Diphosphine Ligand-Enabled Ni-Catalyzed Chelate-Assisted Inner-Selective Migratory Hydroarylation of Alkenes

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The precise control of the regioselectivity in the transition metal-catalyzed migratory hydrofunctionalization of alkenes remains a big challenge. With a transient ketimine directing group, the nickel-catalyzed migratory *β*-selective hydroarylation and hydroalkenylation of alkenyl ketones has been realized with aryl boronic acids using alkyl halide as the mild hydride source for the first time. The key to this success is the use of a diphosphine ligand, which is capable of the generation of a Ni(II)-H species in the presence of alkyl bromide, and enabling the efficient migratory insertion of alkene into Ni(II)-H species and the sequent rapid chain walking process. The present approach diminishes organosilanes reductant, tolerates a wide array of complex functionalities with excellent regioselective control. Moreover, this catalytic system could also be applied to the migratory hydroarylation of alkenyl azahetereoarenes, thus providing a general approach for the preparation of 1,2-aryl heteroaryl motifs with wide potential applications in pharmaceutical discovery.

Introduction

Transition metal-catalyzed migratory hydrofunctionalization of alkenes has emerged as one of the most efficient approaches for the installation of C(sp^3)-tethered functionalities at a distal position on the hydrocarbon chain from the nonpolar carbon-carbon double bond, thus offering a rapid access to highly value-added complex molecules broadly used in pharmaceuticals, agricultural chemicals, and materials

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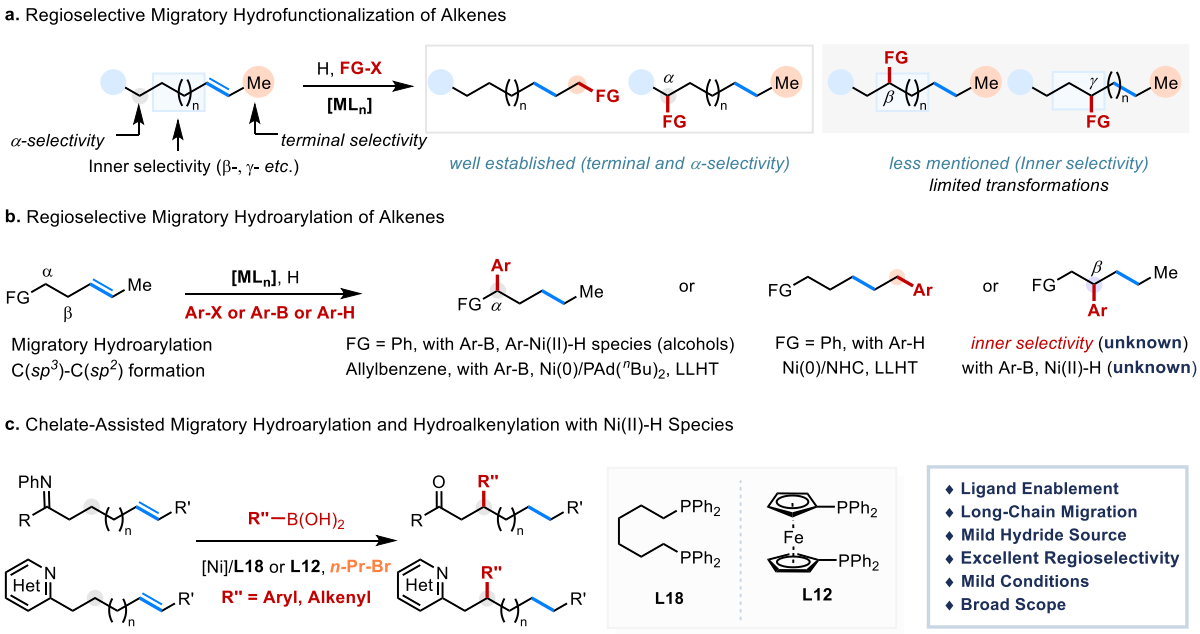
science.[1] In this context, one of the longstanding challenges is the precise control of the regioselectivity during the metal migration and sequential functionalization due to the complications from alkylmetal chain-walking (Scheme 1a). Normally, the terminal linear selective hydrofunctionalization of alkenes is favored.[2] The internal regioselectivity could also be controlled with thermodynamic factors,[3-5] including locating functionalities including carbonyl,[3] phenyl,[4] boronic acid ester[5] etc. and a directing group[6], by the formation of the most stable alkylmetal species. Among those well-established regioselective processes, the inner-selective (*β*- or *γ*-selectivitive) migratory hydrofunctionalizations beyond the α-position to functional group and terminal position are relatively less mentioned in the literature and remains a big challenge.[3-6] Moreover, the inner-selective transformations are currently largely limited to hydroamination[6b, 6l, 6m], hydroamidation[6c, 6e], hydroalkylation[6a, 6f-k] and hydroboronation[4l, 6d]. Hence, there is still a lot space for the development of inner-selective (*β*- or *γ*-selective etc.) migratory hydrofucntionalization reactions with the exceptional regioselectivity control.



Scheme 1. Synopsis of Ni-catalyzed migratory hydroarylation of unactivated alkenes.

The transition metal-catalyzed hydroarylation and hydroalkenylation reaction has the capability of direct construction of C(sp^2)-C(sp^3) bond, which is fundamentally essential in synthetic chemistry.[7] Recently, significant advances have been made in the development of novel regioselective hydroarylation of unactivated alkenes[4c, 8-11] mainly thanks to the rapid developments on metal-hydride chemistry[8] and the

directing group approach[9]. Among those elegant examples, the successes on the migratory hydroarylation and alkenylation reactions of unactivated alkenes are rather limited. Using aryl halides as the arylating regent, Zhu and coworkers[4c] have reported the α-selective hydroarylation of ω-arylated alkenes via the Ni(I)–H initiated chain-walking process using aryl group as the locating group and organosilanes as the reductant (Scheme 1b). Zhu[11a] and our group[12b] has also mentioned the Ar–Ni(II)–H species could be used for the migratory hydroarylation of ω-arylated alkenes employing arylborons as the arylating reagent. The α-selective hydroarylation of electron-rich allylbenzene derivatives with arylboronic acids has also been realized by Iwamoto and Ogoshi using a Ni(0)/mono-phosphine catalytic system via a ligand-ligand hydrogen transfer (LLHT) mechanism[11b]. With arenes as the arylating reagent, Nakao and Hartwig realized an elegant Ni(0)/NHC-catalyzed linear selective hydroarylation of internal unactivated olefins via a LLHT mechanism[11c] (Scheme 1b). Despite of the notable advances, the migratory hydroarylation and hydroalkenylation with inner regioselectivity beyond the α-selectivity and terminal selectivity (linear selectivity) is not disclosed to date. As our continuous interests on the transition metal-catalyzed functionalizations of unactivated alkenes and internal alkenes,[12] we envisioned that the inner-selective migratory hydroarylation reaction was feasible with the assistance of mono-dentate directing group via a stable metallacycle in the presence of a suitable catalytic system. Herein, we report a nickel-catalyzed migratory *β*-selective hydroarylation and hydroalkenylation of alkenyl ketones with aryl boronic acids using alkyl halide as the mild hydride source and ketimine as the transient directing group[13]. This catalytic system could also be applied to the inner-regioselective migratory hydroarylation of alkenyl azahetereoarenes. Notably, the present approach diminishes organosilanes reductant in comparison to widely studied migratory hydrofunctionalization reactions[1-5], thus tolerates a wide array of complex functionalities with excellent regioselective control. Preliminary mechanistic studies indicate the Ni(II)–H species might be the active species in the catalytic cycle, which could enable the efficient migratory insertion of alkene into Ni(II)–H species and the sequent rapid chain walking process.

Discussion

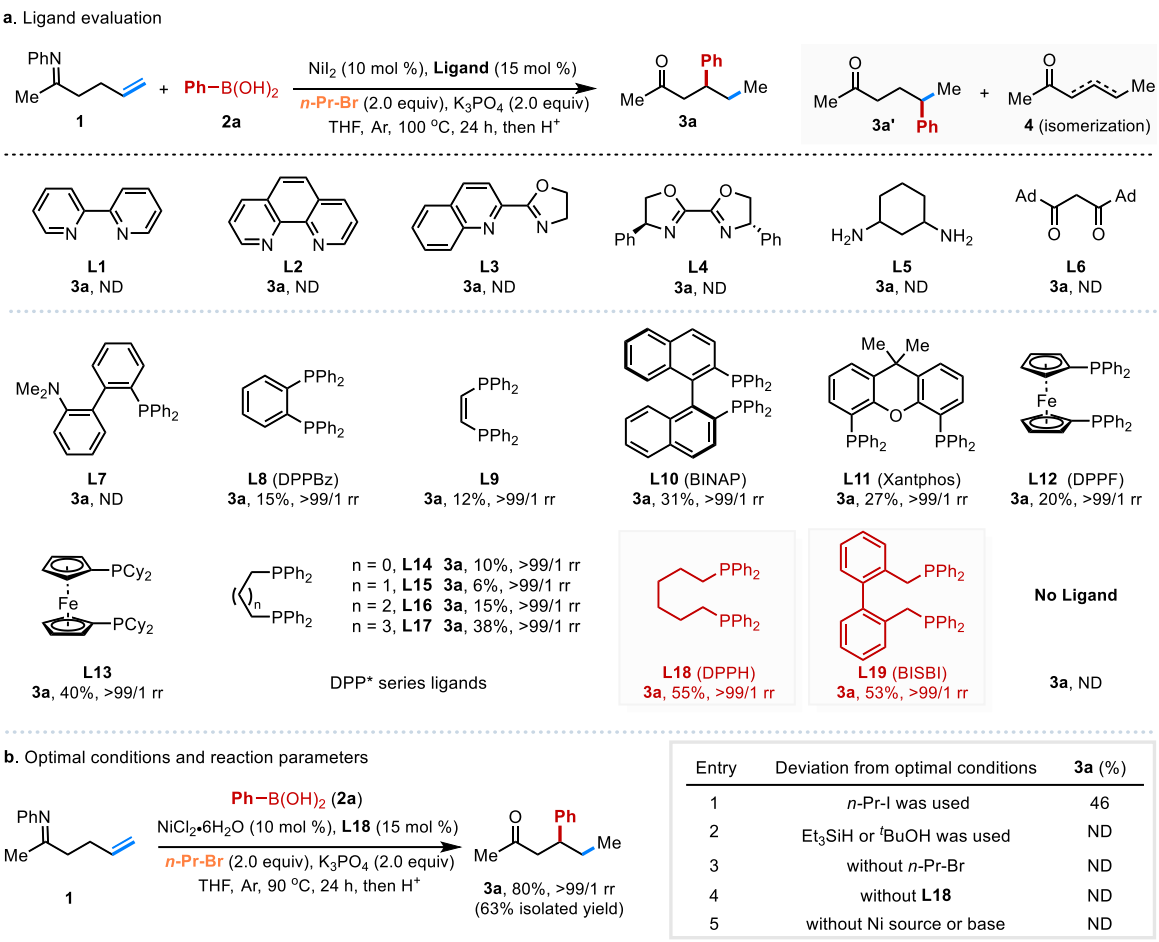
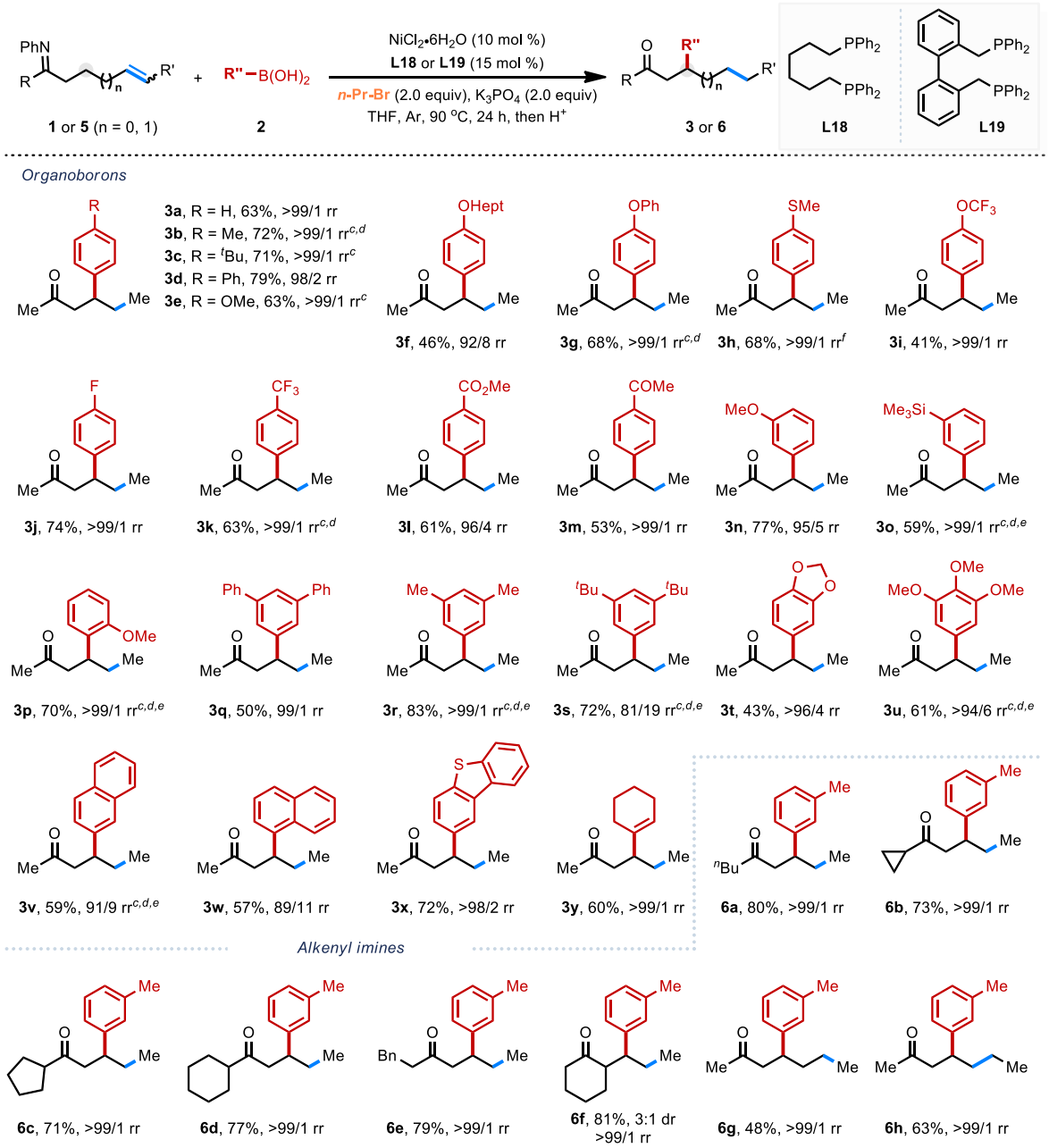


Figure 1. Ligand evaluation, reaction parameters and optimal conditions. a, Ligand evaluation. **b**, Optimal conditions and reaction pa-rameters. ND, not detected.

To explore the feasibility for the Ni-catalyzed migratory *β*-selective hydroarylation reaction of unactivated alkenes, we commenced this study by checking the feasibility of alkenyl ketimine **1** with Ar–Ni(II)–H species, which is superior for the hydroarylation of internal alkenes and migratory hydroarylation of ω-arylated alkenes.[11a,12b] Although the hydroarylation reaction happened in 14% yield in the presence of bulky Adacac ligand **L6**,[12a] the regioselectivity is extremely low (57/7/36 rr). The similar inferior results were obtained in 1,3-diamine ligand (**L5**)-enabled migratory hydroarylation conditions (For details, see supporting information)[11a]. Those initial results indicate the challenge in the precise control of regioselectivity in the migratory hydroarylation reaction. Inspired by the formation of Ni(II)–H species with alkyl halides[14, 6f], we further evaluated the migratory hydroarylation using *n*-Pr–Br as the mild hydride source. Preliminary investigation by using NiI_2 as nickel source, *n*-Pr–Br as hydride source, and K_3PO_4 as base indicated that the desired transformation could not take place in the presence of various common

nitrogen-based bidentate ligands **L1-L5** and bulky acac-type ligand **L6**. Gratifyingly, the use of diphosphine ligand BINAP (**L10**) gave the desired *β*-selective hydroarylated product 3a in 31% yield with excellent regioselectivity (> 99/1 rr), although the monophosphine ligands are inactive. Encouraged by this observation, a series of diphosphine ligands were systematically investigated (Figure 1a). Essentially, all diphosphine ligands are capable of precise controlling the regioselectivities (**L8-L19**). Although the DPPBz (**L8**) and *cis*-1,2-bis(diphenylphosphino)ethene (L9) gave less than 15% GC yields, the Xantphos (**L11**) showed similar reactivity to BINAP. Interesting, the more electron-rich Cy-DPPF (**L13**) gave much higher yield in comparison to DPPF (**L12**). We thus turned to investigate the electron rich DPP* series of ligand with an alkyl linkage. To our great delight, DPPH (**L18**) provides the best outcomes (55% yield, >99/1rr), and other DPP* series ligands with a shorter or longer linkage all resulted in inferior results. Interestingly, BISBI (**L19**) bearing a similar length of linkage to DPPH also gave high yield with excellent regioselectivity (53% yield, >99/1 rr). Upon the systematical optimization of reaction parameters, the yield was improved to 80% GC yield with >99/1 regioselectivity by conducting this reaction at 90 ^{0}C in THF using $NiCl_2 \cdot 6H_2O$ as the optimal nickel source (left, Figure 1b). The screen of versatile types of hydride sources such as alkyl halides, organosilanes and ^{t}BuOH indicates the superior role of *n*-Pr–Br (right, Figure 1b). Moreover, the use of *n*-Pr–I instead of *n*-Pr–Br led to a significant decrease of yield, implying the importance of bromide in the catalytic cycle. Control experiment unveiled that all reaction parameters are essential for this reaction, and this reaction cannot happen in the absence of diphosphine ligand, *n*-Pr–Br, nickel catalyst, or base. This reaction represents the bare examples of metal-catalyzed migratory hydrofunctionalization using alkyl halides as the mild hydride source.

With the optimal conditions in hand, the substrate scope with respect to commercially available aryl boronic acids **2** has been evaluated first using alkenyl ketimine **1** as the model substrate. As shown in Scheme 2, our protocol presents good functional group tolerance, as a variety of aryl boronic acids bearing simple alkyl (**2b–c**), phenyl (**2d**), alkoxyl (**2e–g**), thiomethyl (**2h**), trifluoromethyoxy (**2i**), fluoro (**2j**), trifluoromethyl (**2k**), ester (**2l**) and ketone (**2m**) at the *para*- position of the phenyl ring are compatible, delivering the corresponding products in moderate to good yields (41–79%), and excellent regioselectivity. Noteworthy, our catalytic system can tolerate simple thiomethyl-substituted phenyl boronic acid (**2h**) by



Scheme 2. Ni-Catalyzed migratory hydroarylation of alkenyl ketimines.[a,b] [a]Reaction conditions: **1** or **5** (0.2 mmol), **2** (0.3 mmol, 1.5 equiv), $NiCl_2 \cdot 6H_2O$ (4.8 mg, 10 mol %), **L18** (13.6 mg, 15 mol %), K_3PO_4 (84.9 mg, 2 equiv), *n*-PrBr (39 μL, 0.4 mmol), THF (1.0 mL), 90 °C, 24 hours. [b]Isolated yield, the regioselective ratio (rr value) was determined by GC-MS analysis. [c]Aryl boronic acid (2.0 equiv) was used. [d]K_3PO_4 (3.0 equiv) was used. [e]At 100 °C. [f]With **L19** as ligand.

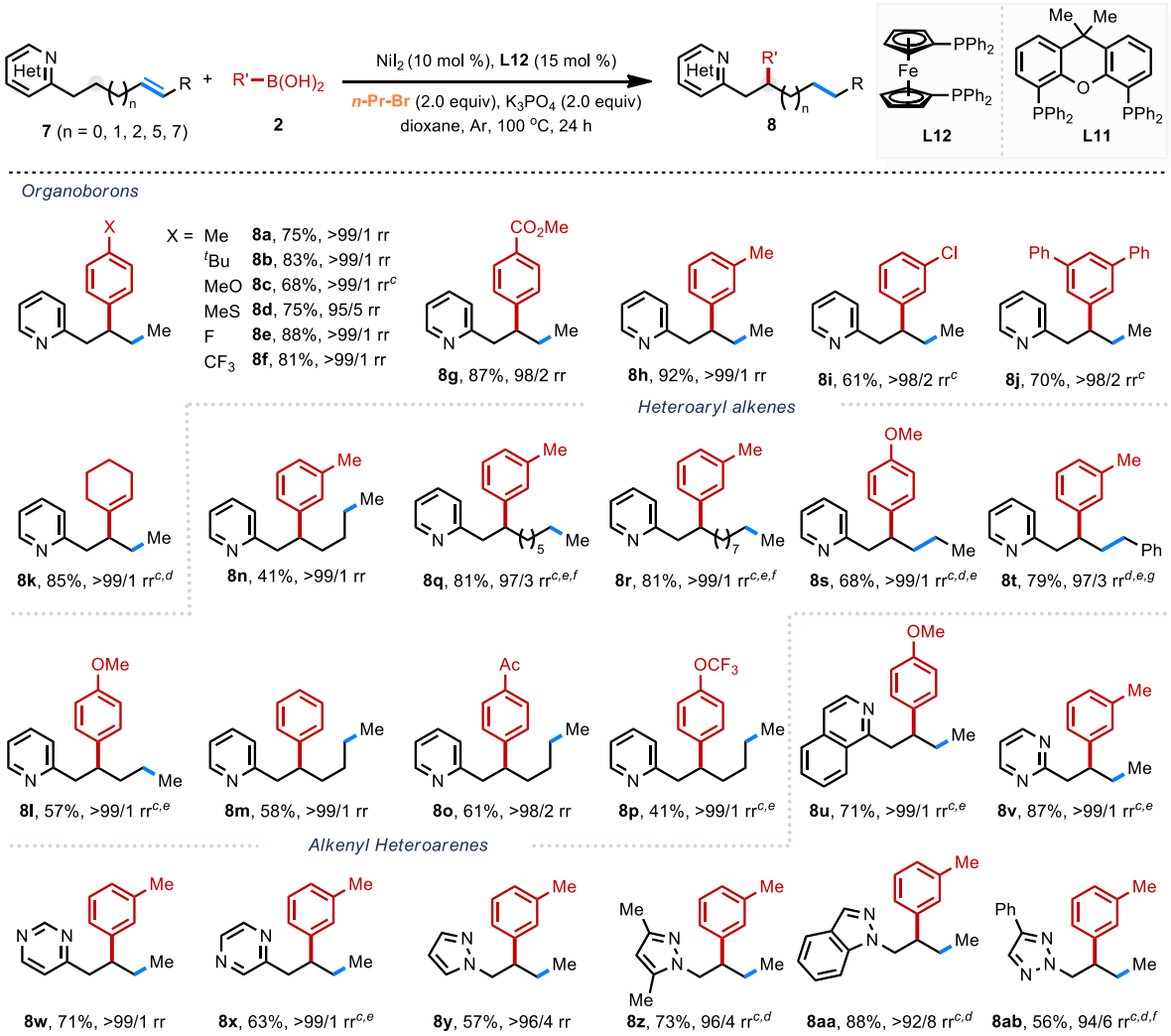
employing **L19** as the optimal ligand, which is normally troublesome in transition metal catalyzed reactions. Similarly, the introduction of alkoxyl or Me_3Si group into the *meta*-position can also deliver the desired products (**3n–o**) with 59–77% yields and excellent regioselectivities. The methoxy group at the *ortho*-, *meta*- or *para*- position didn't significantly affect the efficiency and regioselectivity (**3p** vs **3e** or **3n**). More essentially, the multi-substituted arylboronic acids were all suitable coupling partners for present

regioselective migratory hydroarylation reaction (**3q-u**). Our protocol was also compatible with naphthyl boronic acids (**3v**, **3w**), albeit with moderate yields and a slightly lower regioselectivities. In addition, heterocyclic dibenzo[*b*,*d*]thiophen-2-yl group can be applied for this transformation as well, and **3x** was isolated in 72% yield with >98/2 rr. To our delight, besides aryl boronic acids, the reaction can be compatible with alkenyl boronic acids such as cyclohex-1-en-1-ylboronic acid **2y**, and the anticipated **3y** could be smoothly isolated with 60% yield and >99/1 rr.

Next, the scope of alkenyl ketimines has been further examined. Various alkenyl ketimines substrates with broad range of alkyl moieties such as *n*-butyl (**5a**), cyclopropyl (**5b**), cyclopentyl (**5c**), cyclohexyl (**5d**), and homobenzyl (**5e**) all successfully participated in the regioselective migratory *β*-hydroarylation reaction with moderate to good yields and excellent regioselectivities. As for 2-allyl cyclohexanone (**5f**) containing one alkyl substituent at α-position, the desired *β*-hydroarylation also took place smoothly, albeit with low diastereoselectivity (3:1 dr). Besides, the current protocol is suitable for the *β*-hydroarylation of alkenyl ketimine with one more carbon chain (**5g**). The present transformation is also compatible with alkenyl ketimines substrate bearing an internal double bond, giving 63% yield with >99/1 rr (**6h**). The compatibility with internal alkene and the substrates with longer carbon chain further strengthened the generality of this diphosphine ligand enabled migratory hydroarylation reaction, which might be applied for the functionalization of remote C–H bonds.

Encouraged by the success of migratory *β*-hydroarylation of alkenyl ketimines, we envisioned that the hydrocarbofunctionalization of *N*-heteroaryl alkenes was also possible by using our catalytic system. After a quick attempt of the reaction using 2-(but-3-en-1-yl)pyridine **7a** as the model substrate under the same reaction conditions, we were pleased to find that the desired migratory hydroarylated product **8e** could be obtained in 81% GC yield with a prefect regioselectivity (>99/1) in the presence of DPPH **L18**. The yield could be further improved to 92% GC yield (88% isolated yield) with a slight change of nickel source and ligand to NiI_2 and 1,1'-bis(diphenylphosphino)ferrocene (DPPF) **L12** (For details, see the Supporting Information). Using DPPF as the optimal ligand, we further examined the scope of the present migratory *β*-hydroarylation reaction of alkenyl azaheteroarenes. As depicted in Scheme 3, initial efforts were focused

on the variation in the substitution pattern of the arylboronic acids. Various arylboronic acids bearing *para*- or *meta*-substituents of electron-donating or electron-withdrawing character, such as alkyl, methoxyl, methylthio, phenyl, halogen, ester and trifluoromethyl group, participated in this reaction to deliver *β*-arylated 2-alkyl pyridines **8a**–**j** in good to excellent yields and excellent regioselectivities (>99/1 rr). Besides, the reaction with alkenyl boronic acid could also provide the desired product **8k** with 85% yield and >99/1 rr.



Scheme 3. Ni-Catalyzed migratory hydroarylation of N-heteroaryl alkenes.[a,b] [a]Reaction conditions: **7** (0.2 mmol), **2** (0.3 mmol), *n*-PrBr (0.4 mmol), NiI_2 (10 mol %), **L12** (15 mol %), K_3PO_4 (0.4 mmol, 2.0 equiv), dioxane (1.0 mL), 100 °C, 24 h. [b]Isolated yield; the regioselective ratio (rr value) was determined by GC-MS analysis. [c]Aryl boronic acid (2.0 equiv) was used. [d]K_3PO_4 (3.0 equiv) was used. [e]110 °C. [f]Xantphos **L11** was used instead of **L12**. [g]Ary boronic acid (3 equiv) was used.

Next, the scope with respect to the different alkenyl pyridine derivatives was examined. The reaction typically works well with various alkenyl pyridines with a longer carbon chain under the same conditions, affording the *β*-hydroarylated products in 41-81% yields with excellent regioselectivities (**8l**–**r**). It is noteworthy that the longest carbon chain we had tested is about 8 carbon atoms away from the terminal carbon-carbon double bond (**7r**), which further highlights the efficiency and precise control of this Ni(II)–H initiated migratory process. In addition to terminal alkenes, both methyl- and phenyl-substituted internal alkenes **7s** and **7t** have been evaluated, and the products **8s**–**t** can be obtained with 68–79% yields with excellent regioselectivities. The generality of this protocol was also demonstrated by the compatibility of various aryl boronic acids with a long chain alkenyl pyridines **7b** and **7c**, giving a series of desired products in moderate to high yields (**8l**–**p**). Besides using pyridine as the directing group, other aza-heteroarenes containing substrates have been systematically evaluated. It turns out that the alkenes bearing isoquinoline (**7u**), pyrimidine (**7v**, **7w**), pyrazine (**7x**), pyrazole (**7y**, **7z**), indazole (**7aa**), and 1,2,3-triazole (**7ab**) are all suitable substrates to deliver the corresponding *β*-arylated products with good outcomes.

Mechanistic Studies

To understand this Ni-catalyzed migratory hydroarylation reaction, a variety of mechanistic experiments were carried out. No H/D exchange happened when treating the product **3a** or **8e** under the standard conditions with CD_3CD_2Br (For details, see supporting information). To validate the hydrogen source of this Ni-catalyzed regioselective hydroarylation of alkenes, we first performed the control experiments by using $PhB(OD)_2$ and CD_3CD_2Br, respectively. Although no deuterium in product **3a** was observed for the reaction with $PhB(OD)_2$, partially deuteration at both terminal methyl and the adjacent methylene groups was detected by using CD_3CD_2Br (Figure 2a). These results indicate the alkyl bromide (CD_3CD_2Br) might serve as the sole hydrogen source for the transformation, which is consist with the fact that no reaction happened without the addition of alkyl bromide. Similar to our previous bulky *β*-diketone ligand enabled hydroarylation of internal alkenes,[12b] the $Ni(COD)_2$ is also reactive for this reaction. Hence, we hypothesized that this reaction might undergo the Ni(II)–H species involved process, which might be formed via the single electron oxidative addition of alkyl halide with Ni(0) and sequent *β*-H elimination.

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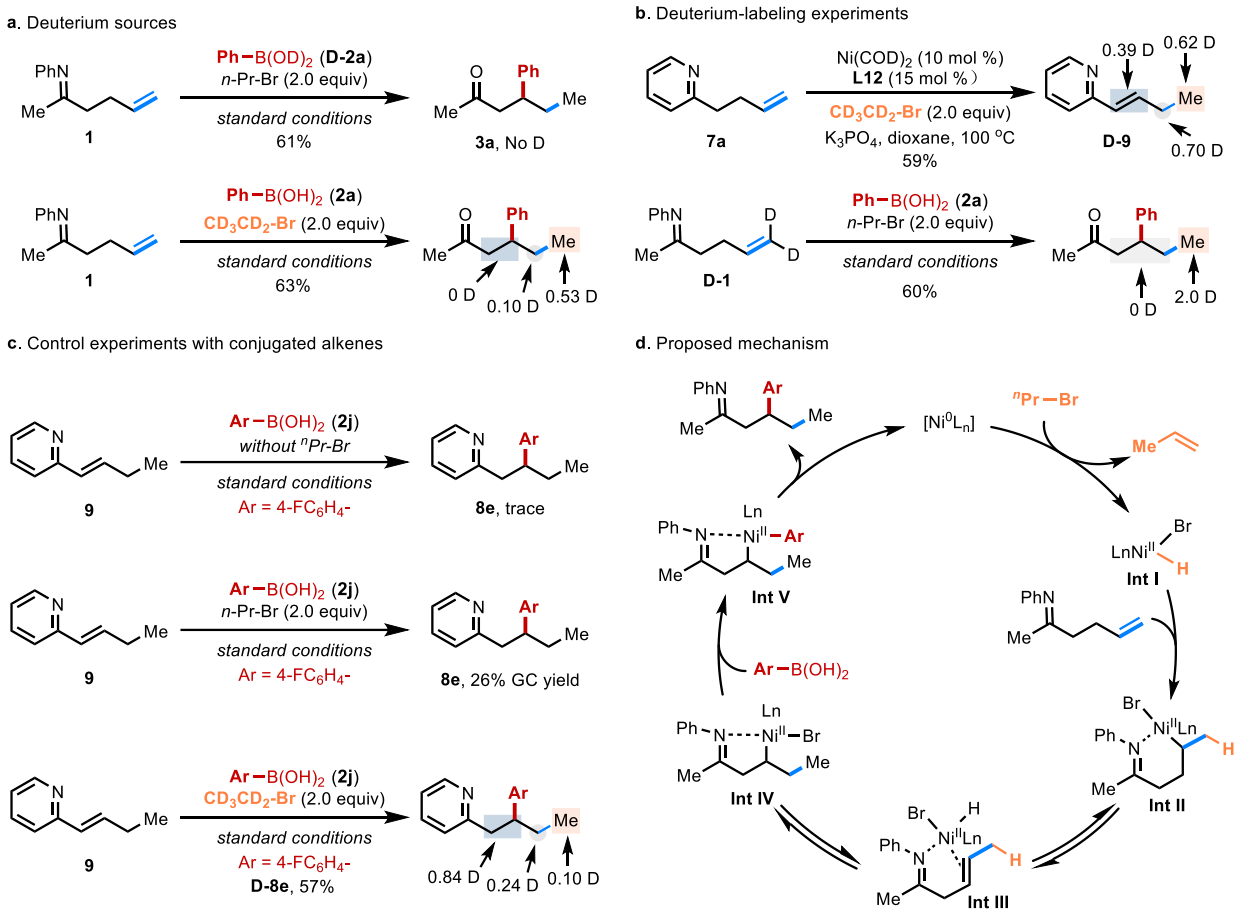

Figure 2. Mechanistic study and proposed reaction mechanism. a, Evaluation of deuterium source. **b**, Deuterium-labeling experiments. **c**, Control experiments with conjugated alkenes. **d**, Proposed mechanism.

addition, the control experiments with $Ni(COD)_2$ in the absence of diphosphine ligand gave no desired product, which further emphasizing the importance of diphosphine ligand in our protocol.

As Ar–(Ln)Ni^{II}–H has been identified as the active species in Ni-catalyzed migratory hydroarylation reaction[11a, 12b], further control experiments were conducted with alkenyl pyridine (**7a**) and CD_3CD_2Br in the absence of arylboronic acid to verify the active Ni(II)–H species [Ar–Ni(II)–H or Ni(II)Br–H)]. That the isomerization of alkenyl pyridine happened with the distribution of deuterium on all the carbon atoms of alkyl chain in the absence of aryl boronic acid concludes the diphosphine ligand attached Ni(II)Br–H is capable of rapid migratory insertion and reversible chain-walking (β-H elimination and reinsertion) (Figure 2b). In addition, the use of deuterium-labelled alkenyl ketimine **D-1** bearing two deuterium atoms at the

terminal position as substrate led to no deuterium disturbance (Figure 2b), implying the rapid chain-walking process and the strong migration tendency probably due to the presence of directing group.

In light of the rapid isomerization to thermodynamic stable conjugated alkene was observed with the active Ni(II)Br–H species, we next turned to explore if the migratory hydroarylation could be accomplished by the Ni-catalyzed Michael addition process with conjugated alkene rather than the coupling with aryl boronic acid. Employing conjugated alkene (*E*)-2-(but-1-en-1-yl)pyridine **9** as the model substrate, only trace amount of *β*-arylated product was observed in the absence of *n*-Pr–Br. In contrast, 26% GC yield of the product was formed with the addition of *n*-Pr–Br (Figure 2c). Those experimental results indicate the Ni-catalyzed Michael addition process might not be involved in our reaction. The *β*-arylated product (formal Michael addition result) might be generated by Ni(II)Br–H initiated hydroarylation process. To further confirm this process, the deuterium-labeled CD_3CD_2Br was employed instead of *n*-Pr–Br. The observation of deuterium distribution at all carbon atom on the carbon chain confirms the formation of Ni(II)–H species rather than Ni(II)–Ar species.

Based on the aforementioned detailed mechanistic studies, a plausible catalytic cycle is shown in Figure 2d. Initially, Ni(0) species could react with *n*-Pr–Br to form Ni(II)Br–H species (**Int I**) via oxidative addition and sequent *β*-H elimination. After the migratory insertion of alkenes into Ni(II)Br–H species with the assistance of a neutral directing group, the stable five-membered nickellacycle **Int IV** was formed via rapid and reversible *β*-H elimination and reinsertion process (metal walking process, **Int II** to **Int IV**). Then, the transmetalation with aryl boronic acid and reductive elimination gave the desired product and regenerated the Ni(0) species.

Conclusion

In summary, we demonstrated a Ni-catalyzed inner-selective migratory hydroarylation and hydroalkenylation of unactivated alkenyl ketimines and alkenyl azaheteroarenes with arylboronic acids by using alkyl halides as the mild hydride source. The present catalytic system is highly reliable, which is compatible with a series of internal alkenes, heterocycle-containing alkenes and the alkenes with long

carbon chain. This reaction features a broad substrate scope and mild conditions, thus providing an efficient method for the preparation of *β*-arylated ketones and 1,2-aryl heteroaryl motifs in high yields and high regioselectivities. Given the large diphosphine ligand inventory, the asymmetric version of current reaction is a ongoing project in our laboratory.

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