hetero)benzo-fused 5- and 6-membered rings via intermolecular carbometalations, due to their widespread prominence as core structural

Clara Jans and Armaan Grewal have contributed equally to this work.

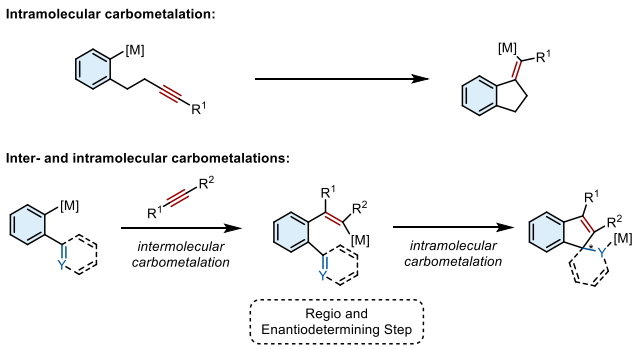


FIGURE 1 | Intra- and intermolecular carbometalations.

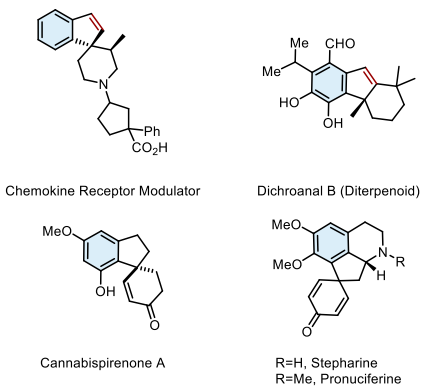


FIGURE 2 | Natural products and pharmaceuticals containing (hetero)benzo-fused 5- and 6- membered rings.

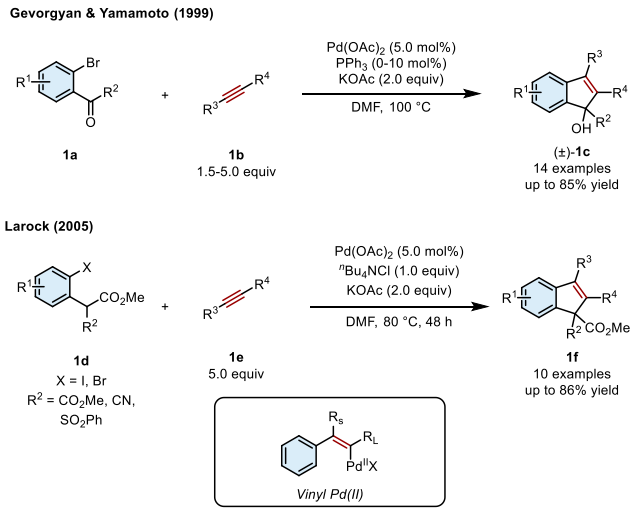
motifs in active pharmaceutical agents and natural products (Figure 2) [6–10]. Given the recent publication of complete and comprehensive reviews on the synthesis of axially chiral molecules [11–13], this review will focus on point chirality and synthesis of enantioenriched tertiary and quaternary centers, while highlighting recent examples on the synthesis of enantiomerically enriched atropoisomers.

2 | Palladium-Catalyzed Reactions

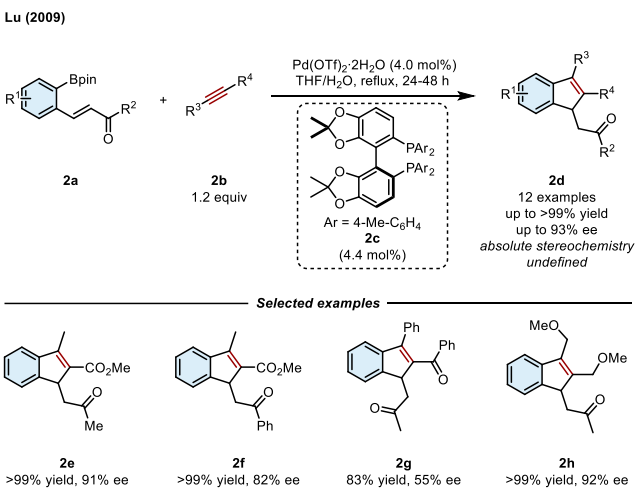
2.1 | Early Studies (RACEMIC)

The racemic synthesis of indenols via an intermolecular carbometalation was developed by Gevorgyan and Yamamoto in 1999 (Scheme 1, top) [14]. Following oxidative addition, the aryl Pd(II) species adds across a disubstituted alkyne to form the corresponding vinyl Pd(II) intermediate. Addition into an electrophilic carbonyl group yields the desired racemic indenol **1c**.

Larock subsequently reported the synthesis of indenes combining disubstituted alkynes and *ortho*-bromobenzaldehydes (Scheme 1, bottom) [15, 16]. Upon deprotonation of the acidic malonate moiety, the resulting carbanion attacks the vinyl-Pd(II) intermediate to form a 6-membered palladacycle. The desired indene **1f** is formed via a final C—C reductive elimination. In both cases, moderate to high regioselectivity was achieved, where the vinyl



SCHEME 1 | Palladium-catalyzed synthesis of racemic indenols and indenes.

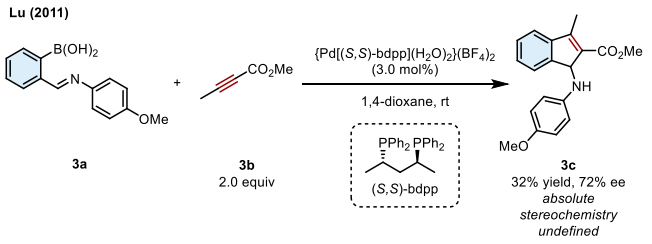


SCHEME 2 | Palladium-catalyzed synthesis of indenes from cinnamic ketones.

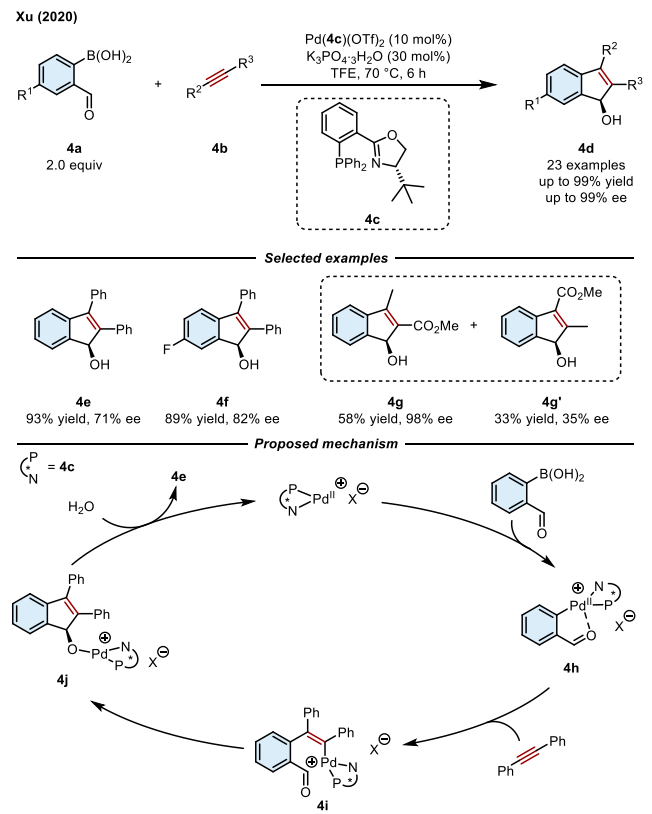
Pd(II) intermediate is bound to the carbon atom bearing the largest substituent of the initial unsymmetrical alkyne.

2.2 | Enantioselectivity Studies

In 2009, Lu and coworkers synthesized enantioenriched indenes from *ortho*-boronate cinnamic ketones (Scheme 2) [17]. Starting from a cationic palladium catalyst, the aryl boronic acid undergoes transmetalation, resulting in a cationic aryl Pd(II) species. Regioselective migratory insertion across an unsymmetrical alkyne occurs, after which conjugate addition to the vinyl ketone followed by protodemetalation furnishes the desired product. Indene **2e** was obtained in quantitative yield and 91% ee using bisphosphine ligand **2c**. Chalcone derivative **2f** was also synthesized in quantitative yield and 82% ee. A limited scope of alkynes was explored, with those bearing a phenyl ketone resulting in poorer enantioinduction, as illustrated by product



SCHEME 3 | Preliminary enantioselective results for the synthesis of aminoindenes.

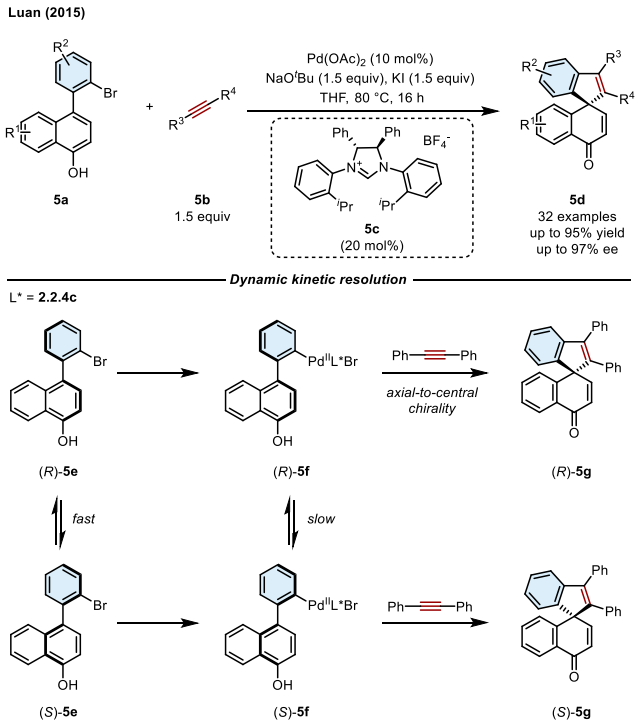


SCHEME 4 | Palladium(II)-catalyzed asymmetric synthesis of indenols.

2 g. Symmetrical bis(methoxymethyl) substituted alkyne gave product **2 h** in quantitative yield and 92% ee.

Shortly after this initial report, Lu et al. synthesized enantioenriched aminoindenes using a cationic palladium catalyst (Scheme 3) [18]. While arylimine **3a** gave the desired aminoindene in a moderate 72% ee using (*S,S*)-bdpp, the yield could not be improved beyond 32%.

In 2020, the Xu group showed that 2-formylphenylboronic acids and diarylacetylenes could be transformed into indenols under palladium catalysis (Scheme 4) [19]. Using chiral phosphinooxazoline ligand **4c**, indenol **4e** was synthesized in 93% yield and 71% ee. Fluorine-substituted substrates generally resulted in improved enantioinduction, as showcased by **4f**. Enantioinduction was shown to be highly dependent on the migratory insertion's

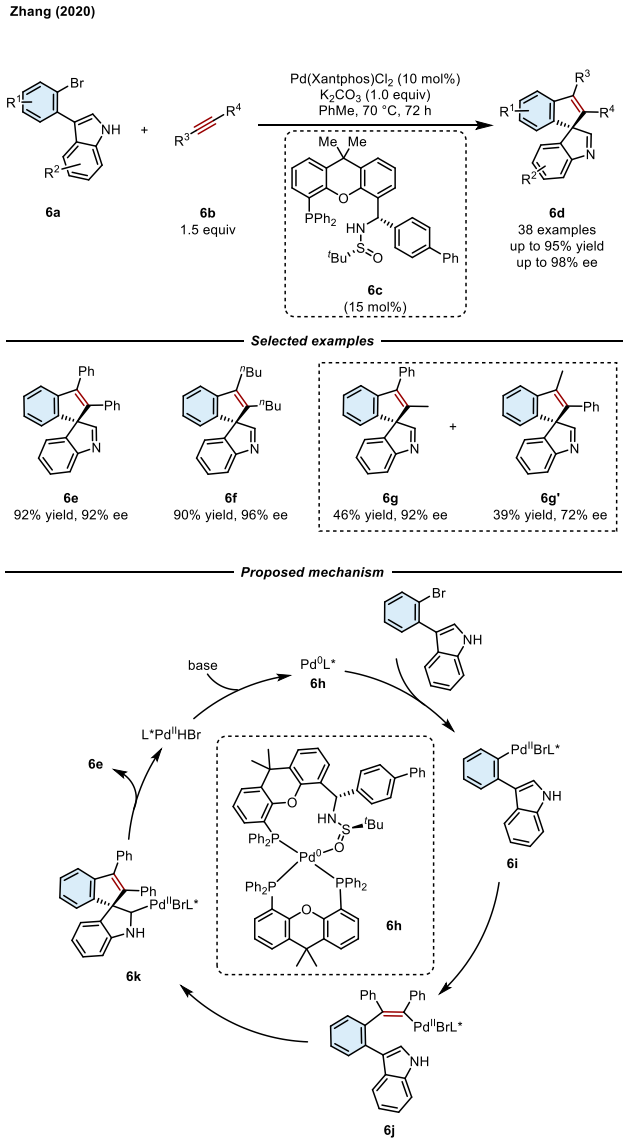


SCHEME 5 | Palladium-catalyzed DYKAT of biaryls for the synthesis of spiroindenes.

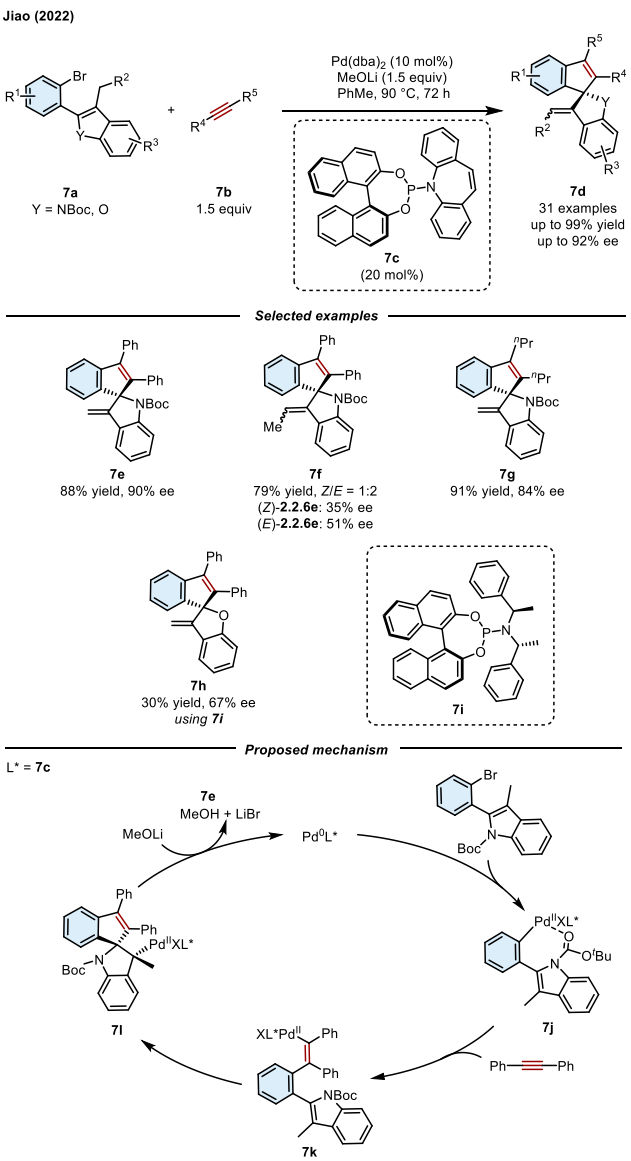
regioselectivity when using unsymmetrical alkynes, as product **4 g** was obtained in 98% ee, while regioisomer **4g'** in 35% ee.

Annulative dearomatization constitutes one of the main methodologies to access enantioenriched spiroindenes. In 2015, the Luan group reported the synthesis of spiroindenes **5d** via the dearomatization of naphthol derivatives (Scheme 5) [20]. A dynamic kinetic asymmetric transformation (DYKAT) strategy was used to transfer axial to central chirality. Fast interconversion between atropoisomers (*S*)- and (*R*)-**5e**, followed by oxidative addition using a palladium catalyst bearing the chiral *N*-heterocyclic carbene **5c** resulted in intermediates (*S*)- and (*R*)-**5f**. Subsequent dearomatization is favored from one face of **5f**, leading to axial-to-central chirality transfer. The desired spiroindenes **5d** were obtained in up to 97% ee.

In 2020, the Zhang group reported the asymmetric dearomatization of 3-(2-bromophenyl)-1*H*-indole **6a** using internal alkynes, resulting in chiral spirocyclopentaneindolines (Scheme 6) [21]. Using PC-Phos **6c** as the chiral sulfinamide ligand and Pd(Xantphos)Cl_2 as the precatalyst, spiroindole **6e** was obtained in 92% yield and 92% ee. Alkyl-substituted alkynes were also tolerated, as showcased by **6f** synthesized in 90% yield and 96% ee. Unsymmetrically substituted alkynes resulted in regioisomeric mixtures, such as **6 g** and **6g'**. The authors noted that the enantioselectivities were higher when the alkyl group is installed closer to the chiral center being formed. Control experiments showed that the catalyst responsible for the enantioinduction was the dual ligand system **6 h**, where both PC-Phos **6c** and Xantphos are coordinated to the metal center.



SCHEME 6 | Synthesis of spirocyclopentaneindolines via an indole dearomatization strategy.

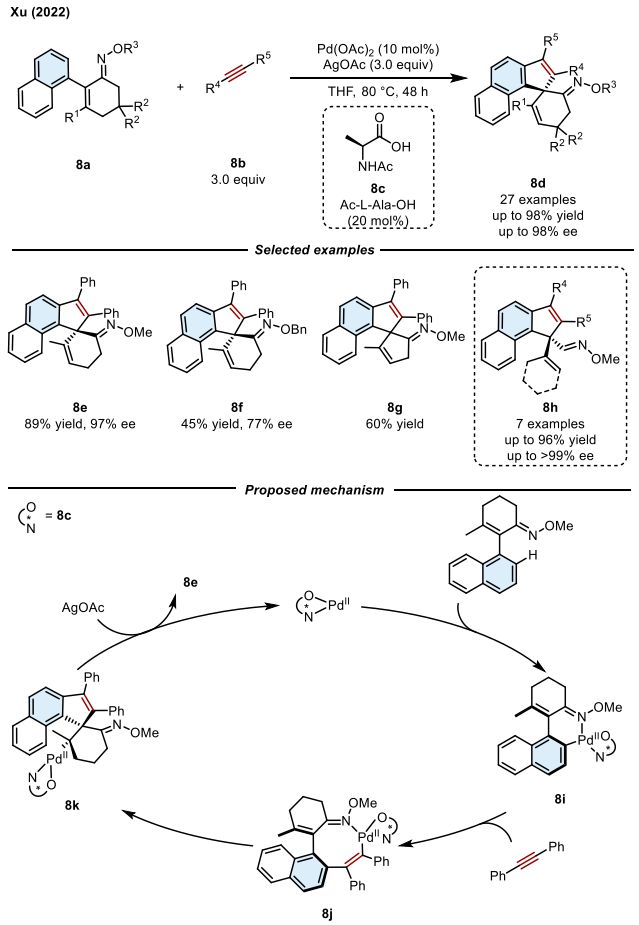


SCHEME 7 | Asymmetric dearomatization of indoles towards the synthesis of spiroindolenines.

In a 2022 report, the Jiao group developed a catalytic asymmetric dearomatization of indole-tethered substrates to access spiro indolenines (Scheme 7) [22]. Using the Carreira ligand **7c** and diphenylacetylene, spiroindene **7e** was successfully obtained from the corresponding Boc-protected indole in 88% yield and 90% ee. A 3-ethylindole-derived substrate led to spiroannulated **7f** as a mixture of 1:2 Z/E isomers, with diminished enantioselectivity. Using an alkyl-substituted dipropylacetylene, product **7 g** was obtained in 91% yield, 84% ee, and was successfully scaled up on a gram-scale in 98% yield and 80% ee. This protocol was also amenable to benzofuran substrates by employing phosphoramidite ligand **7i**. Following DFT studies, the authors propose that the Pd/**7c** complex first undergoes oxidative addition into the corresponding aryl bromide. Subsequent migratory insertion of diphenylacetylene into the C(sp^2)—Pd bond was found to be turnover-limiting and selectivity-determining. Indole dearomatization and β-H elimination eventually provide the product.

Pd(II)-catalyzed C—H activation strategies have additionally been used to access quaternary spiro centers (Scheme 8). Starting from an oxime-substituted substrate, product **8e** was obtained in 89% yield and 97% ee, with protected amino acid **8c** acting as the chiral ligand [23]. The oxime directing group had a large impact on reactivity and enantioselectivity, as *O*-benzyl oxime substituted product **8f** was obtained in 45% yield and 77% ee. Due to a lower rotation energy, 5,5-spirosystem **8 g** was obtained as a racemic mixture. Finally, non-spiro indenes **8 h** could also be synthesized using this methodology. An atroposelective C—H activation using a Pd(II) catalyst, followed by a migration across a disubstituted alkyne leads to **8j**. A second migration across a cyclic or acyclic alkene occurs, where the donation of axial-to-central chirality results in enantioenriched **8k**. β-H elimination yields the desired product.

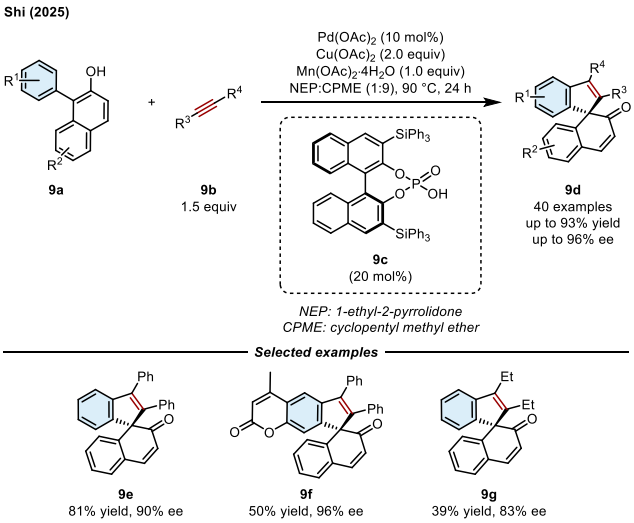
Recently, the Shi group developed the synthesis of spiroindenes via a C—H activation/dearomatization strategy (Scheme 9) [24].



SCHEME 8 | Oxime-directed atroposelective synthesis of spiroindenes.

Similar to Xu's report, the acetate-assisted concerted metalation-deprotonation (CMD) is directed by the naphthol ring, followed by migratory insertion across the alkyne moiety. Axial-to-central chirality transfer provides the final spiro compound in high enantioselectivity. Aryl-substituted alkynes gave moderate to good yields, as exemplified by spiroindenes **9e-f**. Dialkylacetylene substrates were also compatible, although they resulted in lower yields (**9 g**).

In 2025, the Lautens group developed a synthesis of enantioenriched, 2,3-unsubsituted indenes using enantiopure oxabicycles as chiral acetylene surrogates (Scheme 10) [25], building on earlier work [26]. Using the desymmetrized, enantiopure oxabicycle **10b**, bearing a secondary and tertiary amide backbone, indene product **10d** was obtained in 84% yield and 81% ee. An isopropyl-tethered styrene substrate generated the corresponding indene **10e** in 91% ee, while the phenyl-substrate indene **10f** provided a much lower ee of 66%. Electron-poor boronic acids were slightly detrimental to the enantioselectivity, as shown by example **10 g**. The enantioinduction arose from two selective carbopalladations; the first taking place across the unsubstituted alkene moiety on **10b**, resulting in a single regioisomer, and the second across the styrene moiety resulting in high diastereoselectivity. Following a post-catalytic thermal retro-Diels-Alder reaction, the diastereomeric indanes **10i** and **10i'** were converted to the corresponding indene enantiomer **10d**.

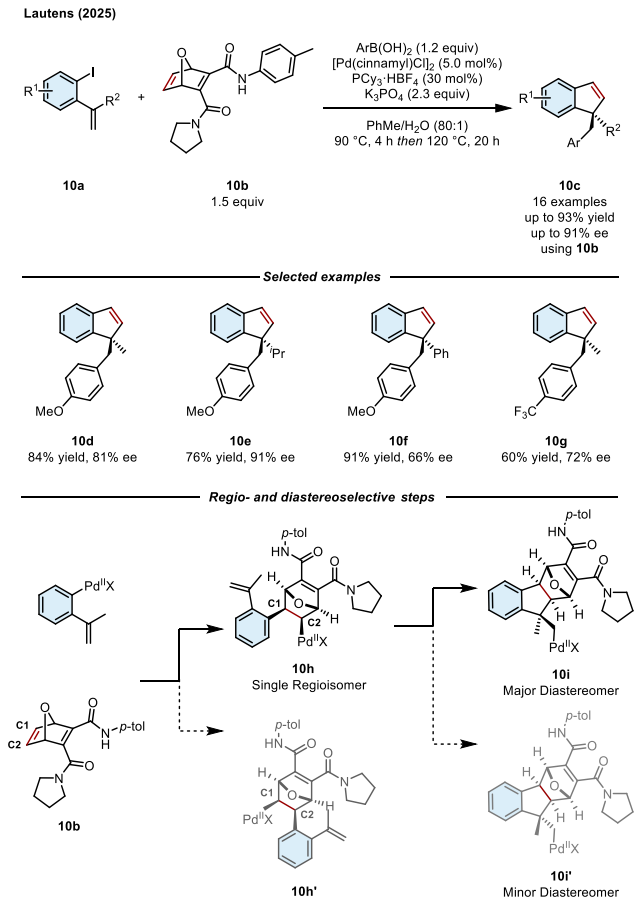


SCHEME 9 | Naphthol-directed CMD-mechanism towards the synthesis of spiroindenes.

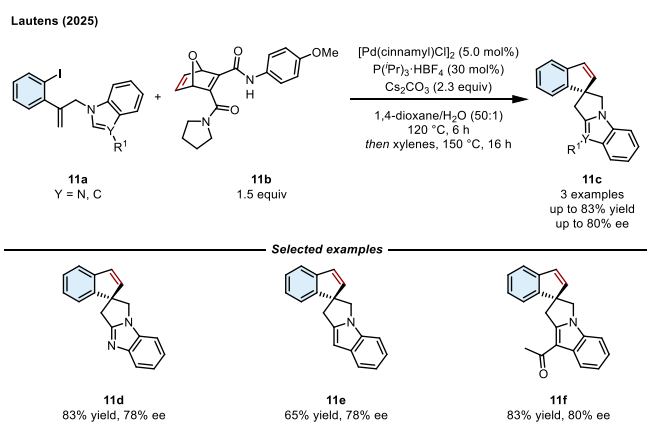
This methodology was later expanded towards the synthesis of spiroindenes via intramolecular C—H activation as the termination step (Scheme 11) [27]. Preliminary enantioselective results using enantiopure oxabicycle **11b** showed the synthesis of heterocycle-tethered spiroindenes **11d-f** in 78% to 80% ee.

Aside from point chirality, there has recently been a considerable effort in developing atroposelective syntheses. In 2024, the Zhang group reported the first asymmetric Larock indole synthesis (Scheme 12) [28]. Using Ming-Phos ligand **12c**, the axially chiral *N*-arylindole **12e** was obtained in 87% yield using an aryl iodide, and 92% yield with the aryl bromide, both in 93% ee. DFT analysis supported that the migratory insertion of the alkyne was the rate-determining step, while reductive elimination constituted the enantiodetermining step. A $\Delta\Delta G^{\ddagger}$ of 2.3 kcal/mol between the two diastereomeric transition states of the latter step was calculated, thereby matching the high levels of experimental ee values.

A similar asymmetric Larock indole synthesis starting from *N*-pyrrolyl-haloanilines was reported by the Li group (Scheme 13) [29]. Using the SPINOL-based phosphoramidite ligand **13c**, the atroposelective synthesis of indole **13e** was achieved in 90% yield and 92% ee using the corresponding iodoarene, and 88% yield and 88% ee with the bromoarene. In some cases, the ee was found to be highly dependent on the arylhalide; disubstituted *n*-propyl indene **13f** was obtained in 73% yield and 67% ee for the iodoarene, as opposed to 83% yield and 87% ee for the bromoarene. Nonlinear effect (NLE) experiments showed a negative NLE, suggesting that more than one equivalent of ligand is bound to the palladium during the enantiodetermining step, which corresponds to the migratory insertion of the alkyne. Mechanistic and DFT investigations suggest that the enantiodetermining step is catalyzed by a [Pd(**13c**)$_2$] species in high enantioselectivity, while the monoligated [Pd(**13c**)] catalyzes the reaction with attenuated enantioselectivity. The calculated $\Delta\Delta G^{\neq}$ between the bisligated Pd transition states was found to be 1.6 kcal/mol, while the corresponding monoligated complex had a smaller $\Delta\Delta G^{\neq}$, at 1.2 kcal/mol.

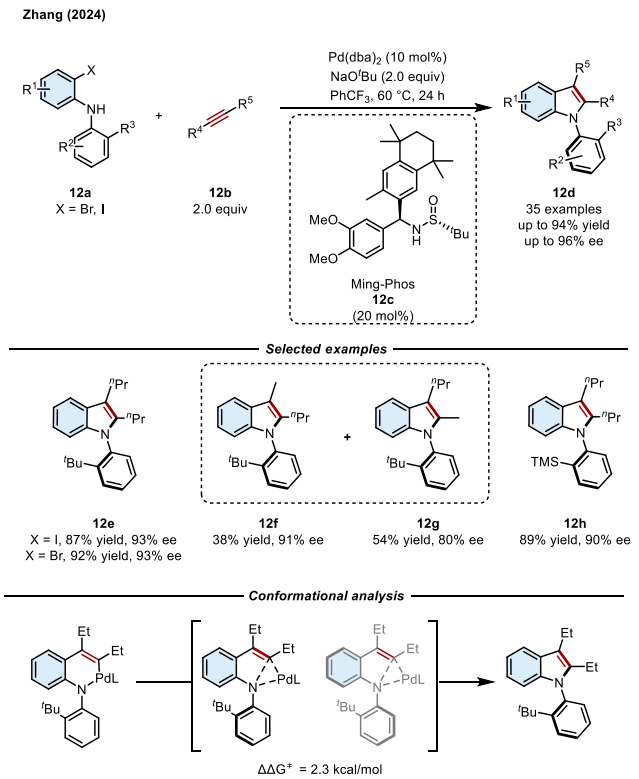


SCHEME 10 | Chiral oxabicycles as acetylene surrogates toward the synthesis of indenes.

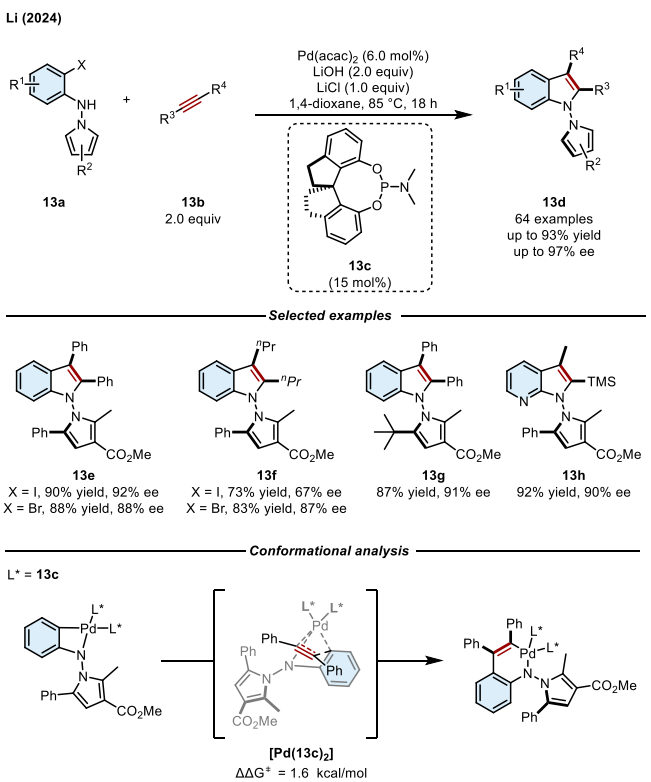


SCHEME 11 | Synthesis of 2,3-unsubstituted spiroindenes using chiral oxabicycles.

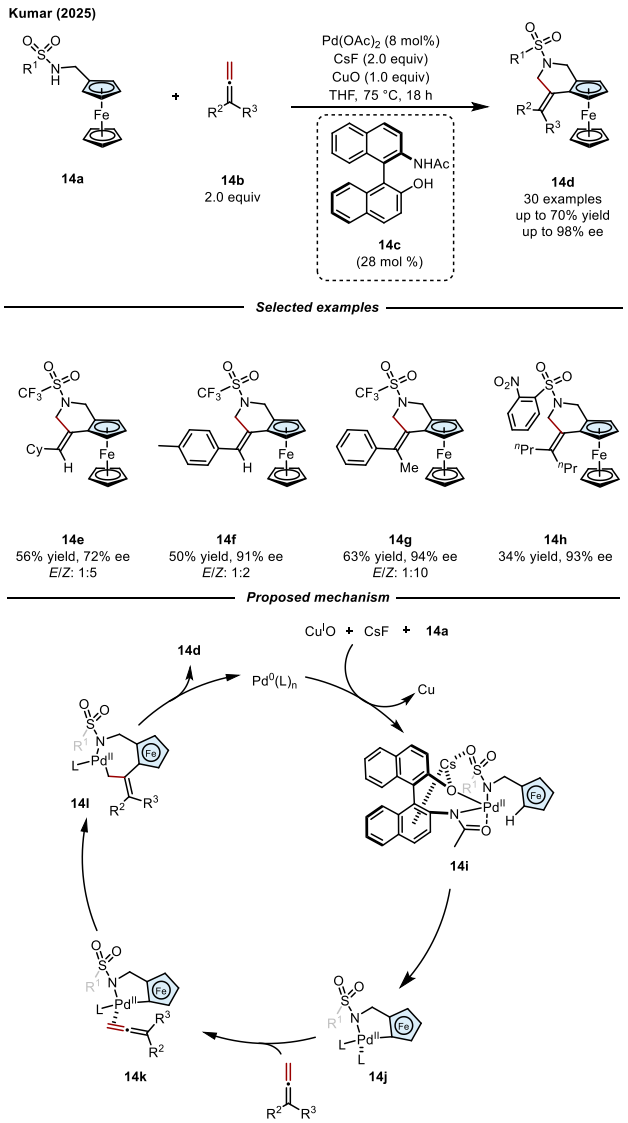
In 2025, the Kumar group reported the synthesis of chiral ferrocene-fused tetrahydropyridines (Scheme 14) [30]. Unsymmetrically-substituted allenes afforded products **14e-g** in moderate to excellent enantioselectivity, and up to 1:10 (*E*/*Z*) selectivity. *Ortho*-nitrophenyl substituted sulfonyl product **14 h** was obtained in modest yield, yet good ee. The enantioselectivity observed is due to intermediate **14i**; the cesium ion interacts with the sulfonyl group and chiral ligand **14c**, creating a chiral



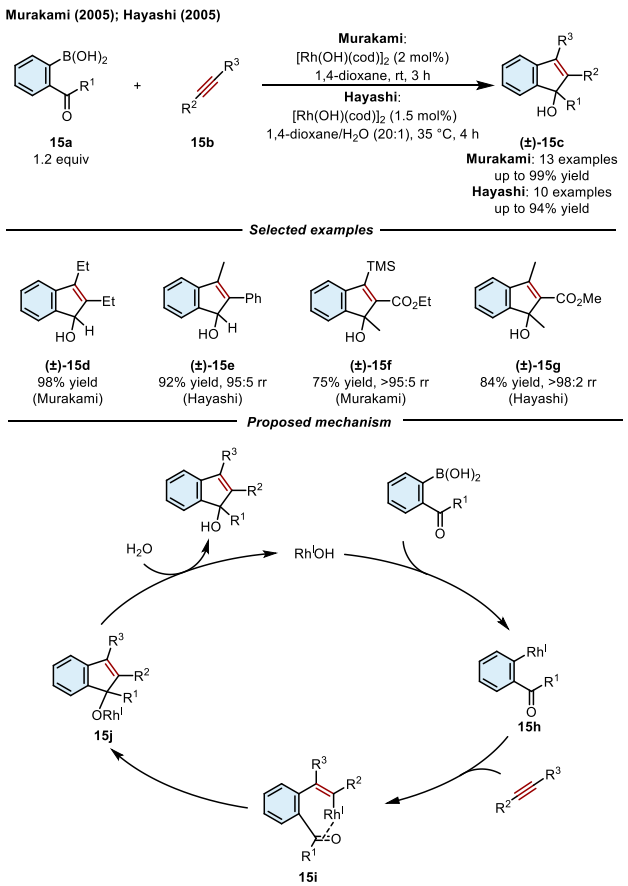
SCHEME 12 | Atroposelective Larock indole synthesis.



SCHEME 13 | Pyrrole-substituted, palladium-catalyzed asymmetric Larock indole synthesis.



SCHEME 14 | Synthesis of chiral ferrocenes via asymmetric palladium catalysis using allenes as coupling partners.



SCHEME 15 | Rhodium-catalyzed racemic synthesis of indenols.

catalytic pocket. The cationic interaction facilitates interaction of the Pd(II) center with the desired enantiotopic C—H bond and prevents undesired β-H elimination from taking place. An enantio-determining C—H activation step via CMD results in intermediate **14j**. Allene insertion into the C(sp^2)—Pd bond followed by reductive elimination affords the 6-membered azacyclic product.

3 | Rhodium-catalyzed Reactions

3.1 | Early Studies (RACEMIC)

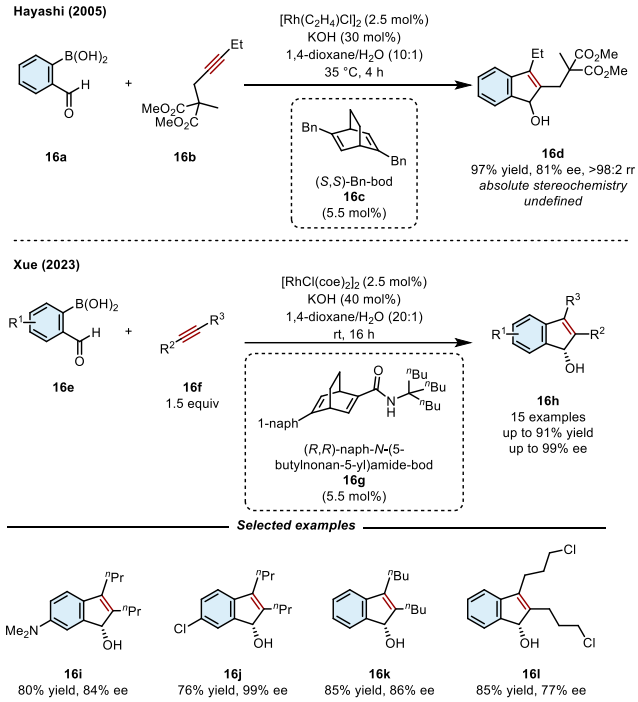
In analogy to Gevorgyan and Yamamoto's work using palladium, Murakami and Hayashi concurrently reported a rhodium-catalyzed racemic synthesis of indenols (Scheme 15) [31, 32]. Transmetalation between the hydroxorhodium(I) catalyst and arylboronic acid **15a** generates arylrhodium(I) intermediate **15 h**. Two sequential carborhodations with the alkyne and carbonyl moieties, respectively, formed the five-membered ring **15j**, followed by protodemetalation to regenerate the Rh(I) catalyst and release the indenol. In general, excellent regioselectivities were observed when using asymmetrical alkynes bearing two significantly different functional groups, as illustrated by examples **15e-g**.

3.2 | Enantioselectivity Studies

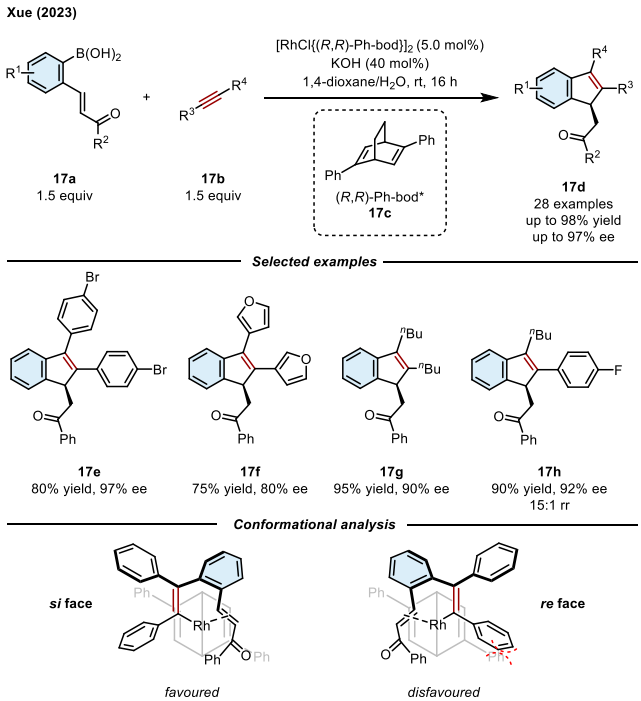
In the same report, Hayashi included preliminary results for the enantioselective synthesis of indenols (Scheme 16) [31], with benzyl-derived (*S,S*)-Bn-bod **16c** providing a result of 81% ee, whereas the phenyl-derived (*R,R*)-Ph-bod resulted in 70% ee.

In 2023, the Xue group was able to improve the selectivity of this reaction in up to 99% ee by harnessing a new chiral bod ligand **16 g** comprising naphthyl and amide substituents [33]. The indenes' ee values fluctuated depending on the position of electron-donating and -withdrawing groups on the boronic acid's aryl ring, as demonstrated by **16i-j**. When substituents other than *n*-propyl were present on the alkyne coupling partner, the selectivity of the transformation decreased slightly as exemplified by **16k-l**.

The same year, Xue reported a related synthesis of enantioenriched indenes using (*R,R*)-Ph-bod **17c** as the chiral ligand (Scheme 17) [34]. Replacing the arylboronic acid's *ortho*-formyl



SCHEME 16 | Rhodium-catalyzed enantioselective synthesis of indenols.



SCHEME 17 | Rhodium-catalyzed enantioselective synthesis of indenes from enone-tethered arylboronic acids.

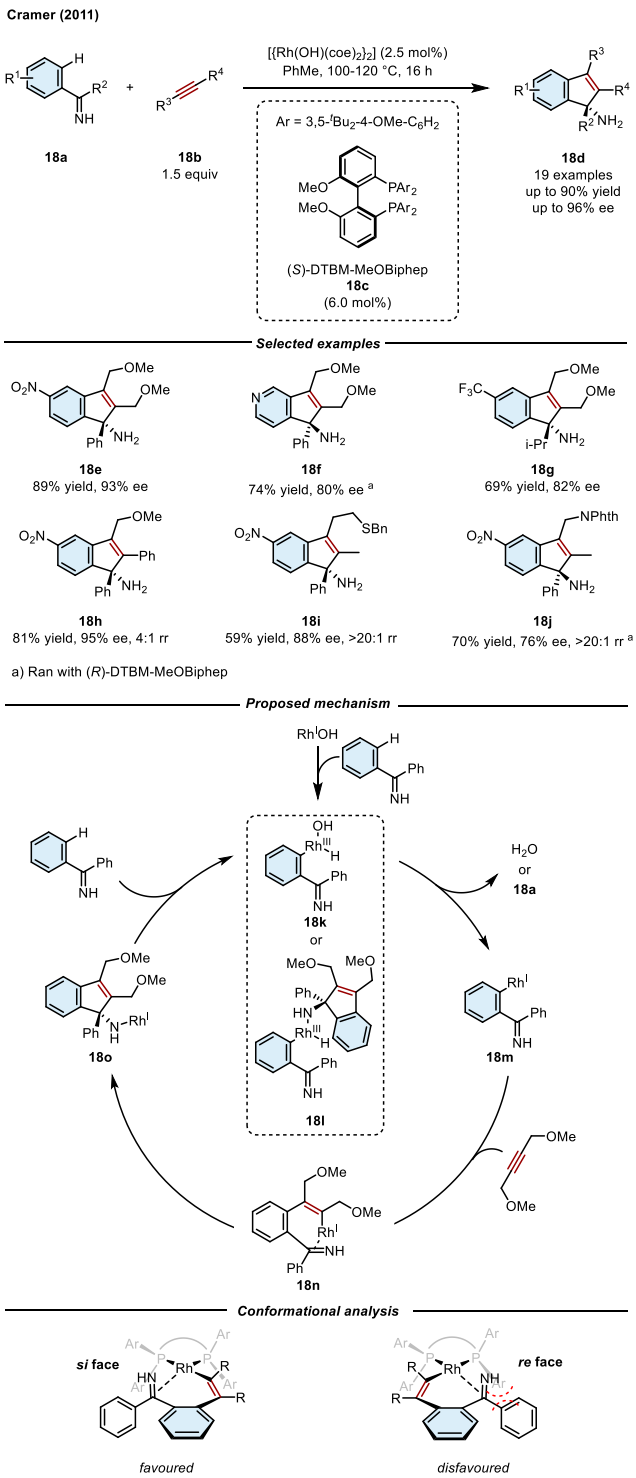
substituent with an activated alkene resulted in a similar cyclization mechanism as in Scheme 15, with protodemetalation occurring on a Rh-enolate intermediate to close the catalytic cycle. Different aryl and alkyl substituents on the alkyne were tolerated, resulting in modest to excellent enantioselectivity as shown by examples **17e-g**. Unsymmetrical alkynes resulted in formation of both regioisomers, in up to 15:1 rr as illustrated by **17 h**. The authors proposed that following the carborhodation onto the alkyne, steric repulsion between one of the ligand's phenyl groups and the aryl group bound to the same carbon as the rhodium atom disfavours 1,4-addition onto the *re* face of the enone. Consequently, addition onto the *si* face is favoured, as the substrate's ketone moiety was deemed to have less pronounced steric interactions with the ligand's phenyl group.

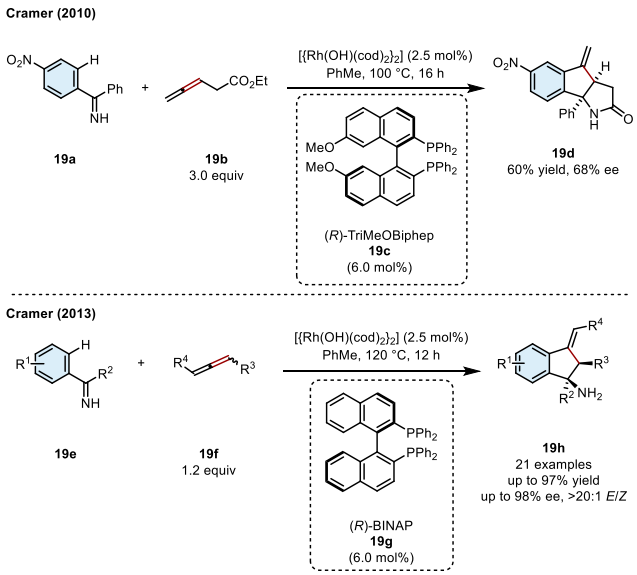
As opposed to the previously shown methodologies that required a functional group handle to commence the catalytic cycle, the Cramer group made use of ketimine-directed C–H activation to access enantioenriched indenamines **18d** (Scheme 18) [35]. This study served as a follow-up to the same group's work on asymmetric carbocyclizations via C—H activation to generate, in part, indanes and indanols [36–42]. Furthermore, a racemic version with preliminary enantioselectivity results had been published the year before by the Zhao lab [43]. Up until then, the enantioselective preparation of chiral primary amines harnessing C—H functionalization remained particularly rare and difficult to achieve.

The catalyst's counterion had a significant impact on conversion and enantioselectivity; only rhodium complexes bearing hydroxide, methoxide, and *tert*-butylamide counteranions led to product formation, as halide- and other oxygen-based counteranions as well as cationic complexes shut down reactivity. It was suggested that the coordinating hydroxide ion converted the Rh(I) complex into the catalytically active Rh(III) species **18k** following C—H activation. Reductive elimination of water in the first catalytic cycle would generate the arylrhodium(I) species **18m** that would undergo the two usual carborhodations. The resulting nitrogen-bound Rh(I)-intermediate **18o** would oxidatively add into the *ortho*-C—H bond of a new molecule of aryl ketimine giving **18l**, followed by reductive elimination to release the desired product.

When the ketimine substrate contained two different aryl groups, C—H activation regioselectively occurred onto the more electron-deficient ring as demonstrated in examples **18e-f** [44]. Unsymmetrical alkynes bearing an alkyl and an aryl group on either side resulted in moderate regioselectivities as seen with **18 h**. When a coordinating group such as a thioether or a phthalimide was placed on one of the alkyne's substituents, a single regioisomer was observed, as displayed in examples **18i-j**. In terms of the stereochemical outcome, the authors rationalized that the imine's *si* face was preferentially attacked by the vinylrhodium(I) moiety due to the absence of steric hindrance that would occur between the ketimine moiety and one of the ligand's DTBM fragment if attack were to happen on the *re* face.

A year prior, Cramer had reported a preliminary enantioselective result for a related transformation (Scheme 19) [45]. Starting from ketimine **19a** and ester-tethered allene **19b**, enantioenriched fused tricycle **19d** was obtained in 68% ee. The lactam moiety results from an intramolecular addition-elimination process between the in situ formed amine and pendant ester moieties. The scope and enantioselectivity of this transformation were improved in 2013, using (*R*)-BINAP, to afford indanylamine products **19 h** in high yields and enantioselectivity [46] .





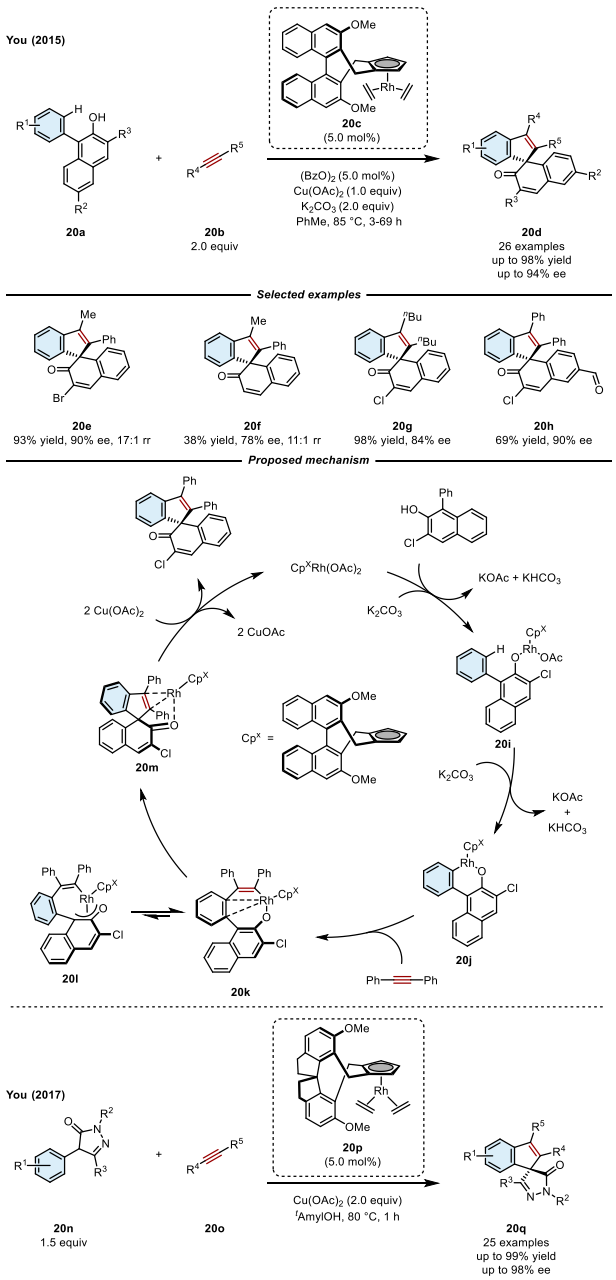
SCHEME 19 | Rhodium-catalyzed enantioselective synthesis indanylamines.

SCHEME 18 | Rhodium-catalyzed enantioselective synthesis of indenamines via directed C–H activation.

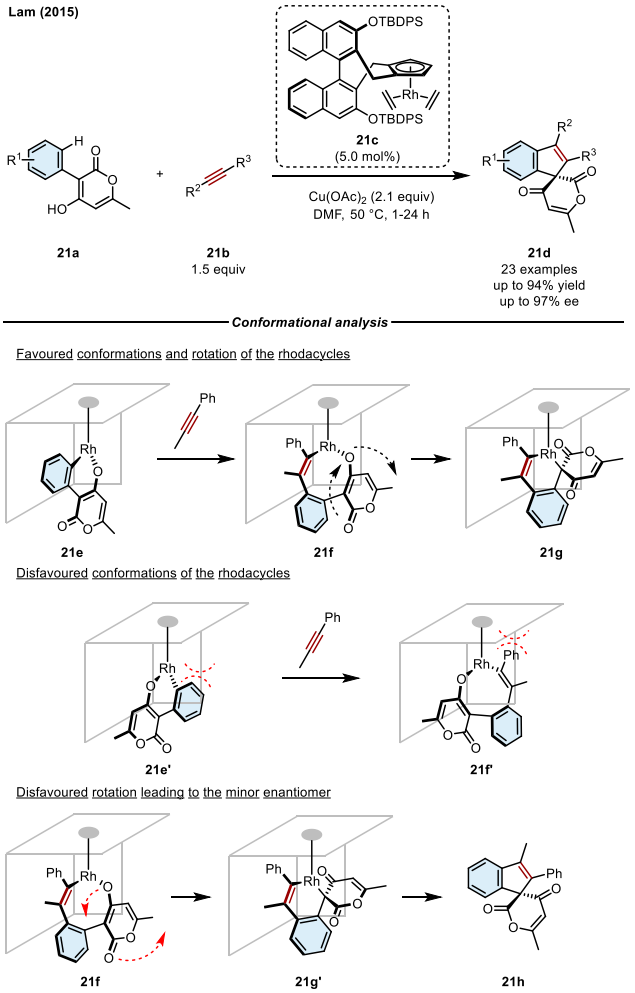
Asymmetric C—H functionalization reactions are well known to be catalyzed by Rh(I) as well as Rh(III) complexes [47, 48]. In 2015, the You lab reported the first transition-metal-catalyzed enantioselecive annulative dearomatization of β-naphthols via an initial C—H functionalization step [49] (SCHEME 20). Similar catalytic syntheses had been previously published, yet only in racemic fashion [50–54]. A Cp^{x}Rh(III) complex was used as the catalyst, as chiral cyclopentadiene ligands remain to date the most effective ligands for Rh(III)-catalyzed asymmetric C—H functionalizations. [48] The reaction is constrained to having halogens on the naphthol's 3-position, as a methyl group and a hydrogen atom resulted in low yields as illustrated by **20f**. Both symmetrical dialkyl- and diarylalkynes **20g-h** were tolerated, and the use of unsymmetrical alkynes resulted in generally good regioselectivity as seen with **20e-f**. Shortly after this report, the You group reported the asymmetric synthesis of spiropyrazolones, following a similar mechanism, using chiral catalyst **20p** [55].

The authors initially proposed a mechanism that lacked information regarding the turnover-limiting and enantiodetermining steps. In order to provide a complete picture, a computational study on the transformation was published a year later. [56] The authors propose that the catalytic cycle commences via ligand exchange between one of the acetate ligands on rhodium and the deprotonated naphthol substrate, resulting in **20i**. C—H activation on the pendant aryl ring would then ensue to form a six-membered rhodacycle **20j**, which is proposed to constitute the turnover-limiting step based on KIE experiments and calculations that determined it has the highest energetic barrier. Potassium carbonate effectively neutralizes the two equivalents of acetic acid that are produced from the reaction, which renders the C—H activation process irreversible. Subsequent migratory insertion to form the eight-membered rhodacycle **20k** was identified as the enantiodetermining step. Although high-energy π-oxaallyl-Rh species **20l** can exist in equilibrium with **20k**, it does not take part in C—C bond formation, contrary to the original proposal. The rhodacycle then undergoes reductive elimination followed by dissociation, forming the desired indene product. The active Rh(III) species is regenerated via oxidation of Rh(I) by copper acetate.

Shortly after You's 2015 report, the Lam group reported a related transformation that also harnessed a Cp^{x}Rh(III) complex



SCHEME 20 | First catalytic asymmetric annulative dearomatization reaction of β-naphthols with alkynes.

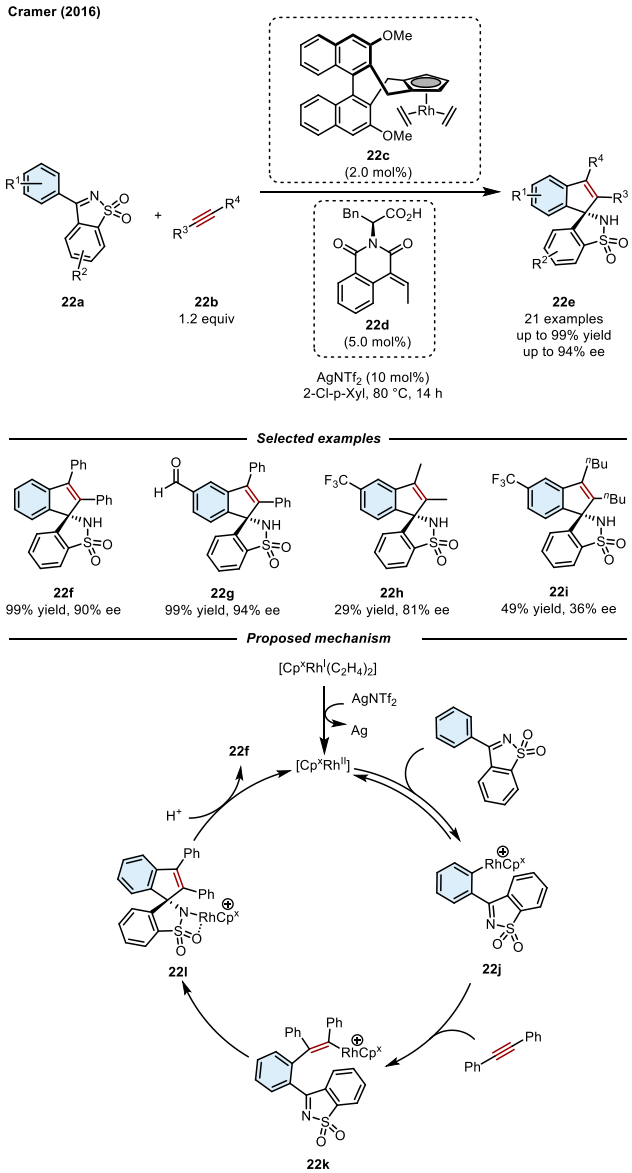


SCHEME 21 | Enantioselective synthesis of spidoindenes from from cyclic 1,3-dicarbonyl compounds and alkynes.

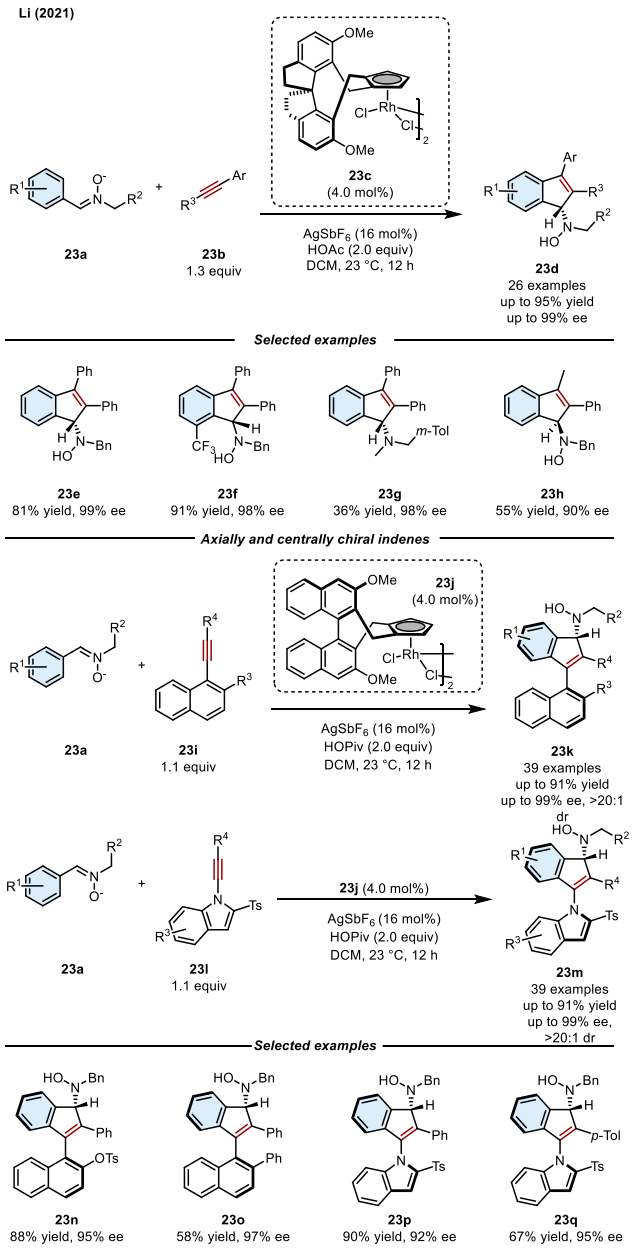
(Scheme 21) [57]. Starting from the aryl-substituted hydroxypyran-2-ones **21a**, spiroindenes **21d** were successfully synthesized. The authors proposed a stereochemical model wherein configuration **21e** is favoured over **21e'** following an enol-directed C—H activation, as the former minimizes arene-ligand interactions. Migratory insertion also favours configuration **21f**, as the arene group next to the rhodium metal center in **21f'** is also clashing with the ligand. Rotation of the 4-alkoxypyran-2-one moiety in **21f** away from the ligand to minimize steric interactions yields the 6-membered rhodacycle, and ultimately, the major enantiomer **21 g**.

In 2016, Cramer reported the synthesis of spirocyclic sultams using a similar $Cp^xRh(III)$ complex (Scheme 22) [58]. The use of an oxidant, $AgNTf_2$, was shown to be essential for reactivity. Chiral *L*-phenylalanine was also used as an additive, improving reactivity without impacting the enantioselectivity; using *D*-phenylalanine also provided the desired product in comparable ee. Dialkyl alkynes displayed lower reactivity and enantioselectivity, as illustrated by example **22i**. The authors propose that the oxidized Rh(II) species undergoes reversible C—H activation, followed by migratory insertion across diphenylacetylene to intermediate **22k**. Addition across the C—N bond sets the chiral center, followed by protonation to get the desired product.

In 2021, a report by the Li group showed the synthesis of three classes of indenes starting from nitrones **23a** (Scheme 23) [59]. Aminoindenes with point chirality were furnished in high enantioselectivity using the Cramer-type catalyst **23c**. Furthermore, naphthyl-substituted spiroindenes **23k** and indole-substituted spiroindenes **23m** were provided in high enantio- and diastereoselectivity. The axially and centrally chiral model product **23n** was obtained in 88% yield and 95% ee, whereas **23p** was obtained in 90% yield and 92% ee. When alkyne **23i** had an alkyl substituent as R^4, the authors noted poor reaction efficiency. This reduced yield was explained following DFT calculations, as the authors noted the importance π–π stacking interactions between the tosyl



SCHEME 22 | Rhodium-catalyzed synthesis of indenyl-spirocyclic sultams.



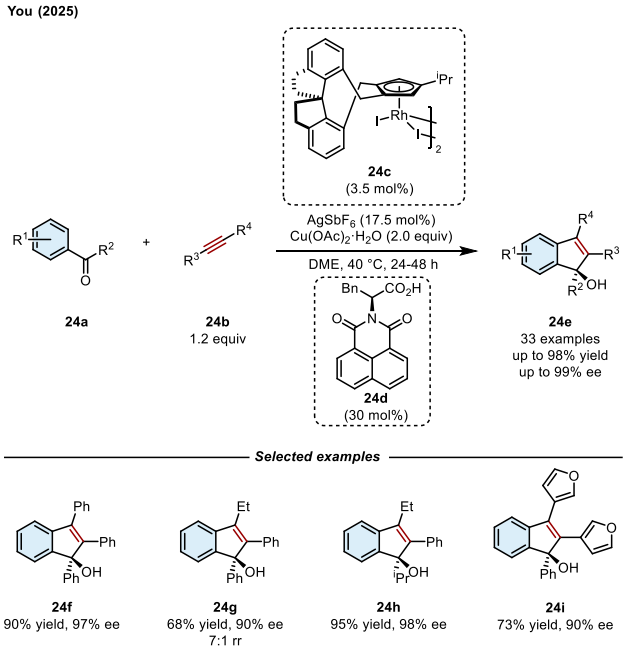
SCHEME 23 | Synthesis of point chiral indenes and axially and centrally chiral indenes via rhodium catalysis.

group's benzene ring (R^3 on **23i**) and the phenyl group (R^4 on **23i**) of the corresponding alkyne.

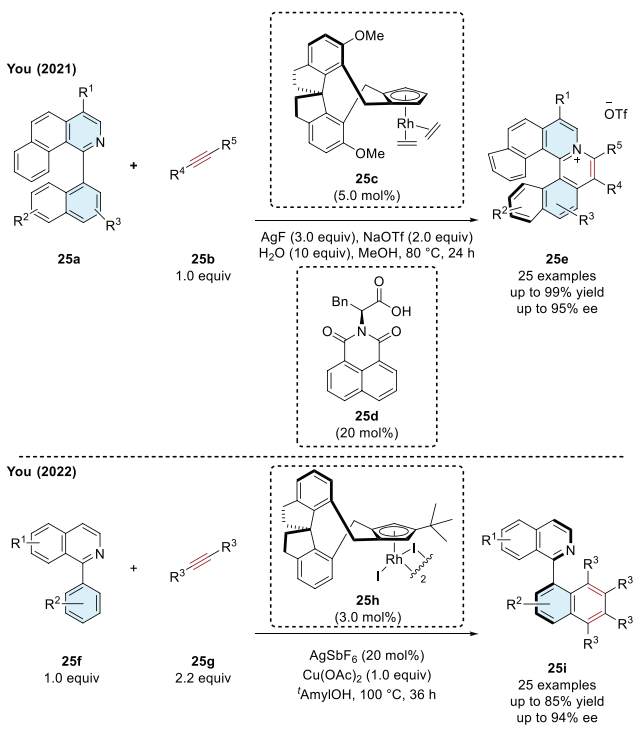
Recently, the You group reported the enantioselective synthesis of indenols (Scheme 24) [60]. Employing the chiral Cp*Rh(III) complex **24c**, the model reaction with benzophenone **24a** and diphenylacetylene furnished the desired indenol **24f** in 90% yield and 97% ee. Following parallel KIE experiments and DFT calculations, the authors proposed that C—H bond cleavage constituted the rate-determining step.

Aside from indenes and indenols, rhodium asymmetric transformations towards the synthesis of atropoisomers have also attracted considerable interest. In particular, the You group has reported multiple enantioselective transformations over the past few years [61–64]. In 2021, the group synthesized azoniahelicenes **25e** from naphthyl-substituted isoquinolines **25a** (Scheme 25) [64]. Products were obtained in excellent enantioselectivity, using chiral Cp*Rh(III) catalyst **25c**. They followed up on this report by synthesizing the Satoh-Miura products **25i** from similar isoquinolines **25f** [61]. The nature of the catalyst's counteranion was found to have a significant impact on product distribution. In the absence of copper, an excess of silver salts acts as both the oxidant and halogen-abstractors. Silver acetate was shown to favor the sole formation of desired Satoh-Miura products **25i**, while AgOTf, $AgNTf_2$, $AgSbF_6$, and $AgPF_6$ saw the formation of azoniahelicenes **25e**.

The You group expanded on this methodology via the synthesis of axially chiral, morpholine-substituted isoquinolines from aromatic imines and alkynes (Scheme 26) [62]. The standard product **26e** was generated in 90% yield, 91% ee, and the reaction conditions tolerated various substitution patterns (**26f**, **26 g**).

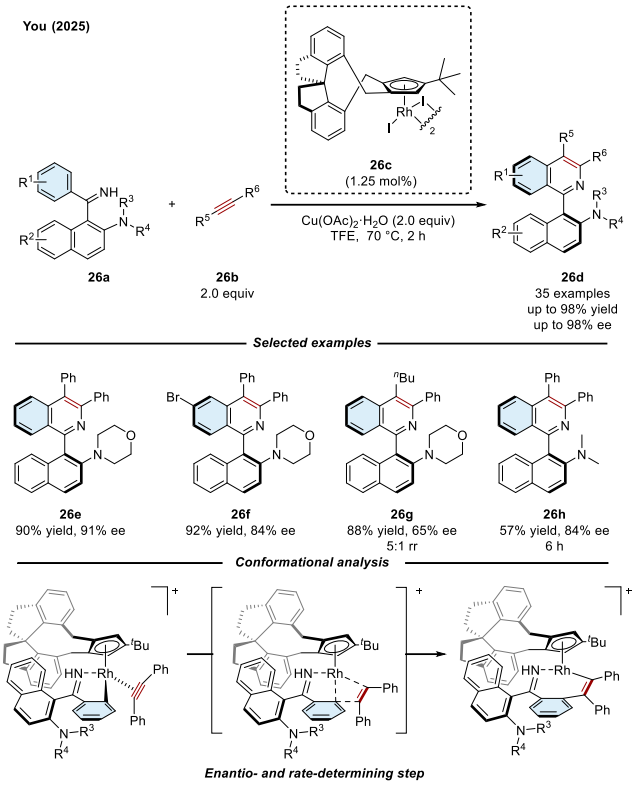


SCHEME 24 | Rhodium(III)-catalyzed synthesis of indenols.



SCHEME 25 | Synthesis of azoniahelicenes and Satoh-Miura products from naphthyl-substituted isoquinolines.

Finally, replacing the morpholine moiety on the naphthyl fragment was also amenable, as dimethyl-amine-derived product **26 h** was obtained in 57% yield and 84% ee. DFT calculations concluded that the migratory insertion of the alkyne into the C—Rh bond constituted the rate- and enantiodetermining step, for which a difference $\Delta\Delta G^{\ddagger}$ of 1.3 kcal/mol was calculated between the diastereomeric transition states.

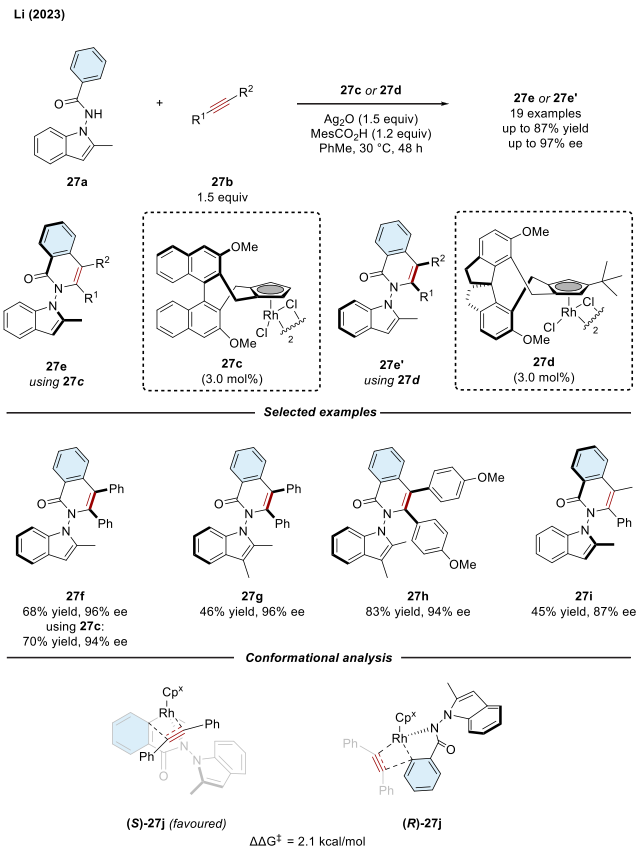


SCHEME 26 | Atroposelective synthesis of morpholine-substituted isoquinolines.

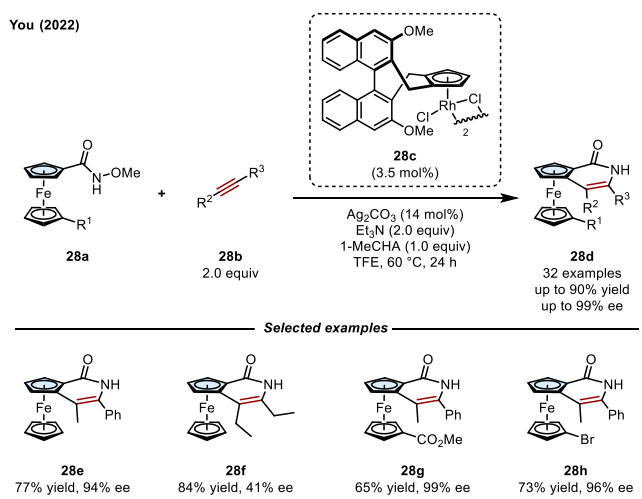
In 2023, the Li group developed the synthesis of N-N axially chiral biaryls **27e** from benzamides **27a** and internal alkynes (Scheme 27) [65]. Product **27f** was obtained in 70% yield and 94% ee employing chiral Rh(III) catalyst **27c**. The opposite enantiomer could be obtained using rhodium catalyst **27d**, in 68% yield and 96% ee. Unsymmetrical alkylarylacetylenes showed high regioselectivity, as shown by product **27i** obtained in 45% yield and 87% ee. Computational studies determined that the alkyne insertion is the rate- and enantiodetermining step. In transition state **(*S*)- 27i**, the 5-membered rhodacycle undergoes a minor distortion relative to diastereomeric **(*R*)- 27j** to create a vacant coordination site for the approaching alkyne.

Additionally, the You group developed a Rh(III)-catalyzed synthesis of planar chiral ferrocene complexes (Scheme 28) [63]. Ferrocene product **28e** was obtained in 77% yield and 94% ee. Dialkylacetylenes were also tolerated in this reaction, as **28f** was obtained in 84% yield, albeit with lower enantiocontrol. Substitution on the ferrocenecarboxamide was also explored, as products **28g** and **28h** were both obtained in moderate yields and high ee. The Kumar group recently developed a diastereoselective variation of this reaction, using allenes under rhodium catalysis [66].

In 2017, Antonchick and Waldmann reported the synthesis of spiropyrazole rings via a rhodium-catalyzed C—H activation approach. Products were obtained in high yields and enantiomeric excess values (Scheme 29) [67]. In 2022, a similar dearomatization strategy was achieved concurrently by the Ackermann and Mei group, via an electrooxidative,

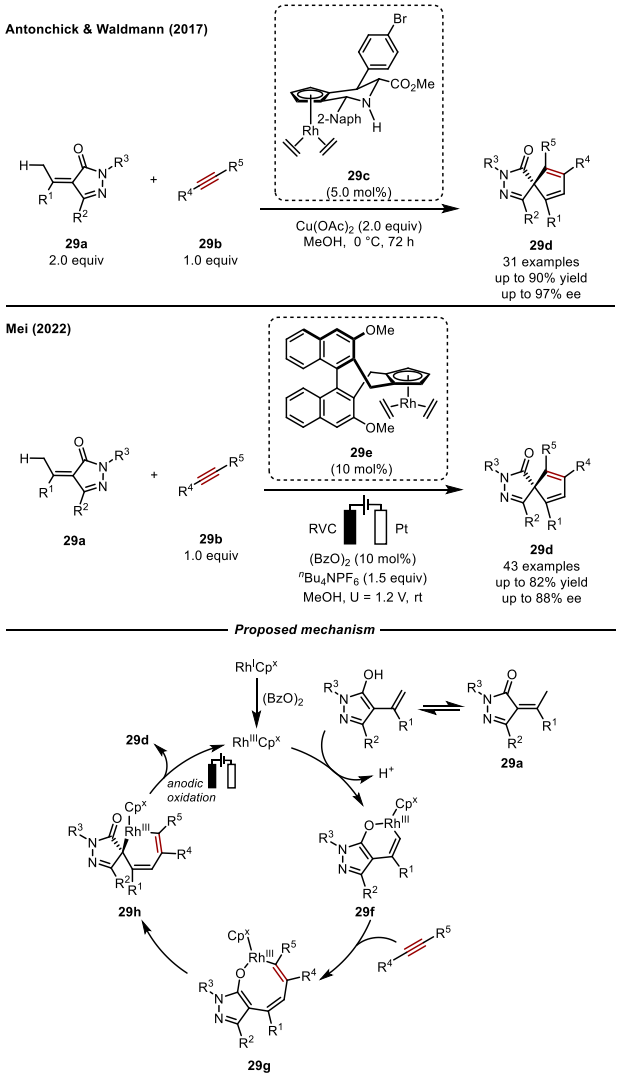


SCHEME 27 | Rhodium-catalyzed synthesis of axially chiral N-N biaryls.



SCHEME 28 | Rhodium-catalyzed asymmetric synthesis of ferrocenecarboxamides.

rhodium-catalyzed annulation [68, 69]. Electrocatalytic methods to synthesize spirocycles enantioselectively remain elusive and as such, these two methods provided an important breakthrough in the field. Cyclic voltametry studies done by the Mei group reveal that catalyst **29e** is oxidized at the anode preferentially over the reactants, product, and $[RhCp^*Cl_2]_2$. In their proposed mechanism, the 6-membered rhodacycle **29f** undergoes migratory insertion, forming an eight-membered ring intermediate.

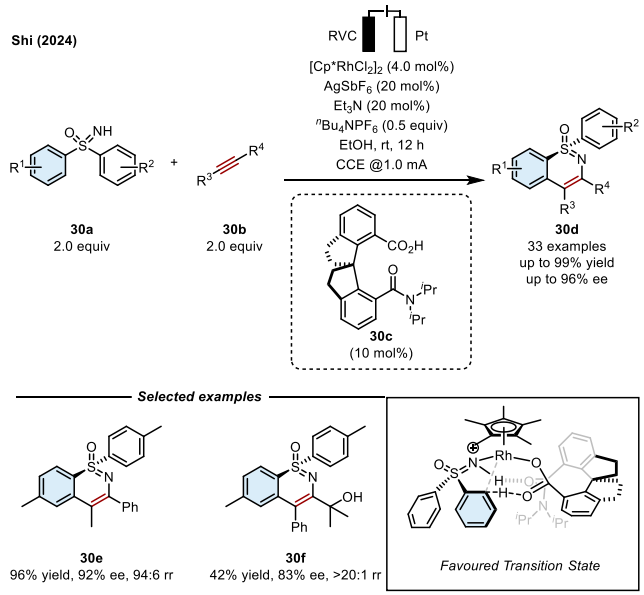


SCHEME 29 | Synthesis of spiropyrazolone via thermal and electrooxidative rhodium catalysis.

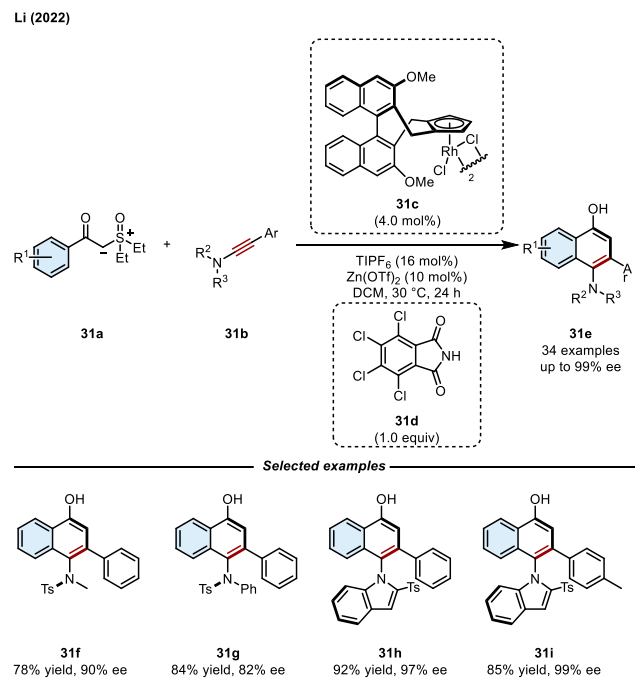
Isomerization to species **29 h** followed by reductive elimination affords product **29d**. The reduced Rh(I) species then gets regenerated to Rh(III), following anodic oxidation.

The Shi group later expanded the use of electrooxidative methods to synthesize chiral sulfoximines **30d** via a rhodium-catalyzed C—H activation sequence from the corresponding meso NH-sulfoximines **30a** (Scheme 30) [70]. This reaction demonstrated high regioselectivity when harnessing unsymmetrical alkylarylacetylenes, where the aromatic substituent ends up proximal to the nitrogen atom (**30e**). The opposite regioselectivity was observed for alcohol-substituted alkynes due to the Rh—O coordination following migratory insertion.

The Li group described the synthesis of axially chiral naphthylamines and C—N biaryls (Scheme 31) [71]. Sulfoxonium ylides **31a** acts as the directing group for C—H activation. Insertion across the amino alkyne occurs with high regio- and enantioselectivity, resulting in naphthylamine products **31f-g**, or indole-substituted, C—N biaryl products **31h-i**.

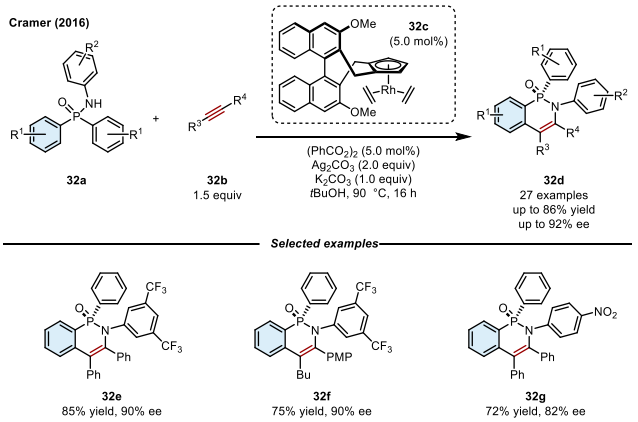


SCHEME 30 | Synthesis of chiral sulfoximines under rhodium-catalyzed and electrooxidative conditions.

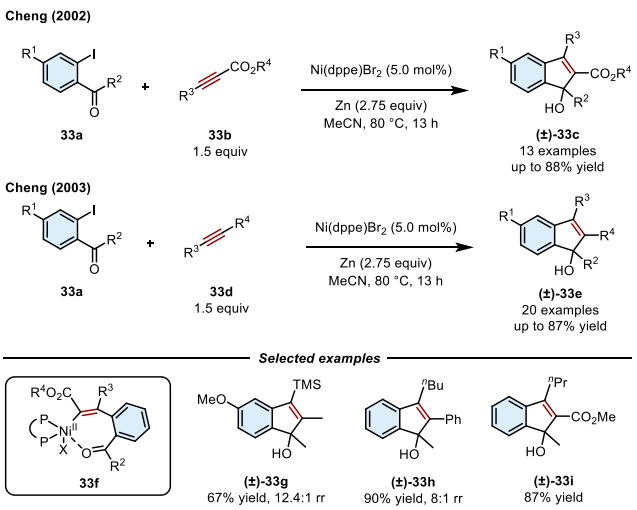


SCHEME 31 | Synthesis of axially chiral naphthylamines.

Similar to Shi's electrochemical report (Scheme 30), Cramer and coworkers reported a chiral-at-phosphorus asymmetric synthesis of phosphinamides (Scheme 32) [72]. The substitution pattern on the aminoaryl moiety was found to have a considerable impact on the yield and enantioselectivity. Strongly electron-withdrawing groups (**32e-g**) provided high reactivity, while *ortho* substitution led to decreased yields. The same group also reported the synthesis of identical phosphinamides motifs via a kinetic resolution [73].



SCHEME 32 | Synthesis of chiral-at-P phosphinamides via rhodium catalysis.

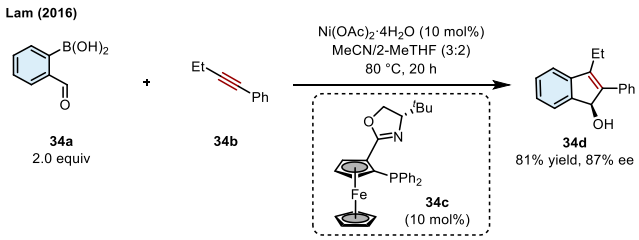


SCHEME 33 | Nickel-catalyzed racemic synthesis of indenols.

4 | Nickel-catalyzed Reactions

4.1 | Early Studies (RACEMIC)

In 2002, the Cheng group developed the racemic and regioselective synthesis of 2,3-disubstituted indenols from a reductive nickel-catalyzed carbocyclization (Scheme 33) [74]. After reduction of the Ni(II) precatalyst to Ni(0), an oxidative addition into the *ortho*-halophenyl ketone **33a** followed by a highly regioselective insertion into the propiolate results in a vinyl Ni(II) intermediate **33f**. Intramolecular nucleophilic addition into the ketone followed by transmetalation with zinc halide and protonation yields the desired product. A year later, Cheng expanded this reductive nickel catalysis to a diverse set of internal alkynes [75]. The migratory insertion across the alkyne was moderately regioselective, with the Ni center being preferentially bound to the carbon with a less electron-donating substituent.



SCHEME 34 | Nickel-catalyzed asymmetric synthesis of an indenol.

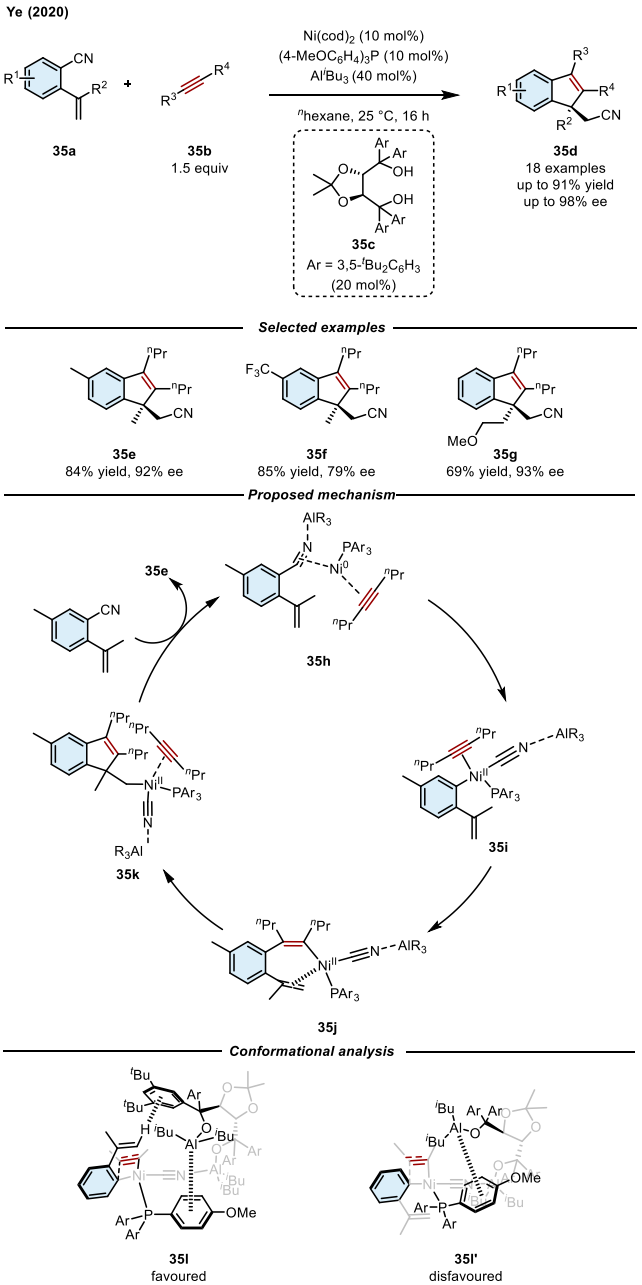
4.2 | Enantioselectivity Studies

In 2016, Lam and coworkers reported a novel asymmetric nickel-catalyzed anti-carbometalative cyclization (Scheme 34) [76]. While the report primarily focused on intramolecular anticarbometalations, one example included an intermolecular syncarbometalation of an alkyne. Reaction of 2-formylphenylboronic acid **34a** with ethyl phenyl acetylene **34b** afforded indenol **34d** in 81% yield and 87% ee.

Ye and coworkers reported the asymmetric nickel-catalyzed synthesis of indenes from aryl nitriles and alkynes (Scheme 35) [77]. $Ni(cod)_2$ in conjunction with Al^tBu_3 as the Lewis acid co-catalyst enabled the carbocyanation to proceed smoothly. A dual ligand system of $P(4\text{-}MeOC_6H_4)_3$ and (*R,R*)-TADDOL ligand **35c** was required to access model substrate **35e** in 84% yield and 92% ee. Oxidative addition of Ni(0) into the C—CN bond is facilitated by coordination of the nitrile to the aluminium complex, leading to intermediate **35i**. A migratory insertion across the alkyne results in **35j**, which undergoes alkene insertion and reductive elimination to afford the desired product. Enantioinduction is controlled by the irreversible alkyne insertion step, where DFT calculations determined that coordination of the two aluminium centers to the TADDOL ligand **35c** occurs. Asymmetric control was achieved by formation of this chiral aluminium complex. In transition state **35l** the σ-donation of the nitrile and π-donation of the arene group on the phosphine ligand to the aluminum/TADDOL species stabilizes the chelation. The authors observed that aryl nitriles with electron-neutral or electron-donating groups worked well within the reaction conditions. However, electron-withdrawing groups resulted in decreased ee.

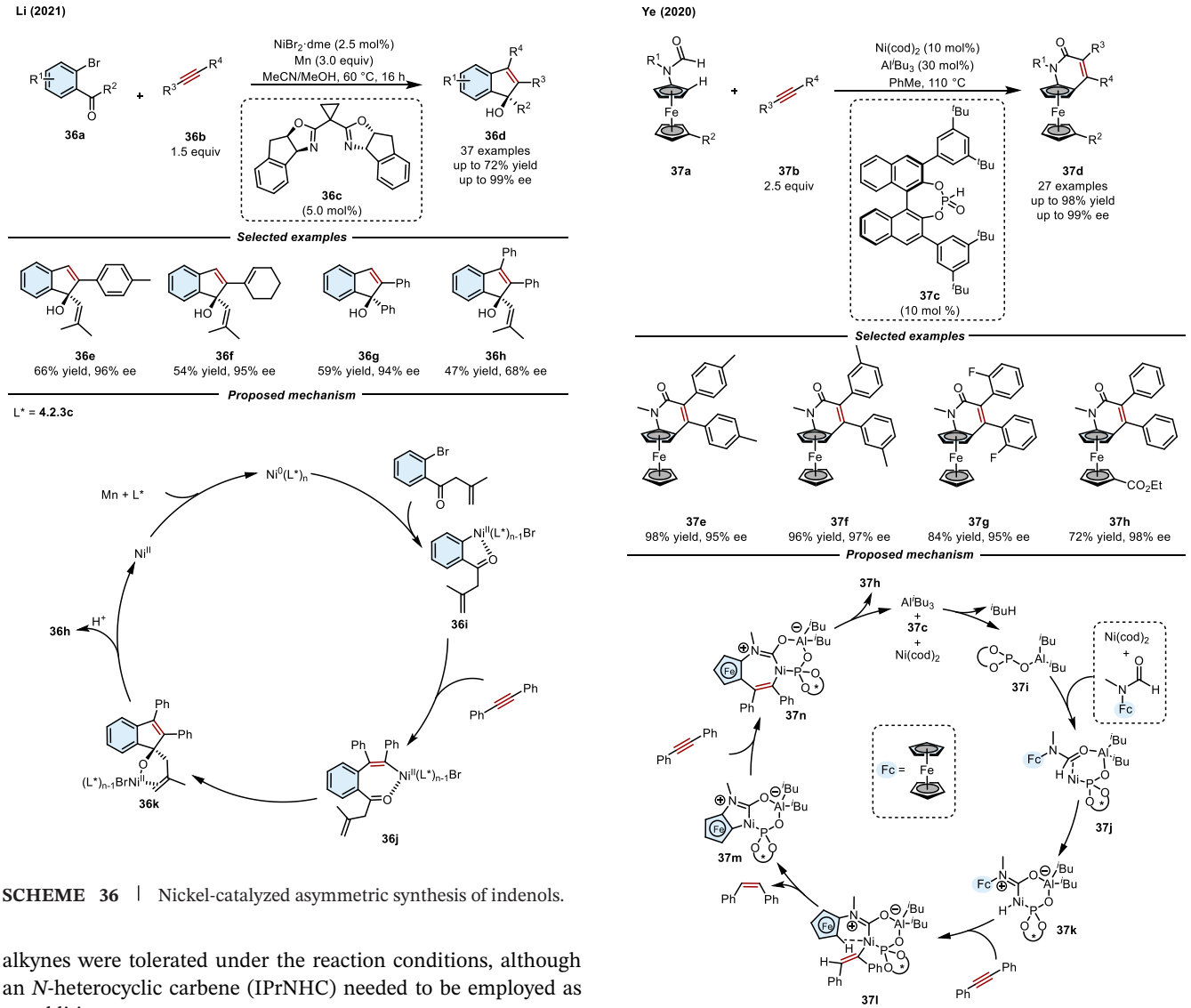
Li and coworkers reported an asymmetric synthesis of indenols starting from either *ortho*-haloaromatic ketones or *ortho*-haloaromatic β-alkenyl ketones (Scheme 36) [78]. Model substrate **36e** was obtained in 66% yield and 96% ee using In-Box chiral ligand **36c**. High ee values were obtained for terminal alkynes, as illustrated by examples **36e-g**. However, the enantioselectivity decreased significantly with internal alkynes. The authors reasoned the selectivity of the *si* face attack may be disfavoured by the hinderance of disubstituted alkynes as showcased by example **36 h**. After oxidative addition, a *cis*-carbonickelation of the alkyne affords formation of vinyl Ni(II) intermediate **36j**, which attacks the *si* face of the carbonyl atom to set the stereocenter, resulting in alkoxide-Ni(II) intermediate **36k**. Protonation and isomerization afford the desired product.

Similar to You's 2022 report (Scheme 28), the Ye group reported two years prior the synthesis of chiral ferrocenes via a nickel-



SCHEME 35 | Nickel- and aluminum-catalyzed asymmetric synthesis of indenes.

and aluminum-catalyzed C—H activation (Scheme 37) [79]. The aluminum catalyst acts as a Lewis acid activator and an anchor for ligand **37c** to allow for enantioinduction to occur; as **37c** coordinates to both nickel and aluminum, allowing for the activation of the formyl C—H bond, giving rise to six-membered nickelacycle **37k**. A second C—H activation via an electrophilic aromatic substitution mechanism generates bicyclic nickel intermediate **37m** and alkene byproduct. Re-insertion of alkyne followed by reductive elimination affords the desired product. While methyl groups on the *meta* and *para* positions of the aryl rings of the alkyne did not hinder the reaction (**37e-f**), *ortho*-methyl substitution led to no reaction, presumably due to steric hindrance. However, *ortho*-fluoro substitution was compatible with the reaction conditions as demonstrated by **37 g**. Dialkyl



SCHEME 36 | Nickel-catalyzed asymmetric synthesis of indenols.

alkynes were tolerated under the reaction conditions, although an *N*-heterocyclic carbene (IPrNHC) needed to be employed as an additive.

In 2025, the Song group reported an enantioselective annulation of *β*-bromoenones with alkynes resulting in five-membered cyclic tertiary alcohols (Scheme 38) [80]. On four instances, chiral tetrasubstituted indenols **38d** could be accessed in good yield and ee via oxidation of the product **38 h**. The products are obtained in enantioselective fashion via an axial-to-central chirality transfer. After a regio- and enantioselective migratory insertion of the alkyne into the C—Ni bond of **38e**, the stable axially chiral 1,3-diene **38f** is obtained. Intramolecular migratory insertion across the carbonyl group, followed by transmetalation, reductive elimination, and protodeboronation affords cyclopentadienol **38 h**, which is aromatized to the corresponding indenol under ambient air.

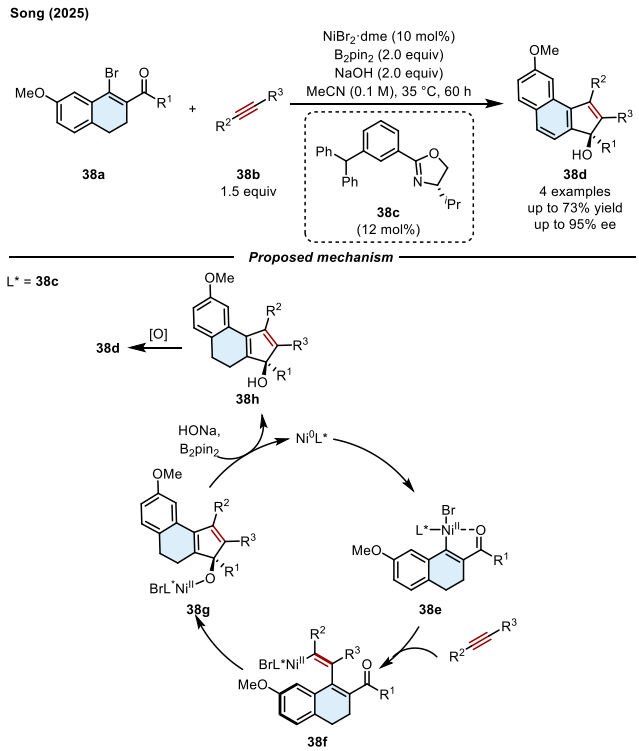
In 2019, the Kong group reported a highly regioselective and enantioselective reaction towards the synthesis of 2,3-fused cyclopentannulated indolines (Scheme 39) [81]. When starting from unsymmetrical alkynes, a single regioisomer is obtained as illustrated by examples **39e-f**. A benzyl substituent was tolerated on the nitrogen atom in **39 g**, allowing straightforward access to the corresponding N-H indoline as the *N*-benzyl group is easily removed.

SCHEME 37 | Nickel-catalyzed asymmetric synthesis of chiral ferrocenes.

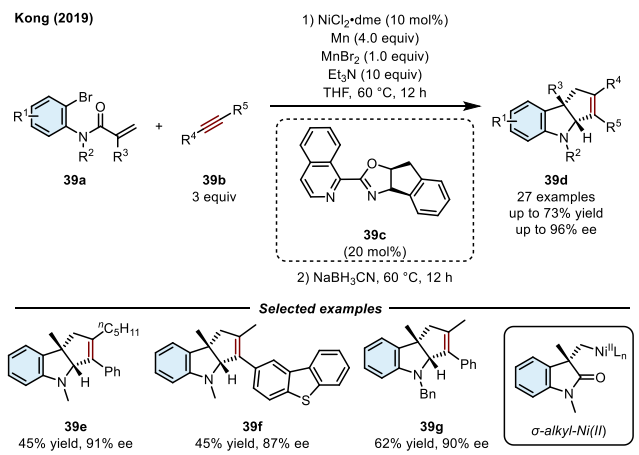
5 | Cobalt-catalyzed Reactions

5.1 | Racemic Studies

The racemic cobalt-catalyzed carbocyclization of *ortho*-iodobenzaldehydes or *ortho*-iodophenyl ketones to access indenols was explored by Cheng in 2003 (Scheme 40, top) [82]. The observed regioselectivity was highly substrate-dependent, ranging from 1:1 to >20:1, as showcased by examples **40d-g**. In terms of the mechanism of the reaction, the Co(II) precatalyst is reduced in the presence of zinc to the active Co(I) catalyst **40k**, which undergoes oxidative addition to give intermediate **40l**. This is followed by insertion of the alkyne into the C—Co bond, resulting in a seven-membered cobaltacycle **40m**, which undergoes intramolecular nucleophilic addition to give **40n**. Reduction with zinc results in Co(I) alkoxide **40o**, which undergoes transmetalation with ZnI_2 to regenerate the Co(I) catalyst. The resulting zinc alkoxide **40p** undergoes hydrolysis to give the final indenol product. Alternatively, reduction of



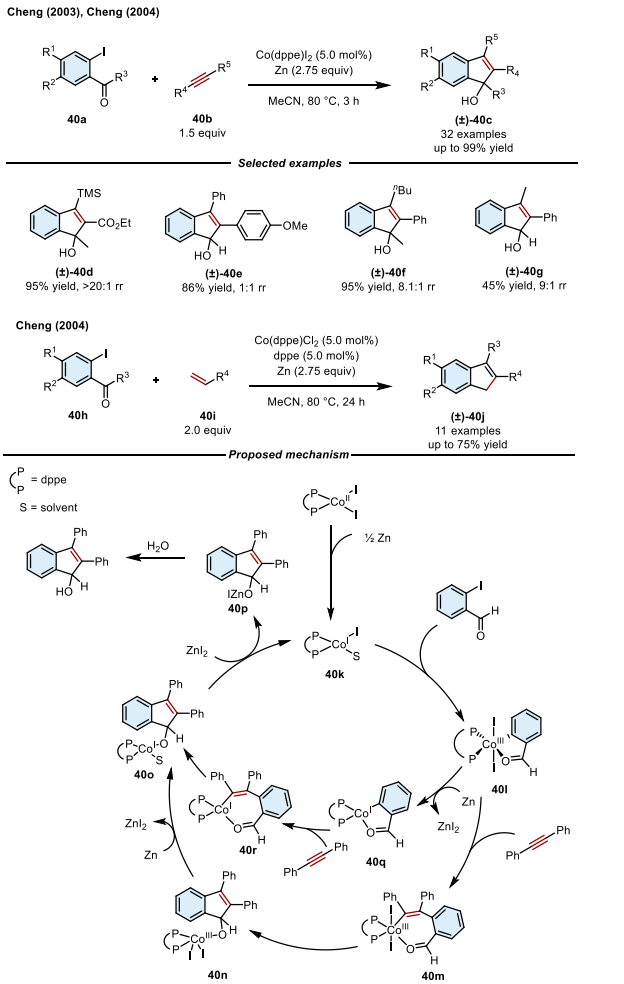
SCHEME 38 | Nickel-catalyzed asymmetric synthesis of chiral tertiary alcohols.



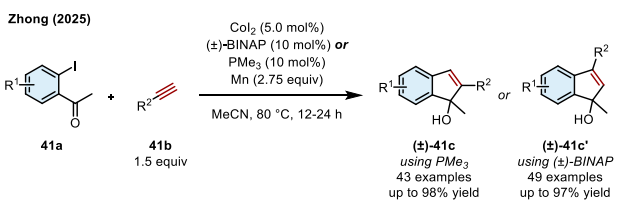
SCHEME 39 | Nickel-catalyzed asymmetric synthesis of indolines.

Co(III) intermediate **40m** to Co(I) intermediate **40q**, followed by migratory insertion across the alkyne to give rise to **40r** couldn't be excluded as another possible mechanistic pathway.

Cheng later utilized cobalt catalysis to access indenes by reacting *ortho*-iodoacetophenones or *ortho*-iodobenzaldehydes with acrylates (Scheme 40, middle) [83]. Conditions utilizing Co(dppe)Cl_2 with an additional equivalent of dppe resulted in product yields up to 75%. The reason for requiring excess ligand was inconclusive, but the authors postulated that the excess ligand may stabilize the cobalt complex over the course of the reaction. When no extra dppe ligand was included, the cobalt complex was found to decompose over time.



SCHEME 40 | Cobalt-catalyzed racemic synthesis of indenes and indenols.

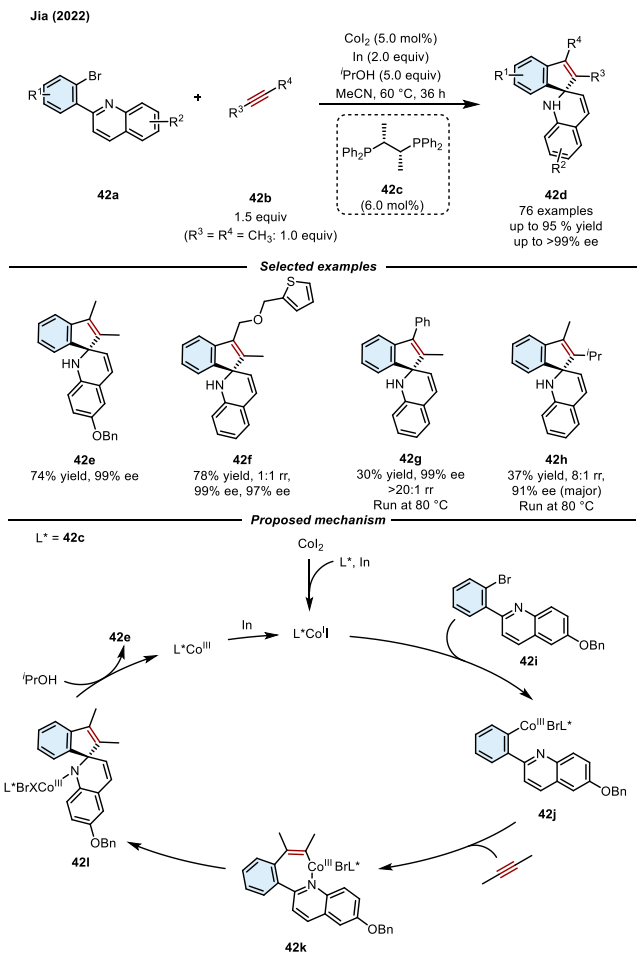


SCHEME 41 | Cobalt-catalyzed and ligand-directed regioselective synthesis of racemic indenols.

In 2025, Zhong and coworkers extended this cobalt catalyzed carbocylization to terminal alkynes, allowing for the regiodivergent synthesis of 2- or 3- substituted indenols (Scheme 41) [84]. Trimethyl phosphine as the ligand affords exclusively 2-substituted indenols **41c**, whereas utilizing BINAP leads to a reversal in regioselectivity, giving 3-subsituted indenols **41c'**.

5.2 | Enantioselectivity Studies

Jia and co-workers reported an enantioselective cobalt catalyzed reaction of 2-*ortho*-haloraryl-N-heteroarenes to access



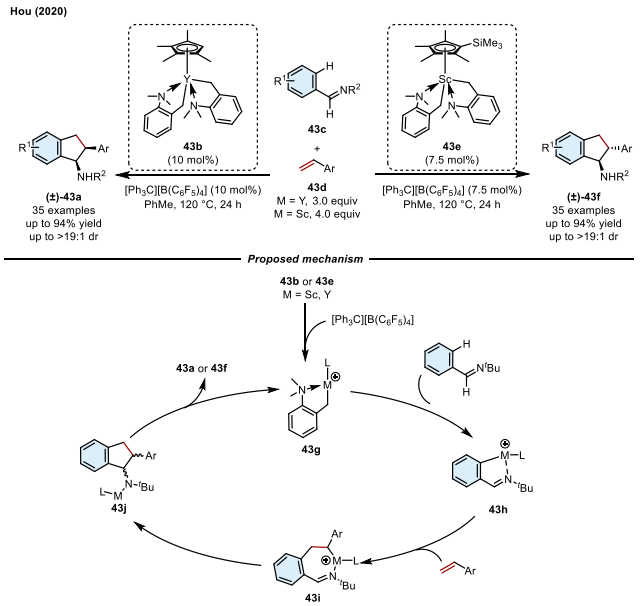
SCHEME 42 | Cobalt-catalyzed asymmetric synthesis of *N*-heterocyclic compounds with spiro quaternary stereocenters.

N-heterocyclic compounds possessing spiro quaternary stereocenters (Scheme 42) [85]. When unsymmetrical alkynes were employed, the regiomeric ratio varied from 1:1 to >20:1 rr, as illustrated by examples **42e-h**. Oxidative addition of Co(I) into the C—Br bond of quinoline-tethered **42i** generates aryl-Co(III) intermediate **42j**. Carbocobaltation of the alkyne results in vinyl-Co intermediate **42k**, which coordinates to the *N*-atom of the quinoline moiety. An intramolecular dearomative migratory insertion into the C═N bond of the azacycle results in intermediate **42l**. Protodemetalation by ^{i}PrOH releases both the product **42e** and Co(III), which is reduced by indium to regenerate Co(I).

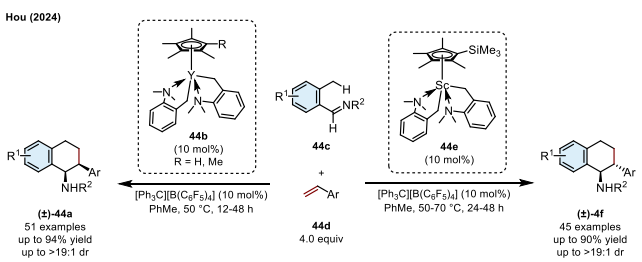
6 | Other Rare-Earth-Metal-Catalyzed Reactions

6.1 | Early Studies (RACEMIC)

The Hou group has made considerable progress in accessing benzofused 5- and 6-membered rings within the space of rare-earth-metal-catalyzed reactions. In 2020, they reported a catalyst controlled diastereodivergent synthesis of aminoindanes via the coupling of aldimines and alkenes (Scheme 43) [86]. Yttrium catalyst **43b** led to synthesis of the *cis*-diastereomer **43a**, whereas scandium catalyst **43e** resulted in the formation of the *trans*-diastereomer **43f**, with both products being obtained in up to >19:1 dr. The active cationic catalyst **43 g**, generated from reaction with co-catalyst $[Ph_3C][B(C_6F_5)_4]$, can undergo C(sp^2)—H activation at the aldimine substrate's *ortho* position to result in **43 h**. Regioselective migratory insertion of a styrene derivative into the metal-aryl bond gives seven-membered metallacycle **43l**, which undergoes intramolecular nucleophilic addition and protodemetalation to afford the desired aminoindane products. The difference in diastereoselectivity was attributed to the olefin insertion step, where the yttrium catalyst and styrene interact favorably during the insertion step due to a smaller orbital energy gap between the two species [86, 87]. The less bulky (C_5HMe_4) ligand also favours *cis* selectivity. In the case of the scandium catalyst, the repulsion between bulky ligand ($C_5Me_4SiMe_3$) and benzaldimine results in a C—H π-interaction between the H atom of the N^{t}Bu group and benzene ring of the styrene, resulting in the observed *trans* selectivity.

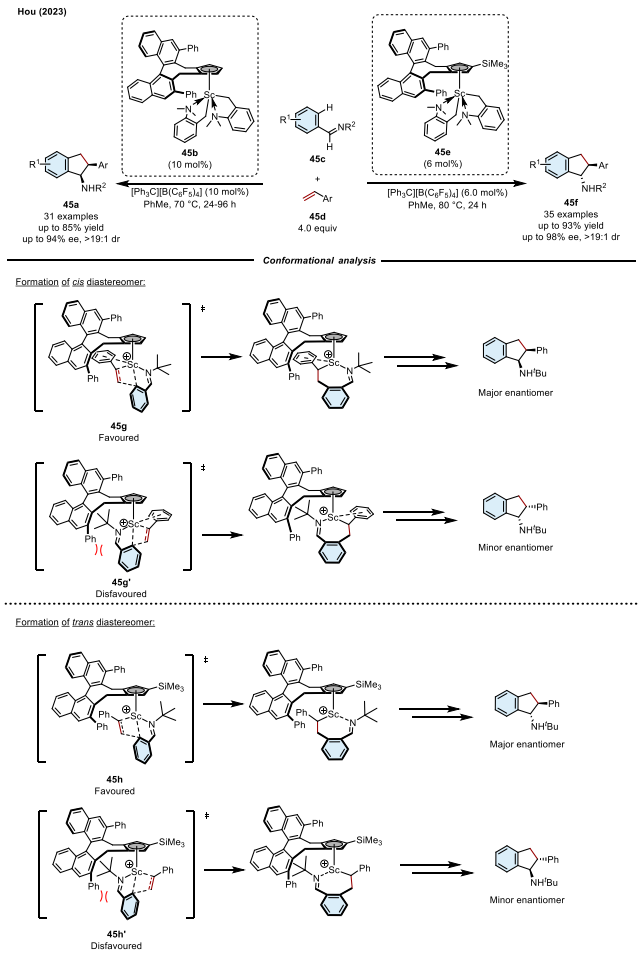


SCHEME 43 | Initial racemic work to access aldimines in a diastereodivergent manner starting from different rare earth catalysts.



SCHEME 44 | Diastereodivergent synthesis of aminotetralins.

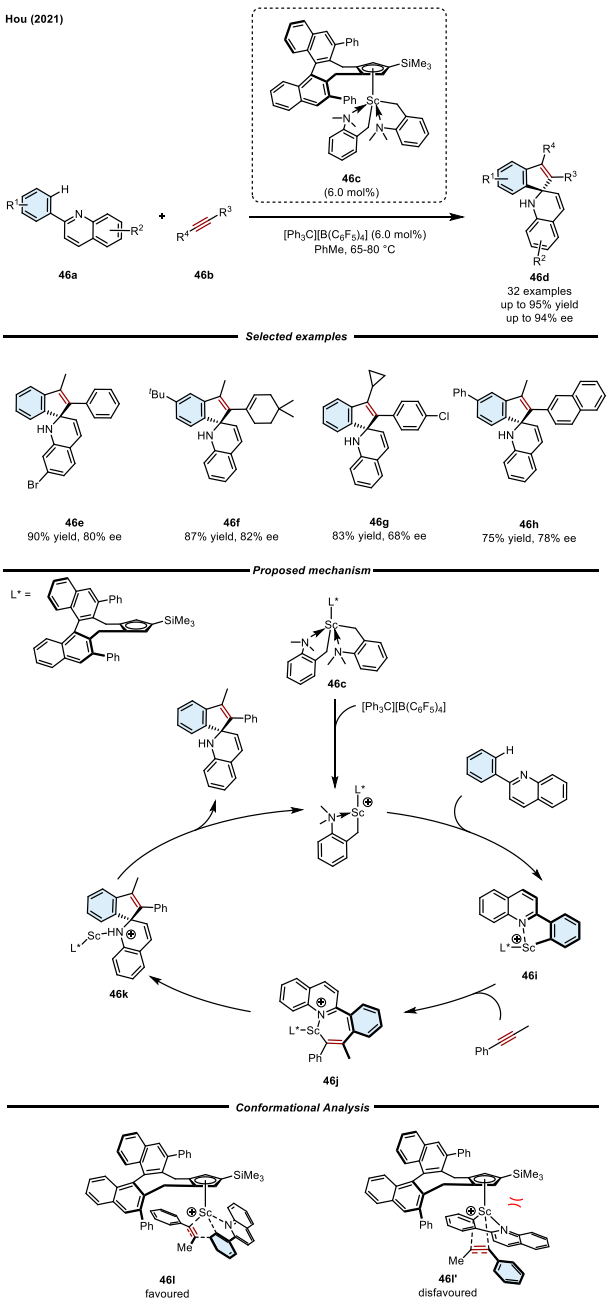
Subsequently, Hou and coworkers were able to extend this methodology to synthesizing aminotetralins via a benzylic C(sp^3)—H activation (Scheme 44) [88]. As established in their earlier work, the use of an yttrium catalyst resulted in the *cis*-diastereomer whereas a scandium catalyst resulted in the *trans*-diastereomer.



SCHEME 45 | Scandium-catalyzed asymmetric synthesis of aminoindanes.

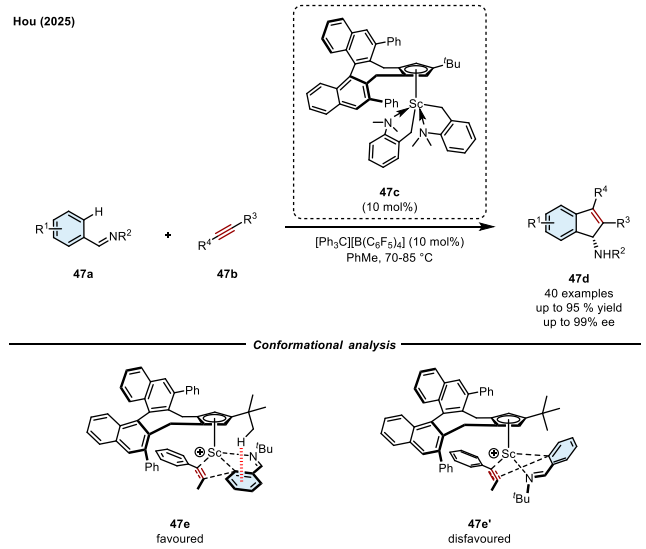
6.2 | Enantioselectivity Studies

In 2023, the Hou group followed up on the diastereodivergent synthesis of aminoindanes with an enantioselective variant utilizing chiral scandium half sandwich catalysts (Scheme 45) [89]. The use of chiral catalyst **45b**, which has a less sterically demanding cyclopentadienyl ligand, results in the exclusive formation of the *cis*-diastereomer with high enantioselectivity. The analogous yttrium complex was effective but displayed lower enantioselectivity. Switching to chiral catalyst **45e** with a more sterically encumbering trimethylsilylcyclopentadienyl ligand reverses selectivity to the *trans*-diastereomer with high enantiocontrol. The formation of the major enantiomer for the *cis*-diastereomer is proposed to occur via transition state **45 g**, where there is minimum repulsion between the styrene's aryl group and the 3,3'-Ph group on chiral catalyst **45b** [89, 90]. Furthermore, the smaller cyclopentadienyl ligand allows for interaction between the scandium atom and aryl group of the styrene, leading to generation of the *cis* product. Formation of the minor enantiomer occurs via transition state **45g'** wherein steric repulsion takes place between the N^{t}Bu group and the 3,3'-Ph group on **45b**. Formation of the major enantiomer for the *trans*-diastereomer occurs via transition state **45 h**, where similarly repulsion is minimized.



SCHEME 46 | Synthesis of enantioenriched dihydroquinolines via scandium catalysis.

Hou and coworkers reported an enantioselective half-sandwich scandium-catalyzed synthesis of N-H spiro-1,2-dihydroquinolines **46d** starting from 2-aryl quinolines **46a** (Scheme 46) [91]. Catalyst **46c**, with phenyl substituents at the 3,3'-positions of the binaphthyl moiety and a TMS substituent on the cyclopentadienyl ring, proved optimal in giving rise to good reactivity and enantioinduction. While Jia and coworkers observed regioselectivity issues in their cobalt catalyzed system to access spiro-1,2-dihydroquinolines (Scheme 42) [85], Hou's system provided single regioisomers. The quinoline's N atom directs the scandium center to the *ortho*-position of its pendant aryl fragment via C—H activation. Migratory insertion of the alkyne affords the seven-membered metallacyle **46j**, which undergoes 1,2 addition to the



SCHEME 47 | Asymmetric synthesis of aminoindenes via scandium catalysis.

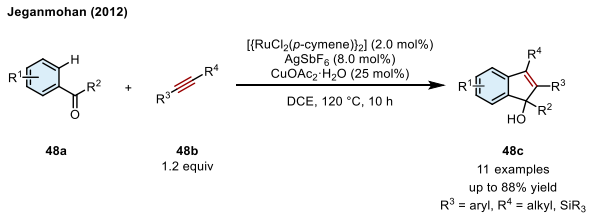
C═N bond of the quinoline moiety to afford a quaternary spiro center. The active catalyst is regenerated by an acid base reaction between the Sc–amido bond and the phenyl *ortho* C—H bond of another molecule of substrate. DFT studies suggested that the driving force for the dearomative spiroannulation results from the scandium alkenyl species **46j** bearing a strongly nucleophilic character. In contrast, an analogous rhodium alkenyl species possesses almost no nucleophilic character. The TMS group on the chiral catalyst was found to play a key role in the high ee values observed. Migratory insertion of the alkyne into the Sc–aryl bond constitutes the enantioselectivity determining step. The authors surmised that the transition state **46l'** for the minor enantiomer shows steric repulsion between the TMS substituent and the 2-phenyl group of the starting material, whereas less repulsion was observed in transition state **46l** leading to the major enantiomer.

Hou and coworkers later reported a scandium-catalyzed enantioselective 3+2 annulation of aldimines with internal alkynes to afford 1-aminoindenes (Scheme 47) [92]. Out of the many chiral scandium half sandwich catalysts that were screened, ^{t}butylcylopentadienyl-ligated catalyst, **47c**, afforded the highest ee values. The enantioselectivity is determined by the alkyne insertion, with the ^{t}butyl substituent playing a key role. En route to the major enantiomer, a C—H π-noncovalent interaction between the ^{t}butyl substituent on the Cp ligand and phenyl group of the benzaldimine was observed, as shown in transition **47e**. No such noncovalent interaction was observed in transition state **47e'** leading to the minor enantiomer.

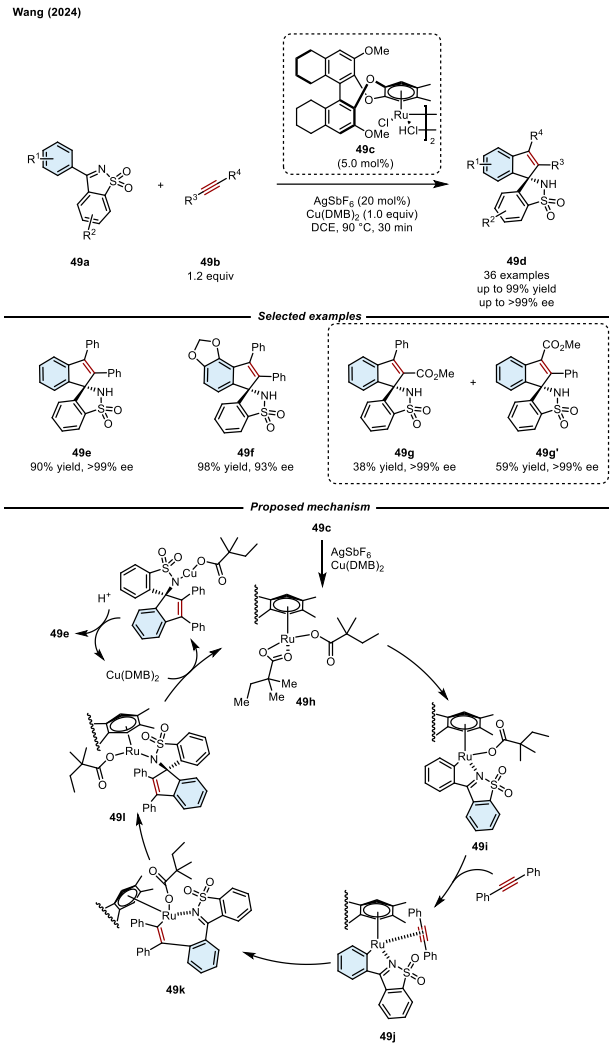
7 | Ruthenium-Catalyzed Reactions

7.1 | Early Studies (RACEMIC)

A report by Jeganmohan and coworkers in 2012 describes the ruthenium-catalyzed synthesis of indenols (Scheme 48) [93]. Notably, carbonyl-directed C—H activation followed by migratory insertion across disubstituted alkynes occurs with high regioselectivity.



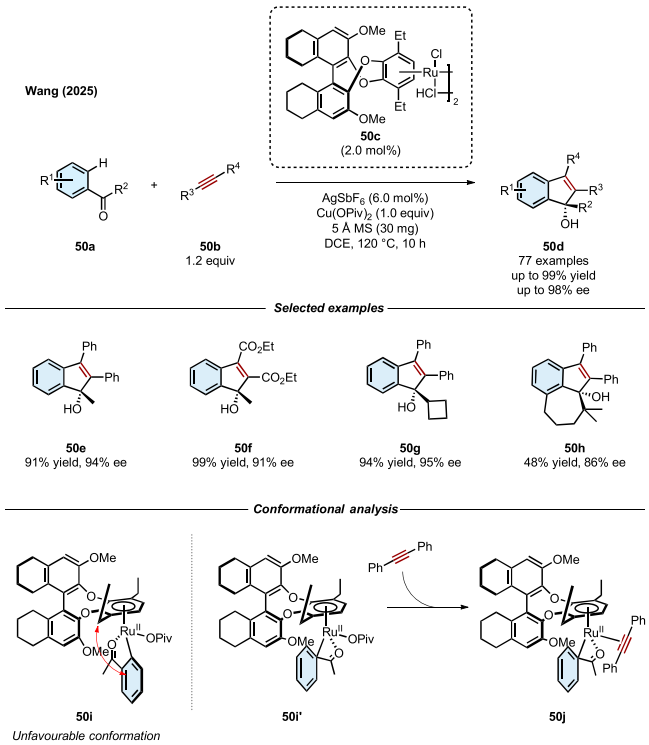
SCHEME 48 | Racemic synthesis of indenols via ruthenium catalysis.



SCHEME 49 | Ruthenium-catalyzed synthesis of spirosultams using BenRu catalyst.

7.2 | Enantioselectivity Studies

In analogy to Cramer's 2016 report (Scheme 22) [58], the Wang group reported the synthesis of spirocyclic sultams using the newly reported BenRu complex **49c** (Scheme 49) [94]. The proposed mechanism starts by forming the catalytically active ruthenium-DMB (3,3-Dimethyl-1-butanol) complex, followed by imine-directed C—H activation. Coordination and insertion of the disubstituted alkyne results in a seven-membered ruthenacycle.

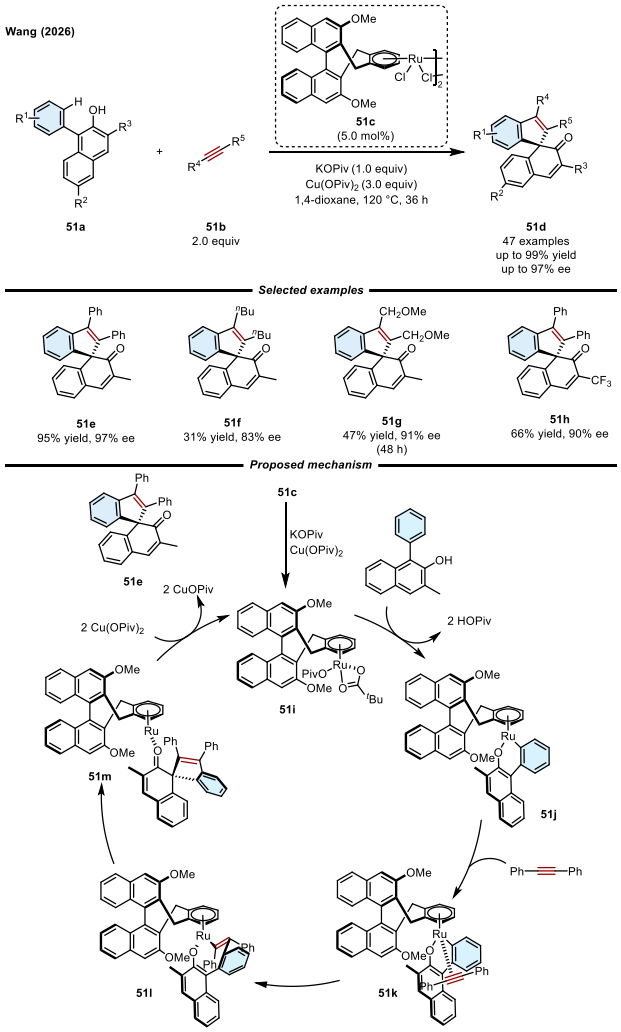


SCHEME 50 | Ruthenium-catalyzed synthesis of enantioenriched indenols.

Addition across the C═N bond, followed by transmetalation with $Cu(DMB)_2$ and protonation yields the desired product **49e**.

Very recently, a report by Wang and coworkers showed the application of the newly designed Ben ligands towards the synthesis of indenols (Scheme 50) [95]. The use of tetrasubstituted Ben ligand **50c** led to the desired indenol product **50e** in 91% yield and 94% ee. These reaction conditions were amenable to a wide substrate scope, with different alkyne partners (**50f**), carbonyl substitution (**50 g**) and aryl substitution (**50 h**) being tolerated. Based on KIE experiments, the authors proposed that C—H bond cleavage towards the formation of the Ru-arene intermediate constitutes the turnover-limiting step. In the minor diastereomer's C—H activation intermediate, there is an unfavorable interaction between the bulky phenyl ring on the acetophenone and the ligand's ethyl group [96]. Alternatively, in the favorable conformation, a stabilizing π-π interaction between the substrate's and ligand's arene rings help lock the substrate prior to alkyne coordination.

Wang and coworkers followed up on their report using a new class of Ben ligands to make indanols by extending the methodology to phenol directed asymmetric C—H activation of β-naphthols with alkynes to access spirocyclic indenes (Scheme 51) [97]. The desired spirocyclic product **51e** was obtained in 95% yield and 94% ee utilizing chiral BenRu catalyst **51c**. Dialkyl alkynes were tolerated in the reaction conditions as well, as illustrated by **51f-g**. The authors propose that the migratory insertion of the alkyne to afford eight membered intermediate **51l** is the enantio-determining step. Based on KIE experiments, the authors proposed that C—H bond cleavage resulting in **51j** is likely the turnover-limiting step.



SCHEME 51 | Ruthenium-catalyzed asymmetric annulative dearomatization of β-naphthols with alkynes.

8 | Conclusion and Perspectives

This review summarizes the progress carried out in the first quarter of the 21st century in transition metal-catalyzed asymmetric intermolecular carbometalations for the construction of enantioenriched molecules bearing stereodefined tertiary and quaternary centers as well as axial chirality. There remains a significant gap in the literature as to potential dual metal-photocatalytic methods to synthesize stereodefined centers, as most procedures require elevated reaction temperatures. However, the diversity of metals and ligands that facilitate reactions showcase a variety of mechanistic pathways and conformational effects, leading to high asymmetric induction.

Author Contributions

Clara Jans: conceptualization, writing - original draft, writing - review and editing. **Armaan Grewal:** conceptualization, writing - original draft, writing - review and editing. **Xavier Abel-snape:** conceptualization, writing - original draft, writing - review and editing. **Mark Lautens:** writing - review and editing, supervision, resources, conceptualization.

Acknowledgments

‡ C.J. and A.G. contributed equally. The authors thank the University of Toronto, the Natural Sciences and Engineering Research Council of Canada (NSERC), and Paraza Pharma Inc. for financial support. C.J. thanks NSERC (CGS-D) for funding. X.A.-S. thanks NSERC (CGS-D) for funding. Dr. Arthur Flaget is thanked for proofreading and insightful discussions.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

References

1. K. W. Quasdorf and L. E. Overman, "Catalytic Enantioselective Synthesis of Quaternary Carbon Stereocentres," *Nature* 516 (2014): 181–191, https://doi.org/10.1038/nature14007.

2. R. C. Larock and E. K. Yum, "Synthesis of Indoles via Palladium-Catalyzed Heteroannulation of Internal Alkynes," *Journal of the American Chemical Society* 113 (1991): 6689–6690, https://doi.org/10.1021/ja00017a059.

3. R. Chinchilla and C. Nájera, "The Sonogashira Reaction: a Booming Methodology in Synthetic Organic Chemistry," *Chemical Reviews* 107 (2007): 874–922, https://doi.org/10.1021/cr050992x.

4. J. N. Shepherd and J. R. Stenzel, "Synthesis of Unsymmetrical Alkynes via the Alkylation of Sodium Acetylides. An Introduction to Synthetic Design for Organic Chemistry Students," *Journal of Chemical Education* 83 (2006): 425, https://doi.org/10.1021/ed083p425.

5. T. H. Vaughn, G. F. Hennion, R. R. Vogt, and J. A. Nieuwland, "The Preparation and Alkylation of Metal Acetylides in Liquid Ammonia*," *The Journal of Organic Chemistry* 02 (1937): 1–22, https://doi.org/10.1021/jo01224a001.

6. C. Bailly, "A Systematic Review of Proaporphine Alkaloids and a Pharmacological Update," *Phytomedicine Plus* 5 (2025): 100689, https://doi.org/10.1016/j.phyplu.2024.100689.

7. H.-G. Cheng, S. Jia, and Q. Zhou, "Benzo-Fused-Ring Toolbox Based on Palladium/Norbornene Cooperative Catalysis: Methodology Development and Applications in Natural Product Synthesis," *Accounts of Chemical Research* 56 (2023): 573–591, https://doi.org/10.1021/acs.accounts.2c00781.

8. A. Rinaldi, D. Scarpi, and E. G. Occhiato, "Recent Advances in the Synthesis of Indenes," *European Journal of Organic Chemistry* 2019 (2019): 7401–7419, https://doi.org/10.1002/ejoc.201901425.

9. G. Majetich and J. M. Shimkus, "The Taiwaniaquinoids: A Review," *Journal of Natural Products* 73 (2010): 284–298, https://doi.org/10.1021/np9004695.

10. C. A. L. Bercht, J. P. C. M. van Dongen, W. Heerma, R. J. J. C. Lousberg, and F. J. E. M. Küppers, "Cannabispirone and Cannabispirenone, Two Naturally Occurring Spiro-Compounds," *Tetrahedron* 32 (1976): 2939–2943, https://doi.org/10.1016/0040-4020(76)80149-4.

11. Z. Zhang and L. Dai, "Construction of Axially Chiral Molecules Enabled by Photoinduced Enantioselective Reactions," *Chemical Science* 15 (2024): 12636–12643, https://doi.org/10.1039/D4SC03766A.

12. W.-Y. Cai, Q.-N. Ding, L. Zhou, and J. Chen, "Asymmetric Synthesis of Axially Chiral Molecules via Organocatalytic Cycloaddition and Cyclization Reactions," *Molecules (Basel, Switzerland)* 28 (2023): 4306, https://doi.org/10.3390/molecules28114306.

13. T. Zhou and B.-F. Shi, "Metal-Catalyzed Asymmetric Synthesis of Biaryl Atropisomers," in *Axially Chiral Compounds* (2021), 13–45, https://doi.org/10.1002/9783527825172.

14. L. G. Quan, V. Gevorgyan, and Y. Yamamoto, "Intramolecular Nucleophilic Addition of Vinylpalladiums to Aryl Ketones," *Journal of the American Chemical Society* 121 (1999): 3545–3546, https://doi.org/10.1021/ja983645w.

15. D. Zhang, E. K. Yum, Z. Liu, and R. C. Larock, "Synthesis of Indenes by the Palladium-Catalyzed Carboannulation of Internal Alkynes," *Organic Letters* 7 (2005): 4963–4966, https://doi.org/10.1021/ol051907a.

16. D. Zhang, Z. Liu, E. K. Yum, and R. C. Larock, "Synthesis of Indenes by the Transition Metal-Mediated Carboannulation of Alkynes," *The Journal of Organic Chemistry* 72 (2007): 251–262, https://doi.org/10.1021/jo0620563.

17. F. Zhou, M. Yang, and X. Lu, "Cationic Palladium(II)-Catalyzed Highly Enantioselective Tandem Reactions of Ortho-Boronate-Substituted Cinnamic Ketones and Internal Alkynes: A Convenient Synthesis of Optically Active Indenes," *Organic Letters* 11 (2009): 1405–1408, https://doi.org/10.1021/ol9001015.

18. X. Yu and X. Lu, "Cationic Palladium Complex-Catalyzed Diastereoselective Tandem Annulation of 2-Iminoarylboronic Acids With Substituted Alkynes: Enantioselective Synthesis of Aminoindene Derivatives by Double Asymmetric Induction," *Advanced Synthesis & Catalysis* 353 (2011): 2805–2813, https://doi.org/10.1002/adsc.201100363.

19. C.-X. Gu, W.-W. Chen, and M.-H. Xu, "Pd(II)-Catalyzed Asymmetric Annulation Toward the Synthesis of 2,3-Disubstituted Chiral Indenols," *The Journal of Organic Chemistry* 85 (2020): 3887–3893, https://doi.org/10.1021/acs.joc.9b02958.

20. L. Yang, H. Zheng, L. Luo, et al., "Palladium-Catalyzed Dynamic Kinetic Asymmetric Transformation of Racemic Biaryls: Axial-to-Central Chirality Transfer," *Journal of the American Chemical Society* 137 (2015): 4876–4879, https://doi.org/10.1021/jacs.5b01285.

21. H. Chu, J. Cheng, J. Yang, Y.-L. Guo, and J. Zhang, "Asymmetric Dearomatization of Indole by Palladium/PC-Phos-Catalyzed Dynamic Kinetic Transformation," *Angewandte Chemie International Edition* 59 (2020): 21991–21996, https://doi.org/10.1002/anie.202010164.

22. D. Gao and L. Jiao, "Divergent Synthesis of Indolenine and Indoline Ring Systems by Palladium-Catalyzed Asymmetric Dearomatization of Indoles," *Angewandte Chemie International Edition* 61 (2022): e202116024, https://doi.org/10.1002/anie.202116024.

23. L.-L. Han, Y.-M. Cui, Q. Yang, L.-L. Fang, and L.-W. Xu, "Palladium-Catalyzed Transient Chirality Transfer and Atroposelective C-H Functionalization to Access Quaternary Stereocenters," *Angewandte Chemie International Edition* 61 (2022): e202211922, https://doi.org/10.1002/anie.202211922.

24. K.-X. Kong, T. Zhou, W.-K. Yuan, X.-S. Hui, Y. Li, and B.-F. Shi, "Pd(II)-Catalyzed Asymmetric C–H Functionalization/Dearomatization of Naphthols Through Axial-to-Central Chirality Transfer," *ACS Catalysis* 15 (2025): 4280–4286, https://doi.org/10.1021/acscatal.5c00136.

25. X. Abel-Snape, C. Jans, B. Mirabi, et al., "Remote Asymmetric Induction via a Chiral Acetylene Equivalent," *ACS Catalysis* 15 (2025): 14239–14251, https://doi.org/10.1021/acscatal.5c03724.

26. X. Abel-Snape, G. Wycich, and M. Lautens, "Synthesis of Indenes and Benzofulvenes via a Palladium-Catalyzed Three-Component Reaction," *ACS Catalysis* 12 (2022): 3291–3301, https://doi.org/10.1021/acscatal.1c06046.

27. C. Jans, A. Grewal, X. Abel-Snape, L. Rizzo, G. J. Hughes, and M. Lautens, "Synthesis of Spiroindenes via Palladium Catalysis Using Oxabicycles as Acetylene Surrogates," *Organic Letters* 27 (2025): 13559–13564, https://doi.org/10.1021/acs.orglett.5c04430.

28. G. Zhang, B. Yang, J. Yang, and J. Zhang, "Pd-Catalyzed Asymmetric Larock Indole Synthesis to Access Axially Chiral N-Arylindoles," *Journal of the American Chemical Society* 146 (2024): 5493–5501, https://doi.org/10.1021/jacs.3c13356.

29. J. Wang, D. Pan, F. Wang, S. Yu, G. Huang, and X. Li, "Pd-Catalyzed Asymmetric Larock Reaction for the Atroposelective Synthesis of N—N

Chiral Indoles," *Science Advances* 10 (2024): eado4489, https://doi.org/10.1126/sciadv.ado4489.

30. D. Parganiha, R. A. Thorat, A. D. Dhumale, et al., "Substrate NOBINAc Ligand Affinity for PdII-Catalyzed Enantioselective C–H Activation Over Reactive β-C–H Bonds in Ferrocenyl Amines," *Chemical Science* 16 (2025): 700–708, https://doi.org/10.1039/D4SC06867J.

31. R. Shintani, K. Okamoto, and T. Hayashi, "Rhodium-Catalyzed Synthesis of Indenols by Regioselective Coupling of Alkynes With Ortho-Carbonylated Arylboronic Acids," *Chemistry Letters* 34 (2005): 1294–1295, https://doi.org/10.1246/cl.2005.1294.

32. T. Matsuda, M. Makino, and M. Murakami, "Synthesis of 1H-Inden-1-ol Derivatives via Rhodium-Catalyzed Annulation of o-Acylphenylboronic Acids With Alkynes," *Chemistry Letters* 34 (2005): 1416–1417, https://doi.org/10.1246/cl.2005.1416.

33. Y. Sun, Y. Li, X. Wang, et al., "Preparation of New Chiral Diene Ligands and Their Use in the Rhodium Catalyzed Asymmetric Annulation of 2-Formylarylboronic Acid With Dialkylalkynes," *Chemical Communications* 59 (2023): 9102–9105, https://doi.org/10.1039/D3CC02330C.

34. Y. Sun, J. Pan, X. Wang, X. Bu, M. Ma, and F. Xue, "Rhodium-Catalyzed Asymmetric Annulation of Unactivated Alkynes With 3-(Ortho-Boronated Aryl) Conjugated Enones: Enantioselective Synthesis of 2,3-Disubstituted Indenes," *The Journal of Organic Chemistry* 88 (2023): 6140–6145, https://doi.org/10.1021/acs.joc.2c02957.

35. D. N. Tran and N. Cramer, "Enantioselective Rhodium(I)-Catalyzed [3+2] Annulations of Aromatic Ketimines Induced by Directed C–H Activations," *Angewandte Chemie International Edition* 50 (2011): 11098–11102, https://doi.org/10.1002/anie.201105766.

36. T. Seiser, O. A. Roth, and N. Cramer, "Enantioselective Synthesis of Indanols From Tert-Cyclobutanols Using a Rhodium-Catalyzed C–C/C–H Activation Sequence," *Angewandte Chemie International Edition* 48 (2009): 6320–6323, https://doi.org/10.1002/anie.200903189.

37. T. Seiser and N. Cramer, "Rhodium(I)-Catalyzed Enantioselective Activation of Cyclobutanols: Formation of Cyclohexane Derivatives With Quaternary Stereogenic Centers," *Chemistry – A European Journal* 16 (2010): 3383–3391, https://doi.org/10.1002/chem.200903225.

38. M. R. Albicker and N. Cramer, "Enantioselective Palladium-Catalyzed Direct Arylations at Ambient Temperature: Access to Indanes With Quaternary Stereocenters," *Angewandte Chemie International Edition* 48 (2009): 9139–9142, https://doi.org/10.1002/anie.200905060.

39. T. Seiser, G. Cathomen, and N. Cramer, "Enantioselective Construction of Indanones From Cyclobutanols Using a Rhodium-Catalyzed C-C/C-H/C-C Bond Activation Process," *Synlett* 2010 (2010): 1699–1703, https://doi.org/10.1055/s-0029-1219959.

40. M. Waibel and N. Cramer, "Palladium-Catalyzed Arylative Ring-Opening Reactions of Norbornenols: Entry to Highly Substituted Cyclohexenes, Quinolines, and Tetrahydroquinolines," *Angewandte Chemie International Edition* 49 (2010): 4455–4458, https://doi.org/10.1002/anie.201001752.

41. T. Seiser and N. Cramer, "Rhodium(I)-Catalyzed 1,4-Silicon Shift of Unactivated Silanes From Aryl to Alkyl: Enantioselective Synthesis of Indanol Derivatives," *Angewandte Chemie International Edition* 49 (2010): 10163–10167, https://doi.org/10.1002/anie.201005399.

42. M. Waibel and N. Cramer, "Desymmetrizations of Meso-Tert-Norbornenols by Rhodium(i)-Catalyzed Enantioselective Retro-Allylations," *Chemical Communications* 47 (2011): 346–348, https://doi.org/10.1039/C0CC01950J.

43. Z.-M. Sun, S.-P. Chen, and P. Zhao, "Tertiary Carbinamine Synthesis by Rhodium-Catalyzed [3+2] Annulation of N-Unsubstituted Aromatic Ketimines and Alkynes," *Chemistry – A European Journal* 16 (2010): 2619–2627, https://doi.org/10.1002/chem.200902814.

44. D. García-Cuadrado, P. de Mendoza, A. A. C. Braga, F. Maseras, and A. M. Echavarren, "Proton-Abstraction Mechanism in the Palladium-Catalyzed Intramolecular Arylation: Substituent Effects," *Journal of the American Chemical Society* 129 (2007): 6880–6886, https://doi.org/10.1021/ja071034a.

45. D. N. Tran and N. Cramer, "Syn-Selective Rhodium(I)-Catalyzed Allylations of Ketimines Proceeding Through a Directed C–H Activation/Allene Addition Sequence," *Angewandte Chemie International Edition* 49 (2010): 8181–8184, https://doi.org/10.1002/anie.201004179.

46. D. N. Tran and N. Cramer, "Rhodium-Catalyzed Dynamic Kinetic Asymmetric Transformations of Racemic Allenes by the [3+2] Annulation of Aryl Ketimines," *Angewandte Chemie International Edition* 52 (2013): 10630–10634, https://doi.org/10.1002/anie.201304919.

47. Y. Zhang, J.-J. Zhang, L. Lou, et al., "Recent Advances in Rh(i)-Catalyzed Enantioselective C–H Functionalization," *Chemical Society Reviews* 53 (2024): 3457–3484, https://doi.org/10.1039/D3CS00762F.

48. C.-X. Liu, S.-Y. Yin, F. Zhao, et al., "Rhodium-Catalyzed Asymmetric C–H Functionalization Reactions," *Chemical Reviews* 123 (2023): 10079–10134, https://doi.org/10.1021/acs.chemrev.3c00149.

49. J. Zheng, S.-B. Wang, C. Zheng, and S.-L. You, "Asymmetric Dearomatization of Naphthols via a Rh-Catalyzed C(sp^2)–H Functionalization/Annulation Reaction," *Journal of the American Chemical Society* 137 (2015): 4880–4883, https://doi.org/10.1021/jacs.5b01707.

50. J. Nan, Z. Zuo, L. Luo, et al., "RuII-Catalyzed Vinylative Dearomatization of Naphthols via a C(sp^2)–H Bond Activation Approach," *Journal of the American Chemical Society* 135 (2013): 17306–17309, https://doi.org/10.1021/ja410060e.

51. H. Zheng, L. Bai, J. Liu, et al., "Pd(0)-Catalyzed Chemoselective Construction of Spirocarbocycles via an Alkyne Insertion/β-Naphthol Dearomatization Cascade," *Chemical Communications* 51 (2015): 3061–3064, https://doi.org/10.1039/C4CC09099C.

52. A. Seoane, N. Casanova, N. Quiñones, J. L. Mascareñas, and M. Gulías, "Rhodium(III)-Catalyzed Dearomatizing (3 + 2) Annulation of 2-Alkenylphenols and Alkynes," *Journal of the American Chemical Society* 136 (2014): 7607–7610, https://doi.org/10.1021/ja5034952.

53. S. Kujawa, D. Best, D. J. Burns, and H. W. Lam, "Synthesis of Spirocyclic Enones by Rhodium-Catalyzed Dearomatizing Oxidative Annulation of 2-Alkenylphenols With Alkynes and Enynes," *Chemistry – A European Journal* 20 (2014): 8599–8602, https://doi.org/10.1002/chem.201403454.

54. S. Gu, L. Luo, J. Liu, et al., "Palladium(II)-Catalyzed Oxidative Dearomatization of Free Naphthols With Two Alkyne Units," *Organic Letters* 16 (2014): 6132–6135, https://doi.org/10.1021/ol502997d.

55. J. Zheng, S.-B. Wang, C. Zheng, and S.-L. You, "Asymmetric Synthesis of Spiropyrazolones by Rhodium-Catalyzed C(sp^2)–H Functionalization/Annulation Reactions," *Angewandte Chemie International Edition* 56 (2017): 4540–4544, https://doi.org/10.1002/anie.201700021.

56. C. Zheng, J. Zheng, and S.-L. You, "A DFT Study on Rh-Catalyzed Asymmetric Dearomatization of 2-Naphthols Initiated With C–H Activation: A Refined Reaction Mechanism and Origins of Multiple Selectivity," *ACS Catalysis* 6 (2016): 262–271, https://doi.org/10.1021/acscatal.5b01891.

57. S. Reddy Chidipudi, D. J. Burns, I. Khan, and H. W. Lam, "Enantioselective Synthesis of Spiroindenes by Enol-Directed Rhodium(III)-Catalyzed C–H Functionalization and Spiroannulation," *Angewandte Chemie International Edition* 54 (2015): 13975–13979, https://doi.org/10.1002/anie.201507029.

58. M. V. Pham and N. Cramer, "Enantioselective Access to Spirocyclic Sultams by Chiral Cpx–Rhodium(III)-Catalyzed Annulations," *Chemistry – A European Journal* 22 (2016): 2270–2273, https://doi.org/10.1002/chem.201504998.

59. F. Wang, J. Jing, Y. Zhao, et al., "Rhodium-Catalyzed C–H Activation-Based Construction of Axially and Centrally Chiral Indenes Through Two Discrete Insertions," *Angewandte Chemie International Edition* 60 (2021): 16628–16633, https://doi.org/10.1002/anie.202105093.

60. B.-B. Gou, W.-J. Shen, Y.-J. Gao, Q. Gu, and S.-L. You, "Enantioselective Synthesis of Indenols via Rhodium(III)–Catalyzed C-H Activa-

tion/Annulation of Ketones With Alkynes," *Science China Chemistry* 68 (2025): 3147–3153, https://doi.org/10.1007/s11426-024-2514-1.

61. W.-W. Zhang, Q. Wang, S.-Z. Zhang, C. Zheng, and S.-L. You, "(SCp)Rhodium-Catalyzed Asymmetric Satoh–Miura Reaction for Building-up Axial Chirality: Counteranion-Directed Switching of Reaction Pathways," *Angewandte Chemie International Edition* 62 (2023): e202214460, https://doi.org/10.1002/anie.202214460.

62. B.-B. Gou, W.-J. Shen, Y.-J. Gao, Q. Gu, and S.-L. You, "Rhodium-Catalyzed Atroposelective Synthesis of Axially Chiral 1-Aryl Isoquinolines via De Novo Isoquinoline Formation," *Angewandte Chemie International Edition* 64 (2025): e202502131, https://doi.org/10.1002/anie.202502131.

63. Q. Wang, Y.-H. Nie, C.-X. Liu, et al., "Rhodium(III)-Catalyzed Enantioselective C–H Activation/Annulation of Ferrocenecarboxamides With Internal Alkynes," *ACS Catalysis* 12 (2022): 3083–3093, https://doi.org/10.1021/acscatal.2c00083.

64. Q. Wang, W.-W. Zhang, C. Zheng, Q. Gu, and S.-L. You, "Enantioselective Synthesis of Azoniahelicenes by Rh-Catalyzed C–H Annulation With Alkynes," *Journal of the American Chemical Society* 143 (2021): 114–120, https://doi.org/10.1021/jacs.0c11735.

65. X. Zhu, H. Wu, Y. Wang, G. Huang, F. Wang, and X. Li, "Rhodium-Catalyzed Annulative Approach to N–N Axially Chiral Biaryls via C–H Activation and Dynamic Kinetic Transformation," *Chemical Science* 14 (2023): 8564–8569, https://doi.org/10.1039/D3SC02800C.

66. R. A. Thorat, D. Parganiha, S. Jain, et al., "Temperature-Dependent Diastereodivergent [4 + 3] Annulation: Synthesis of Ferrocene-Fused Azepines via Rh(III) Catalysis," *Organic Letters* 27 (2025): 552–558, https://doi.org/10.1021/acs.orglett.4c03954.

67. H. Li, R. Gontla, J. Flegel, et al., "Enantioselective Formal C(sp^3)–H Bond Activation in the Synthesis of Bioactive Spiropyrazolone Derivatives," *Angewandte Chemie International Edition* 58 (2019): 307–311, https://doi.org/10.1002/anie.201811041.

68. W. Wei, A. Scheremetjew, and L. Ackermann, "Electrooxidative Palladium- and Enantioselective Rhodium-Catalyzed [3 + 2] Spiroannulations," *Chemical Science* 13 (2022): 2783–2788, https://doi.org/10.1039/D1SC07124F.

69. H. Yuan-Qiong, W. Zhi-Jie, Z. Li, et al., "Electrochemical Rhodium-Catalyzed Enantioselective C–H Annulation With Alkynes," *CCS Chemistry* 4 (2021): 3181–3189, https://doi.org/10.31635/ccschem.021.202101376.

70. G. Zhou, T. Zhou, A.-L. Jiang, et al., "Electrooxidative Rhodium(III)/Chiral Carboxylic Acid-Catalyzed Enantioselective C–H Annulation of Sulfoximines With Alkynes," *Angewandte Chemie International Edition* 63 (2024): e202319871, https://doi.org/10.1002/anie.202319871.

71. P. Wang, Y. Huang, J. Jing, F. Wang, and X. Li, "Rhodium(III)-Catalyzed Atroposelective Synthesis of C–N Axially Chiral Naphthylamines and Variants via C–H Activation," *Organic Letters* 24 (2022): 2531–2535, https://doi.org/10.1021/acs.orglett.2c00686.

72. Y. Sun and N. Cramer, "Rhodium(III)-Catalyzed Enantiotopic C–H Activation Enables Access to P-Chiral Cyclic Phosphinamides," *Angewandte Chemie International Edition* 56 (2017): 364–367, https://doi.org/10.1002/anie.201606637.

73. Y. Sun and N. Cramer, "Tailored Trisubstituted Chiral CpxRhIII Catalysts for Kinetic Resolutions of Phosphinic Amides," *Chemical Science* 9 (2018): 2981–2985, https://doi.org/10.1039/C7SC05411D.

74. D. K. Rayabarapu and C.-H. Cheng, "Nickel-Catalyzed Regioselective Carbocyclization of Ortho-Halophenyl Ketones With Propiolates: An Efficient Route to Disubstituted Indenols," *Chemical Communications* 9 (2002): 942–943, https://doi.org/10.1039/b201473d.

75. D. K. Rayabarapu, C.-H. Yang, and C.-H. Cheng, "Regioselective Synthesis of Indenols via Nickel-Catalyzed Carbocyclization Reaction," *The Journal of Organic Chemistry* 68 (2003): 6726–6731, https://doi.org/10.1021/jo0346508.

76. C. Clarke, C. A. Incerti-Pradillos, and H. W. Lam, "Enantioselective Nickel-Catalyzed Anti-Carbometallative Cyclizations of Alkynyl Electrophiles Enabled by Reversible Alkenylnickel E/Z Isomerization," *Journal of the American Chemical Society* 138 (2016): 8068–8071, https://doi.org/10.1021/jacs.6b04206.

77. T. Zhang, Y.-X. Luan, S.-J. Zheng, Q. Peng, and M. Ye, "Chiral Aluminum Complex Controls Enantioselective Nickel-Catalyzed Synthesis of Indenes: C−CN Bond Activation," *Angewandte Chemie International Edition* 59 (2020): 7439–7443, https://doi.org/10.1002/anie.202001142.

78. Y.-F. Han, Y. Li, X.-H. Ouyang, M. Hu, Z. Tan, and J.-H. Li, "Nickel-Catalyzed Asymmetric Reductive [3 + 2] Annulation of o-Haloaromatic β-Alkenyl Ketones With Alkynes via Alkene Isomerization: Enantioselective Synthesis of 1-Alkenyl 1H-Inden-1-Ols," *ACS Catalysis* 11 (2021): 10115–10122, https://doi.org/10.1021/acscatal.1c02613.

79. H. Chen, Y.-X. Wang, Y.-X. Luan, and M. Ye, "Enantioselective Twofold C−H Annulation of Formamides and Alkynes Without Built-in Chelating Groups," *Angewandte Chemie International Edition* 59 (2020): 9428–9432, https://doi.org/10.1002/anie.202001267.

80. W. Li, Y. Zheng, Y. Gu, et al., "Bis(Pinacolato)Diboron-Enabled Nickel-Catalyzed Regio- and Enantioselective Reductive [3 + 2] Annulation of β-Bromoenones With Alkynes," *Angewandte Chemie International Edition* 64 (2025): e202506873, https://doi.org/10.1002/anie.202506873.

81. Y. Ping, K. Wang, Q. Pan, et al., "Ni-Catalyzed Regio- and Enantioselective Domino Reductive Cyclization: One-Pot Synthesis of 2,3-Fused Cyclopentannulated Indolines," *ACS Catalysis* 9 (2019): 7335–7342, https://doi.org/10.1021/acscatal.9b02081.

82. K.-J. Chang, D. K. Rayabarapu, and C.-H. Cheng, "Cobalt-Catalyzed Carbocyclization of o-Iodobenzaldehydes and o-Iodophenylketones With Alkynes," *Organic Letters* 5 (2003): 3963–3966, https://doi.org/10.1021/ol035514s.

83. K.-J. Chang, D. K. Rayabarapu, and C.-H. Cheng, "Cobalt-Catalyzed Regioselective Carbocyclization Reaction of o-Iodophenyl Ketones and Aldehydes With Alkynes, Acrylates, and Acrylonitrile: a Facile Route to Indenols and Indenes," *The Journal of Organic Chemistry* 69 (2004): 4781–4787, https://doi.org/10.1021/jo049506g.

84. G.-F. Qian, R.-B. Chen, T.-T. Miao, et al., "Ligand-Controlled Cobalt-Catalyzed Regioselective Annulation: Divergent Synthesis of Indenols From o-Haloaromatic Ketones and Terminal Alkynes," *Organic Letters* 27 (2025): 7188–7193, https://doi.org/10.1021/acs.orglett.5c02125.

85. P. Yang, Q. Wang, B.-H. Cui, et al., "Enantioselective Dearomative [3 + 2] Umpolung Annulation of N-Heteroarenes With Alkynes," *Journal of the American Chemical Society* 144 (2022): 1087–1093, https://doi.org/10.1021/jacs.1c11092.

86. X. Cong, G. Zhan, Z. Mo, M. Nishiura, and Z. Hou, "Diastereodivergent [3 + 2] Annulation of Aromatic Aldimines With Alkenes via C–H Activation by Half-Sandwich Rare-Earth Catalysts," *Journal of the American Chemical Society* 142 (2020): 5531–5537, https://doi.org/10.1021/jacs.0c01171.

87. P. Wang, G. Luo, J. Yang, X. Cong, Z. Hou, and Y. Luo, "Theoretical Studies of Rare-Earth-Catalyzed [3 + 2] Annulation of Aromatic Aldimine With Styrene: Mechanism and Origin of Diastereoselectivity," *The Journal of Organic Chemistry* 86 (2021): 4236–4244, https://doi.org/10.1021/acs.joc.0c03060.

88. X. Cong, Q. Zhuo, N. Hao, A. Mishra, M. Nishiura, and Z. Hou, "Divergent Synthesis of Multi-Substituted Aminotetralins via [4+2] Annulation of Aldimines With Alkenes by Rare-Earth-Catalyzed Benzylic C(sp3)–H Activation," *Angewandte Chemie International Edition* 63 (2024): e202318203, https://doi.org/10.1002/anie.202318203.

89. A. Mishra, X. Cong, M. Nishiura, and Z. Hou, "Enantioselective Synthesis of 1-Aminoindanes via [3 + 2] Annulation of Aldimines With Alkenes by Scandium-Catalyzed C–H Activation," *Journal of the American Chemical Society* 145 (2023): 17468–17477, https://doi.org/10.1021/jacs.3c06482.

90. J. Hu, X. Tan, Y. Li, et al., "Theoretical Insights Into Rare-Earth-Catalyst-Controlled Diastereo- and Enantioselective [3 + 2] Annulation of Aromatic Aldimines With Styrenes," *Inorganic Chemistry* 64 (2025): 3120–3128, https://doi.org/10.1021/acs.inorgchem.4c05543.

91. S.-J. Lou, G. Luo, S. Yamaguchi, K. An, M. Nishiura, and Z. Hou, "Modular Access to Spiro-Dihydroquinolines via Scandium-Catalyzed Dearomative Annulation of Quinolines With Alkynes," *Journal of the American Chemical Society* 143 (2021): 20462–20471, https://doi.org/10.1021/jacs.1c10743.

92. A. Mishra, J. Hu, X. Cong, et al., "Enantioselective [3+2] Annulation of Aldimines With Alkynes by Scandium-Catalyzed C−H Activation," *Angewandte Chemie International Edition* 64 (2025): e202419567, https://doi.org/10.1002/anie.202419567.

93. R. K. Chinnagolla and M. Jeganmohan, "Ruthenium-Catalyzed Regioselective Cyclization of Aromatic Ketones With Alkynes: An Efficient Route to Indenols and Benzofulvenes," *European Journal of Organic Chemistry* 2012 (2012): 417–423, https://doi.org/10.1002/ejoc.201101364.

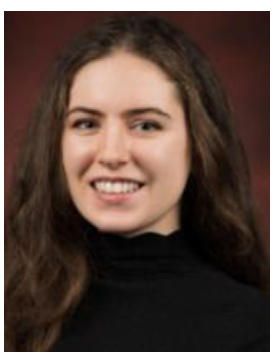
94. J. Li, G. Wang, W. Guo, J. Jiang, and J. Wang, "H8-BINOL-Derived Chiral η^6-Benzene Ligands: New Opportunities for the Ruthenium-Catalyzed Asymmetric C−H Activation," *Angewandte Chemie International Edition* 63 (2024): e202405782, https://doi.org/10.1002/anie.202405782.

95. X. Pang, D. Long, P. Zhai, J.-J. Jiang, and J. Wang, "1,2,3,4-Tetrasubstituted Chiral η^6-Benzene Ligand: Design and Application in Ruthenium-Catalyzed Asymmetric Synthesis of Tertiary Indenols via C–H Activation," *Journal of the American Chemical Society* 147 (2025): 43707–43716, https://doi.org/10.1021/jacs.5c13928.

96. H. Liu, J.-J. Jiang, and J. Wang, "Catalytic Asymmetric C–H Activation/Cyclization of Sulfoximines with Sulfoxonium Ylides by a Chiral η^6-Benzene Ruthenium(II) Catalyst" *ACS Catalysis* 14 (2024): 17398–17404, https://doi.org/10.1021/acscatal.4c04798.

97. X. Mai, H. Liu, J. Jiang, and J. Wang, "Chiral Binaphthyldimethyl η6-Benzene Ligands: Design, Synthesis, and Application in Ruthenium-Catalyzed Asymmetric C–H Activation," *Journal of the American Chemical Society* 148 (2026): 13426–13432, https://doi.org/10.1021/jacs.6c02447.

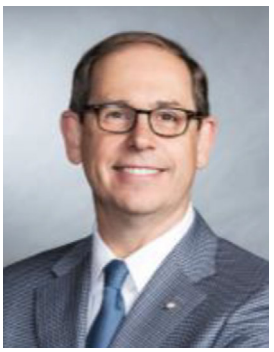
Biographies



Clara Jans was born in Montréal, Québec, Canada in 2000. She obtained her Bachelor of Science from McGill University in 2022, while working with Prof. Lena Simine and Prof. Nathan Luedtke. She is currently attending the University of Toronto working with Prof. Mark Lautens. Her research focuses on palladium catalyzed domino reactions, asymmetric catalysis and the use of oxabicycles as acetylene surrogates.

Armaan Grewal was born in Etobicoke, Ontario, Canada in 2001. She received her B.Sc. Degree from Trent University in 2023, where she worked with Dr. Eric Keske on nickel-catalyzed reactions. She is now doing a PhD at the University of Toronto under the supervision of Prof. Mark Lautens, where she is interested in exploring dual metal catalysis.

Xavier Abel-Snape was born in Hong Kong SAR in 1996. He received his B.Sc Degree at Université de Montréal in 2019. His PhD research in the Lautens group has mainly focused on palladium catalysis involving the use of strained bicycles to generate medicinally relevant scaffolds. The later part of his PhD involved a mechanistic study on how enantiopure chiral oxabicyclic derivatives can be used to generate the corresponding enantioenriched indenes via unprecedented remote effects. He is currently a postdoctoral researcher in the Martin group at ICIQ in Spain, working on photocatalytic methods to modify macrocyclic cores.



Mark Lautens, O.C. was born in Hamilton, Canada. He graduated with a B.Sc. (Distinction) from the University of Guelph working with G.L. Lange. He completed a Ph.D. (University of Wisconsin-Madison) with Barry M. Trost, and did postdoctoral work at Harvard with David. A. Evans. He joined the University of Toronto in 1987 and is University Professor, AstraZeneca Endowed Chair, and Department Chair. He is a Fellow of the Royal Society of Canada, and Officer of the Order of Canada. Most recently he was selected for the H.C. Brown Award from the ACS, and the E.C. Taylor Award from the ISHC.