Enantioselective Construction of Trialkyl Tertiary Centers via Ni-Catalyzed Markovnikov Hydrocarbofunctionalizations of Unactivated Olefins and Electrophiles

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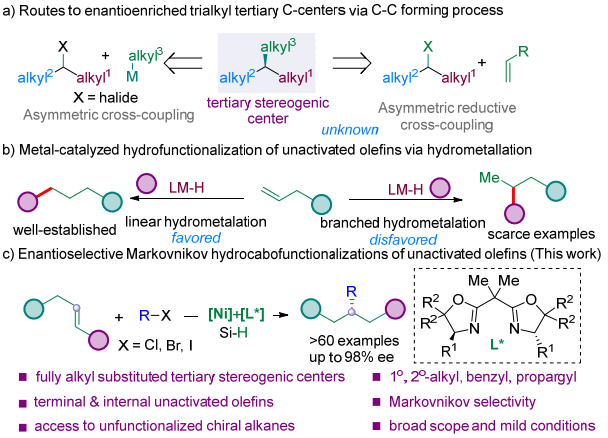
ABSTRACT: Routes to efficient construction of fully aliphatic substituted tertiary chiral centers are highly challenging and desirable. Herein, a Ni-catalyzed enantioselective hydroalkylation of unactivated alkenes at room temperature is described, providing a general and practical access to tertiary stereogenic carbon centers with three alkyl substituents. This reaction involves the regio- and stereoselective hydrometalation of unactivated alkenes with Markovnikov selectivity, followed by coupling with unactivated alkyl electrophiles to access tertiary chiral centers with full alkyl substituents. The mild and robust conditions enable the use of terminal and internal unactivated alkenes as well as primary and secondary unactivated alkyl, benzyl, propargyl halides for the construction of diverse trialkyl tertiary stereogenic carbon centers with broad functional group tolerance.

Carbon-Carbon bonds between sp^3-hybridized carbon centers compromise the major portion framework of organic molecules.[1] Thus, great efforts have been attracted to build the saturated stereogenic carbon centers and to avoid flat molecules, which play a crucial rule in chiral auxiliaries, pharmaceutical agents, natural products and bioactive molecules.[2] Transition-metal-catalyzed enantioselective cross-coupling of alkyl halides with alkyl metal nucleophiles is a powerful and established strategy for sp^3-hybridized C-C bonds forming (Scheme 1a, left).[3,4] This strategy requires the use of stoichiometric amount ofgennerally reactive and sensitive organometallic reagents, which usually require time-consuming preformation.[5] Alternatively, reductive cross-coupling would be an appealing alternative due to the mild conditions and avoiding use of metallic reagents. Specifically, cross-coupling between two alkyl electrophiles using chiral metal catalyst under reductive conditions to forge alkyl-alkyl bonds with good levels of enantiomeric excess is a promising alternative to construct saturated carbon centers yet challenging (Scheme 1a, right).[6] On the other hand, olefins are among the most important feedstock to synthesize value-added targets due to their easy accessibility and diverse reactivity profiles.[7] Consequently, catalytic asymmetric intermolecular carbofunctionalizations of olefins have been emerging as an attractive strategy to access stereogenic carbon centers by constructing C-C bonds to increase saturation of molecules.[8] Among these transformations, enantioselective reductive C-C bond forming processes involving olefins are particularly attractive.[8a,9] Recently, significant progresses have been achieved on the reductive enantioselective carbofunctionalizations of activated olefins,[10] including alkylarylation,[10a-c] hydroarylation,[10d-f] and hydroalkylation[10g-k] of activated olefins. The reductive enantioselective hydrofunctionalizations of unactivated olefins remain a formidable challenge because of their low reactivity and poor selectivity control issues.[11] Seminal

Scheme 1. Construction of Saturated Tertiary Stereogenic Centers.

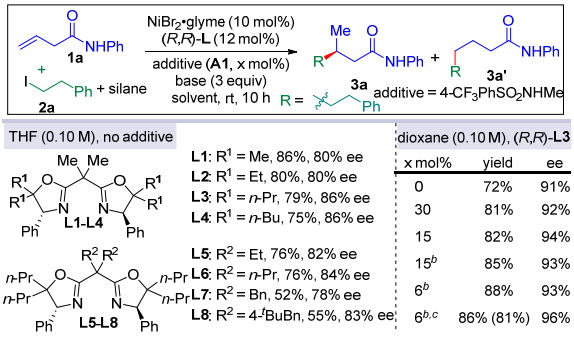


work from Buchwald disclosed the anti-Markovnikov hydroamination of unactivated olefins to deliver linear alkyl amines by copper catalysis.[11b,12] Catalytic hydrofunctionalization of unactivated of olefins in Markovnikov selectivity remains elusive due to the repulsion of ligated metal center with alkyl chain (Scheme 1b).[13] To date, only a few examples for racemic transformations of Markovnikov hydrofunctionalization of unactivated olefins are developed.[14-16] In 2020, Hong reported a racemic Ni-catalyzed Markovnikov hydroamination of unactivated olefins assisted by 8-aminoquinoline (AQ) amide group, which could suppress β-H elimination of alkyl-metal species by its rigid and saturated coordination.[14] In particular, catalytic Markovnikov hydrocarbofunctionalizations of unactivated olefins are attractive by introducing one stereogenic carbon center not adjacent to heteroatoms or carbonyls. In 2020,

Koh and Wang reported Ni/Mn-catalyzed hydroarylation/alkylation of unactivated olefins in a racemic fashion facilitated by a bidentate 8-aminoquinoline.[15] No example of intermolecular, enantioselective, Markovnikov hydrofunctionalization of unactivated olefins has been reported (Scheme 1c). As part of our continuous interests in asymmetric alkyl-alkyl cross-coupling,[10g,k] we envisioned developing an enantio- and Markovnikov-selective hydrocarbofunctionalization of unactivated olefins. To address the challenging enantioselective C_{sp3}-C_{sp3} coupling of both electrophiles nonadjacent to an activating group (aryl, vinyl, carbonyl, heteroatom), we reported a regio- and enantioselective hydroalkylation, hydrobenzylation, hydropropargylation of unactivated olefins with unactivated electrophiles in the presence of a weak coordinating and removable directing group.

To test the feasibility of the proposal, we commenced to identify the reaction parameters using terminal olefin **1a** and 1-iodo-2-phenylpropane **2a** as prototype substrates in the presence of silane and base. After extensive preliminary optimization, we chose $NiBr_2$·glyme (10 mol%) as the nickel catalyst precursor, $(MeO)_3SiH$ as hydride source and potassium phosphate monohydrate as base in THF (0.1 M) for further evaluation (Tables S1-10). Then, a wide range of chiral ligands were tested for this reaction (**L1-L8**). To our delight, using the chiral BOX ligand **L1** with a methyl substituent at 5-position of oxazolidine ring could catalyze the regio- and enantioselective hydroalkylation reaction of unactivated olefin, delivering the Markovnikov hydroalkylated product **3a** in 86% yield with 80% ee. Only trace amount of anti-Markovnikov hydroalkylated regioisomer **3a'** was detected. Increasing the steric hindrance at 5-position of the chiral ligand from methyl to propyl improved the enantioselectivity of the desired product (**L1-L3**), furnishing **3a** in 79% yield with 86% ee with **L3** as anchoring ligand. Further increasing the size of the substituent at 5-position of the BOX ligand (**L4**) delivered **3a** in diminished yield with identical enantioselectivity. Alternating the substituent R^2 on BOX ligand from methyl to ethyl (**L5**), *n*-propyl (**L6**), benzyl (**L7**), or 4-*tert*-butylbenzyl (**L8**) led to lower yields and enantioselectivities. Further evaluation the solvent effect of this reaction disclosed that **3a** was obtained in 72% yield with 91% ee in dioxane (0.1 M).

Table 1. Condition Evaluation of the Reaction[a]

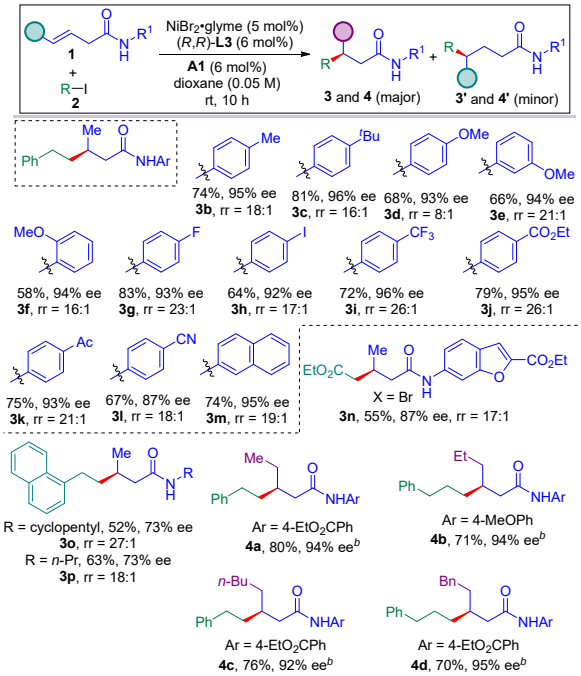


[a] The reaction was conducted using **1a** (0.1 mmol) and **2a** (0.2 mmol) in the presence of $(MeO)_3SiH$ (0.6 mmol) and potassium phosphate monohydrate (0.6 mmol) in 1 mL of solvent under indicated conditions for 10 h unless otherwise stated. Yield was determined by GC using *n*-dodecane as internal standard. Isolated yield is shown in the parentheses. The enantiomeric excess was determined by HPLC using a chiral stationary phase. [b] $NiBr_2$·glyme (5 mol%), (*R*,*R*)-**L3** (6 mol%) were used. [c] The reaction was run in dioxane (0.05 M).

Testing the effect of additives revealed that the use of N-methyl-4-trifluoromethylphenylsulfonamide (**A1**, 30 mol%) increased the yield of **3a** to 81% with 92% ee. Decreasing the loading of **A1** could further increase the enantioselectivity of **3a** without erasing the efficiency of this reaction. After routine optimization, we defined the use of $NiBr_2$·glyme (5 mol%) and (*R*,*R*)-**L3** (6 mol%) as catalyst, **A1** (6 mol%) as additive in the presence of $(MeO)_3SiH$ (0.6 mmol) and potassium phosphate monohydrate (0.6 mmol) in dioxane (0.05 M) as standard conditions, affording the desired product **3a** in 86% yield with 96% ee.[16]

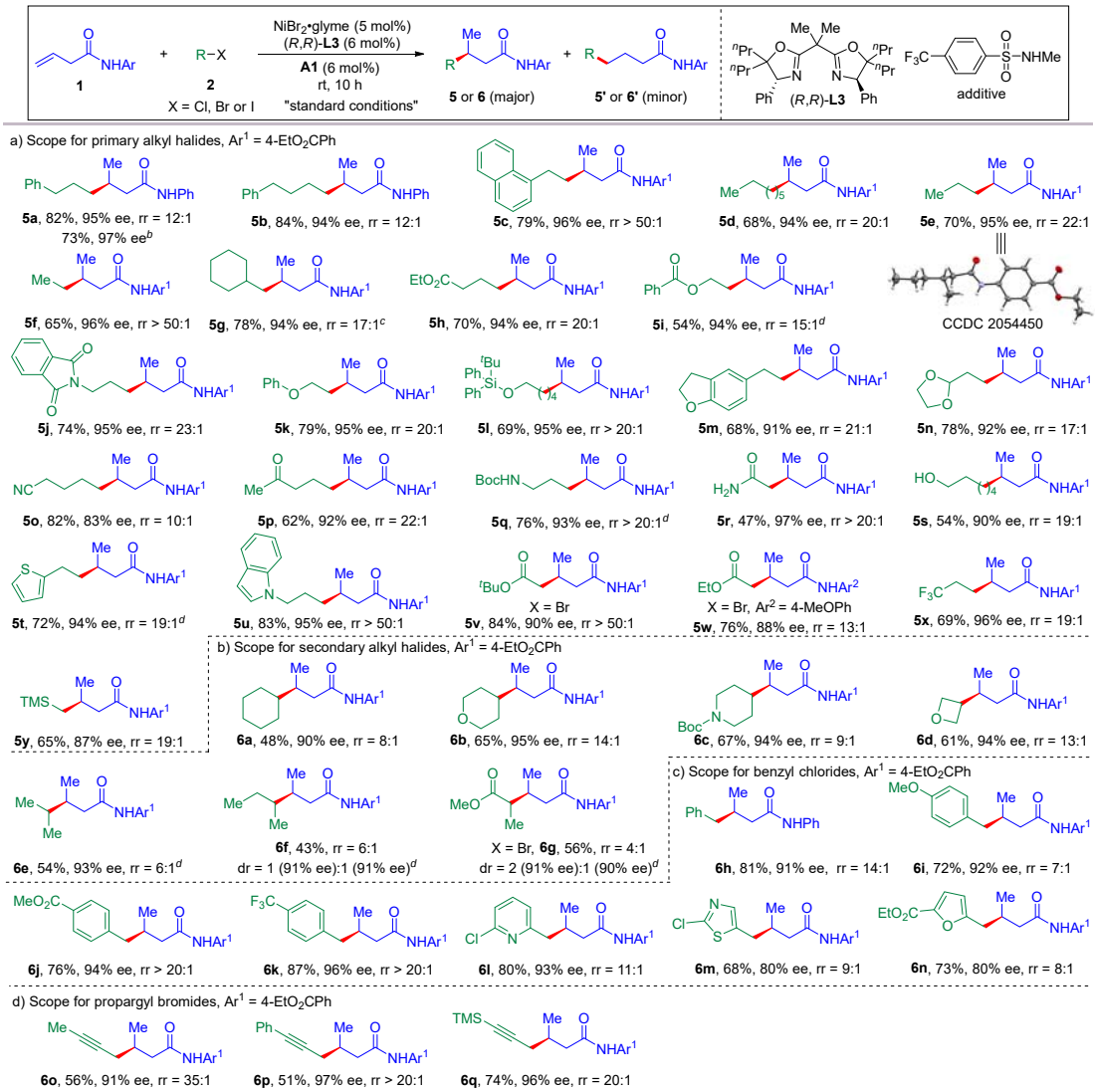
With the optimized conditions in hand, we turned to evaluate the scope of this reaction. The protocol tolerated a wide variety of functional groups and substitution patterns for this enantioselective Markovnikov hydrocarbofunctionalization of unactivated olefins (Figures 1 and 2). In general, this reaction afforded tertiary stereogenic carbon center with full alkyl substitution in high effeciency with excellent regioselectivity. First, we tested the scope of unactivated olefins (Figure 1). N-Aryl 3-enamides with electron-withdrawing or electron-donating groups on the aromatic ring were well-tolerated under the standard conditions, undergoing Markovnikov hydroalkyation in good yields (58-83% yield) with excellent regio- (rr = 8:1 to 26:1) and enantioselectivities (87-96% ee) (**3b-3m**). Notably, aryl halides, such as fluorides and iodides were compatible in the reaction, delivering the desired products (**3g** and **3h**) in 83% and 64% yields with 93% and 92% ee, respectively. Unsaturated functional groups, including ester (**3j**), ketone with acidic protons (**3k**), nitrile (**3l**), were compatible in the reaction, furnishing corresponding products (**3j-3k**) in 67-79% yields with 87-95% ee. Heteroaromatic aniline derived olefin underwent the desired transformation smoothly,

Table 2. Scope for the Reaction in Terms of Olefins[a]



[a] Standard conditions, see Table 1 for detail. rr = ratio of branched product and linear product (**3**:**3'** or **4**:**4'**). rr was determined by GC. [b] The reaction was conducted using $NiBr_2$·glyme (10 mol%), (*R*,*R*)-**L3** (12 mol%), **A1** (1.0 equiv) in dioxane (0.1 M).

Table 3. Scope for the Enantioselective Hydrofunctionalizations of Unactivated Alkenes with Respect to Organohalides[a]



[a] Standard conditions, see Table 1 for detail. Alkyl iodide was used unless otherwise noted. rr = ratio of branched product and linear product. rr was determined by GC. [b] The reaction was conducted on 2.0 mmol scale. [c] 3.0 equiv of alkyl halide was used. [d] $NiBr_2$·glyme (10 mol%), (*R*,*R*)-**L3** (12 mol%), **A1** (50 mol%) were used.

delivering **3n** in 55% yield with 87% ee. Alkyl amine based amide tethered olefins could be tranformed into corresponding amides with a trialkyl substituted tertiary stereogenic center in synthetic useful yields with 73% ee (**3o** and **3p**). Notably, internal olefins were also good substrates for this reaction, giving diverse trialkyl steregenic carbon centers in good yields (70%-80%) with 92-95% ee (**4a**-**4d**), representing one of the few examples for transition metal-catalyzed enantioselective conversion of unactivated internal olefins with high levels of enantiocontrol.[11b]

Next, the scope of organic halides for this reaction was evaluated (Table 3). A wide variety of alkylhalides (including iodides and bromides), benzylchlorides, and propargyl bromides are tolerated in this reaction, delivering a myriad of enantioenriched trialkyl tertiary stereogenic carbon center in high efficiency with excellent levels of enantioselectivity. First, primary alkyl halides were tested. 2-Phenyl-1-iodopropane was converted to trialkyl chiral amide **5a** in 82% yield with 95% ee. The reaction worked well on 2.0 mmol scale, affording **5a** in 73% yield with 97% ee. Linear and α-branched alkyl iodides could be transformed into corresponding amides (**5b**-**5g**) in 65%-84% yields with 94%-96% ee. Functional groups, such as esters, amides, ethers, silyl ethers, acetals, and nitriles were compatible in the reaction, delivering the desired hydroalkylation products (**5h**-**5o**) in 67%-82% yields with 83%-95% ee. Ketone with acidic protons could be tolerated to give corresponding hydroalkylation product **5p** in 62% yield with 92% ee. Amides with free N-H bond were also tolerated in the reaction, delivering desired products (**5q** and **5r**) in synthetic useful yields with 93% and 97% ee. Free alcohol could be tolerated in the reaction, giving desired product **5s** in 54% yield with 90% ee. Heterocycles, such thiophene, indole, derived alkyl iodides were transformed to desired products (**5t** and **5u**) in 72% and 83% yields with 94%

and 95% ee, respectively. Moreover, α-bromoesters could be coupled in the reaction to give desired products (**5v** and **5w**) in 76% and 84% yields with 88% and 90% ee, respectively.1,1,1-Trifluoro-3-iodopropane and (iodomethyl)trimethylsilane were successfully converted to corresponding products (**5x** and **5y**) in 69% and 65% yields with 96% and 87% ee. Next, secondary alkyl halides were tested. Interestingly, cyclic and acyclic secondary alkyl halides were all good substrates for this reaction (**6a-6g**). Carbon, nitrogen or oxygen tethered cyclic secondary alkyl iodides could be transformed to corresponding products (**6a-6d**) in moderate to good yields with 90-95% ee. 2-Iodopropane was coupled to give the hydroalkylated product **6e** in 54% yield with 93% ee. Unsymmetrical acyclic iodides were successfully involved in the reaction to give the desired products (**6f** and **6g**) in moderate yields with the same level of enantioselectivity for both diastereomers (91% ee), indicating the facile control of vicinal saturated carbon centers from two unactivated racemic electrophiles.[4h,17] Next, benzyl halides were tested for this reaction. It is found that benzyl chlorides with electron-donating or electron-withdrawing group could undergo Markovnikov hydrobenzylation to give corresponding products with a trialkyl substituted tertiary stereogenic center (**6h-6k**) in 72-87% yields with 91-96% ee. Heretoaryl containing benzyl chlorides were well-tolerated under the reaction conditions, giving desired products (**6l** and **6m**) in 80% and 68% yields with 93% and 80% ee, respectively. Furthermore, propargyl bromides were examined for this reaction. Methyl, phenyl, and trimethylsilyl substituted propargyl could be coupled to give the desired hydropropargylation products (**6o-6q**) in moderate to good yields with 91%-97% ee, representing the first example of enantioselective hydropropargylation of unactivated olefins.

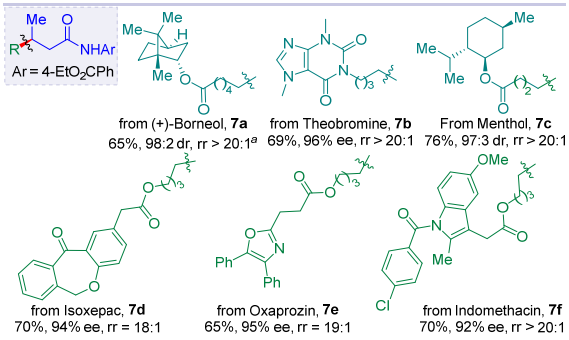


Figure 1. Application of the reaction for late-stage functionalization using alkyl iodide. For reaction conditions, see Table 1 for detail. rr = ratio of branched product and linear product. rr was determined by GC. [a] $NiBr_2$·glyme (10 mol%), (*R*,*R*)-**L3** (12 mol%), **A1** (50 mol%) were used.

To demonstrate the robustness and usefulness of this protocol, we applied this condition to late-stage functionalization of complex molecules, including natural product and drug molecules (Figure 1). (+)-Borneol derivative could be tolerated to give construct the trialkyl tertiary carbon center **7a** in 65% yield with 98:2 dr. Theobromine derived alkyl iodide was converted to corresponding product **7b** in 69% yield with 96% ee. Menthol was also compatible under the reaction conditions, providing menthol containing product **7c** in 76% yield with 97:3 dr. Drug molecules, such as isoxepac and oxaprozin, were transformed into corresponding products **7d** and **7e** in 70% and 65% yields with 94% and 95% ee. Moreover, Indomethacin could be incorporated in the reaction to deliver **7f** in 70% yield with 92% ee.

To further prove the synthetic potential of this protocol, the enantioenriched β-chiral amide product was employed to convert to other functionalized compounds (Figure 2). First, enantioselective γ-chiral amine **8a** was obtained from **5a** (97% ee) in 81% yield with 97% ee. Second, **5a** could be transformed into γ-chiral alcohol **8b** in 74% yield with 98% ee. Moreover, β-chiral carboxylic acid **8c** could be furnished from **5a** in 79% yield with 96% ee. Furthermore, **3a** was converted to unfunctionalized enantiopure alkane **8d** with a trialkyl tertiary stereogenic carbon center in 65% yield with 95% ee, providing a route to pure carbon chiral molecules challenging to access otherwise. The aforementioned derivatizations render this protocol amenable to diverse chiral compounds bearing different functional groups with excellent levels of enantioselectivity.

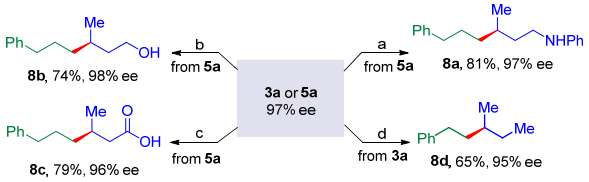


Figure 2. Synthetic application of product. For detailed reaction conditions, see Supporting Information. a) BH_3·Me_2S, THF, 0 °C to reflux. b) 1) NaH, BnBr, DMF, 0 °C to rt; 2) LAH, THF, 0 °C to reflux. c) 1) 2-FPyr, $(CF_3SO_2)O$, DCM, -78 °C to 0 °C; 2) $CeCl_3$, EtMgBr, THF, -78 °C. d) 1) $(Boc)_2O$, Et_3N, DMAP, DCM, 0 °C to rt; 2) LiOH, H_2O_2, THF/H_2O = 3:1, 0 °C to rt, THF, 0 °C to reflux. e) 1) NaH, BnBr, DMF, 0 °C to rt; 2) LAH, THF, 0 °C to reflux; 3) Et_3SiH, tris(pentafluorophenyl)borane, DCM, rt.

To gain insight into the reaction process, we carried out a series of experiments to probe the reaction mechanism. First, reactions using deuterated silane were conducted (Fig. 3a). The reaction of terminal olefin with deuterated silane ($PhSiD_2$) under otherwise identical to standard conditions afforded deuterated hydroalkylation product **9** in 70% yield with 95% ee. Deuterium incorporation (>94% D) was exclusively delivered to γ-position of **9**. No deuterium incorporation was found at β- or α-position of **9**. The reaction of internal olefin with deuterated silane ($PhSiD_2$) delivered the desired product **10** in 63% yield with 89% ee in single diastereosisomer. The results indicated that Ni-H insertion onto olefin to form alkyl-Ni species

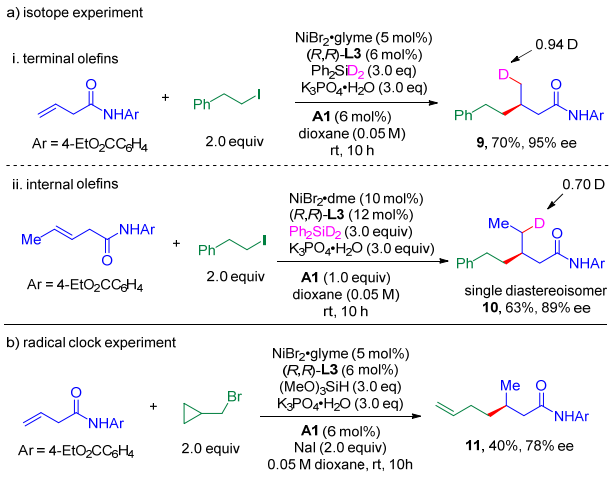


Figure 3. Mechanistic investigation of the reaction.

might be irreversible and enantio-determining. Furthermore, the reaction of olefin with (bromomethyl)cyclopropane afforded the hydroalkylation product **11** in 40% yield with 78% ee with

the ring-opening of cyclopropane (Fig. 3b), indicating the radical nature of oxidative addition step of alkyl halides to nickel intermediate.

Based on the mechanistic results and literature,[10] a tentative mechanism is proposed and depicted in Fig. 4. Nickel hydride species (Ni-H) could be generated from ligated Ni(I) precursor in the presence of silane and base. Ni-H would coordinate with unactivated alkenes (**1**) to form **M1** in the assistance of a coordinating group, which could undergo regio- and enantioselective hydrometalation to give alkyl nickel intermediate **M2**. **M2** could undergo oxidative addition with alkyl halides (**2**) in a stepwise fashion to form Ni(III) intermediate **M3**, which could undergo reductive elimination to give the product bearing a tertiary carbon center **3** and regenerate Ni(I) catalyst.

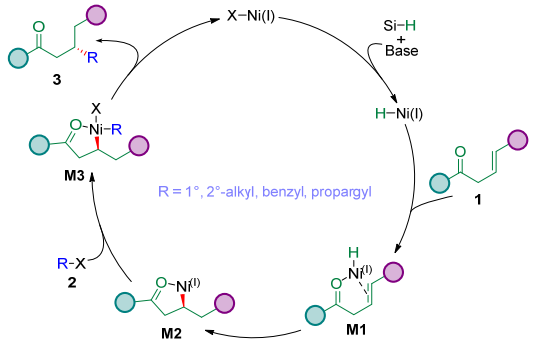


Figure 4. Tentative mechanism for the reaction. Ligand is omitted for clarity.

In summary, a unified protocol for Ni-catalyzed regio- and enantioselective hydrocarbofunctionalizations of unactivated olefins with organohalides under mild conditions has been developed. The use of a modified chiral bisoxazolidine ligand enables the Markovnikov hydroalkylation, hydrobenzylation, and hydropropargylation of unactivated olefins in the presence of a removable and transformable directing group in good yields with excellent levels of enantioselectivity, providing a straightforward access to fully alkyl substituted tertiary saturated carbon centers which are otherwise challenging to access.

ASSOCIATED CONTENT

General procedures for the enantioselective hydrocarbofunctionalizations of unactivated olefins, condition optimization, characterization of new compounds, X-ray data of **5e** (CCDC 2054450), copies of NMR spectra, and HPLC traces (PDF). The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interests.

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16. For more details on the condition optimization, see Supporting Information.

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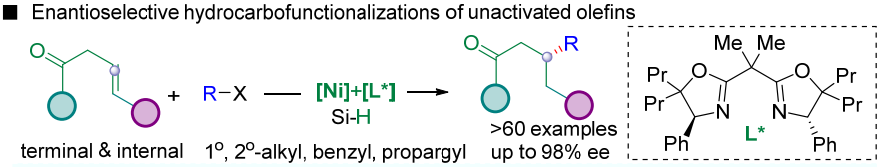
■ Enantioselective hydrocarbofunctionalizations of unactivated olefins



terminal & internal 1°, 2°-alkyl, benzyl, propargyl >60 examples up to 98% ee

- fully alkyl substituted tertiary stereogenic centers
- access to unfunctionalized chiral alkanes
- high branched & enantioselectivity
- mild conditions and broad scope