Streamlined Alkylation via Nickel-Hydride-Catalyzed Hydrocarbonation of Alkenes

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ABSTRACT: Compounds rich in sp^3-hybridized carbons are desirable in drug discovery. Nickel-catalyzed hydrocarbonation of alkenes is a potentially efficient method to synthesize these compounds. By using abundant, readily available, and stable alkenes as pro-nucleophiles, these reactions can have broad scope and high functional group tolerance. However, this methodology is still in an early stage of development, as the first efficient examples were reported only in 2016. Herein, we summarize the progress of this emerging field, with an emphasis on enantioselective reactions. We highlight major developments, critically discuss a wide range of possible mechanisms, and offer our perspective of the state and challenges of the field. We hope this article will stimulate future works in this area, making the methodology widely applicable in organic synthesis.

1. INTRODUCTION

Organic compounds with a greater 3-dimensional (3D) shape than flat aromatics are more likely to succeed as drug candidates because of a better match with biological targets which have 3D structures.[1-3] A useful descriptor for 3D shape is the fraction of sp^3 carbon.[2] Methods for introducing alkyl moieties into organic molecules, especially in an enantioselective manner, are therefore highly relevant to drug discovery. Alkylation by nucleophilic substitution on alkyl electrophiles through an S_N1 or S_N2 pathway is straightforward.[4-5] However, S_N1 reactions suffer from side reactions such as elimination and rearrangement, and the S_N2 reactions have limited scope for hindered primary and secondary alkyl electrophiles. Moreover, it is difficult to create enantiomerically pure C(sp^3) centers by nucleophilic substitution reactions. S_N1 reactions will racemize enantiomerically pure alkyl electrophiles. S_N2 reactions might be stereospecific, but enantiomerically pure alkyl electrophiles can be challenging to prepare. As an alternative to nucleophilic substitution, transition metal-catalyzed cross-coupling of alkyl electrophiles[6-9] can introduce sp^3 carbons in a parallel manner, thereby streamlining alkylation reactions. These reactions, especially the coupling of non-activated alkyl electrophiles containing β-hydrogens, had been challenging due to β-H elimination of metal alkyl intermediates. In the last two decades, many new methods, approaches, and catalysts have been developed so that cross-coupling of alkyl electrophiles in a racemic manner is now readily achieved.[6-9] Nickel catalysis is particularly versatile for these reactions, as Ni can span a wide range of oxidation states and engage in both one- and two-electron oxidative addition reactions.[10-11]

In conventional cross-coupling reactions, organometallic reagents are used as nucleophiles.[12-15] Many of these reagents such as Grignard and organozinc reagents are sensitive to air and moisture and have limited functional group compatibility. Organoboron reagents are relatively stable and have high functional group tolerance, but they are typically made in multiple-step reactions, compromising the step-economy of the overall process. These drawback can be potentially overcome by metal-catalyzed hydrocarbonation of alkenes (Figure 1), which employs stable and abundant alkenes as pro-nucleophiles.[16-20] In these reactions, insertion of an alkene into a metal hydride species generates a metal alkyl species in-situ, which then reacts with a carbon electrophile in a similar manner to a C-C cross-coupling reaction to form a new C(sp^3)-C bond (Figure 1). While many first-row transition metal hydrides can catalyze hydrocarbonation of alkenes,[17] methods based on Cu-H and Ni-H are most versatile. Cu-H catalyzed hydrofunctionalization of alkenes has been developed into a powerful synthetic strategy, with a high level of chemoselectivity and stereochemical control.[18] Nevertheless, Cu alkyl species normally only react with an active alkyl electrophile, such as allylic and benzylic halides, in nucleophilic substitution-type reactions.[18] Elegant strategies based on dual metal catalysis,[21] where transmetalation of a Cu alkyl intermediate to another metal such as Pd, have been developed for hydrocarbonation of alkenes with an unactivated carbon electrophiles such as aryl bromide.[22-23] The scope of these transformations remains limited. In contrast to Cu alkyl species, Ni alkyl species react readily with a wide range of carbon electrophiles in cross-coupling-type reactions. Indeed, a considerable amount of reports of Ni-catalyzed hydrocarbonation of alkenes have emerged in recent years. In this perspective we summarize the key developments in this area, with a focus in enantioselective reactions. We do not include related works in hydrocarbonation of alkynes,[24-27] as these reactions do not generate a new C(sp^3) center. We also do not discuss Ni-catalyzed dicarbofunctionalization of alkenes[28-30] because these reactions typically do not involve Ni-H catalysis.[28-30] Note that metal hydride-catalyzed hydrocarbonation of alkenes should be distinguished from conjugated addition.[31-33] In the latter reactions, carbon nucleophiles, often reactive organometallic reagents, are added to activated alkenes. In the hydrocarbonation reactions

discussed here, stable and readily available carbon electrophiles are added to alkenes, including non-activated ones. For this reason we do not include Ni-catalyzed conjugate addition[34] neither.

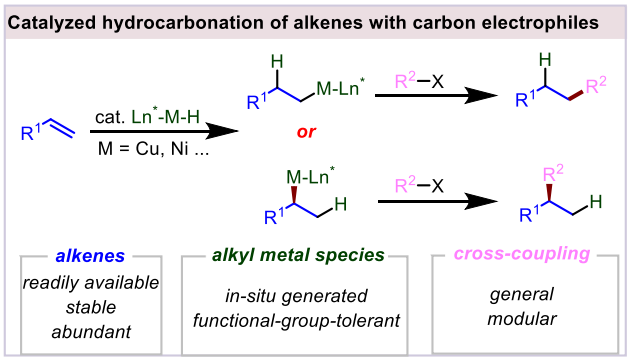

Figure 1. Metal-catalyzed hydrocarbonation of alkenes with carbon electrophiles to introduce a new C(sp^3) center

2. CHEMISTRY OF NICKEL HYDRIDE

Spectroscopically (NMR) characterized Ni-H species were first reported in 1959 as products of the reduction of triphenylphosphine Ni chloride by borohydride.[35] The next several decades saw only sporadic new examples. Ni-H species have gained increased attention in last two decades.[36] In addition to being present in the catalytic cycles of many Ni-catalyzed organic reactions such as alkene isomerization and polymerization, Heck reaction, hydrogenation, as well as hydrosilylation, Ni-H species are also intermediates for Ni-catalyzed hydrogen evolution and oxidation, reactions relevant to hydrogen generation and utilization.[37] Furthermore, Ni-H species are present in the biological systems, being involved in the catalysis of methyl-coenzyme M reductase and [NiFe]-hydrogenase.[38-39] Numerous Ni-H complexes have been isolated and characterized, and they are described in a recent comprehensive review.[36] A selection of these complexes supported by ligands similar to those used in Ni-catalyzed hydrofunctionalization reactions are shown in Figure 2a.[36]

In general, nickel hydride complexes can be synthesized from reactions of nickel precursor complexes and hydride sources in either an oxidative or a non-oxidative pathway (Figure 2b and Figure 2c).[36] In a typical oxidative process, a low-valent Ni complex, such as a Ni(0) species, undergoes oxidative addition with proton or an A-H substrate where A = H, R_3C, and R_3Si (Figure 2b). The non-oxidative process, on the other hand, often involves the reaction of a Ni halide or related complex with a main group hydride such as borohydrides and $LiAlH_4$ (Figure 2c). Of relevance to hydrocarbonation reactions is the generation of Ni-H complexes through σ-bond metathesis with a silane or borane. For example, the pincer bis(amino)amide Ni methoxide complex [($^{Me}N_2N$)Ni-OMe] (**1**) reacted with Ph_2SiH_2 at -70 °C to give the corresponding Ni-H complex (**2**) (Figure 2d).[40]

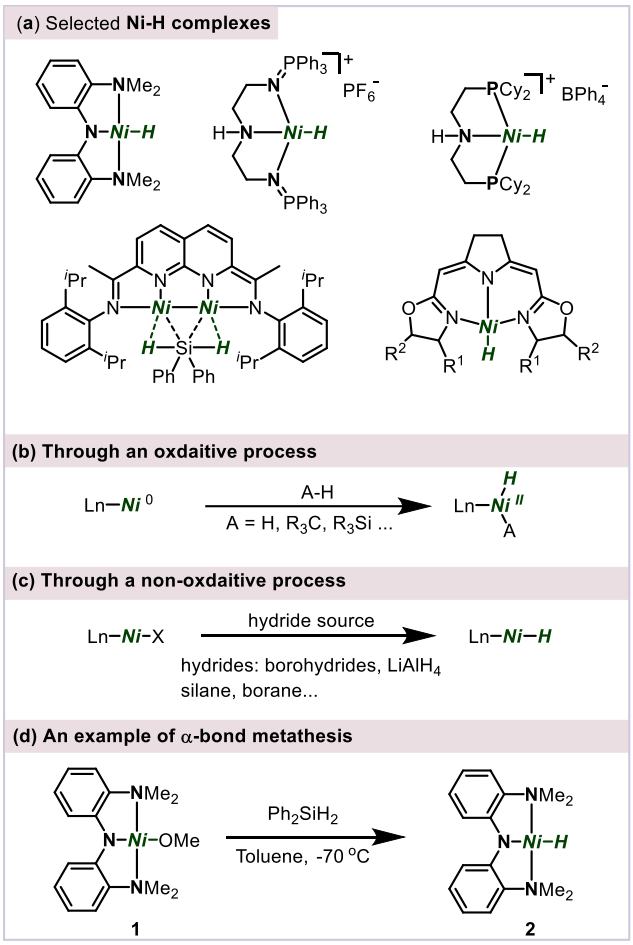

Figure 2. (a) Selected examples of isolated Ni-H complexes; (b-d) Methods for the synthesis of nickel hydrides.

The insertion of alkenes into a Ni-H bond is commonly reported.[36] An open coordination site or a labile ligand on the Ni-H complex is often required. For [($^{Me}N_2N$)Ni-H)] (**2**), the insertion of ethylene is thermodynamically downhill by about 12 kcal/mol.[41] The regioselectivity of the insertion is influenced by how the C=C bond is polarized. Electron-withdrawing groups such as phenyl and ester groups favor the 2, 1-insertion to give a branched Ni alkyl species, whereas normal alkyl groups favor the 1,2-insertion to give a linear Ni alkyl species.[42] Considering the steric environment of the Ni center, the linear alkyl species is likely more stable than its branched counterpart. According to DFT computations,[41] [($^{Me}N_2N$)Ni-^{n}Pr] (**3**) is about 6 kcal/mol more stable than [($^{Me}N_2N$)Ni-^{i}Pr] (**4**). The insertion is often reversible, which forms the mechanistic basis for Ni-catalyzed isomerization of alkenes.

The insertion of carbonyl groups (in ketones or aldehydes) into a Ni-H bond is an essential step in Ni-catalyzed reduction of carbonyl compounds.[43] This insertion is reported for several Ni pincer hydride complexes. Computational studies indicated that the insertion of HCHO into bis(phophinite)- and bis(phosphine)-based pincer Ni-H complexes have a similar Gibbs free energy of about -6 kcal/mol.[44-45] Assuming a small influence of pincer ligands in reaction energies, the insertion of

carbonyl groups into a Ni-H bond appears to be thermodynamically less favourable than the insertion of alkenes. This energetic difference might be responsible for the reactivity difference of [($^{Me}N_2$N)Ni-H)] (**2**) towards alkenes and carbonyl compounds. Insertion of ethylene to **2** completed in 0.5 h at room temperature, whereas insertion of acetone to 2 required about 12 h at the same temperature.[40] The higher activity of certain Ni-H species towards alkenes over carbonyl compounds can be quite advantageous for synthetic applications: it suggests the feasibility of chemoselective hydrofunctionalization of alkenes in the presence of carbonyl groups.

Certain reactivities of Ni-H species can compromise their efficiency in catalytic hydrocarbonation reactions. They include proton transfer, protonation, loss of hydrogen via reductive processes, X-H reductive elimination, as well as halogen exchange reactions with organic halides.[36] A successful hydrocarbonation method requires a relatively high stability of Ni-H against undesired reactions or conditions that avoid those side reactions.

3. DEVELOPMENT OF NI-H-CATALYZED HYDROCARBONATION

An early attempt to Ni-catalyzed hydroalkylation of alkenes was made by our group using ($^{Me}N_2$N)Ni-Cl) (**5**, commonly called Nickamine) (Figure 3). This Ni complex is an efficient (pre)catalyst for cross-coupling of alkyl halides.[46] The stoichiometric reaction cycle for hydroalkylation of an alkenes using an alkyl halide as electrophile and a hydrosilane (diethoxymethylsilane, DEMS) as a hydride source had been demonstrated (Figure 3a).[40] Despite this, in a reaction using 10 mol% **5** as catalyst, NaOMe as base, Me(EtO)$_2$SiH as hydride source, decene as olefin, and dodecyl iodide as electrophile, the hydroalkylation product was obtained in only 10% yield (Figure 3b). The majority of the regents, namely, decene and dodecyl iodide, remained unreacted. The low reaction efficiency was attributed to the instability of the corresponding Ni-H species (**2**). It was shown that complex **2** decomposed readily by N-H reductive elimination or by bimolecular H-H reductive elimination to give eventually Ni nanoparticles.

A breakthrough was made by the groups of Fu (Y.) and Liu in 2016 who reported a method for efficient hydroalkylation and hydroarylation of terminal alkenes (Figure 4a).[47] Their method employed 10% NiBr$_2$·diglyme as precursor to the Ni catalyst (diglyme = diethylene glycol dimethyl ether), 15% of 4,4'-di-*tert*-butyl-2,2'-bipyridine as ligand, 3 equiv. of diethoxymethylsilane (DEMS) as hydride source, and 3 equiv. of Na_2CO_3 as base. The reactions presumably went through a catalytic cycle similar to that in Figure 3a. The choice of ligand dictated the efficiency of the catalysis. Tri-dentate nitrogen ligands such as the $^{Me}N_2$N pincer ligand in **5**, terpyridines, and pybox gave very low yields, so did monodentate phosphine and N-heterocyclic carbene ligands. Bidentate nitrogen ligands such as phenanthrolines and bipyridines gave much better yields. The scope of electrophiles encompassed both alkyl halides and aryl iodides, including secondary alkyl halides. The alkene partners included both mono-substituted and 1,1-disubstituted terminal alkenes. Because of the mild reaction conditions, the method tolerated many functional groups including notably aldehyde, epoxide, and free OH groups.

Taking advantage of the reversibility of the insertion of alkenes into Ni-H species as well as the relative stability of Ni benzyl species over normal Ni alkyl species, the group of Zhu reported a method for Ni-catalyzed benzylic C-H arylation using alkenes and aryl iodides as starting reagents under hydroarylation conditions (Figure 4b).[48] In this case both terminal and internal alkenes could serve as substrates. While the optimized ligand was based on bipyridine, the two methyl groups at the ortho positions were essential. Use of the parent bipyridine ligand gave no arylation product. The group then applied a similar method for hydroalkylation of simple alkyl alkenes, where alkylation occurred always at the terminal position.[49] A similar method was reported by the group of Wang,[50] where a bis(oxazoline) (Box) ligand was more effective than pyridines and phenanthrolines. On the other hand, the group of Lalic developed a method for Ni- catalyzed anti-Markovnikov hydroarylation of alkenes, where they obtained liner products even for styrenes.[51] This unusual activity might be due to the formation of "ligand-less" Ni nanoparticles.

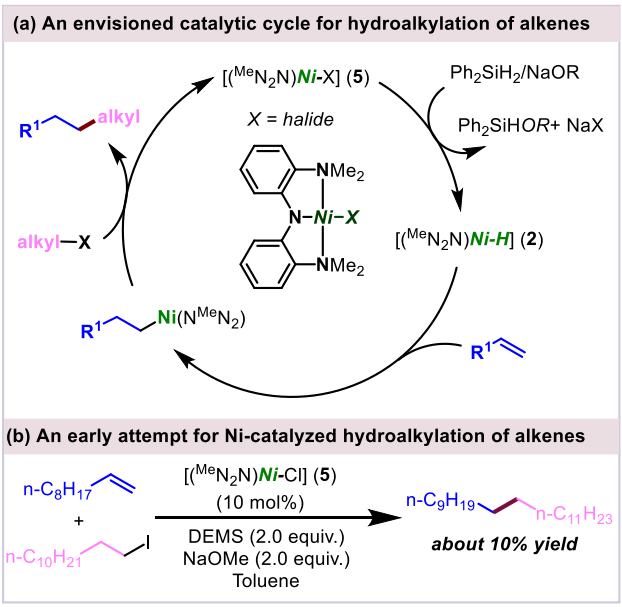

Figure 3. (a) A catalytic cycle envisioned for hydroalkylation of alkenes catalyzed by Ni pincer complex **5**. (b) An attempt for hydroalkylation of alkene using complex **5** as catalyst.

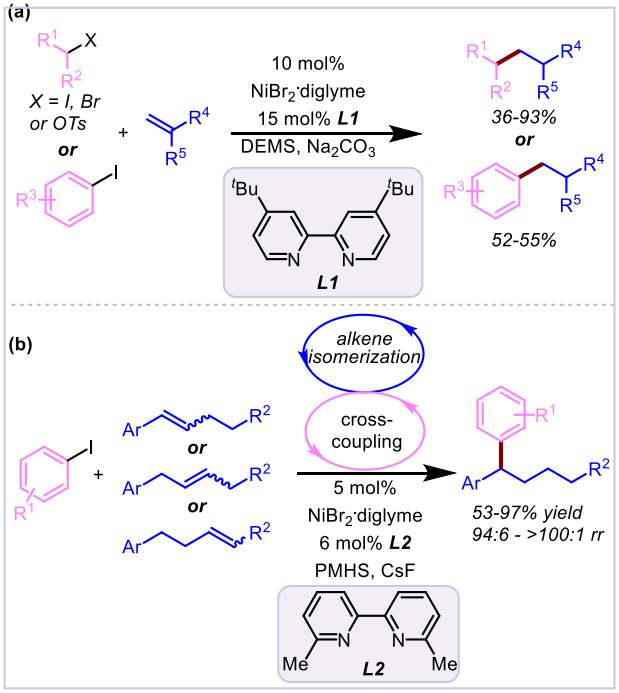

Figure 4. (a) Ni-catalyzed hydroalkylation of alkenes; (b) Ni-catalyzed arylation of remote and proximal alkenes. DEMS: diethoxymethylsilane; PMHS: polymethylhydrosiloxane.

The group of Martin employed α-haloboranes as the electrophiles for Ni-catalyzed hydroalkylation of alkenes (Figure 5a).[52] For both terminal and internal alkenes, alkylation occurred site-selectively at the terminal position. This result indicated a chain-walking process that isomerize an internal olefin to a terminal one via reversible insertion into Ni-H. Again bipyridine ligands were most effective, and the best ligand was 6-methyl, 4,4'-dimethoxy-2,2'-bipyridine. Two different mechanistic pathways were considered by the authors: (1) the addition of a boron-stabilized alkyl radical to an alkene (Figure 5b, path 1); (2) cross-coupling of a Ni-alkyl species with an α-haloborane (Figure 5b, path 2). By using heterocyclic substrates **6** and **7** (Figure 5b, control experiment), they obtained indirect evidence favouring the cross-coupling pathway. Alkylation was found to occur exclusively in the 2-position of the heterocycles.

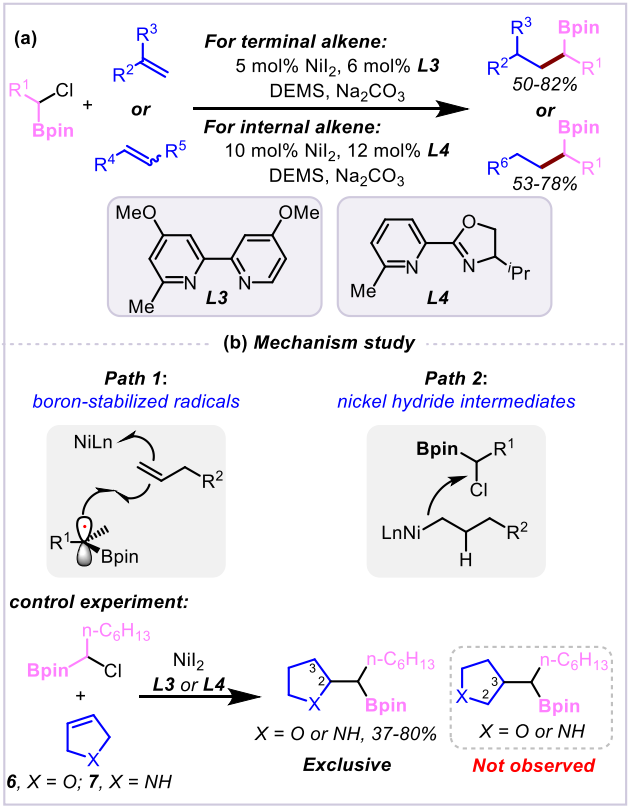

Figure 5. (a) Ni-catalyzed coupling of α-haloboranes with unactivated alkenes; (b) An associated mechanism study for the reaction in (a). DEMS: diethoxymethylsilane.

Our group explored the possibility of an α-boryl group as directing group for regioselective hydrocarbonation. We reasoned that if the synthetically versatile boronic pinacol ester (Bpin) group could direct α-carbonation, branch-selective hydrocarbonation can be achieved after transformation of the Bpin group by many well-established methods.[53] By judicious choices of catalysts and conditions, we succeeded in developing a method for Ni-catalyzed regioselective hydroalkylation and hydroarylation of alkenyl boronic esters (Figure 6a). The best ligand was 2-(2-oxazolinyl)pyridine, while bipyridines and phenanthrolines were not effective. The substrate scope was broad, and notably the method could be used to form a sterically congested secondary-secondary C(sp^3)-C(sp^3) bond. The method also enabled a new type of iterative synthesis. For example, hydroalkylation of **8** and **9** gave the secondary alkyl Bpin product **10**, which was easily converted into the secondary alkyl iodide **11** (Figure 6b). A second hydroalkylation of **12** with **11** then gave a new secondary alkyl Bpin product **13**. The group of Zhu then combined Ni-H catalyzed alkene isomerization with Bpin-directed hydroarylation for remote hydroarylation of boron-containing internal alkenes.[54] Besides aryl and alkyl halides, alkenyl halides or halogenoids were also used as electrophiles in an similar transformation to give allyl boric esters.[55]

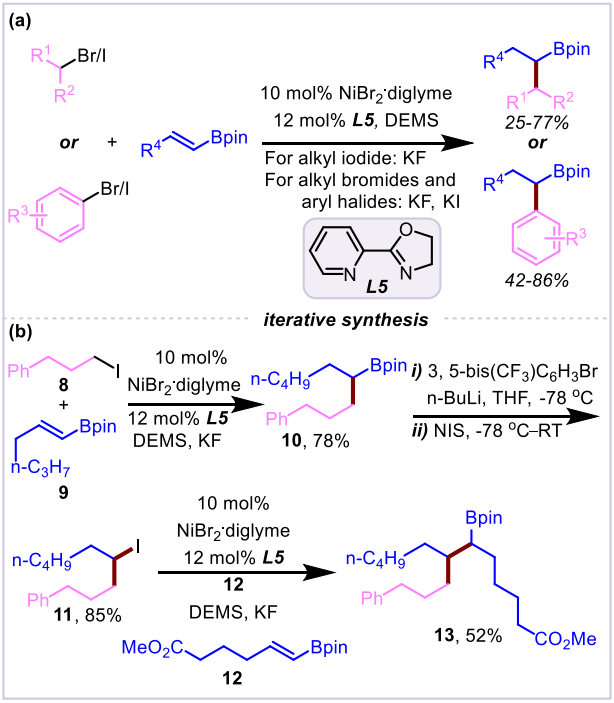

Figure 6. (a) Ni-catalyzed regioselective hydroalkylation and hydroarylation of alkenyl boronic esters; (b) Iterative synthesis using the method in (a). DEMS: diethoxymethylsilane.

In the above examples, the regioselectivity of the hydrocarbonation is dictated by substrates. A strong directing group such as an aryl or boryl group can switch the selectivity to form branched products instead of linear products. Our group developed a method to obtain two different regioselectivities of hydroalkylation of the same substrates. Our strategy relies on substrates with a weak directing group, which makes the corresponding α- and β-alkyl-Ni intermediates similar in energy. Ligands would then be able to turn their relative stability, leading to regiodivergent hydrocarbonation. We demonstrated this strategy for hydroalkylation of 3-pyrrolines, yielding both 2- and 3-alkylated pyrrolidines (Figure 7).[56] Bipyridine ligands gave C2- and C3-alklyted products in similar yields, while most pyridine oxazoline ligands favoured C3-alkylation. A methyl group at the C6-position of the pyridine moiety of pyridine oxazoline ligands, however, reversed the regioselectivity to C2-selective. The role of ligands was proposed to influence either the relative stability of C2- and C3-Ni intermediates, or the kinetic barrier for alkene isomerization which was necessary for C2-alkylation. Recently, a similar strategy was used in the regioselective hydroarylation of internal enamides with high efficiency.[57]

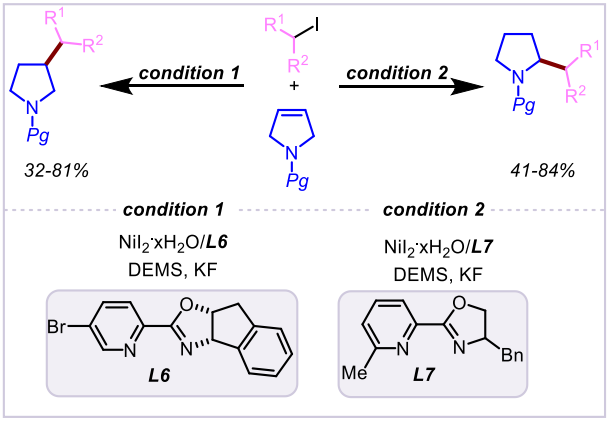

Figure 7. Ligand-controlled regiodivergent hydroalkylation of pyrrolines. DEMS: diethoxymethylsilane.

Further developments have led to methods that employ alternative alkyl electrophiles such as *N*-hydroxyphthalimide esters[58] and pyridinium salt[59] for hydroalkylation reactions. The group of Koh reported that alkyl halides could serve as both hydride and alkyl sources for reductive hydroalkylation of alkenes (Figure 8a).[60] Their method worked for both internal and terminal alkenes bearing an 8-aminoquinaldine end group, which was proposed to provide the right environment for β-H elimination from a putative Ni-alkyl intermediate, generated from activation of alkyl halide by a Ni(0) species. The method used a mild reductant, Mn, to provide the necessary two electrons for the transformation. By avoiding a hydrosilane and a base, this method can potentially improve the functional group tolerance of hydroalkylation. The groups of Zhou and Mei developed an alternative approach for hydrocarbonation using carbon nucleophiles such as organoboron reagents and ketones instead of carbon electrophiles as the coupling partners (Figure 8b).[61-63] Central to their methods was the generation of Ni^{II}-H by oxidative addition of methanol to Ni^0 species. Olefin insertion into Ni-H gave a Ni alkyl species, which upon transmetalation with a carbon nucleophile and reductive elimination yields the hydrocabonation product and regenerate the Ni^0 species. At this moment, only styrenes and 1,3-dienes were suitable alkene substrates, and the reactions were highly regioselective.

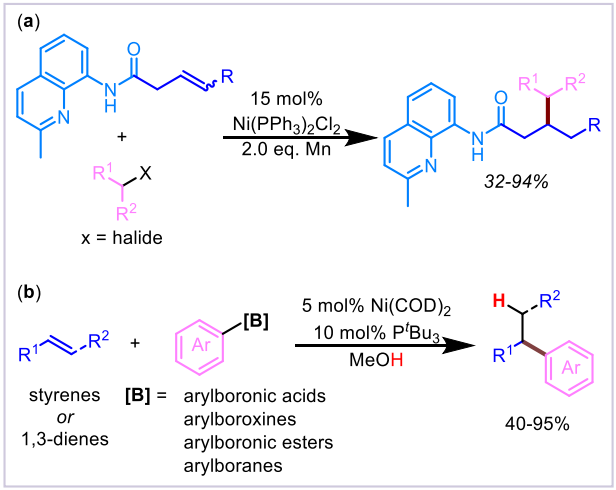

Figure 8. (a) Alkyl halides as both hydride and alkyl sources in catalytic regioselective reductive olefin hydroalkylation; (b) Hydrocarbonation of styrenes and 1,3-dienes using an alcohol as hydride source and organoboron reagents as nucleophiles.

4. DEVELOPMENT OF NI-CATALYZED ENANTIOSELECTIVE CROSS-COUPLING-TYPE ALKYLATION

The reactions described in section 3 are racemic and yield a mixture of two enantiomers in equal amounts. There are two approaches to render these reactions enantioselective (Figure 9). (1) Enantioconvergent cross-coupling of racemic alkyl electrophiles with alkenes, where the enantiomerically enriched carbon center resides on the alkyl fragment from the electrophile (Figure 9a).(2) Enantioselective alkene hydrocarbonation, where the enantiomerically enriched carbon center resides on the alkyl fragment from the alkene (Figure 9b). The first approach is similar to enantioconvergent cross-coupling of racemic alkyl electrophiles, whereas the second approach is analogous to enantioselective hydrofuncitonalization of alkenes. Here we summarize the progress in these two approaches.

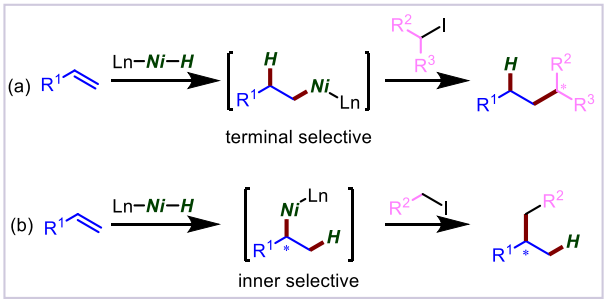

Figure 9. Enantioselective alkylation via nickel-hydride-catalyzed hydrocarbonation of alkenes with alkyl halides. (a) Enantioconvergent cross-coupling of racemic alkyl electrophiles with alkenes; (b) Enantioselective alkene hydrocarbonation. Only reactions with terminal alkenes are shown, but similar reactions with internal alkenes are possible.

4.1. ENANTIOCONVERGENT CROSS-COUPLING OF RACEMIC ELECTROPHILES WITH ALKENES

The group of Fu (G.C) reported the first method for enantioconvergent cross-coupling of racemic alkyl halides with alkenes (Figure 10a).[64] A chiral Ni-bis(oxazoline) ((*R*, *R*)-**L8**) catalyst system was developed to enable enantioselective coupling of α-bromo lactams and esters with alkenes. In addition to alkyl bromides with an adjacent carbonyl, fluorine-containing alkyl electrophiles worked as well. The group of Zhu reported enantioconvergent coupling of α-bromo amides with internal alkenes through an isomerization-coupling sequence to give alkylation at the terminal position of the alkenes (Figure 10b).[65] Reactions were conducted at -25 °C with a nickel-pyrox((*S*)-**L9**) catalyst. The authors found that the methyl group on C6-position of pyrox ligands was essential in achieving the terminal selectivity. Ligands that were less hindered at the C6-position had low reactivity or selectivity. The synthetic utility of this protocol was demonstrated by convergent of isomeric alkene mixtures into enantiomerically enriched α-alkylalkanoic amides.

The group of Fu (G.C.) then applied 1-bromo-alkyl alcohol ester as electrophiles for coupling with alkenes, yielding esters derived from enatioenriched dialkyl carbinols (Figure 11a).[66] These compounds are interesting intermediates and end points in organic, biological, and pharmaceutical chemistry. The reaction conditions were similar to their previous work on the coupling of α-bromo lactams with alkenes.[64] To increase the method's utility, they developed a four-component variant of this method where they generated alkyl halides in situ from aldehydes and acyl bromides and reacted them with alkenes and hydrosilanes (Figure 11b).

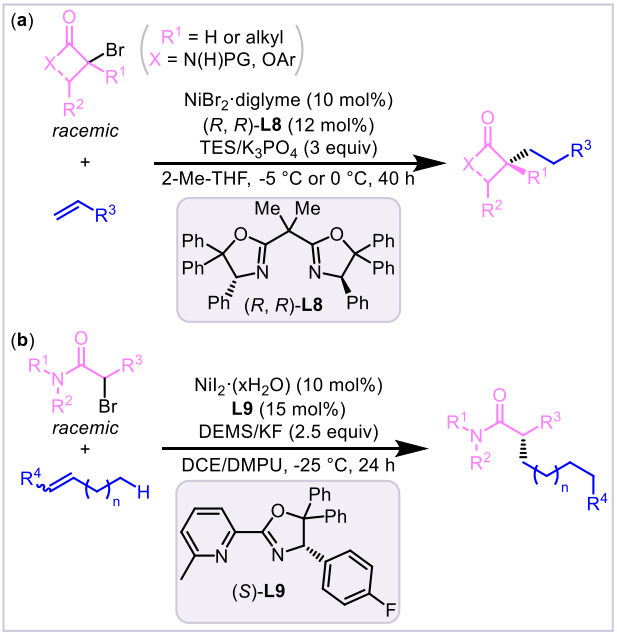

Figure 10. Enantioconvergent cross-coupling of racemic electrophiles with alkenes. (a) With racemic a-bromo carbonyl/fluoroalkyl electrophiles; (b) With racemic a-bromo amide under chain-walking strategy. TES: triethoxysilane; DEMS: diethoxymethylsilane.

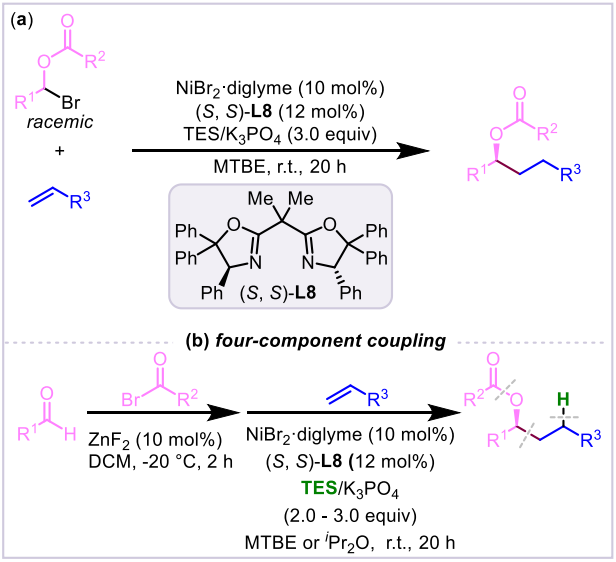

Figure 11. (a) Enantioconvergent cross-coupling of 1-bromo-alkyl alcohol ester with alkenes. (b) A four-component coupling. TES: triethoxysilane.

Considering that chiral phosphorus or sulfur-bearing compounds are important in coordination, materials, and pharmaceutical chemistry, the group of Fu (Y.) developed a method for Ni-catalyzed hydroalkylation of alkenes using racemic α-phosphorus or sulfur alkyl electrophiles (Figure 12).[67] By changing the methyl groups on the connecting carbon ((*S*, *S*)-**L8**) to benzyl groups ((*S*, *S*)-**L10**), both yield and enantioselectivity were largely improved (from 49% yield, 89% ee to 87% yield, 98% ee). The reason for this improvement was not given. Notably, the reactions were not overly sensitive to air and moisture. A wide range of phosphonates, phosphine oxides, sulfonamides and sulfones were obtained in good yields and high enantioselectivity.

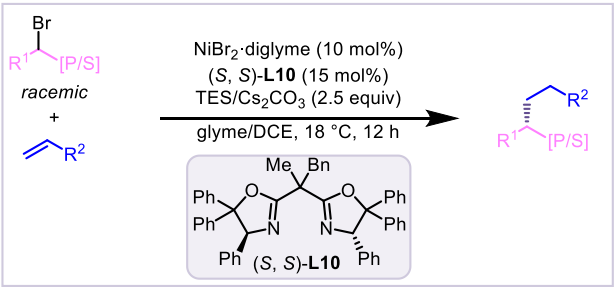

Figure 12. Enantioconvergent cross-coupling of racemic α-phosphorus or sulfur alkyl electrophiles with alkenes. TES: triethoxysilane.

4.2. ENANTIOSELECTIVE HYDROCARBONATION OF ALKENES

4.2.1. Enantioselective C(sp^3)–C(sp^3) cross-coupling

Our group developed a method for Ni-catalyzed enantioselective cross-coupling of alkyl electrophiles with alkenyl boronates (Figure 13).[68] A phenyl-substituted Bi-Ox ligand was the best ligand. Structurally related Py-Ox and Box ligands were inefficient. The yield and enantioselectivity depended on the identity of the metal cations in the alkali-metal fluoride bases. This result suggested that a non-covalent interaction network between the alkali-metal cation, the π-system of the phenyl unit of the ligand, and the oxygen atom of the boronic ester contributed to the enantioselectivity. A variety of hydrosiloxanes could be used as the hydride source, the best of which was diethoxymethylsilane (DEMS). Less electrophilic hydrosilanes (e.g., Et_3SiH, $PhSiH_3$) were unreactive. A pre-formed $NiCl_2$-**L11** complex gave comparable yields and enantioselectivity to the catalyst generated in-situ from $NiCl_2$ and **L11**.

A wide range of primary non-activated alkyl iodides bearing different functional groups could be coupled. The coupling of alkyl bromides required an in-situ halogen exchange with KI as an additive. Alkyl chlorides and triflates were not coupled. Secondary alkyl iodides were coupled in good yields and enantioselectivity as well, giving products with adjacent tertiary C(sp^3) centers. The diastereoselectivity of such coupling, however, was low. Many alkenyl boronate substrates were suitable pro-chiral nucleophiles. On the other hand, the reaction of an analogous alkenyl-9-BBN was not effective. The mild reaction conditions led to high functional group tolerance. As such, the method could be used for synthesizing an array of chiral alkyl Bpins bearing complex or bio-active alkyl fragments derived from drugs and natural products. We showed that the chiral alkyl Bpin products could be easily transformed into other chiral organic compounds without erosion in enantiomeric excess.

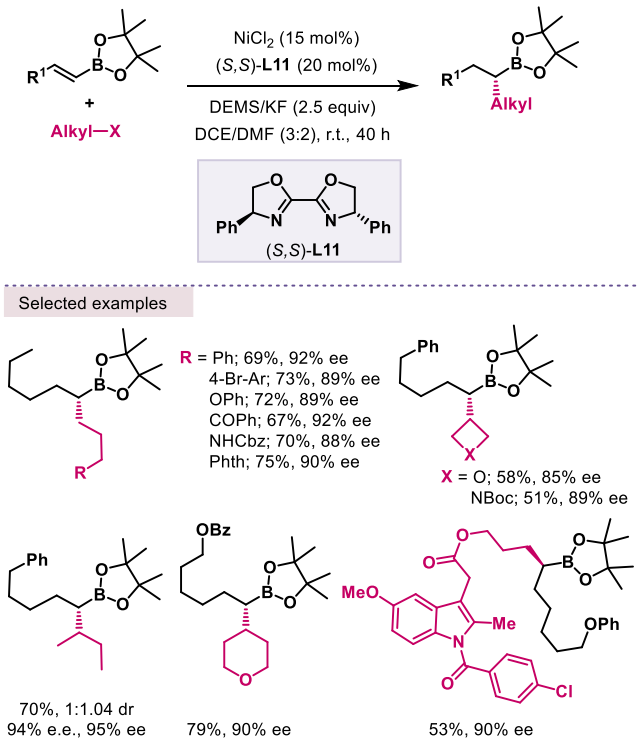

Figure 13. Enantioselective cross-coupling of alkyl halides with alkenyl pinacol boronates. DEMS: diethoxymethylsilane.

Our group then applied the above strategy for the coupling of alkyl halide with (*Z*)-enecarbamates (Figure 14).[69] We recognized that such a method could be used to introduce a diverse set of alkyl groups at the α-position of chiral amines, a difficult task using other methods. We chose Cbz as the *N*-protecting group because this carbamate group could be easily removed. While the optimal Bi-Ox ligand was the same to that

used for analogous coupling of alkenyl boronates, the source of Ni-salt, hydride donor, and solvent had to be changed for the coupling of enecarbamates. Notably HBpin instead of a hydrosilane was the optimal hydride source. Both activated and non-activated alkyl halides could be coupled. Again, broad substrate scope and functional group tolerance were achieved.

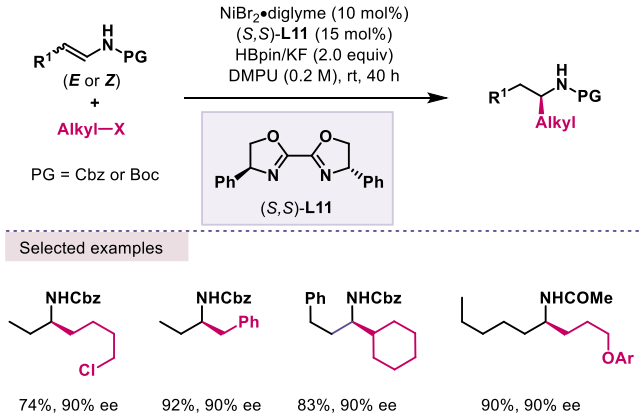

Figure 14. Enantioselective cross-coupling of alkyl halides with enecarbamates.

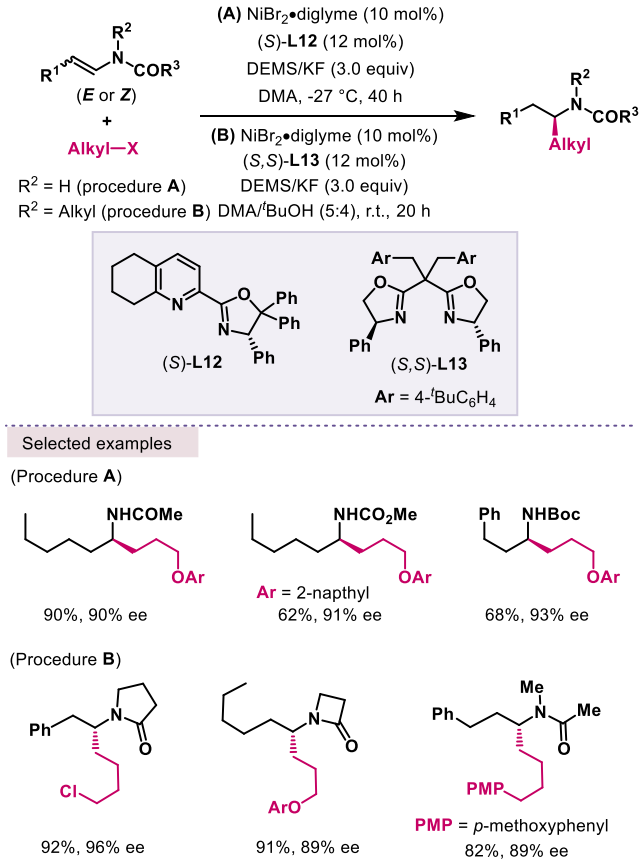

Figure 15. Enantioselective cross-coupling of alkyl halides with enecarbamates and enamides. DEMS: diethoxymethylsilane.

At the around the same time, several groups reported their methods for similar reactions. The groups of Lu and Fu (Y.) developed a method for hydroalkylation of secondary enamides and enecarbamates (Figure 15), where a Py-Ox ligand was the optimal ligand. Both (*E*)- and (*Z*)-substrates afforded comparable coupling yields and enantioselectivity.[70] For the coupling of tertiary enamides, however, they had to modify substantially the conditions. The optimal ligand was a Box ligand. The reactions of (*E*)-substrate had a much higher level of enantioselectivity. In addition to non-activated alkyl halides, the authors also demonstrated hydroalkylation of enamides with racemic α-haloboronates. A low level of diastereoselectivity was observed. Meanwhile, the group of Shu developed Ni-catalzed hydroalkylation of acyl enamines and enol esters, using a chiral Box ligand.[71] The reactions of terminal enamides occurred at room temperature whereas those of internal enamides required a temperature of 45 °C.

The group of Zhu reported Ni-catalyzed enantioselective alkylation at the β-position of α, β-unsaturated amides (Figure 16).[72] This unusual regioselectivity was attributed to the formation of a five-membered metallacycle after syn-hydrometalation of the alkene. Note that a similar mode of action is responsible for the α-alkylation of enamides as described above. The optimal ligands were based on Py-Ox. The reactivity and selectivity depended largely on substituents at the C6 position of pyridine as well as those at the oxazoline ring. Smaller substituents afforded poor results.

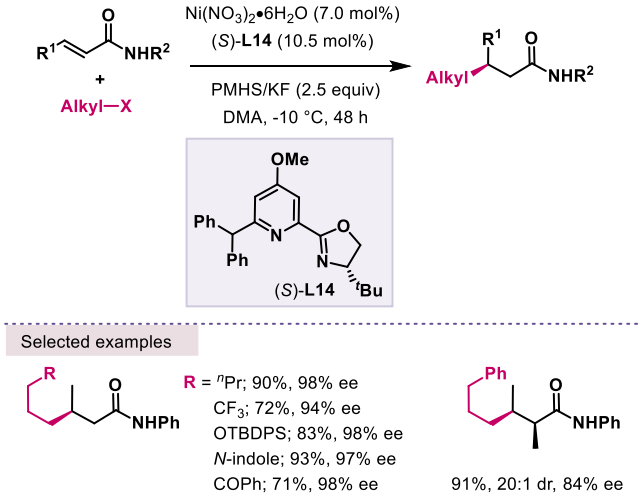

Figure 16. Enantioselective β-selective hydroalkylation of α,β-unsaturated amides. PMHS: polymethylhydrosiloxane.

4.2.2. Enantioselective C(sp^3)–C(sp^2) Cross-Coupling

The Zhu group disclosed Ni-H catalyzed enantioselective hydroarylation of styrene derivatives with aryl halides to access enantioenriched diarylalkanes (Figure 17).[73] Evaluation of various chiral N-based ligands revealed that the highest regio- and enantioselectivity could be only achieved using a chiral bi-imidazoline (Bi-Im) ligand (**L15**). Replacement of KF by CsF as the base only affected the yield but not the enantioselectivity. A change in geometry of the olefin (from *E* to *Z*) did not affect the enantioselectivity. A broad variety of aryl units including heteroaryls in both olefins and aryl halides were well accommodated in these reactions. However, olefins bearing electron-deficient aryl group reacted in a lower level of enantioselectivity, indicating a dependence of enantioselectivity on the stability of the Ni-benzyl intermediate. An aryl bromide was less reactive than an aryl iodide, but the enantioselectivity was similar.

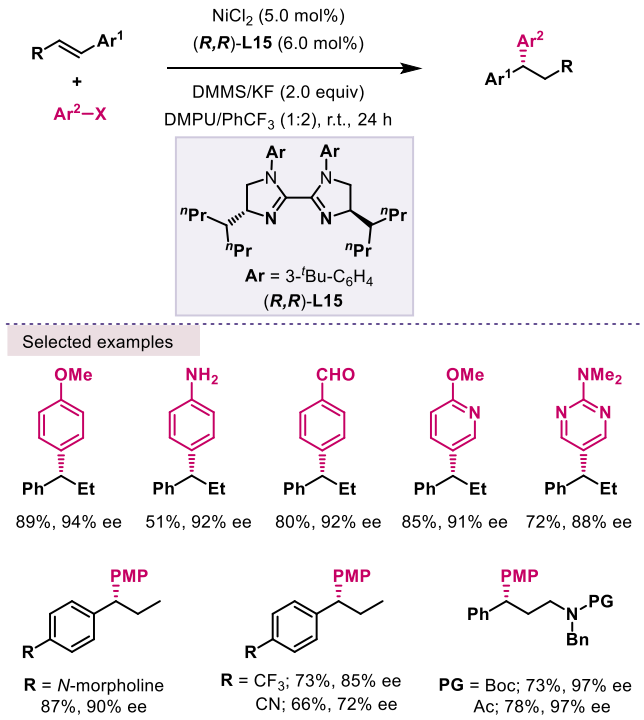

Figure 17. Asymmetric hydroarylation of styrene derivatives. DMMS: dimethoxymethylsilane. PMP: paramethoxyphenyl.

The Nevado group reported a related asymmetric hydroarylation of *N*-vinyl amides for the synthesis of chiral benzylic amine derivatives (Figure 18).[74] The reaction also required a bi-imidazoline (Bi-Im) ligand which was derived from the isoleucine. A super stoichiometric amount of CF_3CH_2OH (TFE) was necessary possibly to promote the NiH generation. Overall, the reactions had moderate to high yields and enantioselectivity. An alkyl vinyl amide was asymmetrically hydroarylated with a similar level of stereoselectivity, but an extended reaction time (40 h) was required. Vinyl amides with a β-substituent were also competent coupling partners but again a longer reaction time was necessary to obtain good yields. Interestingly, (*Z*)-configured vinyl-amide gave higher yield compared to (*E*)-isomer while the enantioselectivity was identical. A vinyl amide with a β-aryl substituent selectively underwent hydroarylation at the carbon -α to the *N*-atom, indicating that the reaction proceeds through a five-membered metallacycle which was more stable than a Ni-benzyl species. An activated alkenyl bromide was a competent coupling partner, although a lower level of enantioselectivity was obtained.

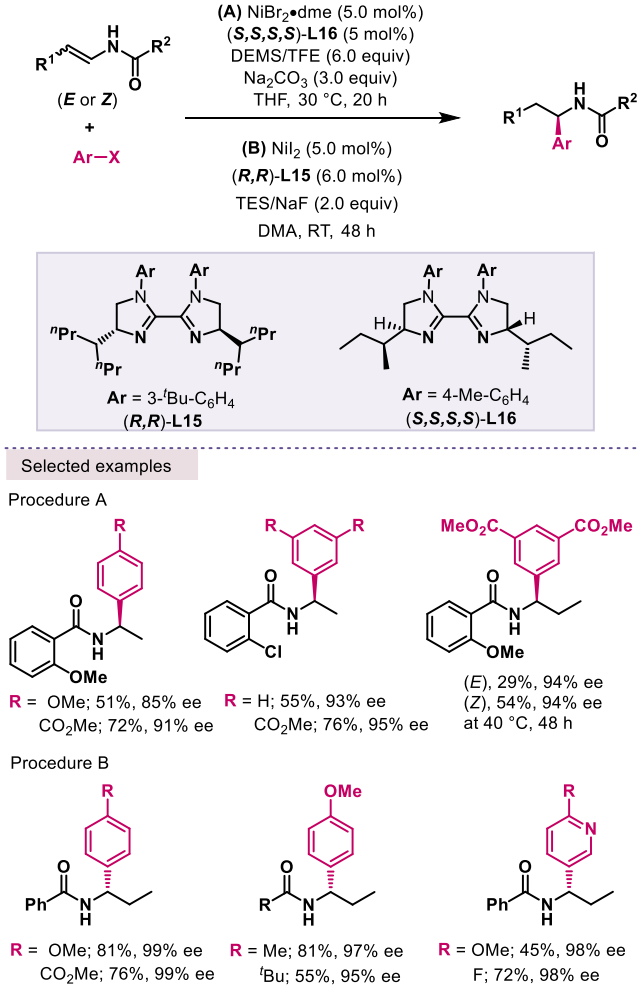

Figure 18. Asymmetric hydroarylation of vinyl enamide derivatives. DEMS: diethoxymethylsilane; TES: triethoxysilane.

At nearly the same time, the group of Zhu reported another protocol for hydroarylation of *N*-vinyl amides (Figure 18).[75] Compared to the method of Nevado, they used a more sterically bulky chiral Bi-Im ligand. In this method, both (*E*)- and (*Z*)-vinyl amides gave similar reaction outcomes. The Zhu group also reported a method for asymmetric cross-coupling between alkenyl bromides and styrene derivatives.[76] A chiral bisoxazoline (Box) ligand was the best ligand. In these reactions, the Ni-H selectively inserted into styrenes instead of alkenyl bromides.

4.2.3. Enantioselective C(sp^3)–C(sp) Cross-Coupling

Taking advantage of NiH catalysis, the Zhu group reported a method for enantioselective coupling of styrenes with alkynyl bromides (Figure 19).[77] The alkynyl group needed to be substituted by a silyl group (preferably TIPS; TIPS = triisopropylsilyl) presumably to impede the insertion of NiH into the alkyne moiety. A chiral Py-Ox ligand (**L17**) turned out as the best ligand. A super stoichiometric amount of NaI was added to promote the regeneration of NiH. Chain-walking and subsequent asymmetric alkynylation at the benzylic position of 3-aryl-1-propene was also obtained (78% yield, 90% ee, 90:10 rr).

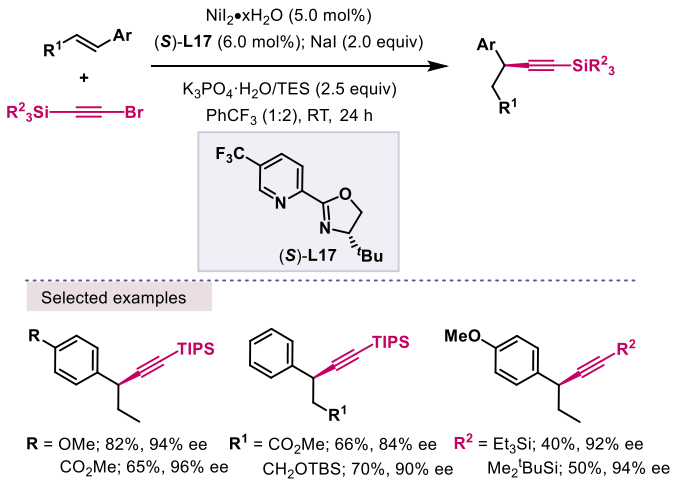

Figure 19. Asymmetric hydroalkynylation of styrene derivatives. TES: triethoxysilane

5. MECHANISMS

The mechanisms of the above-mentioned Ni-catalyzed hydrocarbonation reactions are difficult to establish because the structures and oxidation states of the catalysts throughout the catalytic cycle are rarely known with any precision, and various catalytic cycles can lead to the same reaction outcome. Two general questions can be asked for each catalytic system: (1) the catalytic cycle; (2) the origin of the stereoselectivity.

5.1. CATALYTIC CYCLE

The catalytic cycles likely depend on the nature of the electrophiles. For the coupling with C(sp^2) and C(sp) electrophiles, a Ni^0/Ni^{II} couple might be operating for oxidative addition (Figure 20 (i)[8, 10, 78-79, 15, 80-82] where a Ni^0 species (**A**) activates an electrophile in a 2-e oxidative addition step to form an organo Ni^{II} halide species (**B**). Reaction of the latter with a hydride source in the presence of a base generates a Ni^{II}-H (**C**), which upon insertion of an alkene gives a bis(organo)Ni^{II} species (**D**). Reductive elimination of the coupling product from (**D**) then regenerates the Ni^0 catalyst. Alternatively, oxidation addition occurs on a $Ni^{I/III}$ couple. A Ni^{I}-H (**F**) is generated from the reaction between Ni^{I}-X (**E**) and a hydride donor. This species inserts into an olefin to give a Ni^{I}-alkyl intermediate (**G**) (Figure 20 (ii)). The latter undergoes oxidative addition with an aryl halide to from a Ni^{III}-(aryl)(alkyl) species (**H**), which upon reductive elimination releases the product and regenerates the Ni^{I}-X species (**E**).

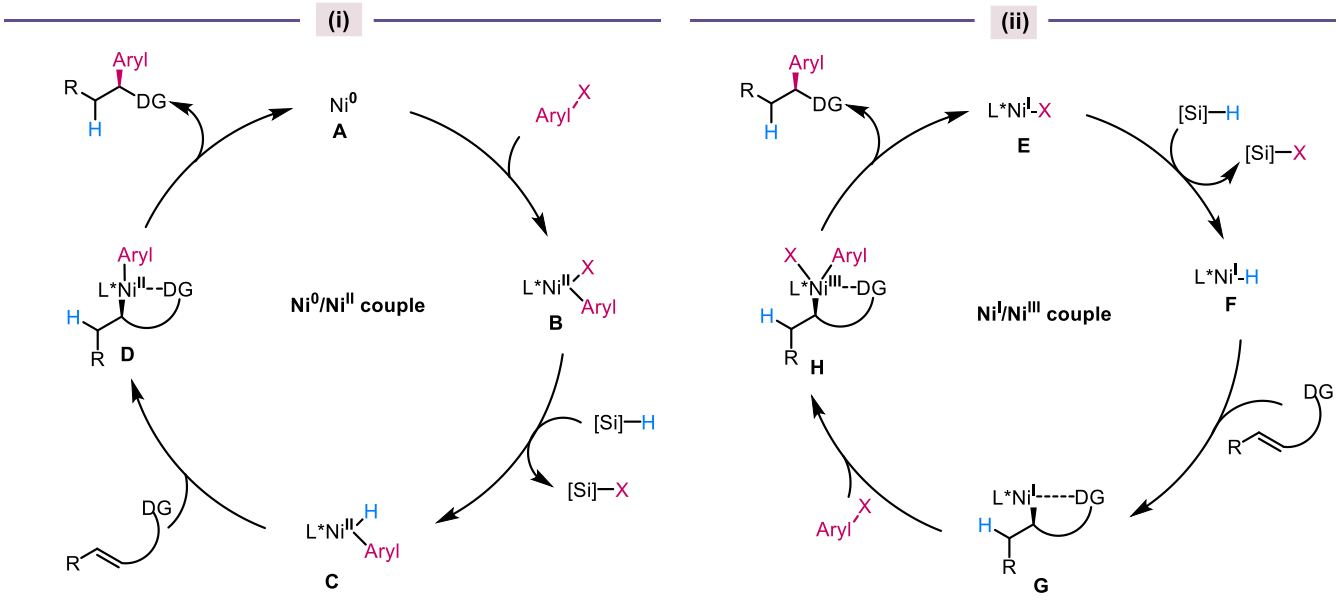

Figure 20: Proposed catalytic cycles for C(sp^3)-C(sp^2) cross-coupling in NiH catalysis

For the coupling with C(sp^3) electrophiles, a Ni^{I} intermediate is often proposed.[83-85] The mechanisms can be divided into two categories involving either a Ni^{I}-H or a Ni^{II}-H intermediate for insertion of alkene (Figure 21a and 21b). In the Ni^{I}-H category, one pathway involves alkene insertion into the hydride species to form a Ni^{I}-alkyl intermediate (**C**, Figure 21a). The latter activates an alkyl electrophile to give a Ni^{II}(alkyl)(X) species (**D**) and an alkyl radical. This radical might recombine with the Ni^{II}(alkyl)(X) species to give a Ni^{III}-bis(alkyl) species (**E**). Reductive elimination from the latter furnishes the coupling product and gives a Ni^{I}-X complex (**A**), which upon reaction with a hydride source regenerates the Ni^{I}-H (**B**). In an alternative pathway, the alkyl radical recombines with the Ni^{I}-alkyl species (**C**) to give a Ni^{II}-bis(alkyl) species (**F**, Figure 21b). Reductive elimination of the coupling product from **F** gives a Ni^0 species **G**, which reacts with the Ni^{II}(alkyl)(X) species (**D**) to give a Ni^{I}-alkyl (**C**) and a Ni^{I}-X (**A**), thereby re-entering the catalytic cycle.

In a third pathway (Figure 21c), the Ni^{I}-H species (**B**) first reacts with an alkyl halide to give an alkyl radical and a Ni^{II}-H (**H**). Alkene insertion into the latter gives a Ni^{II}-alkyl species (**D**), which traps the alkyl radical to give a Ni^{III}-bis(alkyl) species (**E**). Reductive elimination from the latter gives the coupling product and the Ni^{I}-X complex (**A**), which reacts with a hydride source to regenerate the Ni^{I}-H (**B**). In a fourth pathway (Figure 21d), a Ni^{I}-X species (**A**) is proposed to

activate an alkyl halide to give a Ni^{II}-X_2 complex (**I**) and an alkyl radical. Reaction of **I** with a hydride source then gives the Ni^{II}-H (**H**), which upon alkene insertion forms a Ni^{II}-alkyl intermediate (**D**). The latter traps the alkyl radical to give a Ni^{III}-bis(alkyl) species (**E**), which gives the coupling product upon reductive elimination. The Ni^{I}-X (**A**) complex is regenerated in this process. Further pathways involving the activation of an alkyl halide by either the Ni^{II}-H (**H**) or Ni^{II}-alkyl species (**D**) are unlikely given that the ligands used in these reactions are relatively soft. Our group showed that such an activation typically requires a hard ligand for Ni.[40, 84]

Previous studies provided some information on the mechanisms of the various Ni-catalyzed hydrocarbonation of alkenes described above. For example, the group of Zhu and Nevado proposed catalytic cycles based on a Ni^{I}/Ni^{III} couple for the hydroarylation of olefins as depicted in figure 20(ii).[74-75] Ligands used in these reactions are of Bi-Im-types. However, it is unclear whether oxidative addition of an aryl halide to L*Ni^{I} is favorable as compared to L*Ni^{0}, which is well-established for this step.[86-88] More studies are needed to probe the oxidative addition step of hydroarylation. For coupling with alkyl halides, evidences for alkyl intermediates were widely reported from experiments using radical probes. For example, hydroalkylation products derived from the exo-cyclization of 5-iodopent-1-ene as well as ring opening of an alkyl iodide containing a cyclopropyl ring were commonly observed.[68-70] Hydroalkylation reactions were often inhibited in the presence of the radical scavenger (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO). But the latter results might be due to H-atom abstraction from the *in-situ* generated Ni-H species by TEMPO, so they should be viewed with care. Direct addition of an alkyl radical to the olefin substrates is an unlikely pathway as suggested by the observed ipso selectivity in most cases. Various catalytic cycles have been proposed based on preliminary mechanistic studies. For example, the Fu (G.C.) group suggested that the catalytic cycle in Figure 21d, where a Ni^{I}-X species activates alkyl halide, is more likely to operate in enantioconvergent cross-coupling of racemic secondary and tertiary (activated) alkyl electrophiles[77]. They isolated and characterized L*Ni^{II}-complexes which were possible catalytic resting states. No obvious signals for Ni^{I} or Ni^{III} species were detected by EPR during the reaction. Furthermore, UV-vis absorption spectra revealed that around 80% of nickel in the reaction mixture was present as L*$Ni^{II}Br_2$. For the reaction with non-activated primary and secondary alkyl halides with prochiral olefins, a computational study by the groups of Lu and Fu (Y.) suggested a similar catalytic cycle where a Ni^{I}-X species activates alkyl halide (Figure 21d). However, given the high reduction potentials of non-activated alkyl halides (relative to activated alkyl halides), their activation might require a Ni^{I}-alkyl species. Therefore, the catalytic cycle depicted in Figure 21a or 21b is also a possible pathway.

Further experimental studies are needed to establish the most plausible catalytic cycle for a given reaction system. Among the four possible mechanisms in Figure 21, one main difference is the species to activate alkyl halide. Isolation of the relevant Ni^{I}-X, Ni^{I}-H, and Ni^{I}-alkyl and study of their reactivity towards electrophiles will provide key information to the nature of this active species.

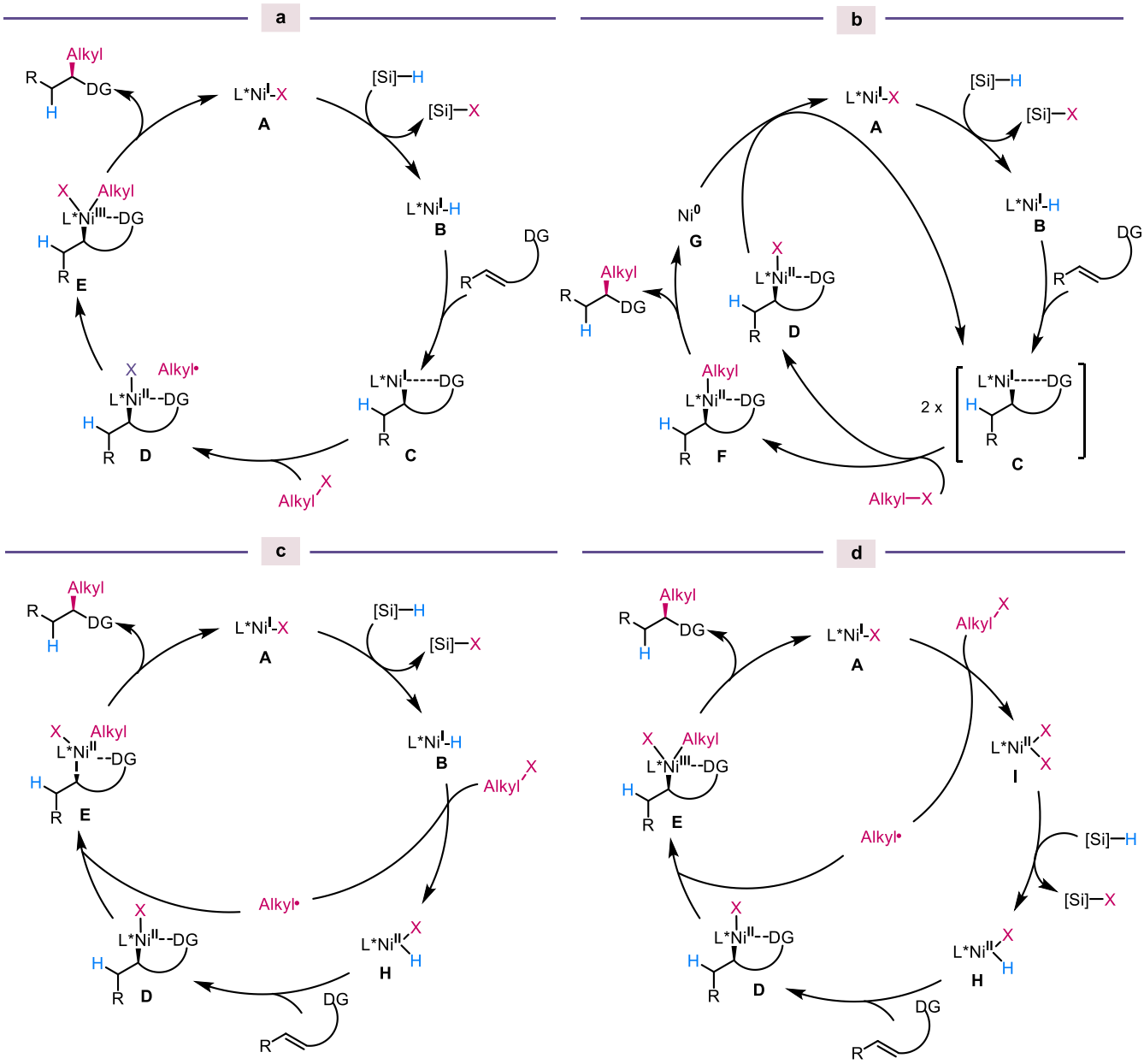

Figure 21: Proposed catalytic cycles for C(sp^3)-C(sp^3) cross-coupling in NiH catalysis

5.2. ENANTIO-DETERMINING STEP

For Ni-catalyzed stereoconvergent coupling of racemic alkyl halides with alkenes, the enantioselective step should be similar to that in analogous coupling of alkyl halides with organometallic nucleophiles. Computational studies by the group of Molander and Kozlowski[86] suggests the stereochemistry is set by reversible homolysis of Ni-alkyl intermediates followed by enantioselective reductive elimination[89]. Alternatively, enantioselective oxidative addition of racemic alkyl halides through a prochiral alkyl radical intermediate was also proposed[90].

For Ni-catalyzed enantioselective hydrocarbonation of alkenes where the alkenes serve as the pro-chiral carbon fragments, the stereoselectivity might be set either by enantioselective alkene insertion into Ni-H or by enantioselective reductive elimination following reversible homolysis of Ni-alkyl intermediates. A common probe for the two possibilities is the diastereomeric ratio of the product in a reaction using a deuterium source (Figure 22). The degree of deuterium incorporation reflects the diastereomeric ratio between two diastereotopic protons. If a prochiral olefin undergoes syn-addition by Ni-D followed by an enantiospecific cross-coupling/reductive elimination with a C-electrophile, then a high diastereomeric ratio between H_A/H_B (depending on the amplitude of enantioinduction) should be observed (Figure 22a). If reversible Ni-C bond homolysis occurs prior to enantioselective reductive elimination, then a low dr value is expected (Figure 22b). A similar strategy was used in Cu-H catalyzed asymmetric hydroamination of olefin, where syn-selective Cu-H addition followed by a stereospecific substitution reaction was found[91]. Nevertheless, complications

arise if there are other mechanisms to scramble hydrogen with deuterium.

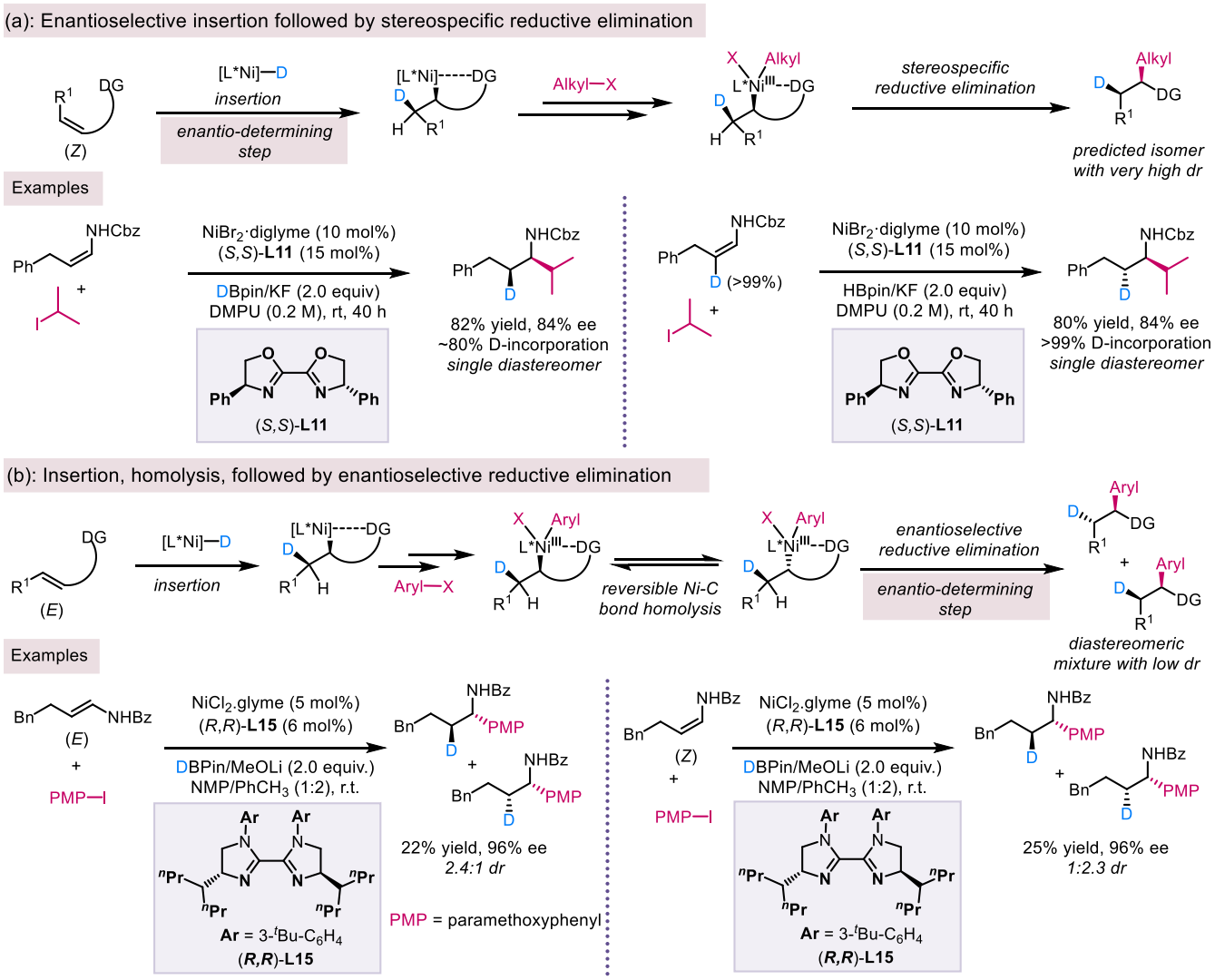

Figure 22. Deuterium labelling experiments to probe the enantioinduction step.

This probe had been applied in several studies of Ni-H catalyzed enantioselective hydrocarbonation. For example, our group used DBpin as the source of deuteride for hydroalkylation of enecarbamates, as well as a β-deuterated enecarbamate as a substrate in combination with HBpin.[69] A high diastereoselectivity was obtained in each case. Moreover, both *E*- and *Z*-configured enecarbamates gave opposite isomers in high diastereomeric ratios. The groups of Lu and Fu (Y.) used Ph_2SiD_2 as a deuteride source for hydroalkylation of enamide and enecarbamate. They found the reaction to be completely diastereoselective as well.[70] These results are consistent with Ni-H insertion into alkene being the enantio-determining step. On the other hand, the group of Zhu found a low level of diastereoselectivity (~2.4:1) in hydroarylation of both *Z*- and *E*- configured enamides. The authors suggested rapid homolysis of Ni-C bond followed by enantioselective reductive elimination is the enantio-determining step.[73, 75] The contrasting diastereoselectivity reported in these examples remain to be reconciled.

6. SUMMARY AND OUTLOOK

In the last few years, Ni-H-catalyzed hydrocarbonation of alkenes has been rapidly developed into a general approach for cross-coupling-type alkylation reactions. The reaction scope has been expanded to include a wide range of alkenes and alkyl electrophiles, including non-activated substrates. Highly enantioselective methods have emerged. By using alkenes as pro-nucleophiles instead of stoichiometric organometallic reagents, a high level of functional group tolerance is achieved. There are many reports describing the application of these reactions for the late-stage functionalization of substrates derived from natural products and bio-active complex molecules.

Despite these advances, the scope of enantioselective hydrocarbonation remains to be improved. Typically, only organic iodides and bromide, but not chlorides, serve as electrophiles. It would be desirable to develop methods using more abundant and available reagents such as chlorides or carboxylic acids or C-H bonds. There are only few examples of enantioselective hydroalkylation using cyclic tertiary alkyl electrophiles,[64] so progress in this area will be welcome. For alkenes, an aryl, boryl, or carbonyl directing group is required for regio- and stereo-selectivity. A major challenge is to use other types of alkenes where the selectivity is controlled by a factor other than a 5-or 6-membered metallacycle originated from the binding of a directing group to the metal. In this context, the group of Lu and Fu (Y) developed a Co-catalyzed hydroalkylation of fluoroalkenes.[92] They proposed that the regio- and stereo-selectivity is catalyst controlled and is due to stabilizing non-covalent C–H···F and destabilizing C–H···H–C repulsion. A directing group is not necessary in this case. Another challenge is to control the chirality of two vicinal tertiary carbon centers in hydrocabonation. In all previous examples, the diastereoselectivity of such a reaction is low.

The mechanistic understanding of the hydrocabonation reactions remains primitive. Various catalytic cycles have been proposed, but comprehensive mechanistic studies are still missing. The key intermediates have not been isolated and their reactivity has not been probed. Although in some cases the enantio-determining steps have been determined, the origin of stereoselectivity is largely speculative. The mechanistic studies of these reactions are inherently difficult due to a large number of accessible oxidation states of Ni, multiple and sometimes co-existing pathways, and the challenge to detect or isolate reactive intermediates (which might be paramagnetic). Nevertheless, these studies are necessary for the further development of Ni-H-catalyzed alkene hydrocarbonation.

Notwithstanding the challenges, the rapid development of Ni-H-catalyzed hydrocarbonation of alkenes in the last few years make us confident that further advances can be achieved in the near future. Thus, we expect these reactions to become widely applicable for enantioselective alkylation, contributing to drug discovery.

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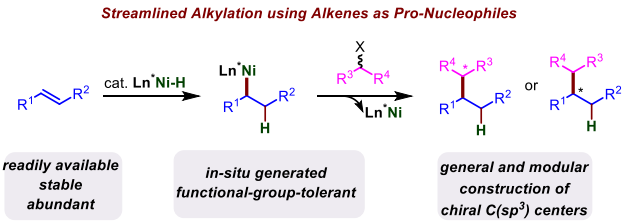

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