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Recent progress on Ni-catalysed alkyl–alkyl cross-coupling enabled by asymmetric hydrofunctionalization of alkenes

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The construction of saturated stereogenic centers, which are of significance in cutting-edge fields such as pharmaceutical research and materials science, represents a fundamental objective in organic synthetic chemistry. In this context, nickel-catalysed hydroalkylation of alkenes has emerged as a promising strategy for efficient construction of chiral carbon centers by $C(sp^3)–C(sp^3)$ cross-coupling with alkyl electrophiles. This reaction mode circumvents the use of stoichiometric alkyl metallic reagents, offering a new opportunity for the synthesis of chiral carbon centers by $C(sp^3)–C(sp^3)$ coupling. By exploiting readily available alkenes as coupling partners, these transformations enable rapid molecular saturation with enantioselectivity control under mild conditions. This review systematically summarizes recent advances in Ni-catalysed alkyl–alkyl coupling enabled by hydroalkylation of alkenes, with an emphasis on strategy development, mechanistic elucidation, and synthetic applications. Despite notable progress, challenges remain in further expanding substrate scope, enhancing catalytic efficiency, and refining mechanistic understanding to advance the synthetic utility of this strategy.

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1 Introduction

Chiral carbon centers, which dominate the structural frameworks of organic molecules, play a critical role in natural products, pharmaceuticals, and functional materials (Scheme 1a).[1–5] The introduction of stereogenic carbon centers into a molecule significantly increases the three-dimensional configuration and alters the properties and functions of the molecule. Moreover, the absolute configuration of saturated carbon centers governs molecular conformation, intermolecular interactions, and biological activity.[6,7] Despite the prevalence of stereogenic carbon centers, the stereoselective construction of such chiral carbon centers remains a long-term challenge in synthetic chemistry.[2] Transition-metal-catalysed asymmetric alkyl–alkyl cross-coupling represents one of the most efficient strategies for the construction of chiral carbon centers, which enables the simultaneous introduction of two saturated carbon centers in a single step.[8–11] Conventional strategies for asymmetric alkyl–alkyl cross-coupling predominantly rely on the use of a stoichiometric amount of alkyl electrophiles (*e.g.*, alkyl halides) and alkyl nucleophiles (*e.g.*, organometallic reagents) by nickel catalysis (Scheme 1b).[12–17] However, this approach suffers from several limitations, including the requirement of prefunctionalized coupling partners, competitive side reactions (*e.g.*, homocoupling and β-hydride elimination), and the use of stoichiometric organometallic reagents, which collectively impede scalability and functional group compatibility issues. To address these challenges, nickel-catalysed hydroalkylation of alkenes has emerged as a powerful alternative for asymmetric alkyl–alkyl bond formation to forge chiral carbon centers (Scheme 1c, top).[18–25] This strategy bypasses the use of stoichiometric alkyl nucleophiles by leveraging a hydrometallation process of alkenes to catalytically generate alkyl nucleophiles. Furthermore, nickel-catalysed asymmetric alkene–alkene cross-coupling represents an even more streamlined approach for asymmetric alkyl–alkyl cross-coupling event by hydrometallation, utilizing alkenes as the sole coupling precursors (Scheme 1c, bottom).[1,3,26,27] On the other hand, alkenes are among the most fundamental and versatile building blocks in organic synthesis, serving as key precursors for polymers, pharmaceuticals, and fine chemicals. The widespread availability, orthogonal reactivity to polar functional groups, and ability to undergo stereoselective transformations of alkenes make them indispensable in synthesis and industrial applications.[28–34] The hydroalkylation strategy of alkenes not only eliminates the reliance on preactivated alkyl precursors, but also enhances atom economy, offering a sustainable and versatile route to build chiral carbon centers by alkyl–alkyl coupling. This review summarizes recent developments in nickel catalysed hydroalkylation of alkenes for the construction of chiral carbon centres. It focuses on alkyl–alkyl cross coupling between alkenes and alkyl halides and alkene–alkene cross coupling. Mechanistic considerations and potential

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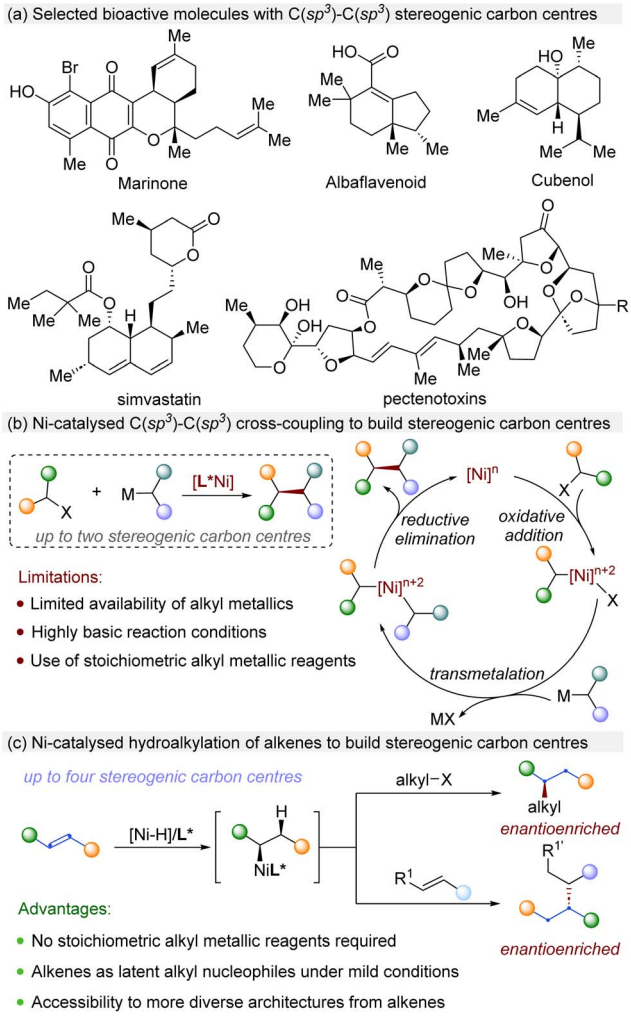

Scheme 1 Ni-catalysed alkyl–alkyl coupling to forge saturated stereogenic carbon centers. (a) Examples of bioactive molecules bearing multiple C(sp^3)–C(sp^3) stereogenic centres, (b) traditional Ni-catalysed alkyl–alkyl cross-coupling, (c) Ni-catalysed alkene hydroalkylation for stereoselective construction of saturated carbon centres.

applications are also discussed. Moreover, future directions for further efforts to flourish nickel-catalysed hydroalkylation of alkenes are also mentioned.

2 Ni-catalysed asymmetric hydroalkylation of alkenes

Nickel-catalysed alkene hydrofunctionalization with C(sp^3)-hybridized electrophiles constitutes a pivotal methodology for the fabrication of saturated stereogenic carbon centres. This synthetic approach takes advantage of the distinctive redox features of nickel catalytic systems to enable efficient C(sp^3)–C(sp^3) bond formation under mild conditions alongside accurate stereochemical control. Importantly, this synthetic strategy enables the construction of up to three stereogenic centres across alkene and alkyl coupling partners.

2.1 Establishing a stereogenic carbon center on alkyl coupling partners

Although Ni-catalysed hydrofunctionalization of alkenes to forge carbon–carbon bonds has been established,[18] the first example of forging chiral carbon centers by Ni-catalysed asymmetric hydroalkylation of alkenes was reported by G. C. Fu in 2018. Moving beyond classical electrophile–nucleophile paradigms that rely on preformed organometallic reagents, this approach leverages terminal alkenes as latent alkyl nucleophile equivalents. As shown in Fig. 1, nickel-catalysed enantioconvergent cross-coupling between racemic secondary/tertiary alkyl electrophiles and terminal alkenes in the presence of a silane has been developed.[19] Using nickel(II) bromide monoglyme adduct ($NiBr_2$ glyme) as catalyst in combination with a chiral bisoxazoline ligand (*R*,*R*)-**L1**, this reaction successfully achieved the asymmetric cross-coupling of racemic α-bromoamides or α-bromo-β-lactams with various alkenes, efficiently constructing asymmetric coupling products containing α-chiral tertiary and quaternary carbon centers. The mild reaction conditions, combined with the use of readily available alkenes, position this methodology as

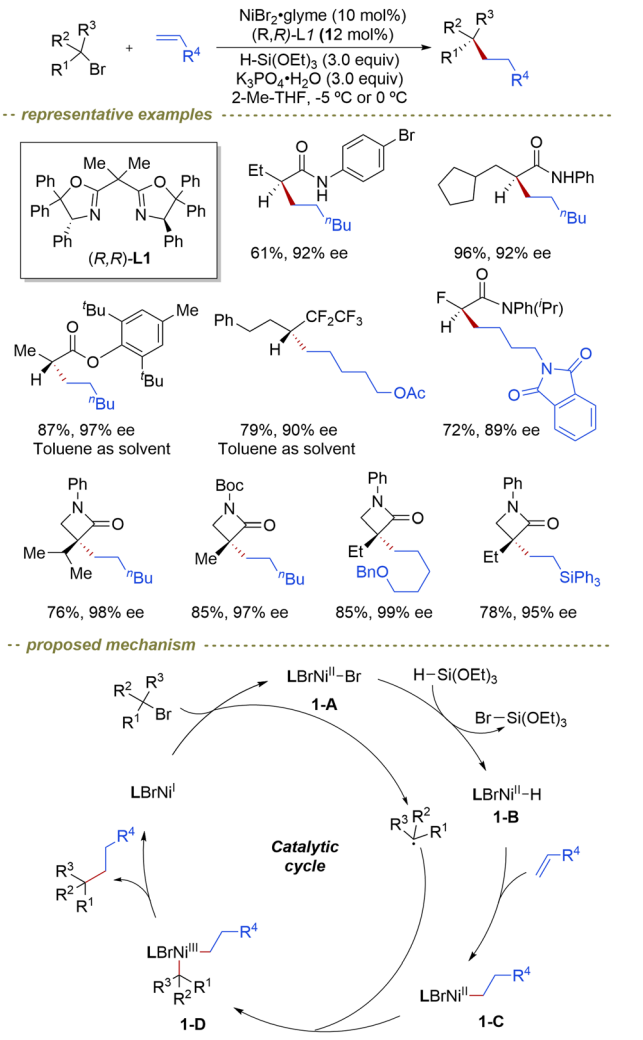

Fig. 1 Ni-catalysed enantioconvergent coupling of secondary and tertiary alkyl electrophiles with alkenes.

a particularly attractive solution to long-standing challenges in stereoselective alkyl–alkyl coupling. This reaction exhibits broad substrate scope and excellent functional group tolerance. Racemic secondary α-haloamides derived from both aryl- and alkyl-substituted scaffolds, irrespective of the electronic nature of the substituents, participate efficiently, furnishing products in high enantiomeric excess. Equally significant is the successful engagement of tertiary electrophiles, particularly α-halo-β-lactams with α-alkyl substituents ranging in steric hindrance from methyl to isopropyl, enabling direct access to enantioenriched quaternary carbon centers that had previously been largely inaccessible through cross-coupling. Notably, amides, esters, lactams, carbonyl-containing or carbonyl-free compounds among secondary electrophiles, and β-lactams with aryl, alkyl, Boc, or alkoxy substituents on the nitrogen atom among tertiary electrophiles, are all well compatible. The alkene partner is similarly versatile. Terminal alkenes bearing ethers, esters, acetals, carbamates, boronate esters, heteroarenes such as benzofurans, indoles, and even complex steroidal frameworks are well tolerated. Mechanistic investigations support a catalytic cycle distinct from conventional cross-coupling manifolds. Initial generation of a Ni–H species **1-B** *via* reaction of a Ni(II) halide complex **1-A** with the hydrosilane enables regioselective hydrometallation of the alkene through β-migratory insertion, furnished a divalent alkyl nickel intermediate **1-C**. Subsequently, intermediate **1-C** then captures an alkyl radical derived from the alkyl halide to generate a complex **1-D**, which undergoes reductive elimination to ultimately produce the coupling product, while regenerating catalyst. Experimental evidence, including the isolation of key Ni(II) intermediates and inhibition by radical traps, substantiates this radical pathway. Overall, this seminal study establishes asymmetric hydroalkylation as a unifying platform that integrates migratory insertion, chain walking, and enantioconvergent radical capture within a single catalytic cycle, thereby exerting a profound influence on the subsequent development of nickel–hydride-mediated asymmetric alkyl–alkyl cross-coupling strategies.

In 2020, the same group further expanded this area to develop a nickel-catalysed enantioconvergent coupling reaction between α-bromo esters and terminal alkenes in the presence of a hydrosilane.[35] This strategy overcomes long-standing challenges associated with preformed alkylmetal nucleophiles, while enabling the direct construction of α-chiral tertiary carbon centers from readily accessible feedstocks. Employing nickel(II) bromide diglyme adduct ($NiBr_2$ diglyme) as catalyst and a chiral bisoxazoline ligand (*S*,*S*)-**L1**, this reaction successfully achieved the enantioconvergent alkyl–alkyl cross-coupling of racemic α-bromo esters (derived from aldehydes and acyl bromides) with various terminal alkenes (Fig. 2). Through asymmetric alkyl–alkyl coupling, this protocol efficiently constructs enantioenriched dialkyl carbinol esters featuring α-chiral tertiary carbon centers. From a substrate-scope perspective, the reaction displays notable generality on both coupling partners. α-Bromo esters derived from both aryl- and alkyl-substituted acyl groups as well as a wide range of aldehydes consistently deliver products with high enantioselectivity. Sterically diverse α-substituents, from methyl to neopentyl, are

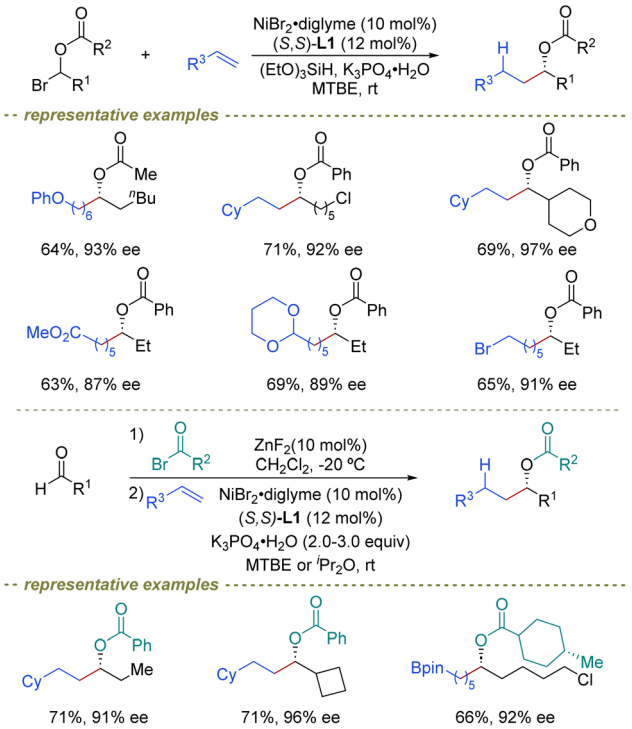

Fig. 2 Ni-catalysed enantioconvergent hydroalkylation of alkenes with α-ester alkyl bromides.

well tolerated, underscoring the robustness of the enantioconvergent process. The reaction accommodates a diverse array of alkenes, including simple α-alkenes and substrates bearing heterocycles, acetals, carbonates, boronate esters, benzofurans, and benzothiophenes, as well as electrophiles containing pendant alkyl bromides and chlorides. Nevertheless, the reaction shows low compatibility with alkyl chlorides, affording less than 1% yield under standard conditions. It also performs poorly with 1,1-disubstituted alkenes such as methylenecyclohexane. These observations define the current limitations of the method and highlight opportunities for further development. An additional conceptual advance is embodied in the four-component, wherein the α-bromo ester is generated *in situ* from an aldehyde and an acyl bromide prior to coupling. This highly convergent design enables the formation of multiple C–H, C–C, and C–O bonds in a single catalytic operation, substantially streamlining access to complex, enantioenriched dialkyl carbinol esters. Successful application of this strategy to the synthesis of bioactive molecules and advanced intermediates highlights its synthetic utility and positions it as a powerful platform for late-stage diversification.

In the same year, Y. Fu group described a nickel-catalysed asymmetric hydroalkylation of alkenes with racemic α-phosphorus or α-sulfur alkyl electrophiles (Fig. 3).[36] Utilizing $NiBr_2$ diglyme as precatalyst in conjunction with a chiral bisoxazoline ligand (*S*,*S*)-**L2**, this method enables the efficient formation of α-chiral tertiary carbon centers adjacent to phosphorus or sulfur atoms through $C(sp^3)$–$C(sp^3)$ coupling. The protocol proceeds under mild conditions and delivers products with excellent enantioselectivity and broad functional group tolerance,

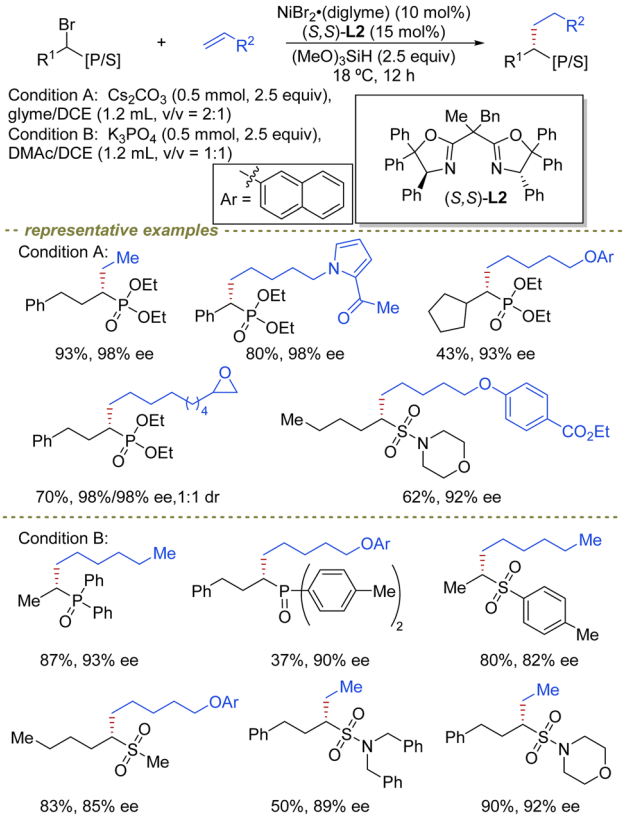

Fig. 3 Ni-catalysed enantioconvergent hydroalkylation of alkenes with α-phosphorus or sulfur alkyl bromides.

offering an attractive alternative to conventional heteroatom-directed cross-coupling strategies. The substrate scope of this methodology is particularly noteworthy.

A wide array of unactivated alkenes including acyclic and cyclic alkenes as well as those bearing functional groups such as ethers, esters, nitrile, silyl ethers, and heterocycles are effectively transformed under the catalytic conditions. Likewise, α-phosphorus and α-sulfur alkyl electrophiles with diverse alkyl, aryl, and heterocyclic groups are converted into the corresponding chiral heteroatom-substituted alkane derivatives in good yields and high enantioselectivity. The reaction also exhibits excellent compatibility with substrates containing sensitive functional groups such as epoxides, aryl chlorides, and aryl bromides. Limitations are observed with sterically hindered α-*tert*-butyl-substituted electrophiles, where yield and enantioselectivity are compromised, and the applicability to tertiary α-P/S-substituted electrophiles remains underexplored, highlighting avenues for further methodological refinement. The study establishes a nickel–hydride-mediated migratory insertion mechanism, in line with the mechanism proposed by the G. C. Fu group, wherein regioselective Ni–H insertion into the alkene generates an alkyl nickel intermediate that undergoes oxidative addition with a racemic α-heteroatom alkyl electrophile followed by reductive elimination to deliver enantioenriched C(sp^3)–C(sp^3) products. Notably, this method constitutes the first example of the asymmetric hydroalkylation of alkenes adjacent to heteroatoms under nickel-catalysed conditions, providing an efficient and highly selective new approach for the construction of asymmetric C(sp^3)–C(sp^3) bonds.

Almost simultaneously, Wu and co-workers disclosed a nickel-catalysed enantioconvergent hydroalkylation reaction between trifluoromethyl-containing α-alkyl bromides and alkenes.[37] As shown in Fig. 4, using $NiBr_2$ diglyme as catalyst along with a chiral bisoxazoline ligand (*S*,*S*)-**L3**, this reaction successfully achieved the asymmetric hydroalkylation of trifluoromethyl-containing α-alkyl bromides with various alkenes, efficiently synthesizing enantioenriched trifluoromethylated alkanes. The study is particularly significant in the context of asymmetric hydrofunctionalization, as it overcomes the long-standing difficulty associated with controlling stereochemistry in reactions involving alkyl radicals and non-activated alkenes, while simultaneously incorporating fluorinated motifs of high medicinal relevance.

This reaction exhibits excellent substrate scope and functional group tolerance. A wide range of terminal alkenes bearing aliphatic or heteroatom-containing substituents, including alcohols, ethers, esters, amides, and heteroarenes such as indoles and furans, are all well tolerated. Trifluoromethyl- and perfluoroethyl-substituted α-alkyl bromides serve as highly competent electrophiles, accommodating a wide range of functional groups, including esters, ketones, carbamates, and additional halides, as well as structurally complex and bio-relevant motifs such as piperidines and ferrocene, while even

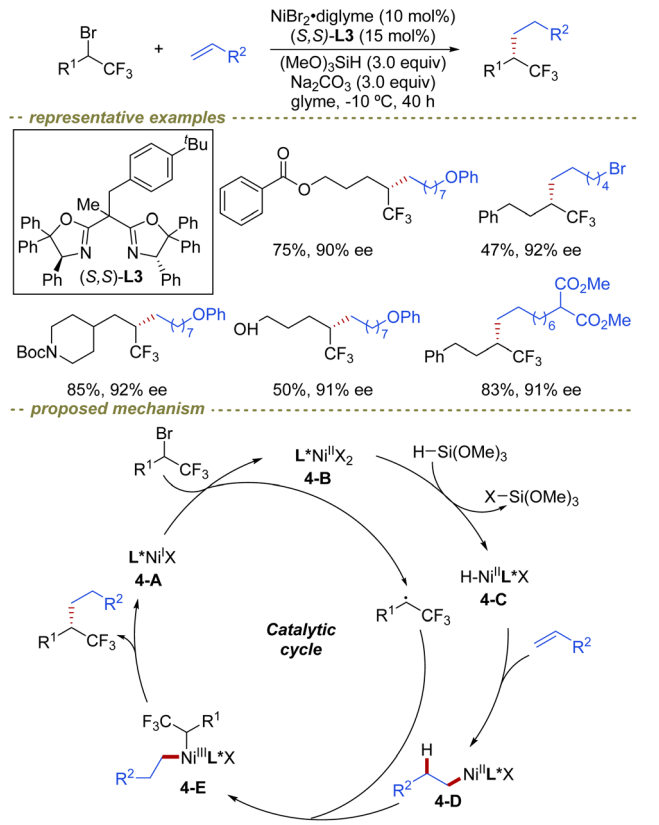

Fig. 4 Ni-catalysed enantioconvergent hydroalkylation of alkenes with trifluoromethyl-containing α-alkyl bromides.

sensitive functionalities like free alcohols are well tolerated, underscoring the high chemoselectivity of the catalytic system. In contrast, 1,1-disubstituted alkenes remain a persistent limitation, affording the desired products only in moderate yields and enantioselectivity. Mechanistic investigations support a catalytic cycle operating through Ni(I)/Ni(III) redox manifolds and radical intermediates. A chiral LNi(I) species **4-A** initiates the process *via* single-electron transfer (SET) to the α-alkyl bromide, generating an alkyl radical and a Ni(II) halide complex **4-B**. Subsequent formation of a Ni–H species **4-C**, enabled by hydrosilane activation, allows regioselective hydronickelation of the alkene to furnish a Ni(II)–alkyl intermediate **4-D**. Radical capture then delivers a high-valent Ni(III) species **4-E**, from which stereodefining reductive elimination affords the chiral trifluoromethylated product and regenerates the active Ni(I) catalyst **4-A**, completing the catalytic cycle. Overall, this work elegantly merges radical chemistry with Ni–H catalysis to enable efficient asymmetric alkyl–alkyl bond formation, providing streamlined access to chiral trifluoromethylated alkanes and highlighting the importance of Ni-catalysed asymmetric alkene functionalization for fluorine-rich molecules.

In the following year, Cai and co-workers developed a nickel-catalysed enantioconvergent hydroalkylation of unactivated alkenes with α-pyridyl alkyl bromides, further expanding the scope of Ni–H asymmetric catalysis. Employing triethoxysilane as hydride source, $NiBr_2$ (diglyme) as catalyst and (*S*,*S*)-**L4**/(*S*,*S*)-**L5** chiral bisoxazoline, this reaction efficiently synthesizes compounds bearing pyridine-substituted sp^3 chiral centers, with excellent efficiency and enantioselectivity (Fig. 5).[38] This work significantly advances Ni–H catalysis by enabling asymmetric hydrofunctionalization of underexplored azaarene-activated alkyl electrophiles, thereby providing a solution to the longstanding challenge of stereoselective access to saturated heteroaryl motifs relevant to medicinal chemistry. This catalytic system demonstrates a remarkably broad substrate scope, encompassing a wide range of terminal alkenes, including simple aliphatic chains such as 1-octene, as well as nitrogen- and oxygen-containing functionalized alkenes. Structurally complex alkenes derived from natural products such as β-pinene cholesterol and estrone as well as drug-like molecules such as probenecid and gemfibrozil can participate smoothly in this reaction. This observation highlights the excellent functional group tolerance of the catalytic system and great potential for late-stage molecular diversification. Limitations are primarily electronic rather than steric: electron-rich alkenes such as vinyl ethers fail to participate, which is attributed to competitive π-allyl formation and Tsuji–Trost-type decomposition pathways rather than catalyst deactivation. The α-pyridyl alkyl bromide coupling partners exhibit substantial versatility: α-alkyl groups ranging from methyl to *n*-butyl, as well as functionalized substrates bearing methoxy or terminal alkene moieties, provide high yields with excellent enantioselectivity. Substitution on the pyridine ring is highly position-dependent, with C4- and C5-substituted pyridines and heterocyclic analogues such as 2-ethylpyrimidine being well tolerated, whereas C3 substitution or replacement with weaker coordinating arenes significantly diminishes reactivity. Steric

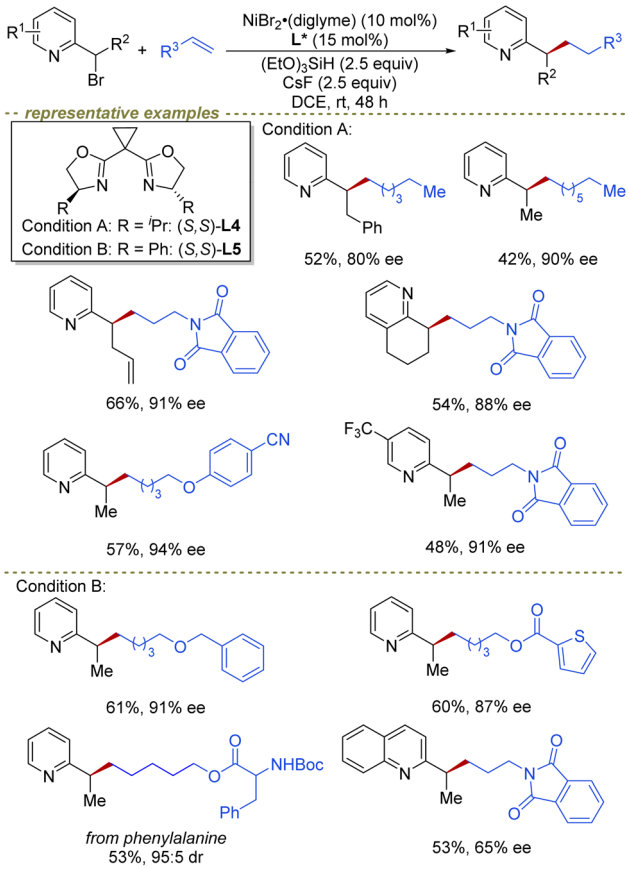

Fig. 5 Ni-catalysed enantioconvergent hydroalkylation of unactivated alkenes with α-pyridyl alkyl bromides.

hindrance at the α-carbon or the C6 position of the pyridine ring also reduces both yield and enantioselectivity, underscoring the critical interplay of steric and electronic factors in the enantiofacial control of C–C bond formation. Mechanistic studies verify that the transformation proceeds *via* a radical chain catalytic cycle. This mechanistic profile is consistent with previously established nickel-catalysed asymmetric cross-coupling between alkyl electrophiles and alkenes. In the field of nickel-catalysed alkyl–alkyl cross-coupling, this work demonstrates that asymmetric hydrofunctionalization can effectively merge radical reactivity with rigorous enantiocontrol. Such a synthetic strategy enables the facile construction of sophisticated heteroaryl-substituted sp^3-hybridized molecular frameworks.

In 2025, Kong *et. al.* reported the integration of the hydrogen atom transfer (HAT) strategy with nickel-catalysed asymmetric alkyl–alkyl cross-coupling, establishing a dual HAT/Ni catalytic system for the enantioselective C(sp^3)–H alkylation of saturated heterocycles with alkenes.[39] As shown in Fig. 6, this reaction is conducted in the presence of $NiBr_2$ glyme and ligand (*R*,*R*)-**L3**/(*S*,*S*)-**L6**, with dicumyl peroxide (DCP) or di-*tert*-butyl peroxide (DTBP) as HAT reagent and hydrosilane $(MeO)_3SiH$ or polymethylhydrosiloxane (PMHS) as hydrogen source. The method provides efficient access to chiral heterocycles and alkyl boronic esters bearing 1,2-adjacent stereogenic centers, delivering high

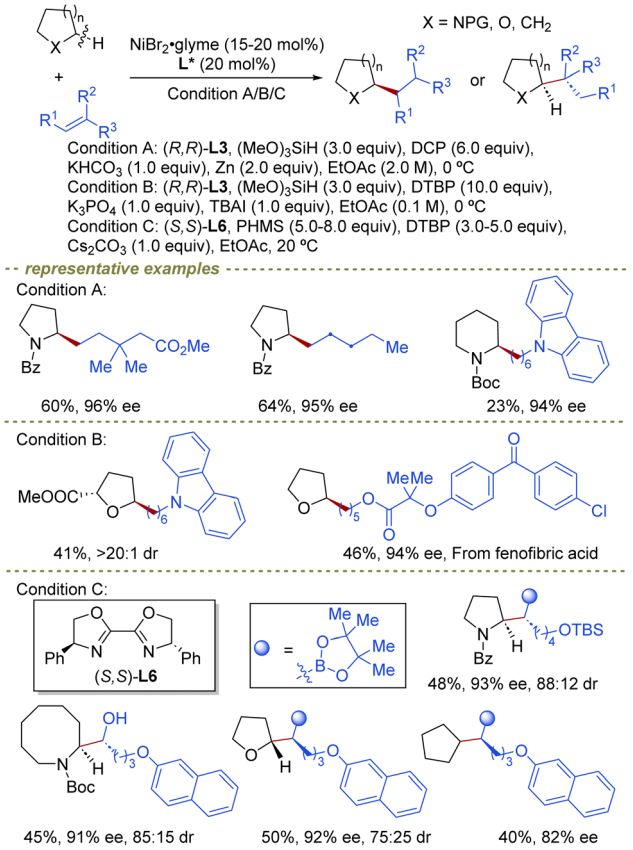

Fig. 6 Enantioselective C(sp^3)–H alkylation of saturated heterocycles with alkenes.

levels of enantio- and diastereoselectivity under mild conditions.

An array of unactivated alkenes, including terminal, 1,1-disubstituted, and cyclic alkenes, participate efficiently in the reaction, delivering asymmetric C(sp^3)–C(sp^3) coupling products. Alkenes bearing heteroaromatic motifs such as indole, carbazole, and furan are well-tolerated, underscoring the chemoselectivity of the nickel manifold. Notably, mixtures of internal alkene regioisomers are transformed in a regioconvergent fashion into a single enantioenriched product, consistent with reversible Ni–H insertion and chain-walking processes. In addition, diverse saturated nitrogen- and oxygen-containing heterocycles, ranging from pyrrolidines and piperidines to oxacycles of varying ring sizes are selectively alkylated, with common *N*-protecting groups such as benzoyl, Boc, and pivaloyl remaining intact. Substrates bearing pre-existing stereocentres undergo highly diastereoselective functionalization, further enhancing the synthetic utility of the method. Mechanistic investigations reveal that the stereochemical outcome of this transformation is governed by a HAT–nickel dual catalytic manifold, wherein peroxide-derived alkoxyl radicals initiate site-selective C(sp^3)–H abstraction from saturated heterocycles to generate carbon-centered radicals. These radicals are subsequently intercepted by alkyl–nickel intermediates formed *via* Ni–H hydrometallation of alkenes, culminating in enantioselective C(sp^3)–C(sp^3) bond formation through Ni(II)/Ni(III) radical capture and reductive elimination. Both enantio- and diastereoselectivity are synergistically dictated by the steric and electronic features of the chiral ligand during the key steps of radical combination and reductive elimination. In reactions involving alkenyl boronic esters, the α-boryl substituent exerts a stabilizing and directing influence on the organonickel intermediate, effectively suppressing chain walking and thereby enhancing diastereocontrol. Notably, this protocol represents the first nickel-catalysed enantioselective C(sp^3)–H alkylation of saturated heterocycles with alkenes under a HAT-enabled strategy, providing a powerful and general approach for the construction of chiral heterocycles and densely functionalized, multi-stereocenter architectures of significance in medicinal chemistry and natural product synthesis.

In nickel-catalysed asymmetric migratory hydroalkylation of alkenes, the simultaneous control of stereoselectivity and site-selectivity represents a formidable challenge, owing to the intrinsic complexity of migratory processes and the involvement of multiple competing reaction pathways.[40–43] In 2019, Zhu and co-workers developed a nickel-catalysed enantioconvergent remote asymmetric hydroalkylation reaction between unactivated alkenes and racemic α-bromoamides (Fig. 7).[20] Using a chiral NiH catalyst system featuring a C6-methyl-substituted Pyrox ligand (*S*)-**L7**, racemic α-bromoamides were coupled with simple alkenes through a sequence involving reversible alkene isomerization (chain walking) followed by enantioconvergent C(sp^3)–C(sp^3) bond formation. This strategy enables remote asymmetric hydroalkylation, introducing unsymmetrical secondary alkyl groups at distal positions of the alkene framework and furnishing enantioenriched α-alkylalkanoic amides with excellent regio- and stereocontrol. Notably, the protocol provides efficient access to amide products bearing α-tertiary stereogenic centers from readily available alkene

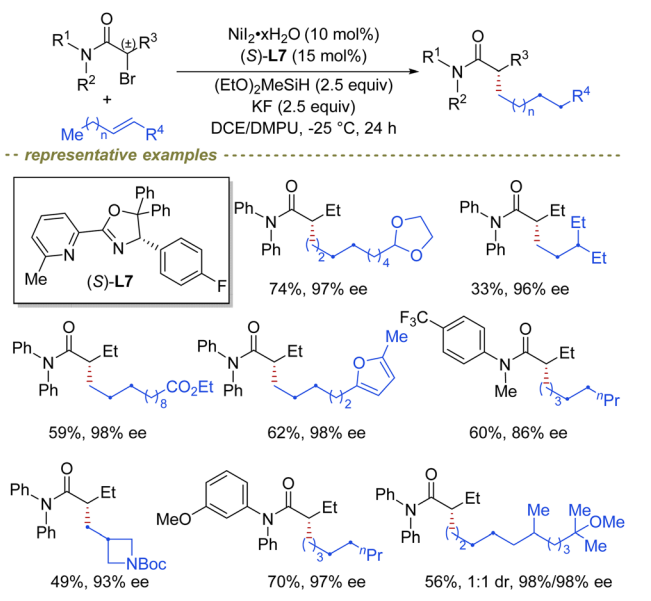

Fig. 7 Ni-catalysed remote asymmetric hydroalkylation of alkenes with racemic α-bromoamides.

feedstocks, underscoring the importance of NiH catalysis in stereoselective alkyl–alkyl cross-coupling. This protocol exhibits excellent substrate scope and functional group tolerance. Both *E*- and *Z*-internal alkenes, as well as inseparable *E*/*Z* mixtures, undergo efficient migratory hydroalkylation with essentially complete terminal regioselectivity, underscoring the robustness of the NiH-mediated chain-walking process. Functional groups such as acetals, ethers, esters, nitriles, carbamates, and heteroaromatic motifs are well tolerated, highlighting the mildness and chemoselectivity of the catalytic system. Notably, more substituted alkenes, including 1,1-disubstituted alkenes and even trisubstituted internal alkenes, can serve as viable precursors to primary alkylnickel intermediates; although the latter display reduced conversion, they nevertheless furnish the desired migratory coupling products. On the electrophile side, a diverse array of racemic α-bromoamides is compatible, encompassing diarylamides and aryl–alkyl amides with both electron-donating and electron-withdrawing substituents, as well as aryl chlorides that remain intact for downstream functionalization. The reaction proceeds *via* a chiral Ni–H initiated, regioselective hydrometallation and chain-walking process, followed by enantioconvergent oxidative addition of a racemic α-bromoamide to a migrated alkyl nickel intermediate and stereocontrolled C–C bond-forming reductive elimination to furnish enantioenriched α-alkylated amides. This work highlights NiH-catalysed asymmetric alkyl–alkyl cross-coupling as an effective approach that leverages chain-walking alkene isomerization to achieve both regio- and enantioconvergent remote stereocontrol from readily available substrates, providing a framework for constructing chiral sp^3-rich architectures.

Very recently, Martin and co-workers reported a photoinduced nickel-catalysed enantioconvergent sp^3–sp^3 cross-coupling between unactivated terminal and internal alkenes and racemic aziridines, representing a major advance in asymmetric hydrofunctionalization of alkenes (Fig. 8).[44] Utilizing nickel(II) acetylacetonate $Ni(acac)_2$ in combination with the chiral bis(imidazole) ligand (*S*,*S*)-**L8**, the protocol exploits the hydrozirconation ability of Schwartz's reagent (Cp_2ZrHCl) to generate alkylzirconium intermediates *in situ*, which undergo a radical-mediated Ni(I/III) catalytic cycle to afford chiral β-alkylated amines. This strategy overcomes the longstanding challenge of enantioconvergent sp^3–sp^3 bond formation from simple alkene substrates, providing direct access to stereodefined saturated amines that are ubiquitous in pharmaceuticals and natural products. The reaction features an excellent substrate scope and high functional group tolerance. Racemic aziridines modified with electron-donating methyl and methoxy units, electron-withdrawing fluoro, trifluoromethyl, and cyano groups as well as heteroaryl fragments such as thiophene can be efficiently transformed into chiral amine products. These reactions deliver high yields and excellent enantioselectivities across different substrates. On the other hand, terminal alkenes with diverse functionalities can be efficiently utilised. Suitable substituents include halides, hydroxyl groups, esters, ethers, and polyunsaturated structural units are also compatible. Internal alkenes undergo selective chain walking to enable site and regioselective distal C–H functionalization regardless of *Z* and *E* geometric configurations. Notably, the methodology tolerates complex molecular scaffolds such as estrone and α-tocopherol, as well as industrially relevant light alkenes like ethylene under mild conditions, highlighting its broad applicability, synthetic versatility, and potential for late-stage functionalization. Mechanistic studies revealed a multi-step pathway initiated by hydrozirconation of terminal/internal alkenes with Schwartz's reagent, where internal alkenes undergo chain-walking to form uniform terminal alkylzirconium species. Subsequent homolytic cleavage of the C–Zr bond under visible-light conditions generates alkyl radicals alongside $Cp_2Zr^{3+}Cl$, which in turn reduces the Ni(II) complex coordinated by a chiral bis(imidazole) ligand (**L8**) to the catalytically active Ni(I) species. The Ni(I) center captures the alkyl radical and mediates a stereoablative ring-opening of racemic aziridines, forming a dialkyl–Ni(III) intermediate that undergoes reductive elimination to deliver chiral β-alkylated amines. Control experiments with enantioenriched aziridines demonstrate that enantioselectivity is exclusively ligand-controlled, highlighting the robustness of the catalytic design. Overall, this method overcomes prior aziridine-based sp^3–sp^3 coupling limitations, offering a direct route to enantioenriched β-alkyl amines and valuable insights for feedstock-derived enantioconvergent reactions.

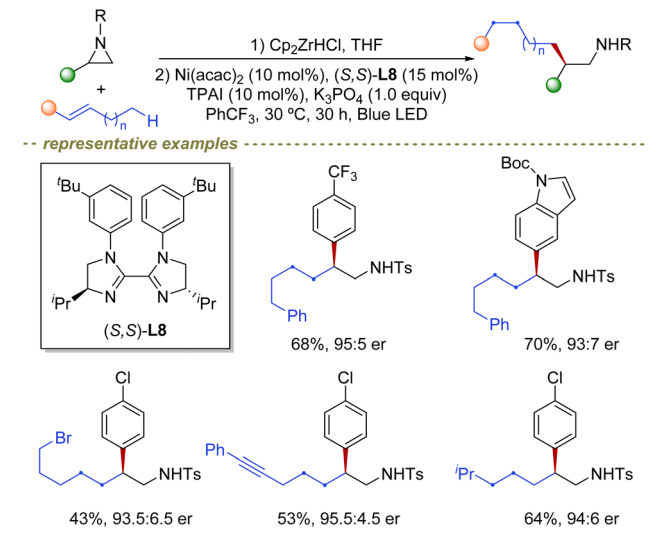

Fig. 8 Ni-catalysed photoinduced enantioconvergent $C(sp^3)$–$C(sp^3)$ coupling of unactivated alkenes with aziridines.

2.2 Establishing chiral carbon centers on alkenes

In the nickel-catalysed reaction between alkenes and alkyl halides, chiral centers are generated through highly regio- and enantioselective hydronickelation of the alkene. The nickel catalyst and chiral ligand work synergistically to direct the insertion of the Ni–H species into the alkene double bond with precise stereocontrol, enabling the formation of chiral centers

selectively at either the α- or β-position. In 2021, Shu and co-workers were the first to report nickel-catalysed enantioconvergent formal hydrofunctionalization reaction of acrylamides with alkyl halides, benzyl halides, and propargyl halides (Fig. 9).[45] Utilizing $NiBr_2$ glyme in combination with the chiral bisoxazoline ligand (*R*,*R*)-**L9**, this methodology enables the efficient construction of α-chiral tertiary amides *via* asymmetric alkyl–alkyl coupling.

The reaction exhibits remarkable enantioselectivity and regioselectivity, providing a versatile platform for synthesizing stereochemically defined α-tertiary centers, which are of high relevance in drug development and natural product synthesis. From a substrate scope perspective, aryl-substituted acrylamides bearing electron-donating, electron-withdrawing, or multiple substituents are efficiently converted into chiral α-alkyl amides. Alkyl-substituted alkenes with varying chain lengths and diverse functional groups also proceed smoothly under standard conditions. Compatible functional groups include halogens, nitrile, free hydroxyl moieties, esters, ethers, and

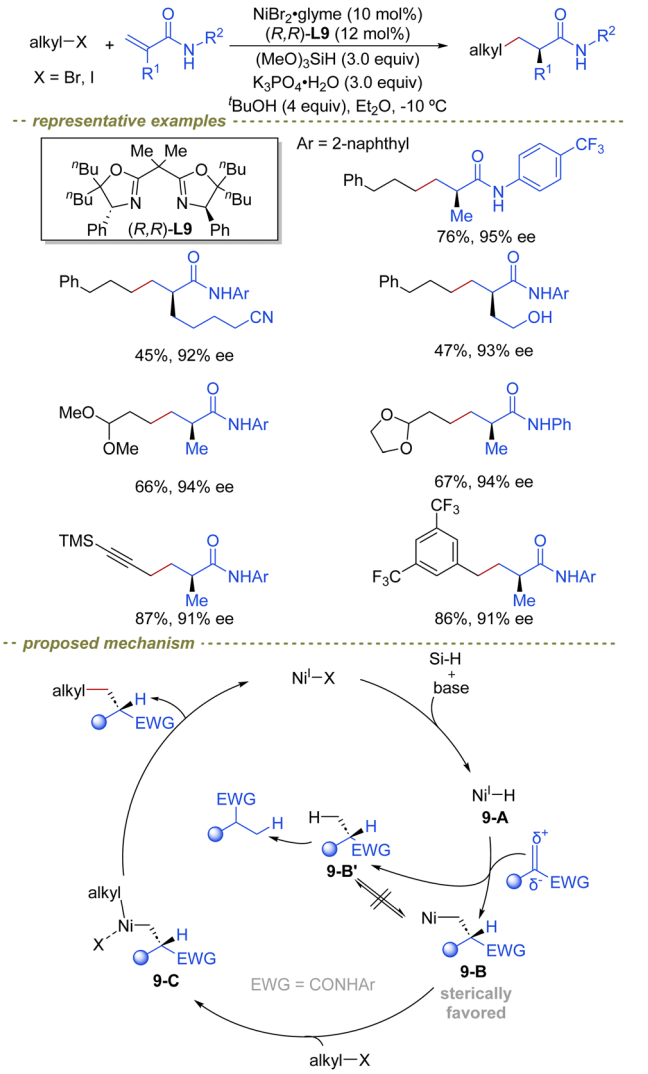

Fig. 9 Ni-catalysed enantioselective hydroalkylation of acrylamides with alkyl halides.

trisubstituted structural motifs. Notably, the reaction shows excellent compatibility with alkyl halides bearing sensitive functional groups. Primary and secondary alkyl iodides and bromides with ether linkages, acetals, esters, nitriles, amides and heterocyclic units can undergo the reaction efficiently. Benzyl bromides modified with electron-donating, electron-withdrawing or ester substituents also proceed smoothly. Propargyl bromides carrying alkyl aryl or silyl substituents are similarly compatible under standard conditions. In addition, the reaction is compatible with complex structures found in natural products and drug molecules, enabling smooth late-stage asymmetric modification to generate the corresponding chiral amide derivatives. Despite this broad applicability, the methodology exhibits limitations with unsymmetrical secondary alkyl halides, which afford lower yields and enantioselectivities, and non-amide alkenes, which preferentially undergo reduction rather than hydroalkylation. Mechanistic investigations reveal that Ni(II) is initially reduced to Ni(I), which is transformed into a Ni–H species **9-A** in the presence of a base and silane. The Ni–H intermediate **9-A** undergoes stereoselective migratory insertion into the alkene to form alkyl intermediates **9-B** or **9-B′**, one of which **9-B′**, directed by the amide functionality, undergoes oxidative addition with the electrophile to generate intermediate **9-C**. Subsequent reductive elimination furnishes the α-tertiary chiral amide while regenerating Ni(I), thereby closing the catalytic cycle. Overall, this work establishes the first nickel-catalysed enantioselective hydroalkylation, hydrobenzylation, and hydropropargylation of acrylamides, with alkyl halides, benzyl halides, and propargyl halides, providing an efficient and highly selective route for constructing α-chiral tertiary amides with broad functional group tolerance and enabling future advances in enantioconvergent alkene cross-couplings.

Shortly thereafter, Y. Fu group advanced nickel-catalysed asymmetric hydroalkylation by developing a robust method for the enantioselective coupling of enamides and enecarbamates with alkyl halides.[46] As shown in Fig. 10, this reaction is carried out in the presence of $NiBr_2$ (diglyme) and chiral bisoxazoline ligands (*S*,*S*)-**L10** for tertiary enamides, and (*S*)-**L11** for secondary enamides/enecarbamates. It successfully achieves the asymmetric hydroalkylation of tertiary/secondary enamides and enecarbamates with primary alkyl iodides (or alkyl bromides, requiring the addition of NaI), and efficiently constructs aliphatic amine compounds with α-chiral centers through asymmetric $C(sp^3)$–$C(sp^3)$ coupling. This reaction exhibits excellent substrate scope and functional group tolerance. Both aromatic enamides (with either electron-donating or electron-withdrawing groups on the aromatic ring) and aliphatic enamides (with linear or α-branched alkyl chains), including sterically demanding β,β-dialkyl-substituted variants, as well as secondary and tertiary enamides and enecarbamates readily undergo asymmetric hydroalkylation. The reaction tolerates a broad scope of primary alkyl halides. These substrates span from short chain methyl to long chain *n*-hexyl derivatives. Compounds carrying sensitive functional groups are also compatible. Representative examples include esters, nitrile, ethers, alkenes, acetals, aryl chlorides, and heterocyclic

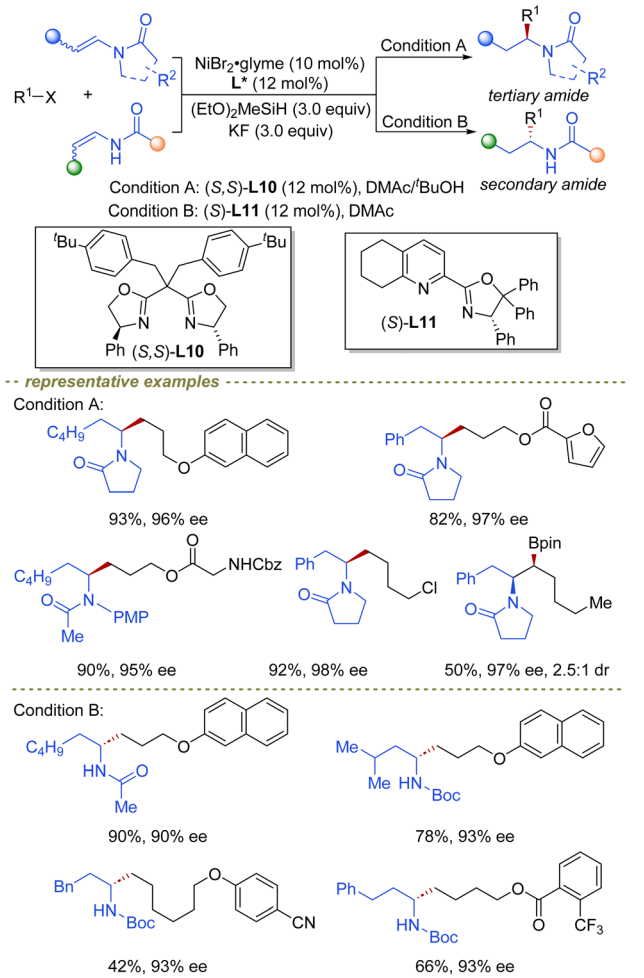

Fig. 10 Ni-catalysed asymmetric hydroalkylation of enamides and enecarbamates with alkyl halides.

units. Suitable heterocycles cover thiophene indole and coumarin. All these substrates can afford the desired asymmetric hydroalkylation products efficiently. Furthermore, racemic α-haloboronates can be efficiently converted into β-aminoboronates bearing two chiral centers, providing versatile intermediates for the synthesis of chiral amino alcohols and related motifs. The authors emphasized that the mechanism of this reaction is fundamentally different from the classical Ni-catalysed alkyl–alkyl cross-coupling mechanism reported by G. C. Fu group.[19] Unlike Fu's earlier mechanism, where stereocontrol is exerted on the electrophilic alkyl halide *via* oxidative addition, the current hydroalkylation strategy relies on stereoselective *syn*-addition of a Ni(II)–H species to the nucleophilic enamide. This step generates a chiral Ni(II) intermediate whose configuration dictates the absolute stereochemistry of the product. Subsequent transmetalation with the alkyl halide and reductive elimination furnishes the enantioenriched amine. This mechanism emphasizes that the nucleophilic partner, rather than the electrophile, is the stereocontrol element, providing an orthogonal strategy for asymmetric $C(sp^3)$–$C(sp^3)$ bond formation. Overall, this work provides a complementary approach to traditional enantioselective nickel catalysis, exhibiting broad substrate scope and high enantioselectivity. It enables the efficient synthesis of structurally diverse, enantioenriched aliphatic amines, with profound implications for pharmaceutical development.

The asymmetric hydroalkylation of enecarbamates reported by Hu and co-workers represents a pivotal advance in nickel-catalysed alkyl–alkyl cross-coupling through alkene hydrofunctionalization. In this study, a chiral Ni–H manifold was strategically harnessed to address a long-standing challenge in asymmetric $C(sp^3)$–$C(sp^3)$ bond formation, namely the construction of α-stereogenic amines bearing minimally differentiated alkyl substituents. By combining $NiBr_2$ (diglyme) with a chiral bisoxazoline-derived ligand (*S*,*S*)-**L6**, the authors achieved a highly enantioselective hydroalkylation of *N*-protected enecarbamates with alkyl halides (Fig. 11).[47] Conceptually, this transformation merges asymmetric hydrometallation with radical alkyl capture, offering a distinct and complementary alternative to classical cross-electrophile coupling strategies that often suffer from limited stereochemical control at fully aliphatic carbon centers. This reaction exhibits excellent substrate scope and functional group tolerance. A wide array of enecarbamates derived from aromatic and aliphatic aldehydes, including both *N*-Cbz- and *N*-Boc-protected variants, undergo smooth coupling to furnish α-chiral amine derivatives with consistently high enantioselectivity. Notably, β,β-disubstituted enecarbamates, enecarbamates containing alkyl chloride or ester groups, and even synthetically challenging vinylamine-type substrates ($NiI_2 \cdot xH_2O$/(3*S*,8*R*)-**L12**), are all well compatible with the reaction system. On the electrophile side, primary unactivated alkyl iodides with varying carbon chain lengths are well accommodated in this reaction. Primary and secondary alkyl halides carrying diverse functional groups also proceed efficiently under standard conditions. Suitable functional groups include chloride esters, acetals, ethers, amines, and heterocyclic units. Representative heterocycles are phthalimide

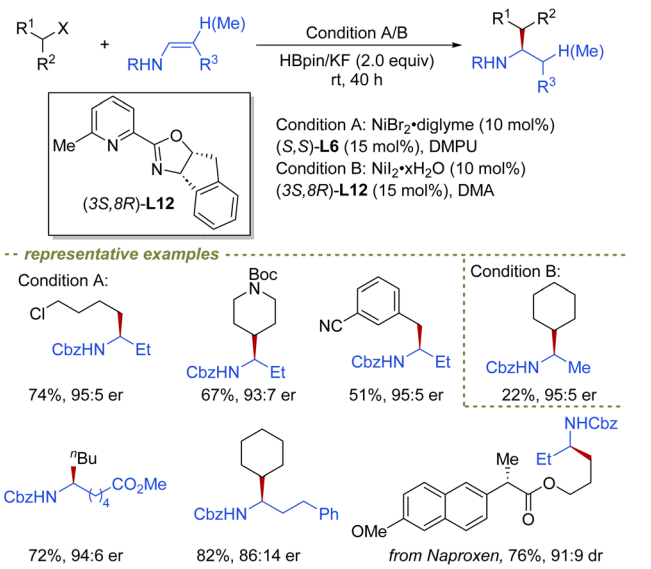

Fig. 11 Ni-catalysed asymmetric hydroalkylation at the α-position of enamides.

and indole. All these electrophilic substrates afford the corresponding asymmetric hydroalkylation products smoothly. Furthermore, activated alkyl halides including benzyl bromides are well compatible with this catalytic system. In contrast, tertiary alkyl halides and trisubstituted enecarbamates fail to participate in the transformation. *tert*-Butyl iodide serves as a typical incompatible substrate in this category. Such reactivity discrepancies originate from the intrinsic steric constraints within the catalytic cycle. Two potential catalytic pathways exist for the reaction mechanism, but their core reaction processes are highly consistent. First, the Ni(I) active species is converted into the key Ni–H intermediate under the synergistic effect of the hydride source and base. Subsequently, the Ni–H intermediate undergoes stereoselective *syn*-addition to the double bond of the enecarbamate, generating a well-defined Ni(II)-alkyl intermediate. In parallel, activation of the alkyl halide generates an alkyl radical, which then intercepts the Ni(II)–alkyl species to furnish a high-valent Ni(III) dialkyl intermediate. Finally, the Ni(III) intermediate undergoes reductive elimination to form the target C(sp^3)–C(sp^3) bond, while regenerating the Ni(I) active species to complete the catalytic cycle. Notably, the *N*-Cbz protecting group of the enecarbamate plays a decisive directing role: coordination of the carbamate moiety to the nickel center enables the formation of a stabilized five-membered nickelacyclic intermediate, effectively governing the regioselectivity of Ni–H insertion and suppressing undesired chain-walking or non-selective hydrometallation pathways. This directing effect underpins the exclusive formation of the α-alkylated product with high regioselectivity. This work delineates a general and influential design paradigm for Ni-catalysed asymmetric alkyl–alkyl cross-coupling, wherein substrate-directed hydrometallation synergistically merged with radical processes circumvents longstanding constraints of enolate alkylation and hydroalkylation, thereby enabling streamlined access to otherwise elusive chiral amines and shaping subsequent advances in stereoselective C(sp^3)–C(sp^3) bond formation.

In the meantime, Shu group developed a nickel-catalysed enantioselective hydroalkylation reaction of acyl enamines or enol esters with unactivated alkyl iodides, providing a powerful platform for asymmetric alkyl–alkyl cross-coupling *via* hydrofunctionalization of alkenes.[48] Employing bis(1,5-cyclooctadiene)nickel Ni(COD)$_2$ as catalyst and chiral BOX ligands (4*R*,4*R*′,4*S*,4*S*′)-**L13** for acyl enamines and (4*R*,4*R*′,4*S*,4*S*′)-**L14** for enol esters as chiral auxiliaries, the transformation enables highly regio- and enantioselective construction of C(sp^3)–C(sp^3) bonds, furnishing enantioenriched chiral secondary alkyl-substituted amine and alcohol derivatives, addressing a long-standing challenge associated with β-hydride elimination and stereochemical erosion in alkyl–alkyl cross-couplings (Fig. 12). This protocol exhibits a notably broad and synthetically valuable substrate scope, encompassing tertiary and secondary acyl enamines, enol esters, and diverse alkyl iodides with excellent functional group tolerance. Both tertiary and secondary acyl enamines, including sterically demanding internal variants and substrates derived from complex natural products, participate efficiently, highlighting the robustness and generality of the catalytic system.

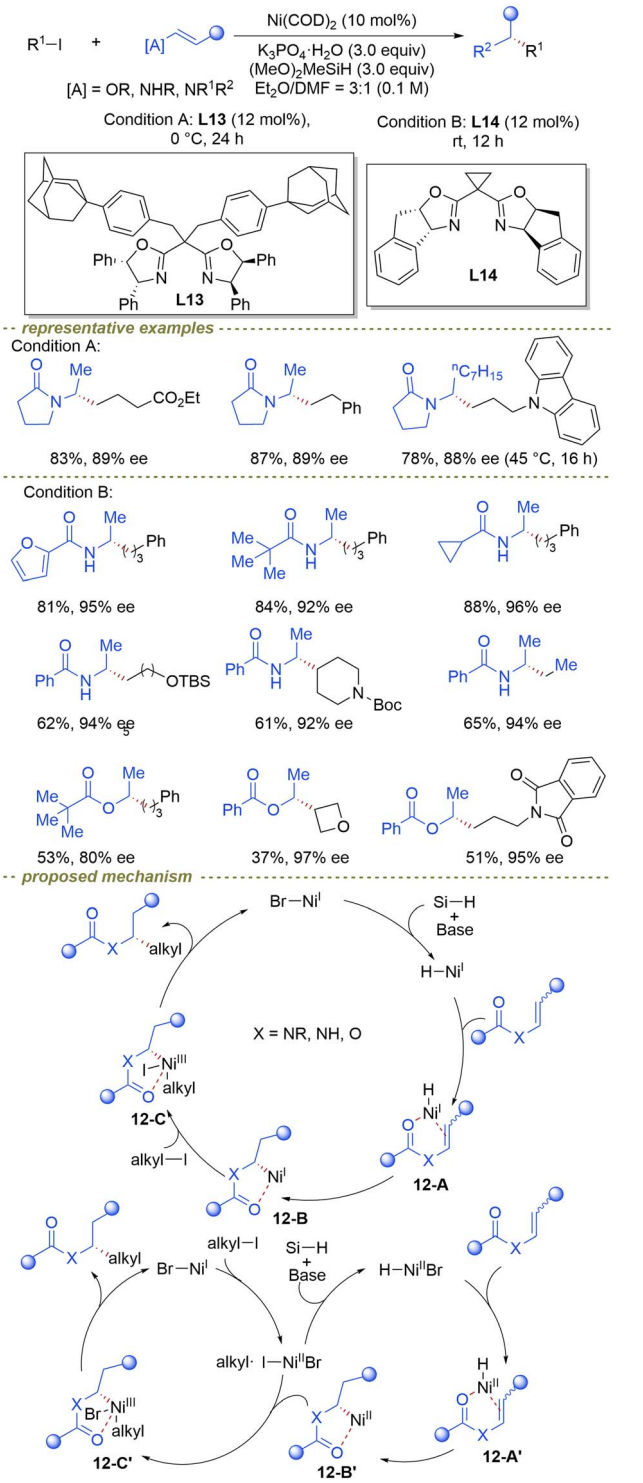

Fig. 12 Ni-catalysed enantioselective hydroalkylation of acyl enamines and enol esters with alkyl halides.

Importantly, internal acyl enamines with both (*E*/*Z*)-configurations, undergo smooth hydroalkylation to furnish structurally diverse α-branched dialkyl amines with high enantioselectivity. The methodology is further extended to enol esters derived from both aromatic and aliphatic carboxylic acids. Both

terminal and internal enol esters with varied alkyl chains are compatible in the reaction. Regarding alkyl iodide substrates, a broad scope of primary and secondary alkyl iodides can be well accommodated in this reaction. Representative substrates cover linear α-branched cyclic and aryl substituted skeletons. Functionalized analogues containing esters, ethers, amides, nitriles, silyl ethers, and heteroaromatic units are also compatible.

These substrates allow the facile construction of diverse chiral amine and alcohol frameworks through asymmetric alkyl–alkyl cross coupling. In contrast, tertiary alkyl halides remain unreactive, consistent with steric constraints and competing radical pathways commonly observed in Ni-catalysed alkyl couplings. Mechanistic studies, supported by precedent and control experiments, delineate a nickel–hydride-driven catalytic manifold in which enantioselectivity is established during migratory insertion of the alkene. Two closely related pathways are proposed by the authors, involving either Ni(I)–H or Ni(II)–H species generated *in situ* from the precatalyst under the combined action of silane and base. In the first pathway, a Ni(I)–H intermediate undergoes stereoselective hydronickellation of acyl enamines or enol esters to form an alkyl–Ni species **12-B**, which subsequently engages in oxidative addition with an alkyl iodide to access a high-valent Ni(III) intermediate **12-C** prior to reductive elimination. The second pathway starts with single-electron transfer from the nickel catalyst to alkyl iodide substrates. This process generates an alkyl radical and a Ni(II) species, which further transforms into a Ni(II)–H intermediate. Subsequent stereoselective hydrometallation delivers an alkylnickel intermediate **12-B′**. The resulting alkylnickel species couples with the alkyl radical to access the Ni(III) manifold **12-C′**. In both pathways, reductive elimination delivers the enantioenriched alkyl–alkyl coupling product while regenerating the catalytically active nickel species. Overall, this synthetic method enables the efficient and highly selective construction of enantiopure aliphatic amine and alcohol derivatives *via* asymmetric hydrofunctionalization enabled $C(sp^3)$–$C(sp^3)$ bond formation. This approach paves the way for further advances in the field of reductive and stereocontrolled alkyl–alkyl bond construction.

Meanwhile, Hu and co-workers further advanced this asymmetric alkyl–alkyl bond formation by developing a nickel hydride-catalysed enantioselective $C(sp^3)$–$C(sp^3)$ cross-coupling between unactivated alkyl halides and alkenyl boronic acid pinacol esters (alkenyl Bpins).[49] As shown in Fig. 13, employing a $NiCl_2$ precursor in combination with a chiral bisoxazoline ligand (*S*,*S*)-**L6** and diethoxymethylsilane as hydride source, the protocol enables efficient coupling of primary and secondary alkyl iodides with alkenyl Bpins to furnish α-chiral alkyl boronate esters with high levels of enantioselectivity. Notably, alkenyl Bpin substrates serve as masked alkyl nucleophile surrogates. These compounds facilitate the stereocontrolled assembly of saturated chiral centres *via* asymmetric hydrometallation and coupling cascades. This synthetic strategy addresses a persistent challenge within Ni–H catalysis associated with stereochemical erosion during chain walking events. This work demonstrates the excellent applicability of

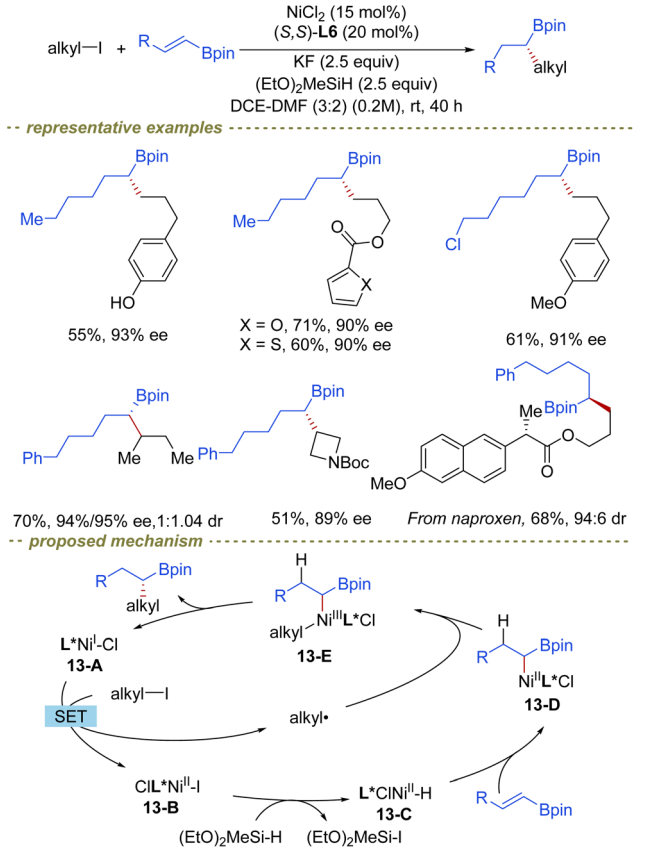

Fig. 13 Ni-catalysed asymmetric alkyl–alkyl cross-coupling of alkyl halides with alkenyl boronic acid pinacol esters.

enantioselective hydrofunctionalization for cross-electrophile C–C bond construction. The substrate scope is notably broad and highlights the synthetic versatility of the method. A wide range of alkenyl Bpins, including those bearing aryl or aliphatic substituents and diverse functional groups such as halides, esters, and ethers, participate efficiently while maintaining excellent enantioselectivity. Notably, sterically hindered β,β-disubstituted alkenyl Bpins and synthetically challenging vinyl boronic acid pinacol esters, are also competent substrates, underscoring the efficiency of the hydrometallation step. However, trisubstituted alkenyl Bpins cannot participate in the reaction due to excessive steric hindrance around the double bond. On the electrophile side, both primary and secondary unactivated alkyl iodides, including acyclic and cyclic variants, are readily engaged, tolerating a broad range of functionalities such as carbonyls, protected amines, heterocycles, and pharmaceutically relevant motifs, with alkyl bromides rendered viable through *in situ* halide exchange. Although tertiary alkyl halides and triflates remain unreactive owing to ineffective interaction with the nickel catalyst, the overall scope, functional-group compatibility, and amenability to late-stage modification of complex molecules (such as naproxen, indomethacin compounds) collectively establish this methodology as a powerful platform for enantioselective $C(sp^3)$–$C(sp^3)$ bond construction. Mechanistic investigations delineate a well-defined Ni(I)/Ni(II)/Ni(III) catalytic manifold in which a chiral

Ni(I)–Cl species **13-A**, generated from Ni(II) and a bisoxazoline ligand, serves as catalytically active initiator. Single-electron transfer from this Ni(I) intermediate to an alkyl iodide produces an alkyl radical alongside a Ni(II) halide **13-B**, which is subsequently converted into a Ni–H species **13-C** upon reaction with a hydrosilane. This intermediate **13-C** undergoes *syn*-addition to alkenyl Bpin to generate a chiral Ni(II)–alkyl intermediate **13-D**, which is also the enantioselectivity-determining step of the reaction. Subsequent radical capture by this organonickel species **13-D** affords a high-valent Ni(III) dialkyl intermediate **13-E**, which undergoes rapid reductive elimination to furnish the enantioenriched alkyl Bpin product while regenerating the catalytically active Ni(I) species, thereby closing an efficient and stereocontrolled catalytic cycle.

Meanwhile, a similar report from the group of Fu demonstrates the efficient coupling of *tert*-butyloxycarbonyl (Boc)-protected enol esters with primary alkyl iodides (Fig. 14).[50] This reaction using $NiCl_2(PPh_3)_2$ as catalyst in combination with chiral bisoxazoline ligand (*S*,*S*)-**L5** enables the stereoselective construction of C(sp^3)–C(sp^3) bonds to furnish α-chiral secondary alkyl-substituted methyl carboxylates with high enantioselectivity (88–97%) and moderate yields (30–52%).

Notably, the reaction proceeds effectively irrespective of the *Z* or *E* configuration of the enol substrate, highlighting the generality and robustness of Boc-protected enol esters as competent substrates for Ni-catalysed asymmetric hydrofunctionalization. The reaction exhibits a remarkable versatility in substrate scope, efficiently coupling both aromatic and aliphatic enol esters, regardless of electronic properties or steric hindrance. Linear primary alkyl iodides of varying chain lengths, including those bearing functional groups such as ethers, trifluoromethyl, acetyl, nitrile, and Boc-protected amines, participate smoothly, while alkyl electrophiles containing *p*-toluenesulfonyloxy (–OTs) or aryl chloride moieties are also compatible, preserving reactive sites for further functionalization. The reaction accommodates enol esters with diverse *E*/*Z* configurations, enabling the construction of α-chiral centers with high enantioselectivity. Limitations are observed with unsymmetrical secondary alkyl iodides and aryl electrophiles, reflecting steric and radical-stability constraints. Mechanistic studies reveal that the enantioselectivity-determining step of this asymmetric reaction is the stereoselective *syn*-addition of the chiral ligand-coordinated Ni(II)–H intermediate to enol esters. The cycle is initiated by the reduction of a Ni(II) precursor to an active Ni(I) species (**14-A**) by silane/base, followed by single-electron transfer with alkyl iodides to generate alkyl radical and Ni(II) species (**14-B**). Subsequent formation of a Ni(II)-hydride species **14-C** enables stereoselective *syn*-addition to the enol ester, affords α-oxoalkyl Ni(II) intermediate **14-D**, which intercepts the alkyl radical to generate a Ni(III) species **14-E**. Finally, reductive elimination from Ni(III) affords the enantioenriched product while regenerating the Ni(I) catalyst, completing the cycle. This study highlights the advancing scope and mechanistic understanding of Ni-catalysed asymmetric hydrofunctionalization, enabling highly enantioselective C(sp^3)–C(sp^3) bond formation and paving the way for applications in complex molecule synthesis and medicinal chemistry. Future directions may involve extending these methodologies to secondary alkyl halides and unactivated alkenes.

Zhu and co-workers reported a nickel hydride-catalysed enantioselective regio-reversed hydroalkylation reaction of α,β-unsaturated amides using $Ni(NO_3)_2 \cdot 6H_2O$ and the chiral ligand (*S*)-**L15** (Fig. 15).[51] This transformation proceeds *via* a regio-reversed *syn*-hydronickellation followed by asymmetric C(sp^3)–C(sp^3) bond formation, enabling the direct construction of β-chiral centers from β-alkyl/aryl-substituted α,β-unsaturated amides and primary or secondary alkyl iodides.

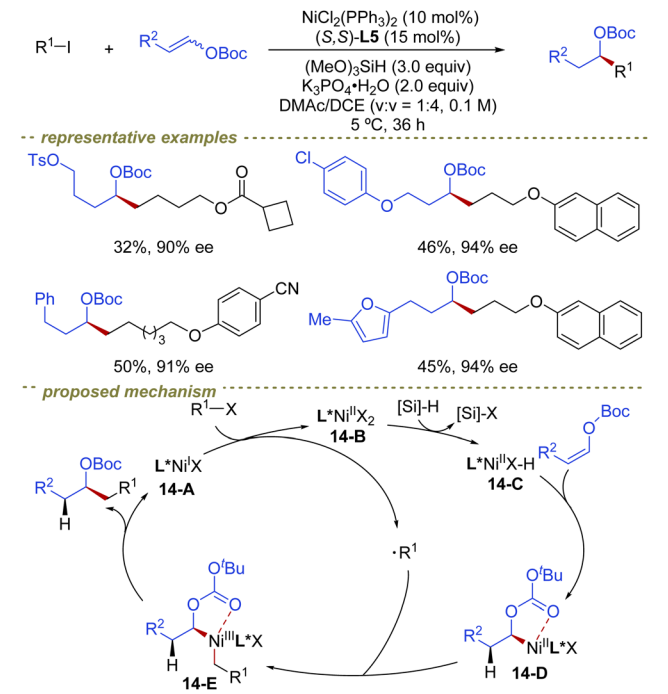

Fig. 14 Ni-catalysed asymmetric hydroalkylation of enol esters with alkyl halides.

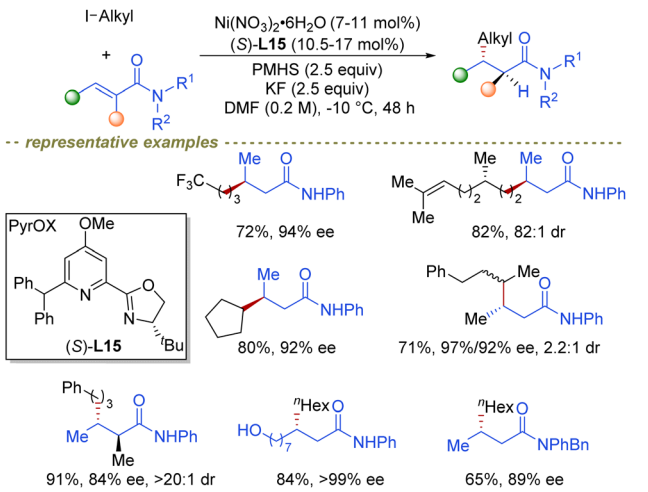

Fig. 15 Enantioselective hydroalkylation of α,β-unsaturated amides with alkyl halides.

The methodology exhibits exceptional stereocontrol and broad substrate compatibility, underscoring the strategic utility of NiH-mediated processes in the streamlined synthesis of complex chiral architectures. A wide range of α,β-unsaturated amides bearing either alkyl or aryl substituents at the β-position, as well as *N*-alkyl- and *N*-aryl-substituted amides, undergo smooth and efficient transformation. Notably, α,β-unsaturated amides containing alkyl chloride, free alcohol, ester, aryl chloride, and unprotected phenol hydroxyl groups, even sterically hindered α,β-disubstituted amides, are all well compatible with the reaction system. Among them, α,β-disubstituted amides can generate a single diastereoisomer with two chiral centers (dr > 20 : 1), whereas β,β-disubstituted α,β-unsaturated amides cannot participate in the reaction because of excessive steric hindrance around the double bond. On the electrophile side, a diverse array of primary and secondary unactivated alkyl iodides is compatible in this transformation. These substrates include short and long linear alkyl chains as well as structurally diverse molecules containing nitriles, esters, ethers, phosphonates, acetals, *N*-*tert*-butoxycarbonyl (*N*-Boc) carbamates, phthalimides, and heteroaromatic moieties such as pyrroles. All these substrates act as competent coupling partners, collectively validating the robustness and synthetic versatility of this asymmetric nickel-catalysed hydroalkylation system. Synergistic cooperation between regioselective hydronickellation and ligand-governed enantioselective coupling enables nickel hydride catalysis to efficiently assemble structurally complex and stereodefined molecules under mild synthetic conditions, further broadening the practical utility of this catalytic platform.

In continuation of their efforts on Ni–H catalysis, Shu group expanded their research to Ni–H catalysed asymmetric hydroalkylation of unactivated alkenes with alkyl halides, which substantially advanced Ni-catalysed alkyl–alkyl cross-coupling chemistry. Employing a $NiBr_2$ glyme precatalyst in combination with a chiral bisoxazoline ligand (*R*,*R*)-**L16**, this transformation enables the efficient enantioselective formation of fully alkyl-substituted saturated tertiary stereogenic centers through asymmetric C(sp^3)–C(sp^3) bond construction, notably exhibiting a rare and highly controlled Markovnikov selectivity (Fig. 16).[52,53] Importantly, the inclusion of *N*-methyl-4-(trifluoromethyl)benzenesulfonamide (**A1**) was shown to significantly enhance both reaction efficiency and enantioselectivity. This study addressed a long-standing challenge in asymmetric hydrofunctionalization, namely the formation of saturated tertiary carbon centers which are remote from classical activating groups, and demonstrated that careful ligand design and reaction engineering can override the intrinsic anti-Markovnikov bias typical of first-row transition-metal hydride catalysis. This reaction exhibits high enantioselectivity, excellent regioselectivity, and broad substrate scope. For alkenes, *N*-aryl-3-enamides with electron-donating groups, electron-withdrawing groups, or heterocyclic structures on the aromatic ring participate smoothly, delivering products with high levels of enantio- and regioselectivity. Meanwhile, *N*-alkyl-3-enamides can smoothly afford the target products, albeit with a slight decrease in enantioselectivity. Both terminal and

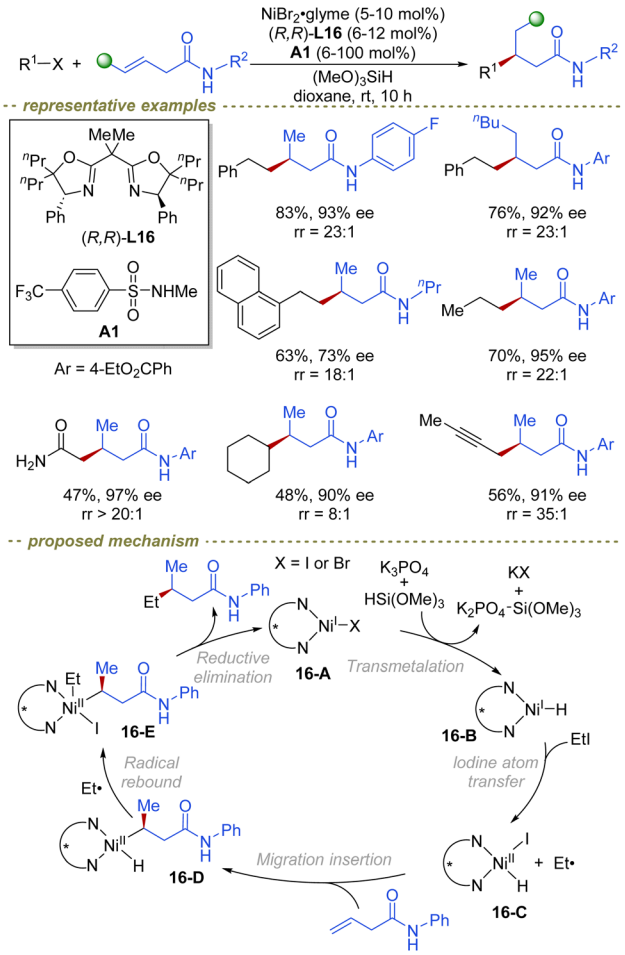

Fig. 16 Ni-catalysed regio- and enantioselective hydroalkylation of unactivated alkenes.

internal alkenes are efficiently converted, whereas γ,δ-unsaturated amides remain unreactive, highlighting a defined geometric requirement for productive insertion. A wide array of alkyl halides exhibits satisfactory reactivity under standard catalytic conditions. Valid substrates include primary alkyl iodides and bromides, alongside cyclic and acyclic secondary alkyl iodides. Benzyl chlorides bearing electron donating or electron withdrawing substituents, as well as propargyl bromides functionalised with methyl, phenyl and trimethylsilyl groups, are also well tolerated. This catalytic system accommodates diverse functional moieties such as esters, amides, silyl ethers, acetals, nitriles, free N–H bonds, unprotected hydroxyl groups and ketones featuring acidic protons. Halide substrates derived from heterocyclic scaffolds including thiophene and indole are also synthetically viable. Notably, asymmetric acyclic secondary halides enable the precise assembly of vicinal saturated stereogenic carbon centres. Functionalized halide substrates such as α-bromo esters and trifluoromethyl-modified derivatives are also compatible with this catalytic system. Furthermore, alkyl iodide scaffolds sourced from natural product frameworks and pharmaceutical skeletons can undergo efficient transformation under standard conditions.

Representative substrate classes include derivatives of (+)-borneol and indomethacin.

Mechanistic studies, supported by experimental evidence and density functional theory calculations, reveal a Ni(I)/Ni(II) catalytic manifold in which an active Ni–H species **16-B** is generated from a Ni(I) precursor **16-A** and initiates the reaction *via* single-electron transfer to alkyl halides, producing an alkyl radical and a Ni(II)–H intermediate **16-C**. The latter undergoes a stereoselective Markovnikov migratory insertion with unactivated alkenes, an irreversible step identified as both regio- and enantio-determining, to produce an alkyl–Ni(II) complex **16-D**. Subsequent radical recombination with the alkyl–Ni intermediate and reductive elimination deliver $C(sp^3)$–$C(sp^3)$ bond formation, constructing fully alkyl-substituted tertiary stereogenic centers and regenerating the catalytically active nickel species. This strategy constitutes the first enantioselective Markovnikov convergent hydroalkylation of unactivated alkenes with diverse alkyl halides, establishing a powerful and conceptually distinct platform for asymmetric alkyl–alkyl cross-coupling that enables access to chiral carbon centers remote from directing or activating groups. Overall, this study establishes the first enantioselective and Markovnikov-selective convergent hydroalkylation of unactivated alkenes with alkyl halides. This work provides a mechanistically well-defined and general nickel-catalysed platform to access fully alkyl-substituted tertiary stereocenters. The transformation features excellent functional group compatibility and great synthetic potential for the assembly of structurally complex molecules.

Shortly thereafter, Shu group reported a ligand-controlled, enantioselective β-hydroalkylation of allylamines that constitutes a significant advance in nickel-catalysed alkyl–alkyl cross-coupling *via* asymmetric hydrofunctionalization of alkenes. In the presence of a chiral bisoxazoline ligand (*S*,*S*)-**L17**, allylamines selectively undergo β-enantioselective hydroalkylation to form $C(sp^3)$–$C(sp^3)$ bonds with excellent regio- and enantiocontrol, affording a diverse array of chiral β-branched aliphatic amines that are challenging to access through conventional cross-coupling methodologies (Fig. 17).[54] The substrate scope of this transformation is particularly broad and illustrative of its synthetic robustness. Diverse alkyl iodides with synthetically fragile functional moieties are well accommodated throughout the transformation. Compatible functional groups include alkyl chlorides, silyl ethers, esters, ketones, acetals and imides, with no obvious sacrifice in reaction yield or enantioselective performance. Both aryl and alkyl substituted *N*-acyl allylamines act as reliable alkene coupling partners. This robust catalytic system enables the facile synthesis of various *N*-acyl β-chiral amine derivatives with favourable yields and outstanding enantiomeric excess values. Notably, the method tolerates unactivated alkenes and complex alkyl fragments, emphasizing its potential utility for late-stage functionalization and medicinal chemistry applications. Mechanistic studies revealed that a Ni(I)/Ni(III) catalytic manifold initiated by *in situ* formation of an Ni(I)–H species **17-B** from an LNi(I) precursor **17-A** in the presence of silane and $K_3PO_4 \cdot H_2O$. Intermediate **17-B** undergoes SET with alkyl iodides, producing alkyl radical and the Ni(II)–H intermediate (**17-C**), which subsequently inserts

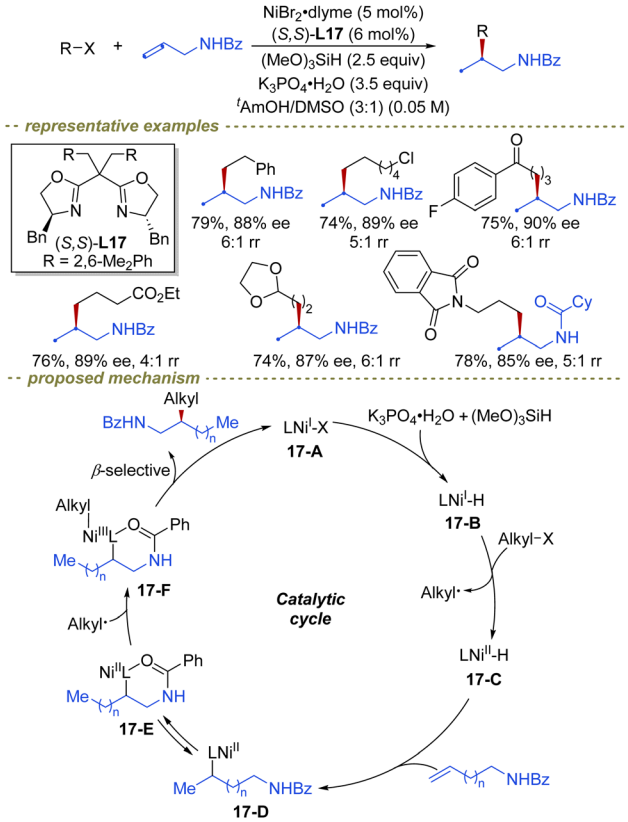

Fig. 17 Enantioselective β-hydroalkylation of alkenyl amines with alkyl halides.

into the double bond of allylamines to form the alkyl–Ni(II) intermediate (**17-D**). Further, intermediate **17-D** undergoes reversible β-H elimination/reinsertion, and under the regulation of the ligand, the β-located intermediate (**17-E**) is generated, which combines with alkyl radicals to form the dialkyl–Ni(III) species (**17-F**). Finally, **17-F** undergoes reductive elimination to yield the target β-branched product, regenerating the Ni(I) species to complete the catalytic cycle. This study showcases how ligand-engineered NiH catalysis integrates radical generation, controlled chain walking, and enantioselective $C(sp^3)$–$C(sp^3)$ reductive elimination to enable asymmetric alkyl–alkyl cross-coupling *via* migratory Ni–alkyl intermediates, providing both a versatile synthetic platform and mechanistic principles for the rational design of future stereocontrolled hydroalkylation reactions.

Lu and co-workers reported, for the first time, a NiH-catalysed diastereo- and enantioselective hydroalkylation reaction between 3,3-disubstituted cyclopropenes and alkyl iodides.[55] As shown in Fig. 18, this reaction is conducted in the presence of $NiCl_2$ and a newly developed *N*-benzyl-substituted DPEN chiral ligand (*S*,*S*)-**L18**, with diethoxymethylsilane $(EtO)_2MeSiH$ (DEMS) as hydride source and KF as base. It successfully achieves the asymmetric hydroalkylation of 3,3-disubstituted cyclopropenes with various unactivated alkyl iodides, efficiently affording alkyl cyclopropane derivatives bearing two chiral centers through the construction of asymmetric $C(sp^3)$–$C(sp^3)$ bonds. Notably, this strategy circumvents

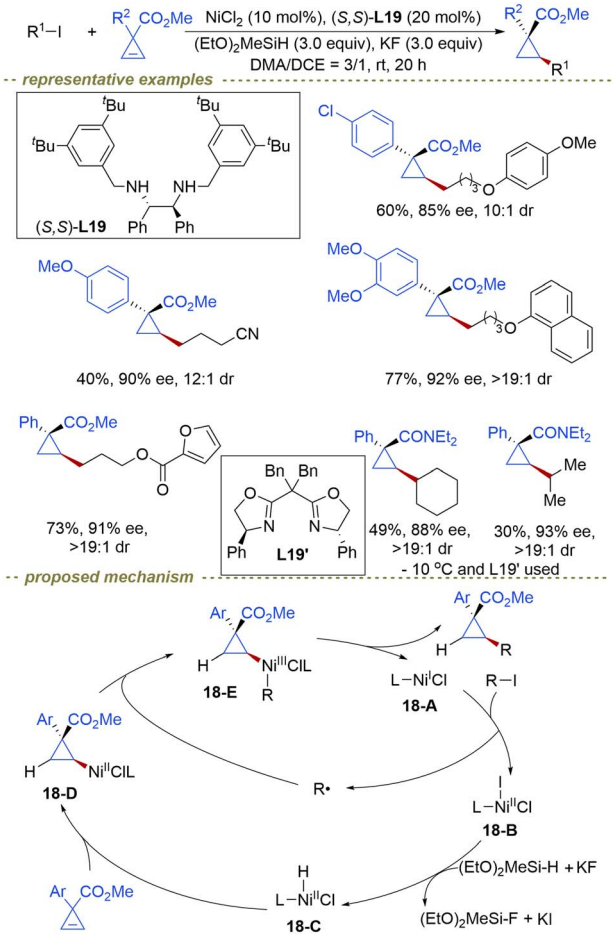

Fig. 18 Ni-catalysed asymmetric hydroalkylation of 3,3-disubstituted cyclopropenes with alkyl iodides.

the limitations of traditional cyclopropanation or carbometallation approaches, which often require prefunctionalized organometallic reagents and display restricted functional-group tolerance. This catalytic system delivers a broad substrate scope and exceptional functional group tolerance. 3,3-Disubstituted cyclopropenes undergo efficient asymmetric hydroalkylation under standard conditions. Aryl-functionalized cyclopropenes with electron donating groups, electron withdrawing groups, and varied benzene ring substitution patterns are all viable substrates. Additionally, cyclopropene derivatives bearing ester or amide substituents are well tolerated within this transformation. Furthermore, cyclopropenes bearing disubstituted aryl frameworks, naphthyl fused skeletons, and diverse ester substituents remain compatible. Suitable ester variants include methyl, ethyl and *tert*-butyl functional groups. These observations demonstrate that the hydronickelation process is insensitive to substrate electronic properties and steric alterations.

With respect to alkyl iodide coupling partners, both unfunctionalized and structurally elaborate primary alkyl iodides participate efficiently in the catalytic transformation. Tolerated functionalities cover esters, nitriles, halides, phenyl groups, imides, acetates, silyl ethers, boronate esters and heterocyclic scaffolds. Such broad compatibility supports the late-stage diversification of structurally sophisticated molecules. Alkyl iodides originating from aromatic alcohols are competent coupling partners in this reaction, furnishing alkyl cyclopropane products bearing two contiguous stereogenic centres. While secondary alkyl iodides deliver slightly diminished enantioselectivity, these substrates remain applicable to the catalytic system. Such substrate tolerance further validates the versatility of this NiH-based platform for the stereoselective assembly of densely functionalized alkyl cyclopropane frameworks. Mechanistic studies reveal that $NiCl_2$ combines with (*S*,*S*)-**L19** to form a Ni(II) precursor, which is reduced to a Ni(I) species (**18-A**) under the action of DEMS/KF. Species **18-A** undergoes SET with alkyl iodide to generate alkyl radical and a Ni(II) species (**18-B**). Subsequent formation of a Ni(II)–H species **18-C** enables regio- and enantioselective hydronickelation of cyclopropenes to afford a chiral Ni–alkyl intermediate **18-D**, which intercepts the alkyl radical to generate a high-valent Ni(III) complex **18-E**. Finally, Stereospecific reductive elimination from this intermediate **18-E** forges the $C(sp^3)$–$C(sp^3)$ bond, delivering alkyl cyclopropanes bearing two contiguous stereocenters in a single step. This transformation constitutes the first NiH-catalysed hydroalkylation protocol targeting cyclopropene substrates. This method addresses the longstanding drawbacks of conventional synthetic strategies that fail to enable direct alkyl chain installation on cyclopropene skeletons.

In the same year, Lu group reported a nickel-catalysed enantioselective β-hydroalkylation method for amine-containing alkenes and alkyl halides, representing a significant advance in asymmetric alkyl–alkyl cross-coupling (Fig. 19).[56] Using a $NiBr_2$ diglyme/bisoxazoline catalytic system (*S*,*S*)-**L10**, this transformation delivers β-chiral branched alkylamines through highly regio- and stereoselective $C(sp^3)$–$C(sp^3)$ bond formation. This strategy leverages alkenes as latent alkyl nucleophile equivalents *via in situ* hydrometallation and chain-walking, enabling nickel-catalysed asymmetric alkyl–alkyl cross-coupling with precise control over regio- and

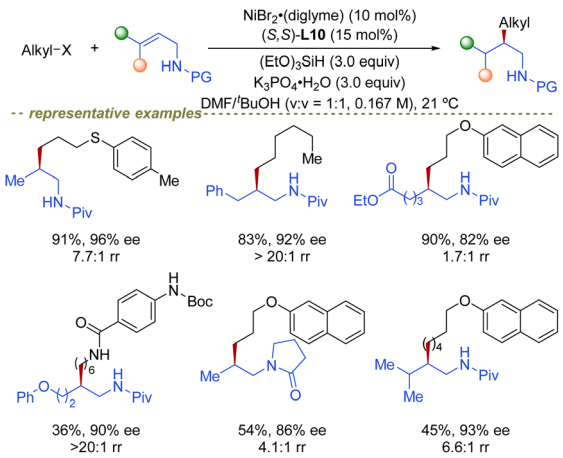

Fig. 19 Ni-catalysed enantioselective β-selective hydroalkylation of amine-containing alkenes with alkyl halides.

enantioselectivity, thereby overcoming enduring challenges in regio- and stereocontrol in alkyl–alkyl cross-coupling. From a substrate scope perspective, aliphatic alkyl halides and heteroatom-containing analogues bearing sulfur and phosphonate moieties can be efficiently converted into corresponding target products. A broad set of functional groups including esters, trifluoromethyl groups, trifluoromethoxy groups, nitrile, aryl chlorides, and base-labile ketone carbonyls remain compatible under mild reaction conditions. Heterocyclic motifs, including phthalimide, furan, and thiophene units, remain intact, rendering the strategy particularly attractive for late-stage diversification. Regarding alkene substrates, amine protected derivatives exhibit broad reaction compatibility. Both benzoyl and lactam based directing groups are well accommodated within this catalytic system, and 2-pyrrolidinone serves as a representative lactam scaffold. Internal disubstituted and trisubstituted alkenes act as competent coupling partners. Less sterically hindered substrates afford products in high yields, while increased steric bulk gradually reduces reaction efficiency. In contrast, tetrasubstituted alkenes remain unreactive under standard conditions. Notably, alkene *Z*/*E* geometry exerts minimal influence on selectivity. Although ester-substituted alkenes may afford regioisomeric mixtures due to competing directing effects, the desired β-branched products are readily isolated. Importantly, the resulting amine-containing products can be further transformed through hydrolysis or reduction to primary or secondary amines, providing expedient access to valuable intermediates for bioactive molecules and their analogues. Mechanistic and computational studies reveal that Ni–H–mediated, ligand-controlled *syn*-hydrometallation coupled with directed chain walking enables regio- and enantioselective C(sp^3)–C(sp^3) bond formation, establishing asymmetric hydrofunctionalization as a powerful strategy to overcome longstanding selectivity challenges in Ni-catalysed alkyl–alkyl cross-coupling.

In 2024, Hu group aimed at further expanding this field by reporting a ligand-controlled, nickel-catalysed regiodivergent and enantioselective hydroalkylation of sulfolenes, constituting a significant advance in asymmetric alkyl–alkyl cross-coupling enabled by Ni–H catalysis.[57] As shown in Fig. 20, through judicious selection of chiral ligands, the protocol enables precise reversal of regioselectivity while maintaining high enantioinduction in reactions with a broad range of alkyl iodides, thereby furnishing both C2- and C3-alkylated cyclic sulfones *via* asymmetric C(sp^3)–C(sp^3) bond formation. Notably, this strategy overcomes a long-standing challenge in hydrofunctionalization chemistry—the simultaneous control of regio- and enantioselectivity in electronically biased alkene systems—without reliance on directing groups, substrate modification, or altered reaction conditions. The reaction exhibits broad substrate scope and high functional group tolerance. Both 2-sulfolene and 3-sulfolene participate efficiently, delivering either C2- or C3-alkylated cyclic sulfones with high enantioselectivities. Diversely functionalized alkyl iodides bearing halogens, unprotected phenols, alkyl hydroxyl groups, nitriles, ketones, esters and heterocyclic scaffolds undergo efficient asymmetric hydroalkylation. Furan and thiophene represent

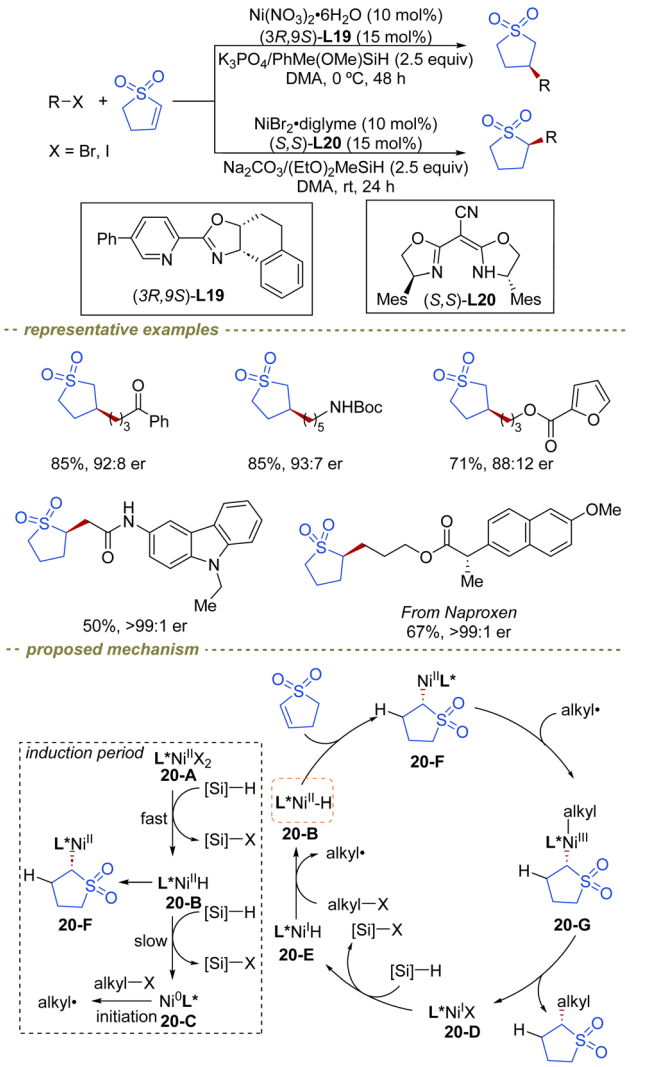

Fig. 20 Ni-catalysed regiodivergent and enantioselective hydroalkylation of sulfolenes for the synthesis of chiral alkylcyclic sulfones.

compatible heterocyclic substrates. Furthermore, alkyl iodides sourced from pharmaceutical and bioactive frameworks proceed smoothly under standard catalytic conditions. These transformations preserve the core structural skeletons of complex bioactive substrates throughout the reaction process. A defining feature of this strategy is the precise control of regioselectivity through ligand modulation: neutral PYROX ligand (3*R*,9*S*)-**L19** selectively promote C3-alkylation, whereas anionic BOX ligand (*S*,*S*)-**L20** favors C2-alkylation, obviating the need for substrate redesign or extensive condition screening. The reaction proceeds through a Ni(I)/Ni(III) catalytic cycle to achieve C2-selective alkylation. Initially, the Ni(II)–H species **20-B** generated from a Ni(II) precursor **20-A** and silane constitutes the predominant resting state. Partial reduction to Ni(0) species **20-C** facilitates single-electron activation of alkyl halides to produce alkyl radicals that initiate turnover, while *syn*-selective migratory insertion of the Ni–H **20-B** into the sulfolene double bond delivers a Ni(II)–alkyl intermediate **20-F** that is both regio- and enantio-determining. Subsequent radical capture forms a high-valent Ni(III) bis(alkyl) species **20-G**, which undergoes

rapid reductive elimination to forge the C(sp^3)–C(sp^3) bond and regenerate a lower-valent nickel species **20-D** that is reconverted to the hydride **20-E**, closing the cycle. Currently, this regioselectivity is attributed to the influence of ligands, though whether this stems from thermodynamic or kinetic control remains unclear. Overall, this work demonstrates that ligand-controlled asymmetric hydrofunctionalization provides a mechanistically informed and broadly applicable strategy to advance Ni-catalysed alkyl–alkyl cross-coupling, enabling regio- and enantioselective construction of chiral sulfones and related architectures from unactivated alkenes with significant relevance to medicinal chemistry.

Y. Fu group achieved a significant advance in Ni-catalysed alkyl–alkyl cross-coupling by merging hydrofunctionalization of alkenes with asymmetric induction, exemplified by the enantioselective hydroalkylation of vinyl pyrroles (Fig. 21).[58] A key feature of this work is the identification of a chiral bisoxazoline ligand, (*S*,*S*)-**L10**, which substantially enhances both reactivity and selectivity. Relative to previous ligand frameworks, this optimized catalytic system affords substantially enhanced product yields and retains excellent enantioselective performance. Representative substrates exhibit improved yield elevating from approximately 55% to over 70%, which demonstrates the indispensable contribution of rational ligand design to efficient NiH-based asymmetric transformations. Notably, modification of the pyrrole nitrogen substituent from methyl to the more labile *tert*-butoxy carbonyl (Boc) group preserves both coupling efficiency and high enantioselectivity, underscoring the robustness and functional-group tolerance of the methodology. From substrate scope perspective, vinyl pyrroles bearing different substitution patterns on the heteroaromatic framework were efficiently transformed, and variation of the *N*-protecting group was well tolerated without compromising reactivity or selectivity. Notably, the protocol accommodates both primary and secondary alkyl iodides, thereby enabling streamlined access to α-branched alkylated pyrrole motifs that are prevalent in medicinally relevant scaffolds.

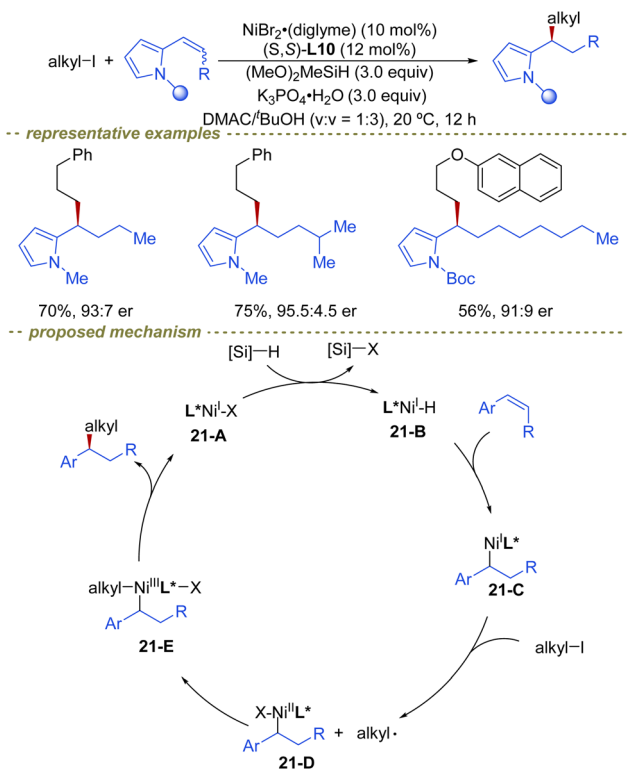

Fig. 21 Ni-catalysed asymmetric hydroalkylation of vinylpyrroles with alkyl iodides.

Mechanistic studies support a catalytic cycle characteristic of NiH-mediated radical cross-coupling processes, proceeding through a Ni(I)/Ni(II)/Ni(III) manifold. Initial hydride transfer from a silane to an LNi(I)X precursor **21-A** generates the catalytically active LNi(I)H species **21-B**, which undergoes regio- and enantioselective migratory insertion into the vinylpyrrole double bond to furnish an alkyl–Ni(I) intermediate **21-C**, with stereocontrol imparted by the chiral bisoxazoline ligand. Subsequent single-electron transfer to the alkyl iodide produces an alkyl radical alongside an alkyl–Ni(II) species **21-D**, followed by radical capture to form a high-valent Ni(III) intermediate **21-E**. Reductive elimination from this species forges the C(sp^3)–C(sp^3) bond, delivering the hydroalkylation product and regenerating the active catalyst, thereby completing the catalytic cycle. Overall, this work highlights the decisive impact of ligand design in overcoming persistent challenges in regio- and stereoselective Ni-catalysed alkyl–alkyl bond construction from simple alkenes under mild conditions, thereby establishing a versatile platform for the construction of saturated three-dimensional carbon architectures.

In 2025, Qian and co-workers reported a nickel-catalysed asymmetric C(sp^3)–C(sp^3) cross-coupling that enables the enantioselective synthesis of α,α-dialkylated indoles through hydrofunctionalization of *N*-indolyl-substituted alkenes with alkyl iodides (Fig. 22).[59] This study addresses a long-standing challenge in asymmetric alkyl–alkyl coupling, namely the differentiation of minimally distinct alkyl groups while maintaining high regio- and enantioselectivity. The use of $NiBr_2$ diglyme in combination with a newly developed chiral bisoxazoline ligand, (*S*,*S*)-**L21**, proved crucial for achieving efficient catalytic turnover under mild conditions, delivering *N*-alkylated indole products bearing fully saturated stereogenic centers at the *N*-α-position in high yields and excellent enantioselectivities. The reaction proceeds under mild conditions, featuring a broad substrate scope and compatibility with various functional groups and complex molecular structures. A diverse array of *N*-indolyl alkenes were competent coupling partners, including those bearing electron-donating or electron-withdrawing groups on the indole ring, carbazole-derived alkenes, and more sterically hindered *N*-alkenyl indoles. Notably, the reaction consistently exhibited exclusive regioselectivity for alkyl–alkyl coupling at the α position relative to the indole nitrogen, even in substrates containing potentially competing aryl directing groups. A variety of primary alkyl iodides, including long-chain *n*-alkyls, functionalized or distally branched ones, and those containing functional groups such as trifluoromethyl, phenyl, silyl ether, and ester, can undergo the reaction smoothly. Although, secondary alkyl iodides could also be engaged when an alternative chiral ligand (*S*,*S*)-**L6** is used in

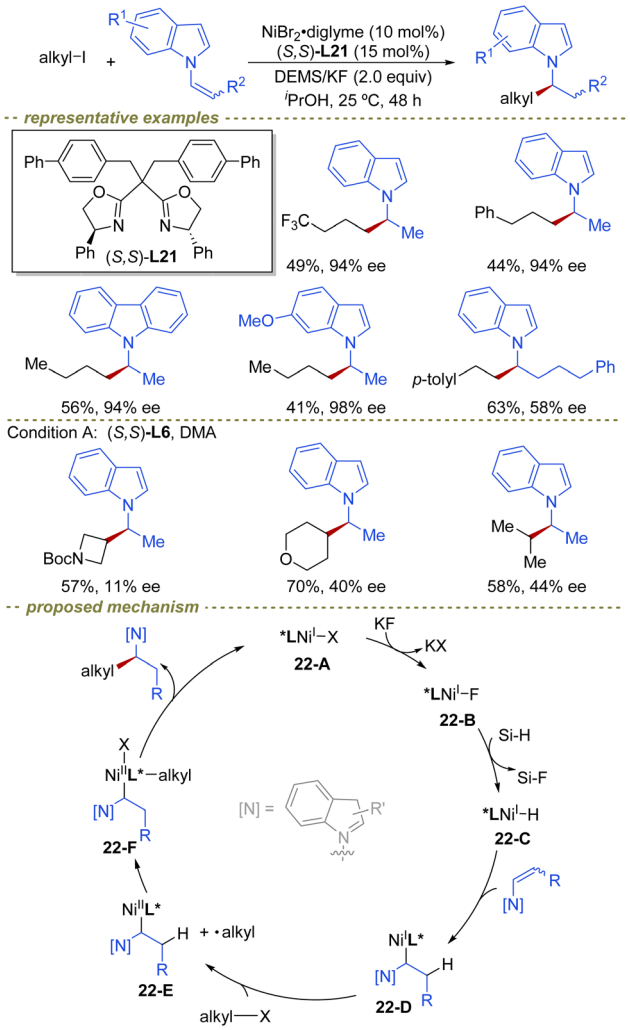

Fig. 22 Ni-catalysed asymmetric hydroalkylation of *N*-indolyl-substituted alkenes and alkyl iodides.

place of (*S*,*S*)-**L21**, albeit with diminished enantioselectivity, reflecting the increased steric and electronic demands of these electrophiles. More importantly, alkyl iodides derived from structurally complex natural products such as estrone and naproxen proved to be competent coupling partners, underscoring its applicability to late-stage functionalization. Mechanistic studies reveal that the chiral ligand-coordinated Ni(I) species (**22-A**) initially forms the active Ni(I)–F intermediate (**22-B**), which is then reduced to the active Ni(I)–H intermediate (**22-C**). Subsequently, species **22-C** undergoes migratory insertion with *N*-indolyl alkene to form the indole *N*-bound Ni(I)-alkyl intermediate (**22-D**). This intermediate further reacts with alkyl iodide *via* SET, induces C–I bond cleavage to generate an alkyl radical and the Ni(II)–I species (**22-E**). Species **22-E** captures the alkyl radical to form a dialkyl–Ni(III) intermediate (**22-F**), which finally undergoes reductive elimination to forge the new C(sp^3)–C(sp^3) bond and deliver the α,α-dialkyl indole compound.

Notable breakthroughs have been achieved in addressing two long-standing challenges in nickel-catalysed asymmetric hydroalkylation of alkenes, namely the precise control of hydrogen migration pathways and the site-specific construction of chiral centers within alkene frameworks. In 2022, Shu group reported the first Ni-catalysed migratory asymmetric hydroalkylation of *N*-acyl alkenyl amines, to construct tertiary stereogenic carbon centers next to nitrogen.[54] The authors reported that increasing the loading of the $NiBr_2$ glyme catalyst to 10 mol% and the chiral ligand (4*R*,4*S*′,4*S*,4*R*′)-**L22** to 12 mol% led to optimal yields and regioselectivity for the desired migratory hydroalkylation products. Notably, this catalytic system afforded two chiral products with high enantiomeric excesses, thereby establishing a valuable strategy for the streamlined synthesis of structurally diverse chiral aliphatic amine derivatives (Fig. 23).

In 2023, Y. Fu group reported a nickel-catalysed remote asymmetric hydroalkylation reaction of alkenyl ethers that integrates controlled alkene migration with enantioselective C(sp^3)–C(sp^3) bond formation.[60] Employing the catalyst $NiBr_2$ diglyme and the bisoxazoline chiral ligand (*S*,*S*)-**L23**, the transformation proceeds *via* sequential chain-walking and asymmetric hydrofunctionalization, enabling the efficient synthesis of dialkyl carbinol ether products bearing an *O*-α-chiral center (Fig. 24). Notably, stereocontrol is exerted at a position distal to the initial alkene, without the assistance of classical directing groups or prefunctionalized organometallic reagents. As such, it addresses a long-standing challenge in migratory hydroalkylation, where maintaining high regio- and enantioselectivity after multiple β-hydride elimination/insertion events is intrinsically difficult. From substrate scope perspective, both monosubstituted and multi-substituted alkenyl ethers are suitable substrates, delivering enantio-enriched target products. Regarding ether-protecting groups, alkenyl ethers protected by benzyl and cyclohexyl groups exhibit the highest reactivity, whereas less sterically demanding methyl ethers afford reduced enantiomeric excess (70% ee), underscoring the importance of steric differentiation around the oxygen substituent during the enantio-determining step. Primary and secondary alkyl iodides exhibit high reactivity in this system. Suitable substrates include structures substituted with esters and heterocyclic units such as furan. Alkyl iodides originating from drug frameworks and bioactive molecules also show good reaction efficiency. Mechanistic studies support a NiH-mediated radical relay pathway that rationalizes both alkene migration and stereocontrol. Ni(I) species (**24-A**) serves as active catalyst, which first reacts with the alkyl iodide to

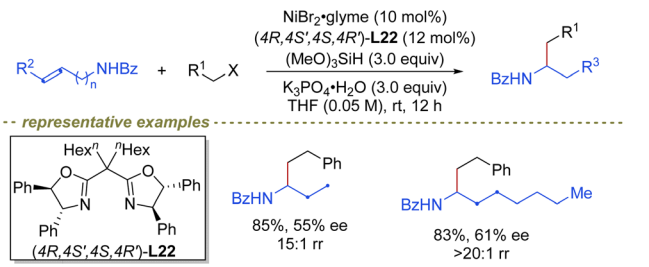

Fig. 23 Ni-catalysed asymmetric α-hydroalkylation of alkenyl amines with alkyl halides.

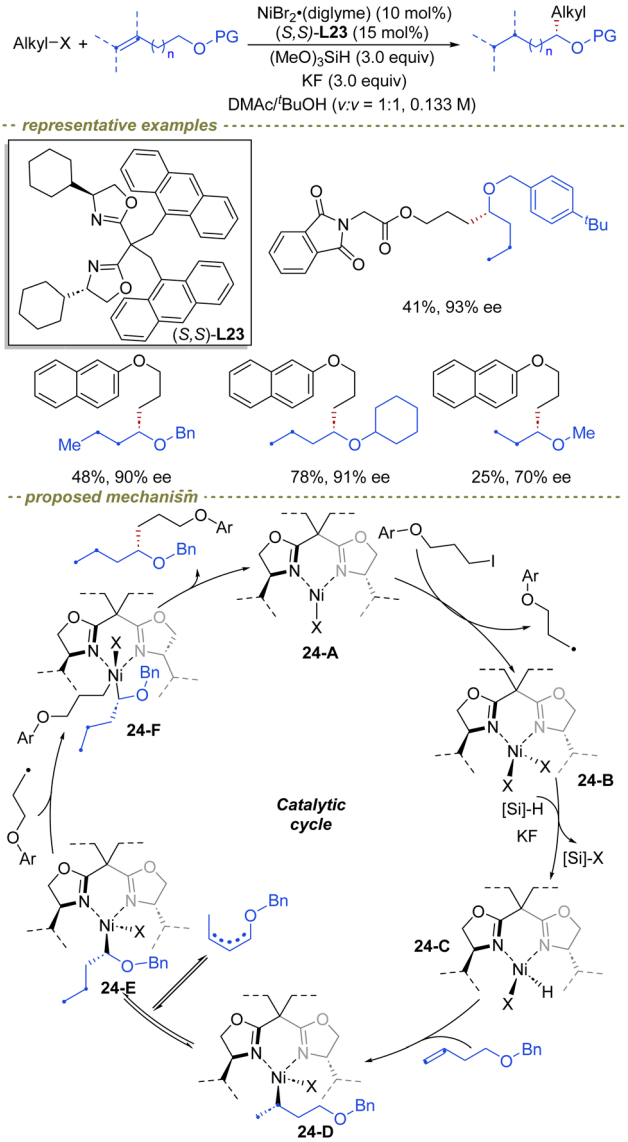

Fig. 24 Ni-catalysed remote asymmetric hydroalkylation of alkenyl ethers with alkyl halides.

generate Ni(II) species (**24-B**) and an alkyl radical. Base-promoted hydrogen transfer with silane converts species **24-B** into Ni(II)–H species (**24-C**). Subsequently, species **24-C** inserts into the alkene molecule to produce alkyl nickel species (**24-D**), which then undergoes β-hydride elimination to give *O*-α-alkyl nickel species (**24-E**). Capture of the transient alkyl radical by *O*-α-alkyl nickel species **24-E**, yielding Ni(III) species **24-F**. Finally, reductive elimination of species **24-F** produces the alkene migratory hydroalkylation product and regenerates the initial catalyst **24-A**, thereby completing the catalytic cycle. Density functional theory calculations and ligand structure–activity correlations indicate that steric repulsion and stabilizing non-covalent interactions between the chiral bisoxazoline ligand and the migrating substrate govern the enantio-determining radical capture/reductive elimination sequence. More importantly, this asymmetric alkene migration reaction enables the efficient synthesis of chiral dialkyl carbinol ethers from commercially available alkenyl ethers and alkyl iodides, thereby providing a convenient route for the preparation of (*R*)-δ-decalactone.

In 2023, Rong and his co-workers reported a distinctive nickel-catalysed asymmetric hydroalkylation of unactivated endocyclic alkenes that constitutes a valuable advance in alkyl–alkyl cross-coupling enabled by hydrofunctionalization. By combining a nickel catalyst with a Ph-BOX-type chiral ligand (4*R*,4*R*′,4*S*,4*S*′)-**L24**, the authors achieved highly regio- and enantioselective C2-functionalization of readily available 3-pyrroline derivatives through a tandem alkene isomerization/hydroalkylation process, enables the efficient synthesis of chiral C2-alkylated pyrrolidine compounds (Fig. 25).[61] This strategy is particularly notable because it enables the desymmetrization of *N*-heteroendocyclic alkenes, a long-standing challenge in asymmetric catalysis, while forging C(sp^3)–C(sp^3) bonds without the need for preformed organometallic nucleophiles. The reaction proceeds under mild conditions, exhibits broad substrate scope, and is compatible with various functional groups and complex molecular structures. Both aryl acyl-substituted and alkyl acyl-substituted 3-pyrroline derivatives can undergo the reaction smoothly, regardless of the electronic nature or substitution pattern on the aryl group. Electron-rich, electron-poor, and fused aromatic systems are all compatible,

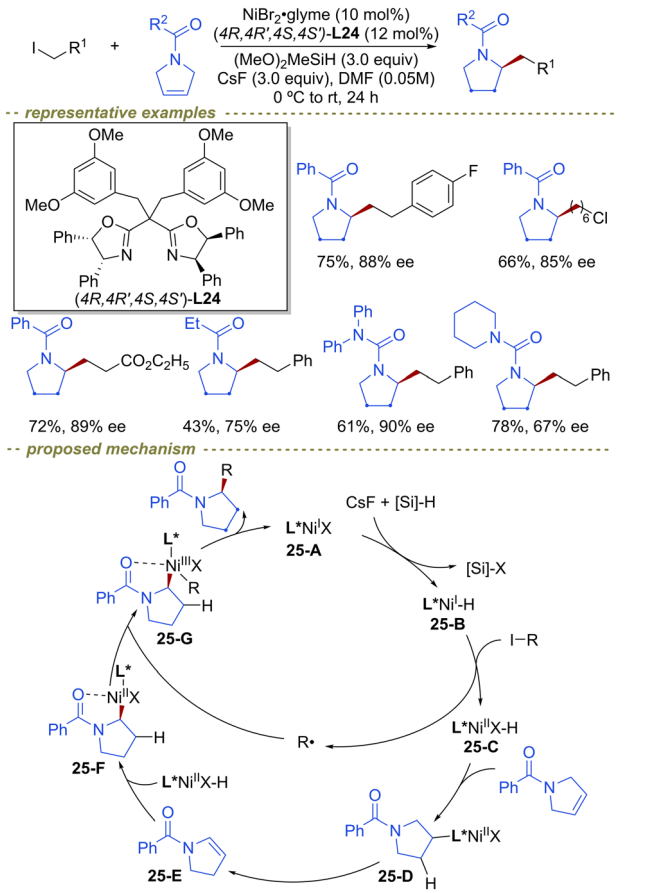

Fig. 25 Ni-catalysed asymmetric C2-selective hydroalkylation of 3-pyrroline alkenes with alkyl halides.

underscoring the robustness of the nickel catalytic manifold. On the electrophile side, primary alkyl iodides including linear aryl substituted and heterocycle containing examples are efficiently incorporated with consistently high enantioselectivities. More importantly, drug-derived alkyl iodides (*e.g.*, estradiol valerate-derived alkyl iodide) and complex heterocyclic/natural product-derived substrates (*e.g.*, dehydroabietylamine-derived substrates) can participate in the reaction efficiently.

Mechanistic studies indicate that the chiral ligand-coordinated Ni(I) species (**25-A**) generates the active Ni(I)–H intermediate (**25-B**) in the presence of the hydride source dimethoxymethylsilane (DMMS) and the base CsF. Intermediate **25-B** undergoes a SET with alkyl iodide, producing an alkyl radical and a Ni(II) species (**25-C**). Subsequently, the Ni(II) species **25-C** undergoes migratory insertion into 3-pyrroline to form a Ni(II)–alkyl intermediate (**25-D**), followed by β-H elimination and alkene reinsertion, enables controlled isomerization to a 2,3-dihydropyrroline intermediate (**25-E**) along with a Ni(II) species. Further, re-insertion at the C2 position and radical capture then furnish a high-valent Ni(III) species (**25-G**), from which reductive elimination delivers the enantioenriched C2-alkylated pyrrolidine and regenerate the Ni(I) catalyst, thus completing the catalytic cycle. Isotopic labeling and radical-clock studies reveal that NiH-mediated irreversible insertion and free-radical intermediates, orchestrated by a chiral BOX ligand, enable regio- and enantioselective alkyl–alkyl cross-coupling of unactivated alkenes, providing a versatile route to chiral C2-alkylated pyrrolidines through migratory asymmetric hydrofunctionalization.

The recent contribution from Hu and co-workers represents a notable advance in Ni–H enabled alkyl–alkyl cross-coupling, extending asymmetric hydrofunctionalization paradigms to phosphorus-containing substrates through a dynamic kinetic asymmetric transformation (DyKAT) manifold (Fig. 26).[62] Employing $NiI_2 \cdot xH_2O$ as nickel source, the 2-naphthyl-substituted oxazoline (*S*,*S*)-**L25** as ligand, triethoxysilane as hydride source, and K_3PO_4 as base, this reaction successfully achieved regio-, diastereo-, and enantioselective hydroalkylation of various cyclic phosphinates with primary alkyl iodides under mild conditions furnished 3-alkylated cyclic phosphinates. By merging nickel hydride catalysis with controlled chain-walking, this work addresses a long-standing challenge in asymmetric catalysis: the simultaneous and selective construction of two nonadjacent stereogenic centers, one at carbon and one at phosphorus. In contrast to earlier Ni–H systems the present strategy leverages reversible alkene migration to interconvert P-chiral substrate enantiomers, thereby enabling efficient enantioconvergent C(sp^3)–C(sp^3) bond formation from readily accessible racemic cyclic phosphinates. This reaction exhibits excellent substrate scope and functional group compatibility. Among alkyl iodide substrates, both arylalkyl iodides regardless of electron-donating/withdrawing substituents and primary alkyl iodides containing functional groups such as *tert*-butyldiphenylsilyl (TBDPS)-protected alcohols, phthalimides, indoles, esters, chloroalkyls, and trisubstituted alkenes undergo efficient coupling. For cyclic phosphinate substrates, aryl esters based on electron-rich phenyl and naphthyl moieties exhibit excellent

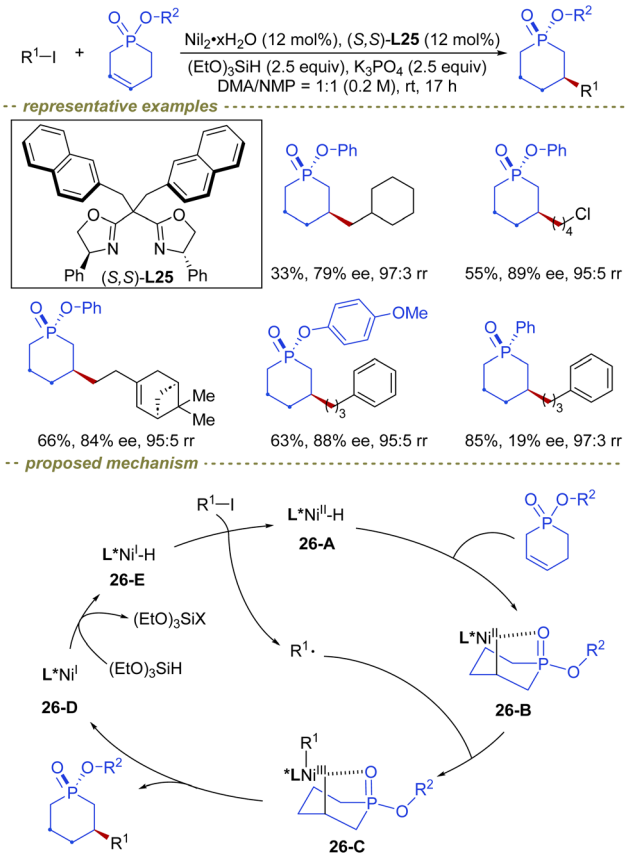

Fig. 26 Ni-catalysed asymmetric hydroalkylation of cyclic phosphinates with alkyl iodides.

reactivity. The corresponding products afford diastereoselectivity values exceeding 97 : 3, enantioselectivity values reaching 89%, and regioselectivity values up to 95 : 5. Notably, all four stereoisomers are accessible through a combination of enantiomeric ligand selection and base-mediated hydrolysis–esterification, underscoring the method's versatility. In contrast, benzyl iodides, branched/secondary alkyl iodides, and aryl esters with electron-withdrawing substituents exhibit poor reactivity, often resulting in diminished enantioselectivity or failure to furnish the desired products. Mechanistic studies reveal the key reaction pathway: the Ni(II)–H species (**26-A**) enables hydronickellation of the cyclic phosphinates, and subsequent chain-walking enables intermediate equilibration and substrate enantiomer interconversion, forming the alkyl–Ni(II) intermediate (**26-B**). Intermediate **26-B** captures an alkyl radical to generate the dialkyl–Ni(III) intermediate (**26-C**), which undergoes stereospecific reductive elimination to produce the target product while releasing the Ni(I) species (**26-D**). Subsequent regeneration of the Ni–H species **26-A** *via* silane-mediated reduction closes the catalytic cycle. The chiral ligand (*S*,*S*)-**L25** precisely regulates the selectivity of key steps including chain-walking, radical capture, and reductive elimination through steric and electronic effects. Although alternative sequences involving Ni(I) intermediates or reversed order of hydride formation and halide reduction cannot be fully excluded, the available experimental evidence strongly supports a DyKAT

pathway. This study demostrates the asymmetric hydroalkylation of cyclic phosphinates under mild conditions, establishing a versatile Ni-catalysed platform for enantioconvergent alkyl–alkyl cross-coupling that enables access to all stereoisomers and broadens strategies for heteroatom-centered chirality.

Recently, Wang group reported a nickel-catalysed asymmetric migratory hydroalkylation of trisubstituted alkenes (Fig. 27).[63] Employing $NiBr_2$ glyme as catalyst and the bisoxazoline (*S*,*S*)-**L26** as ligand, this strategy enables enantio- and diastereoselective formation of C(sp^3)–C(sp^3) bonds between unactivated alkyl fragments through a controlled chain-walking process. Notably, the method provides direct access to acyclic amine derivatives bearing an α-stereogenic center adjacent to nitrogen and a remote γ- or δ-all-alkyl-substituted stereocenter, a motif largely inaccessible *via* conventional cross-coupling approaches. Importantly, careful selection of alkene geometry and ligand configuration allows stereodivergent synthesis of all four possible stereoisomers, highlighting the exceptional versatility and synthetic potential of this single-catalyst system. The reaction exhibits excellent substrate scope and functional group compatibility. Among alkyl halides, primary alkyl bromides and iodides undergo coupling efficiently, while secondary alkyl bromides and iodides enable the challenging secondary–secondary C(sp^3)–C(sp^3) cross-coupling, affording products with high yields and outstanding stereoselectivity. Functional group compatibility encompasses, aryl fluoride/chloride, trifluoromethyl, silyl ether, acetal, phthalimide, and thiophene, underscoring the robustness of the catalytic manifold. However, sterically hindered tertiary alkyl halides (*e.g.*, *tert*-butyl iodide) are incompatible with this catalytic system.

Among alkenes, γ,γ-disubstituted allylamides exhibit optimal reactivity, enabling efficient construction of 1,3-non-adjacent stereocenters irrespective of electronic or steric variations in the alkene substituents. In contrast, δ,δ-disubstituted homoallylamides furnish 1,4-non-adjacent stereocentres with diminished enantio- and diastereoselectivity, due to the weak non-covalent interactions between the amide group and the ligand, as well as alkene isomerization during chain walking. This method is applicable to the late-stage modification of drug-like molecules, gram-scale reactions, and the concise synthesis of drug analogues. Mechanistic investigations, supported by experimental observations and density functional theory (DFT) calculations, reveal that the transformation proceeds through a well-defined nickel catalytic cycle involving the generation of Ni(I) species, formation of alkyl radicals, insertion of Ni(II)–H into the alkene, chain walking (β-H elimination/reinsertion), radical capture, and reductive elimination. Notably, non-covalent interactions between amide moieties and nickel species, coupled with ligand-derived steric and electronic effects, synergistically modulate reaction stereoselectivity. This mechanistic paradigm offers an innovative strategy for the stereodivergent assembly of non-adjacent stereogenic centres.

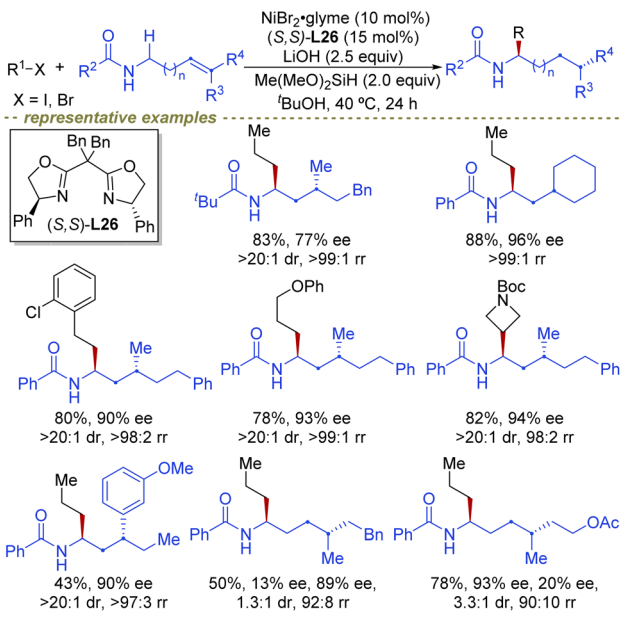

Fig. 27 Ni-catalysed migratory hydroalkylation of trisubstituted alkenes.

2.3 Establishing two chiral carbon centers on alkyl electrophiles and alkenes

The simultaneous formation of chiral centers in both the alkyl halide and alkene moieties is achieved through strategies such as enantioconvergent coupling or tandem hydrometallation-radical capture. This process relies on the redox cycling of nickel catalysts and precise stereocontrol imparted by chiral ligands, enabling the synchronous establishment of chiral centers on both substrate-derived fragments during C(sp^3)–C(sp^3) bond formation.

In 2021, Shu group reported the Ni-catalysed asymmetric hydroalkylation of unactivated alkenes with alkyl halides in the presence of a directing group to construct two continuous stereogenic carbon centers on both alkene and alkyl electrophile parts.[52,53] The reaction tolerates both activated and unactivated alkyl halides to deliver adjacent tertiary carbon centers in good yields and excellent levels of enantioselectivity, albeit in low ratios of diastereoselectivity. In 2022, Hu group reported a Ni-catalysed asymmetric hydroalkylation reaction of alkenyl pinacol boronates with racemic 2-bromo-γ-lactams/lactones, addressing a long-standing challenge associated with the stereocontrolled formation of vicinal C(sp^3)–C(sp^3) bonds (Fig. 28).[64] Using $NiCl_2$ as catalyst and bisoxazoline (*S*,*S*)-**L27** as ligand, this protocol efficiently synthesizes chiral alkyl boronate–lactam/lactone compounds containing vicinal C(sp^3) stereocenters. This reaction exhibits an excellent substrate scope and functional group tolerance. 2-Bromo-γ-lactams bearing *N*-aryl, *N*-heteroaryl, or *N*-alkyl substituents undergo smooth hydroalkylation with consistently high levels of enantio- and diastereocontrol, irrespective of the electronic nature of the substituents on nitrogen. Notably, the protocol is not limited to lactams; structurally related 2-bromo-γ-lactones are also competent electrophiles and, notably, do not require Lewis acid ($BF_3 \cdot OEt_2$) activation to achieve excellent yields and stereoselectivities. It is worth noting that the product derived from acyclic 2-bromoester analogs shows low stereoselectivity, indicating that cyclic substrates are crucial for stereocontrol.

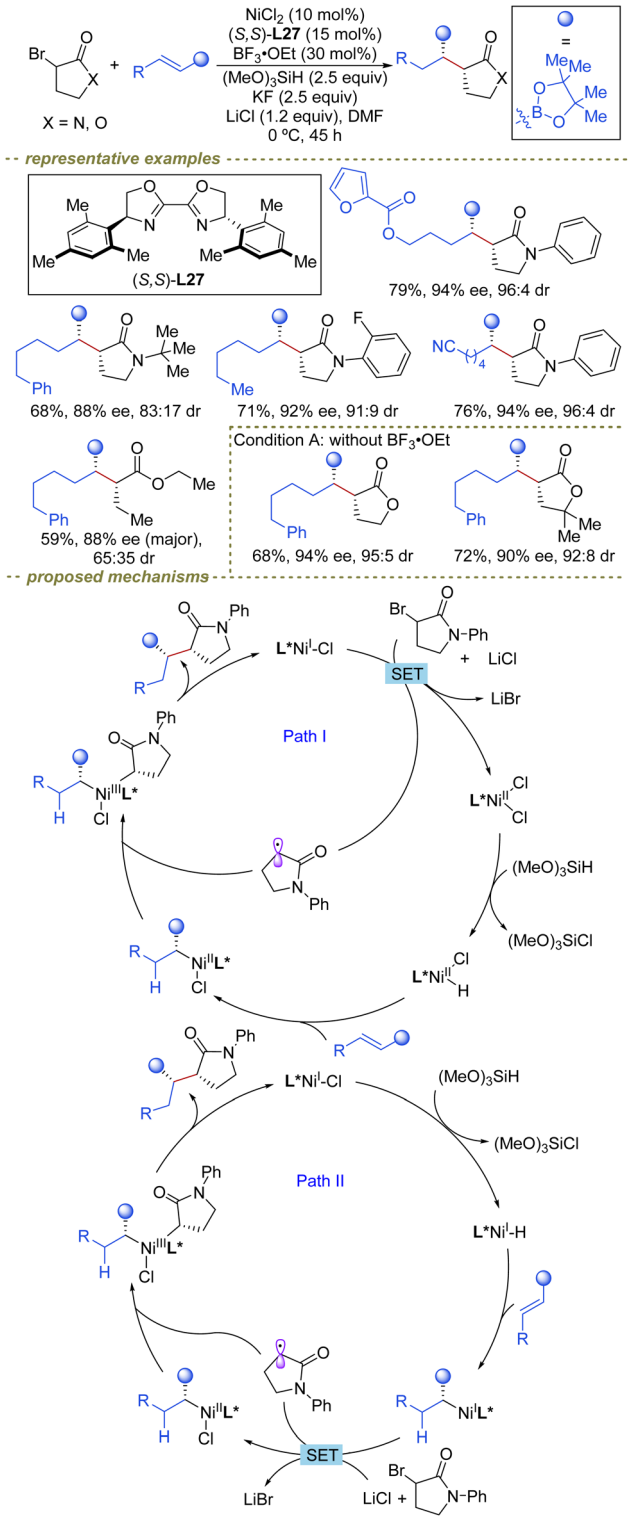

Fig. 28 Ni-catalysed enantio- and diastereoselective hydroalkylation of alkenyl boronic esters with 2-bromo-γ-lactams (or lactones).

Alkenyl pinacol boronates with different carbon chain structures and functional groups such as chlorine, ethers, TBS ethers, esters, nitriles, aryl groups, and benzamides all react smoothly. Alkenyl boronates bearing pharmaceutically valuable heterocyclic scaffolds can serve as competent reaction substrates. Compatible heterocyclic structures include furan, thiophene and tetrahydropyran. Alkenyl boronates and 2-bromo-γ-lactams sourced from bioactive frameworks also proceed efficiently under standard reaction conditions. In contrast, tertiary alkyl bromides fail to engage in the hydroalkylation process, presumably due to pronounced steric hindrance that impedes productive catalyst–substrate interaction. The authors proposed two possible reaction mechanisms. Both pathways follow Ni(I)/Ni(II)/Ni(III) redox transformations to complete the catalytic cycle, with α-carbonyl alkyl radicals as key intermediates. The vicinal C(sp^3) stereocenters are synergistically regulated through a combination of migratory insertion (the enantioselectivity-determining step) and radical trapping (the diastereoselectivity-critical step). The key distinctions between the two pathways are as follows: in Pathway I, the alkyl electrophile is activated by the initially formed Ni(I)–Cl species *via* SET. The catalytic transformation proceeds through sequential nickel speciation evolution starting from Ni(I)–Cl species, followed by Ni(II)–Cl_2 and subsequent Ni(II)–H intermediates. The resulting Ni(II)–H active species undergoes migratory insertion to form the key Ni(II)-α-boryl–alkyl intermediate.

Notably, the hydride source is preferentially utilized for reduction to regenerate the Ni(I)–Cl species. In contrast, Pathway II involves the direct activation of the alkyl electrophile by the Ni(I)-α-boryl–alkyl species. Pathway II enables the generation of Ni(II)-α-boryl–alkyl intermediates within a two-step catalytic sequence, fully bypassing the Ni(II)–Cl_2 speciation stage. Despite both mechanistic routes converging at identical Ni(II)-α-boryl–alkyl intermediates, experimental evidence fails to distinguish these two pathways. This subtle mechanistic ambiguity offers considerable scope for further mechanistic investigation.

In 2023, Zhu and co-workers developed a regio-, enantio-, diastereoselective NiH-catalysed hydroalkylation reaction of enamides/enecarbamates with racemic α-bromoamides (or Katritzky salts).[65] As shown in Fig. 29, using $Ni(NO_3)_2 \cdot 6H_2O$ and a chiral bidentate ligand (4*S*,5*R*)-**L28**, the reaction efficiently synthesizes a series of β-aminoamide compounds containing vicinal tertiary–tertiary C(sp^3) stereocenters with excellent substrate scope. The significance of this transformation is simultaneous control of two adjacent stereogenic centers originating from two distinct, prochiral and racemic partners. Numerous α-bromo secondary amides can serve as suitable substrates, including *N*-aryl-substituted derivatives (compatible with both electron-donating and electron-withdrawing groups), *N*-heteroaryl-substituted derivatives (containing structures such as indole), *N*-alkyl-substituted derivatives, as well as α-bromo Weinreb amides and *N*,*N*-dialkyl-substituted α-bromoamides—all of which participate in the reaction. Beyond halides, Katritzky salts derived from α-amino acids are used as electrophiles, they also enable efficient formation of β-aminoamides with excellent enantioselectivity. In addition, enamides/enecarbamates can perfectly accommodate a variety of functional groups (*e.g.*, alkyl chlorides, ethers, esters, ketones, nitriles, aryl bromides). Beyond enamide substrates, encarbamates are also compatible. Except for secondary enamides

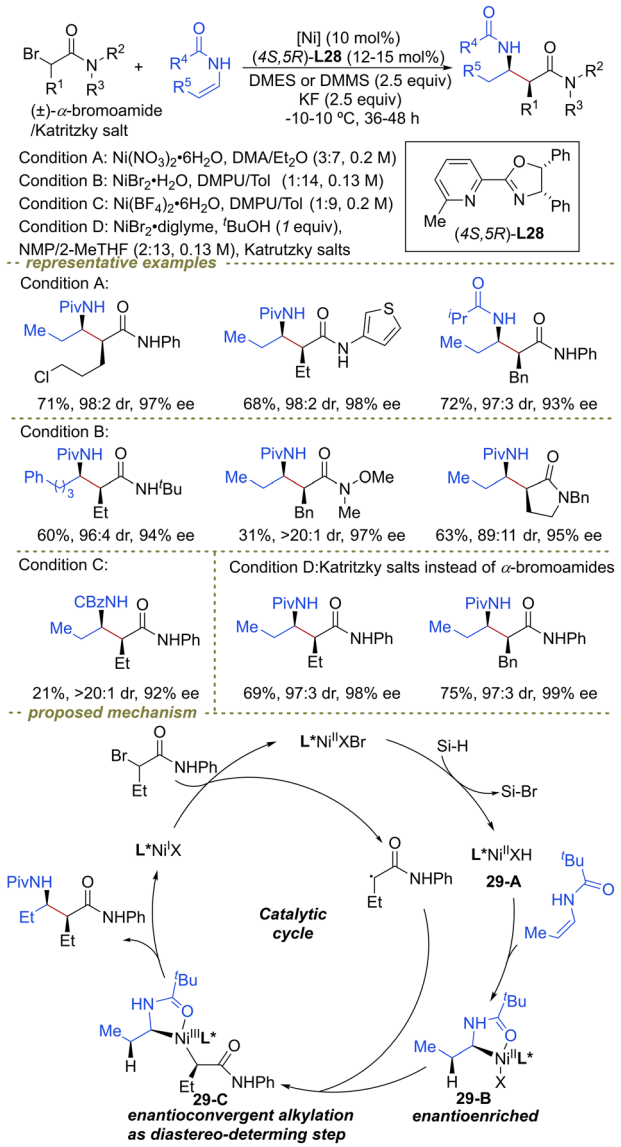

Fig. 29 Ni-catalysed enantioconvergent hydroalkylation of *cis*-enamides (or enecarbamates) with racemic α-bromoamides (or Katritzky salts).

protected with sterically hindered *N-tert*-butyloxycarbonyl groups, enamides with less sterically hindered aliphatic or aromatic acyl protecting groups are also feasible substrates. Mechanistic investigations support a Ni(II)/Ni(III) catalytic cycle that is characteristic of asymmetric NiH-mediated hydroalkylation. Initially, the LNi(II)–H species (**29-A**) undergoes enantioselective *syn*-insertion into enamides to generate a Ni(II)-alkyl intermediate (**29-B**). This step is identified as the enantiodetermining event and is consistent with deuterium-labeling experiments that confirm *syn* insertion. Subsequent reaction with a racemic α-bromoamide or Katritzky salt proceeds through a radical pathway, wherein an alkyl radical adds to the alkyl–Ni(II) species to form a high-valent Ni(III) intermediate (**29-C**). Diastereoselective reductive elimination forges the C(sp^3)–C(sp^3) bond, delivering the product with excellent diastereo- and enantiocontrol while regenerating the Ni(II) catalyst. This work showcases how precise ligand design and mechanistic orchestration can transform simple, readily available starting materials into highly complex, stereochemically rich molecules.

The continuous effort of Hu group resulted in their new reports on Ni–H catalysis. In 2024, they disclosed a directing-group-free nickel–hydride catalysed asymmetric hydroalkylation reaction of fluoroalkenes with secondary alkyl halides (containing cyclic/linear amide moieties) enabling the highly stereocontrolled construction of vicinal C(sp^3)–C(sp^3) bonds bearing fluorine substituents.[66] As shown in Fig. 30, this reaction proceeds in the presence of $NiCl_2$ glyme and a chiral bisoxazoline ligand (*S*,*S*)-**L10**, and efficiently transforms readily accessible (*Z*)-fluoroalkenes into densely functionalized organofluorine motifs containing two adjacent stereogenic centers with excellent yields, enantioselectivities, and diastereoselectivities. This work addresses a long-standing

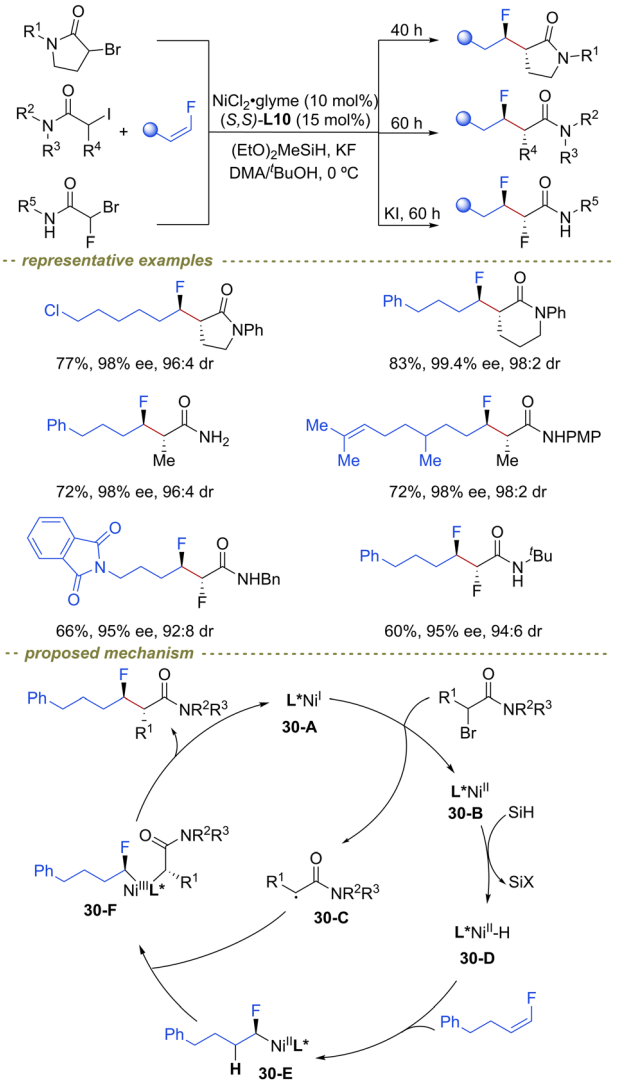

Fig. 30 Ni-catalysed asymmetric hydroalkylation of fluoroalkenes and amide-containing alkyl halides.

challenge in NiH catalysis associated with the simultaneous control of regio- and stereochemical outcomes in the absence of strongly coordinating auxiliaries. The study further demonstrates that a single fluorine substituent can effectively direct hydronickelation and stereochemical induction while suppressing deleterious pathways such as C–F oxidative addition and hydrodefluorination, thereby underscoring the strategic role of fluorine in enabling highly selective alkyl–alkyl cross-coupling processes. The reaction exhibits a remarkably broad substrate scope on both coupling partners.

A wide range of fluoroalkenes undergo asymmetric hydroalkylation smoothly, including substrates bearing alkyl chlorides, silyl ethers, esters, alkenes, protected amines, and heterocycles such as furans, phthalimides, with uniformly high levels of enantio- and diastereocontrol. On the electrophile side, both cyclic lactams with 4-to-6-membered ring skeletons and linear α-iodoamides are competent coupling partners. Notably, more challenging primary and tertiary amides are also well tolerated. Beyond mono-fluorinated products, racemic bromofluoroamides can also serve as substrates, generating vicinal difluorides with two fluorine-containing stereocenters, providing streamlined access to fluorine-rich building blocks of high relevance to medicinal chemistry. Mechanistic investigations support a Ni(I)/Ni(III) catalytic manifold involving radical intermediates. Single-electron transfer from a Ni(I) species (**30-A**) activates secondary alkyl halides generates a Ni(II) species (**30-B**) and an alkyl radical (**30-C**), which is converted into a Ni(II)–H species (**30-D**) upon reaction with the silane. Enantioselective *syn*-hydronickelation of the fluoroalkene constitutes the stereodetermining step, delivering a Ni(II)-α-fluoroalkyl intermediate (**30-E**). Subsequent radical capture forms a high-valent Ni(III) species (**30-F**) that undergoes rapid reductive elimination to afford the target products with vicinal fluorine-containing C(sp^3) stereocenters and regenerate the active Ni(I) catalyst **30-A**. Deuterium-labeling, radical clock, and inhibition experiments collectively corroborate this pathway and underscore the pivotal role of controlled hydrometalation in dictating both regio- and stereochemical outcomes. Overall, this contribution represents the first directing-group-free NiH-catalysed strategy capable of assembling fluorine-containing vicinal stereocenters through asymmetric alkyl–alkyl cross-coupling, establishes a new paradigm for exploiting subtle electronic effects of fluorine in nickel catalysed asymmetric hydrofunctionalization.

3 Ni-catalysed asymmetric alkene–alkene coupling by hydroalkylation

Compared with the well-established hydroalkylation between alkenes and alkyl electrophiles, asymmetric alkene–alkene cross-coupling enabled by Ni–H catalysis is an emerging area yet challenging strategy for constructing asymmetric C(sp^3)–C(sp^3) bonds.[67,68] A remarkable advantage of this approach is its exceptional step- and atom-economy, since it employs two distinct alkenes as the sole coupling partners without relying on prefunctionalized alkyl halides or stoichiometric organometallic reagents. This methodology ingeniously leverages the ambivalent reactivity of alkenes, allowing them to act simultaneously as nucleophiles and electrophiles, thereby enabling precise stereocontrol during C(sp^3)–C(sp^3) bond formation under mild conditions. Nevertheless, the simultaneous realization of chemoselectivity, regioselectivity, and enantioselectivity from two structurally similar alkenes remains a formidable challenge. First, chemoselectivity is difficult to control because the two alkenes often exhibit comparable reactivity toward Ni–H insertion, inevitably leading to uncontrolled homodimerization and low yields of the desired cross-coupling products. Second, regioselectivity is hard to regulate due to the flexible sites for hydrometallation and the inherent tendency of chain walking, which can cause ambiguous regioselectivity in C–C bond formation. Third, enantiocontrol is more sophisticated, as the chiral ligand must simultaneously differentiate the facial selectivity of hydrometallation for both alkenes and precisely govern the stereochemistry during the subsequent reductive elimination. Despite these obstacles, rational design as well as the exploitation of orthogonal reactivity between the two alkenes have enabled effective suppression of side reactions and excellent control of selectivities. Therefore, asymmetric alkene–alkene cross-coupling not only expands the synthetic scope of nickel-catalysed alkyl–alkyl coupling but also provides a unique platform for exploring new reaction modes and mechanisms in asymmetric catalysis.

In 2024, Shu group further advanced the field of nickel-catalysed alkyl–alkyl cross-coupling through the development of a nickel-catalysed asymmetric cross-hydrodimerization reaction of enamides and unactivated alkenes.[69] Using $NiBr_2$ glyme as catalyst, 5,6-dimethylpyridine mono-oxazoline (3*S*,8*R*)-**L29** as chiral ligand, trimethoxysilane ($(MeO)_3SiH$) as hydride source, and 3-bromocyclooctene or 3-bromocyclohexene (**O1** or **O1′**) as single-electron acceptor, the authors established a enantio- and regioselective construction of α-branched aliphatic amines bearing tertiary stereocenters *via* hydrometallation of the polarized enamide and subsequent coupling with unactivated alkenes (Fig. 31). Remarkably, the transformation integrates both reductive and oxidative elements in a single reaction manifold, circumventing the need for preformed organometallic reagents or alkyl electrophiles. This reaction exhibits excellent substrate scope and functional group tolerance. Linear unactivated alkenes with different carbon chain lengths, as well as internal and cyclic unactivated alkenes, participate efficiently, enabling access to both tertiary–primary and secondary–secondary alkyl–alkyl linkages. The reaction accommodates a wide array of functional groups, including halides, esters, nitriles, aldehydes, boronic esters, free alcohols, amides, sulfonamides, and heteroaryl motifs, highlighting its chemoselectivity under redox-neutral yet mechanistically complex conditions. On the enamide side, both aryl- and alkyl-substituted *N*-acyl enamides, cyclic amide derivatives, and even *N*-acyl enamines lacking N–H bonds are competent substrates, collectively enabling streamlined access to α-branched aliphatic amines bearing tertiary stereogenic centers. The successful late-stage modification of drug-like molecules further illustrates the synthetic utility of this cross-hydrodimerization paradigm. Mechanistically, the authors propose two closely related

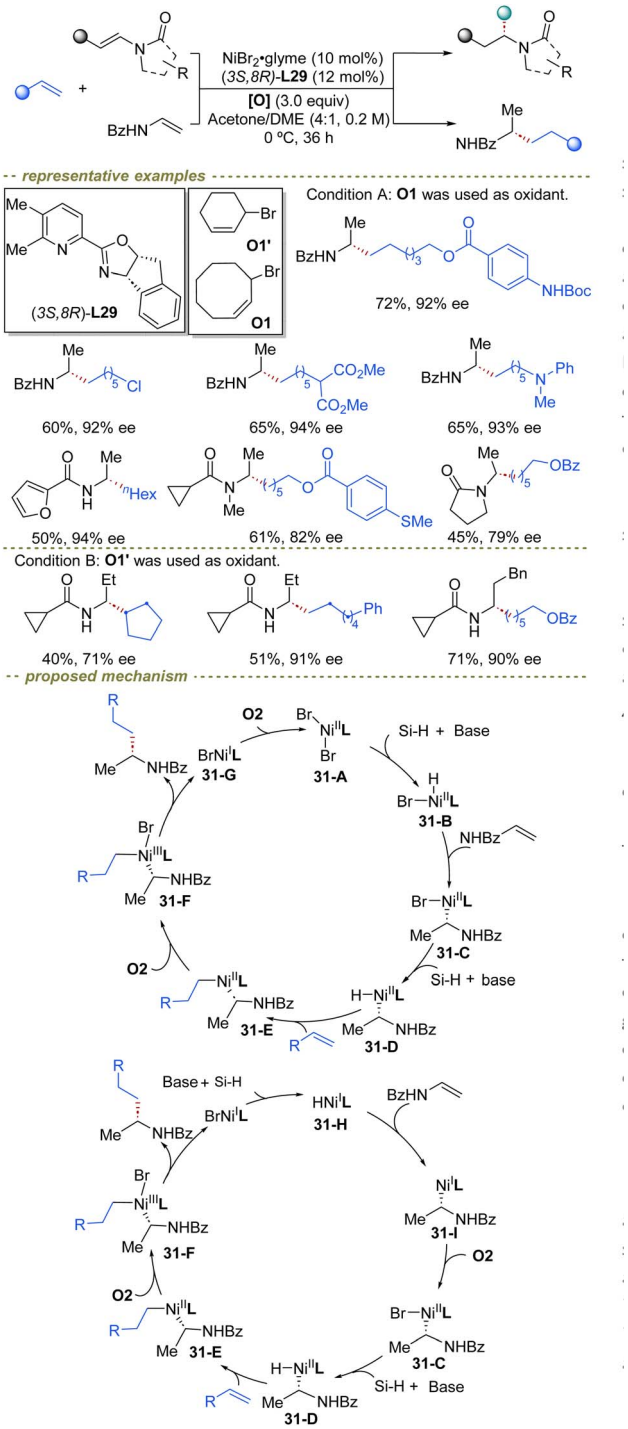

Fig. 31 Ni-catalysed asymmetric cross-hydrodimerization of *N*-acyl enamines with unactivated alkenes.

catalytic cycles that converge on a common dialkylnickel intermediate prior to C–C bond formation. In the first scenario, in the presence of silane and base, the Ni(II) species (**31-A**) is converted to Ni(II)–H (**31-B**), which then undergoes migratory insertion into the enamide to form an alkylnickel species (**31-C**). Species **31-C** reacts with silane and base to generate an alkylnickel hydride intermediate (**31-D**), which undergoes regioselective migratory insertion into the unactivated alkene to form a dialkylnickel species (**31-E**). Species **31-E** is subjected to single-electron oxidation by **O2** to form a Ni(III) intermediate (**31-F**), which finally undergoes reductive elimination to produce the target product and Ni(I) species (**31-G**). Species **31-G** is then oxidized to Ni(II) (**31-A**) to complete the catalytic cycle. In the secondpathway, Ni(I)–H (**31-H**) undergoes migratory insertion into the enamide to form an alkylnickel species (**31-I**), which is oxidized by **O2** to generate intermediate **31-C**. In the presence of base, intermediate **31-C** reacts with silane to form an alkylnickel hydride intermediate (**31-D**), which selectively inserts into the unactivated alkene to form a dialkylnickel species (**31-E**). Intermediate **31-E** undergoes single-electron oxidation with **O2** to form a Ni(III) intermediate (**31-F**), which undergoes reductive elimination to yield the final product and Ni(I) species.

Deuterium-labeling and kinetic experiments support irreversible, enantio-determining hydrometallation of the enamide and reversible insertion into the unactivated alkene, rationalizing the observed head-to-tail regioselectivity and high enantiocontrol. Notably, this reaction proceeds in the coexistence of both a reductant and an oxidant, with alkenes serving as the sole precursors for the enantioselective construction of $C(sp^3)$–$C(sp^3)$ bonds. It demonstrates excellent chemoselectivity, head-to-tail regioselectivity, and high enantioselectivity, providing a novel strategy for the efficient construction of saturated carbon stereocenters containing $C(sp^3)$–$C(sp^3)$ bonds.[70]

In the same year, Shu and co-workers demonstrated a nickel-catalysed enantioselective cross-coupling reaction of two distinct alkenes (enol esters and unactivated alkenes) *via* a reductive-oxidative relay (Fig. 32).[26] Conducted in the presence of $NiBr_2$ glyme and chiral bisoxazoline ligand ((4*S*,4*S*′,4*R*,4*R*′)-**L30**, (4*S*,4*S*′,4*R*,4*R*′)-**L31**, (*S*,*S*)-**L32**), this reaction efficiently synthesizes chiral dialkyl carbinol derivatives through hydrometallation of enol esters followed by hydrometallation of unactivated alkenes. The strategy exploits the orthogonal reactivity of the two alkene classes under nickel hydride catalysis, enabling head-to-tail coupling with high levels of regio- and enantioselective control. Subsequent substrate scope investigations demonstrated the broad applicability of this reaction. A broad array of terminal enol esters, including those bearing electron-rich, electron-deficient, and heteroaryl substituents, participate efficiently while maintaining excellent enantioselectivity, even in the presence of functional groups such as esters, halides, thioethers, and silyl ethers. Sterically demanding β-alkyl-substituted enol esters are well tolerated, underscoring the robustness of the enantio-determining hydrometallation step. Notably, *Z*-configured internal enol esters achieved efficient conversion, whereas the corresponding *E*-isomers are largely unreactive, reflecting the sensitivity of the nickel hydride insertion to steric hindrance around the alkene. On the partner side, a wide range of primary unactivated alkenes with different carbon chain lengths, α-branched, and β-branched unactivated alkenes are compatible, including substrates incorporating heterocycles (*e.g.*, furan, indole, benzimidazole, phthalimide, carbazole) as well as complex

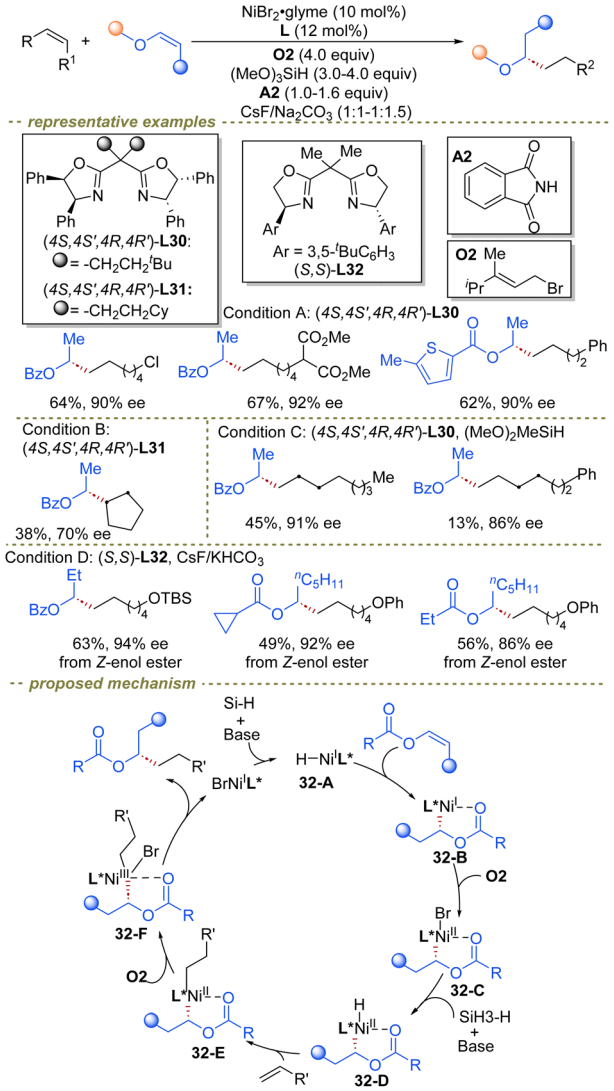

Fig. 32 Ni-catalysed asymmetric hydrodimerization of enol esters with unactivated alkenes.

alkenes derived from indomethacin or estrone, exhibited good compatibility, affording the corresponding asymmetric cross-coupling products. Moreover, cyclic alkenes, such as cyclopentene, could participate in the reaction, albeit in moderate yield and enantioselectivity. In contrast, activated alkenes such as styrenes preferentially undergo homodimerization, revealing an inherent reactivity mismatch that further delineates the scope of this relay process. Mechanistic analysis supports a catalytic cycle in which asymmetric hydrofunctionalization plays a decisive role in stereocontrol. A chiral LNi(I)–H species (**32-A**) is formed under the action of a base and silane, which undergoes regioselective insertion into enol esters to generate a β-ester-substituted Ni(I) intermediate (**32-B**). Subsequent single-electron oxidation by an allyl bromide oxidant (**O2**) converts the alkyl–Ni(I) species into a higher-valent nickel intermediate (**32-C**). Next, intermediate **32-C** reacts with silane to generate a Ni(II)–H intermediate (**32-D**), which then undergoes migratory insertion into unactivated alkenes to form a dialkyl Ni(II) intermediate (**32-E**). The resulting dialkyl–Ni(II) complex (**32-E**) undergoes further oxidation to a Ni(III) state (**32-F**), from which reductive elimination to produce chiral dialkyl carbinol esters and regenerates the Ni(I) catalyst. This method enables efficient construction of asymmetric $C(sp^3)$–$C(sp^3)$ bonds without the need for stoichiometric alkyl nucleophiles or electrophiles. Overall, this study laid a foundation for future developments in Ni-catalysed asymmetric alkene functionalization, demonstrating that careful control over sequential hydrometallation and redox events can unlock otherwise inaccessible stereodefined dialkyl motifs.

Very recently, Shu group reported the first example of a nickel-catalysed asymmetric cross-hydrodimerization between electron-deficient alkenyl phosphine sulfides and unactivated alkenes.[71] As shown in Fig. 33, this reaction is conducted in the presence of $NiBr_2$ glyme and a newly developed pyridine–oxazolidine chiral ligand (3*R*,8*S*)-**L33**, with trimethoxysilane ($(MeO)_3SiH$) as hydride source and 3-bromocyclooctene derivative **O3** as single-electron acceptor, enables direct construction of α-chiral phosphine sulfide derivatives *via* $C(sp^3)$–$C(sp^3)$ bond formation. This strategy overcomes the longstanding challenge of selectively engaging electron-poor alkenes, expanding the

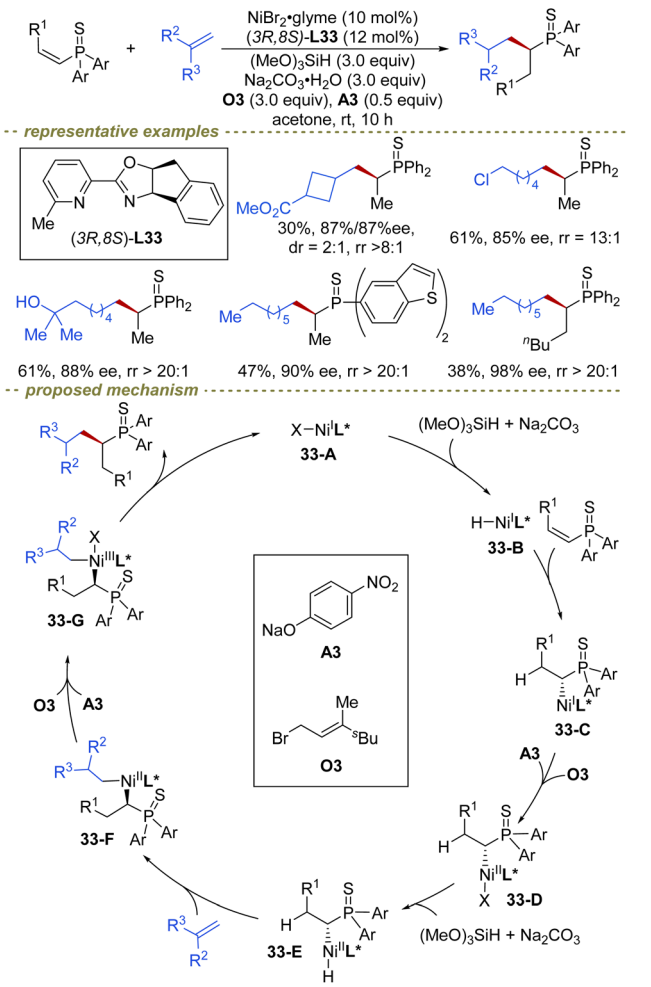

Fig. 33 Ni-catalysed asymmetric hydrodimerization of alkenyl phosphine sulfides with unactivated alkenes.

scope of asymmetric hydrofunctionalization beyond electron-rich systems. By leveraging a Ni-catalytic reductive–oxidative manifold, the approach achieves chemo-, regio-, and enantioselective control in a single catalytic cycle while obviating the need for prefunctionalized alkyl electrophiles or nucleophiles, thus establishing a new paradigm for asymmetric alkene–alkene coupling. This reaction exhibits excellent substrate scope and functional group tolerance. Unactivated alkenes with diverse carbon chain lengths are well tolerated in this transformation. Alkenes functionalized with halogens, boronates, esters, ethers, acetals, aldehydes, sulfonamides, unprotected hydroxyl groups, aromatic rings and heterocyclic scaffolds also serve as competent substrates. Furan represents a typical compatible heterocyclic derivative.

All these substrates efficiently deliver the corresponding asymmetric cross-coupling products under standard catalytic conditions. Additionally, this method can be applied to 1,1-disubstituted alkenes and alkenes derived from certain drug molecules. Alkenyl phosphine sulfides with electron-donating or electron-withdrawing aryl substituents, heteroaryl groups, and even internal alkenes serve as competent partners, whereas vinyl phosphine oxides display reduced reactivity due to strong oxygen coordination, highlighting the crucial role of sulfur coordination in promoting selective Ni–alkene engagement. Based on mechanistic results and relevant literature reports, the authors proposed a plausible reaction mechanism. Under the reaction conditions, a ligand-coordinated LNi(I)–Br species (**33-A**) is converted to LNi(I)–H species (**33-B**) in the presence of silane and base. The species **33-B** undergoes regio- and enantioselective migratory hydrometallation with unsaturated phosphine sulfides to form a secondary alkyl Ni(I) species (**33-C**), which then undergoes single-electron oxidation by the oxidant (**O3**) to generate an alkyl Ni(II) intermediate (**33-D**). The intermediate **33-D** undergoes a second transmetalation reaction with silane in the presence of base, producing an alkyl Ni(II)–H intermediate (**33-E**). Intermediate **33-E** undergoes regioselective hydrometallation with unactivated alkenes to form a dialkyl Ni(II) species (**33-F**), which is oxidized by **O3** to yield a dialkyl Ni(III) intermediate (**33-G**). Finally, reductive elimination of **33-G** affords the alkyl–alkyl cross-coupling product. Deuterium-labeling and kinetic studies support the irreversibility of both hydrometallation events and identify catalyst activation as rate-limiting step, lending strong experimental backing to the proposed mechanism. This reaction achieves, for the first time, the asymmetric coupling between electron-deficient alkenes and electronically neutral alkenes, thereby expanding the boundaries of alkene–alkene asymmetric coupling and injecting new vitality into novel modes of asymmetric alkyl–alkyl bond formation.

4 Conclusion and outlook

In summary, nickel-catalysed hydroalkylation of alkenes represents an emerging approach for constructing stereogenic carbon centers *via* alkyl–alkyl cross-coupling, using alkenes as latent alkyl nucleophiles. This strategy avoids stoichiometric alkyl metallic reagents, making it promising for synthesizing sensitive stereogenic centers. Its mild reaction conditions also open new avenues for accessing diverse stereogenic centers with varied substitution patterns through alkyl–alkyl cross-coupling. Notably, the unprecedented Ni-catalysed asymmetric alkene–alkene cross-coupling enables asymmetric C(alkyl)–C(alkyl) bond formation *via* a redox–relay coupling process, offering an alternative to conventional methods that rely on stoichiometric alkyl nucleophiles or electrophiles. Despite these impressive advances, several critical limitations and challenges still hinder the broader application of this field. Foremost among these is the difficulty in achieving efficient hydroalkylation of tertiary alkyl halides, which is mainly attributed to severe steric hindrance, slow radical formation, and competitive side reactions such as β-hydride elimination. Furthermore, the scope of alkenes is largely limited to terminal and disubstituted substrates, while tri- and tetrasubstituted alkenes still remain largely underexplored. To address these issues, future research should focus on the development of novel chiral ligands with enhanced steric and electronic modulation, more efficient catalytic systems, and deeper mechanistic insights. Merging this chemistry with external stimuli such as photochemistry, electrochemistry, or cooperative catalysis would also open new opportunities. Finally, expanded applications in the synthesis of complex pharmaceuticals, natural products, and late-stage functionalization will further validate the practical utility of these methodologies. We anticipate this reaction mode will emerge as a cornerstone of alkyl–alkyl cross-coupling, offering a versatile platform for the streamlined construction of stereogenic centers with implications for pharmaceutical innovation, materials science, and sustainable chemical synthesis.

Author contributions

The manuscript was written through the contributions of all authors.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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