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Regio- and Enantioselective Ni-Catalyzed Formal Hydroalkylation, Hydrobenzylation and Hydropropargylation of Acrylamides to α-Tertiary Amides

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Dedicated to Shanghai Institute of Organic Chemistry on the occasion of its 70th anniversary

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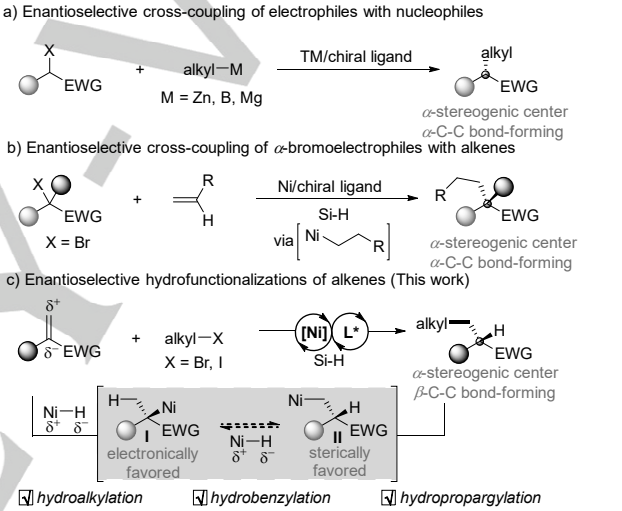
Abstract: To develop enantioselective alkyl-alkyl cross-couplings with coinstantaneous formation of a stereogenic center without the use of sensitive organometallic species is attractive yet challenging. Herein, we report the intermolecular regio- and enantioselective formal hydrofunctionalizations of acrylamides, forging a stereogenic center α-position to the newly formed C_{sp3}-C_{sp3} bond for the first time. The use of a new developed chiral ligand enables the electronically-reversed formal hydrofunctionalizations, including hydroalkylation, hydrobenzylation, and hydropropargylation, offering an efficient way to access diverse enantioenriched amides with a tertiary α-stereogenic carbon center which is facile to racemize. This operationally simple protocol allows for the anti-Markovnikov enantioselective hydroalkylation, and unprecedented hydrobenzylation, hydropropargylation under mild conditions with excellent functional group compatibility, delivering a wide range of amides with excellent levels of enantioselectivity.

As a privileged substructure, α-stereogenic amides are found in a wide range of bioactive molecules, such as peptides, and serve as versatile precursors for many other functional groups.[1,2] As a result, the development of methods to access such stereogenic centers in a highly enantioselective manner is significant and highly desirable.[3] Early efforts have focused on the use of stoichiometric chiral auxiliaries to control the stereochemistry.[4] Recent studies have been increasingly paid to asymmetric catalytic alkyl-alkyl cross-coupling transformations.[5] Over the past decade, extensive progress has been made in transition metal-catalyzed, in particular, nickel-catalyzed enantioselective alkyl-alkyl cross-coupling reactions from racemic secondary alkyl electrophiles with organometallic reagents (Scheme 1a).[6] To circumvent the use of stoichiometric, reactive, and often sensitive organometallic reagents, which usually require time-consuming preformation, one attractive alternative is hydrometallation of alkenes through metal hydride insertion to generate alkylmetallic intermediate in situ.[7] Direct use of readily available alkenes as a surrogate of carbon nucleophile to form alkyl-alkyl carbon bonds with aliphatic stereogenic carbon-centers remains underdeveloped.[8] Fu group reported a seminal work on Ni-H catalyzed enantioselective alkyl-alkyl cross-couplings of 1-substituted alkenes with secondary alkyl bromides adjacent to amides and esters (Scheme 1b).[9] More recently, the same strategy was further extended to secondary alkyl bromides next



Scheme 1. Alkyl-alkyl cross-coupling strategies to construct stereogenic carbon center.

to phosphates and ethers.[10] The current strategy could only be applied to monosubstituted aliphatic alkenes, resulting in a non-enantioselective Ni-H insertion, followed by an enantioselective cross-coupling with activated secondary alkyl bromides adjacent to electron-withdrawing groups to form a stereogenic carbon-center at the newly-formed alkyl-alkyl bond. Unactivated alkyl halides and activated alkenes are unsuccessful substrates with this strategy. Buchwald group discovered that Cu-H could undergo enantioselective insertion into alkenes to form alkyl copper species with a tertiary β-stereogenic carbon center, followed by C-N bond formation to give *β*-stereogenic amines.[11] We questioned whether Ni-H could undergo enantioselective hydride insertion into alkenes to form an alkyl-Ni species with a tertiary stereogenic center (**II**) over electronically favored intermediate (**I**), followed by C_{sp3}-C_{sp3} cross-coupling of unactivated alkyl halides, benzyl halides, and propargyl halides to realize enantioselective hydrofunctionalization of substituted acrylamides. In particular, enantioselective hydrobenzylation,[12] hydropropargylation[13] of acrylamides remains unknown. Herein, we demonstrate the first intermolecular regio- and enantioselective formal hydrofunctionalizations of alkenes enabled by Ni-H insertion into acylamides, followed by a C_{sp3}-C_{sp3} bond-forming process to forge a stereogenic carbon center α-

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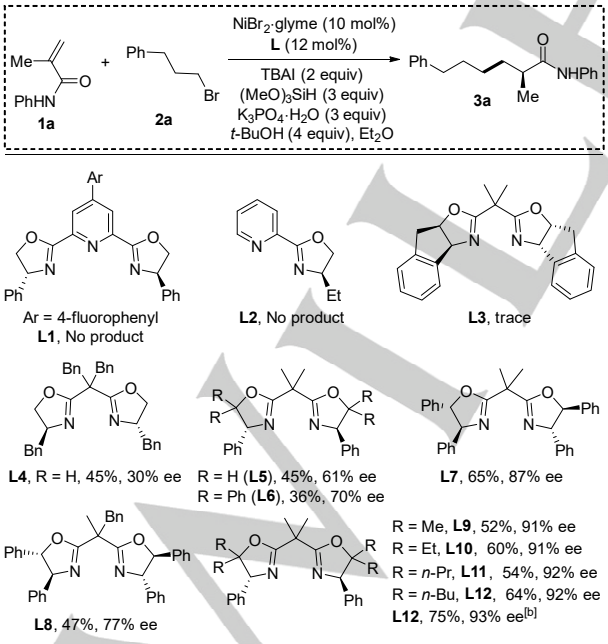
position to the newly formed alkyl-alkyl bond (Scheme 1c). This modular process allows for enantioselective hydroalkylation, hydrobenzylation, hydropropargylation of acrylamides to afford a wide range of enantioenriched amides with an α-tertiary stereogenic carbon center that is facile to racemize.

We set out to explore the hypothesis using N-phenylmethacrylamide **1a** and 3-phenyl-1-bromopropane **2a** as the stereotype substrates (Table 1). After extensive evaluation of preliminary conditions, we found that use of $NiBr_2$·glyme (10 mol%), nitrogen-coordination ligand (**L**, 12 mol%), in the presence of TBAI (2 equiv), trimethoxylsilane (3 equiv), potassium phosphate monohydrate (3 equiv), and *t*-butanol (4 equiv) in diethyl ether delivered optimal yield of **3a**. Using the identified condition, we evaluated the reaction outcome by using different scaffolds of chiral ligands. First, pyridine bisoxazolidine (**L1**) or pyridine oxazolidine (**L2**) led to no formation of desired product **3a**. The use of bisoxazolidine ligand with indanyl substituent (**L3**) only gave trace amount of **3a**. The reaction underwent smoothly in the presence of Bn-BOX ligand (**L4**), delivering the anti-Markovnikov hydroalkylation product **3a** in 45% yield with 30% ee. The use of Ph-BOX ligand derivatives (**L5** or **L6**) improved the results, giving **3a** in moderate efficiency with 61% and 70% ee, respectively. Notably, **L7** further improved the enantiomeric excess to 87%. Modification the sidearm of **L7** from methyl to benzyl (**L8**) decreased the enantioselectivity of **3a** to 77%. To our delight, further modification of the chiral BOX ligand by introducing alkyl substituents onto 5-position of oxazolidine ring substantially improved the efficiency and enantioselectivity of the reaction (**L9**-**L12**). Increasing the steric hindrance of the chiral ligand at 5-position improved both the yield and enantioselectivity of the desired product, furnishing **3a** in 64% yield with 92% ee with **L12** as an anchoring ligand. Chiral amide **3a** was obtained in 75% yield and 93% ee when 3-phenyl-1-iodopropane **2b** was used instead of **2a** in the absence of TBAI.[14]

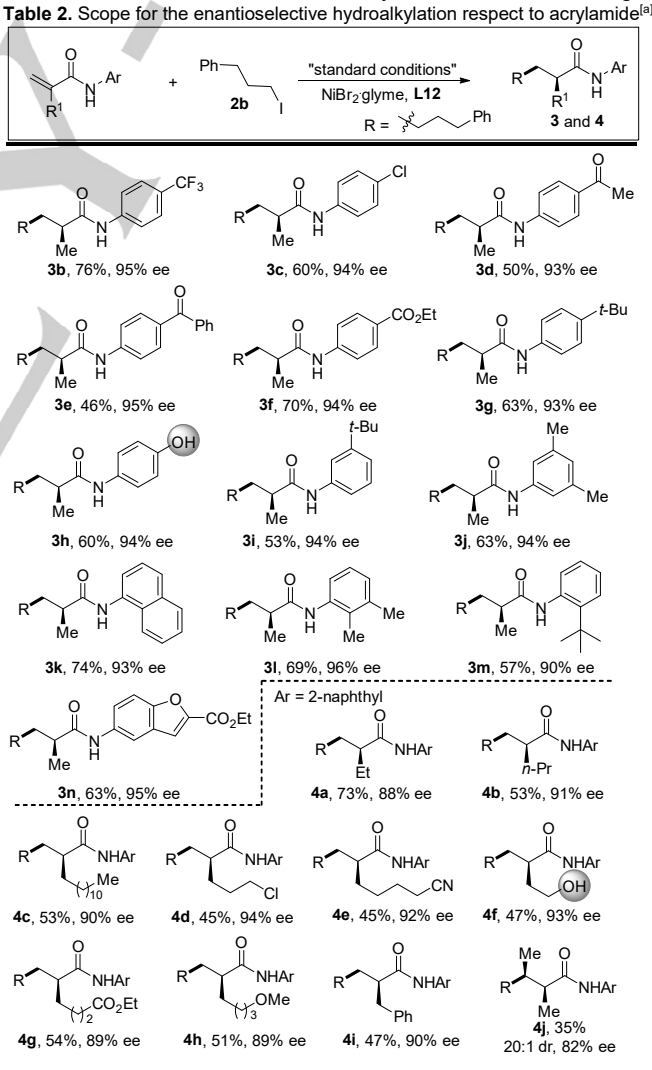
Table 1. Evaluation of the reaction conditions[a]



[a] The reaction was run with 0.1 mmol of **1a**, 0.2 mol of **2a** under indicated conditions in Et_2O (3 mL) at -10 ºC for 40 h. Isolated yields are shown. The enantiomeric excess was determined by HPLC using a chiral column. [b] 4-Phenyl-1-iodobutane (**2b**) was used in the absence of TBAI.

With the optimized conditions in hand, we turned to explore the scope of enantioselective formal hydrofunctionalization reaction. The reaction tolerates a wide variety of functional groups and substitution patterns for diverse hydrofunctionalization processes (Tables 2 and 3). Initially, we tested the scope of acrylamides (Table 2). N-Aryl acrylamides with electron-withdrawing or electron-donating groups are well tolerated under the reaction conditions, affording corresponding hydroalkylated chiral amides in good yields (46-76% yield) with excellent enantioselectivity (93-95% ee) (**3b**-**3g**). Functional groups such as halides (**3c**), ketones (**3d** and **3e**), and esters (**3f**) do not affect the outcome of the reaction, delivering the chiral amides in excellent enantiomeric excess (93-94% ee), leaving an opportunity for further elaboration of the products. Notably, free O-H is also compatible in this reaction, furnishing the desired product **3h** in 60% yield with 94% ee. *meta*- and *ortho*-Substituted anilines were successful substrates for the reaction, delivering the desired α-tertiary chiral amides in 53-74% yields with 90-96% ee (**3i**-**3m**). Herterocyclic aniline derived acrylamide was converted to chiral amide **3n** in 63% yield with 95% ee. N-Methyl-N-phenylmethacrylamide with **2b** led to the formation of corresponding chiral amide in low efficiency. Furthermore, acrylamides with diverse substituents on alkene moieties were examined. Different alkyl chains with varied length

Table 2. Scope for the enantioselective hydroalkylation respect to acrylamide[a]



[a] Standard conditions: $NiBr_2$·glyme (10 mol%), (*R*,*R*)-**L12** (12 mol%), 0.2 mmol of acrylamide, 0.4 mmol of **2b**, trimethoxylsilane (3 equiv), K_3PO_4·H_2O (3 equiv), and *t*-butanol (4 equiv) in Et_2O (3 mL) at -10 ºC.

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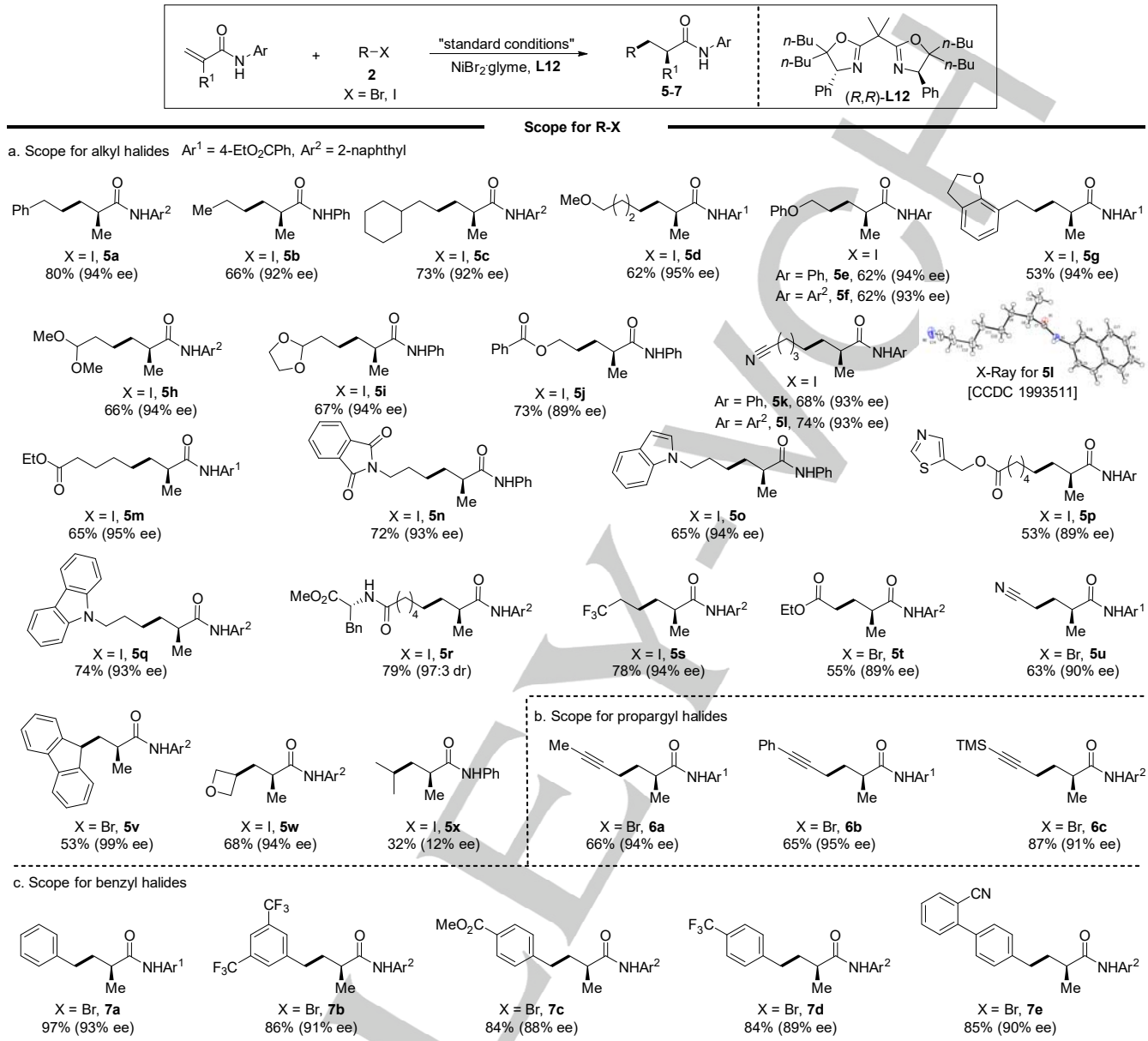
Table 3. Scope for the enantioselective hydroalkylation/hydropropargylation/hydrobenzylation with respect to halides[a]



[a] Standard conditions, see Table 2 for detail.

were tolerated in the reaction, providing the corresponding chiral amides with different alkyl chains in 53%-73% yields with 88%-91% ee (**4a**-**4c**). Alkyl halide and nitrile substituted acrylamides were compatible with the reaction conditions, furnishing the corresponding chiral amides (**4d** and **4e**) in 45% yield with 94% and 92% ee, respectively. Free alcohol substituted acrylamide could be converted to **4f** in 47% yield with 93% ee. Ester and ether were also tolerated under the reaction conditions, delivering the desired hydroalkylation products (**4g** and **4h**) in synthetically useful yields with 89% ee. Benzyl substituted acrylamide could be hydroalkylated enantioselectively to generate **4i** in 47% yield with 90% ee. Trisubstituted acrylamide was converted to desired product **4j** in 35% yield with 82% ee. Unfortunately, ethyl methacrylate gave no desired hydroalkylation product, leading to complete reduction to give ethyl isobutyrate.

Next, we evaluated the organic halides for this reaction. As shown in Table 3, a wide range of alkylhalides (including iodides and bromides) were well tolerated in this reaction, forming a myriad of enantioenriched amides in good efficiency with excellent levels of enantioselectivity. Firstly, primary alkyl halides were tested. 2-Phenyl-1-iodoethane was converted to chiral amide **5a** in 80% yield with 94% ee. Linear and *α*-branched alkyl iodides could be transformed into corresponding amides (**5b** and **5c**) in 66% and 73% yields with 92% ee. Ether tethered alkyl iodides reacted to give corresponding hydroalkylation products **5d**-**5g** in 53-62% yields with 93-95% ee. Acyclic and cyclic acetals were well suited for this reaction that provided corresponding chiral amides (**5h**

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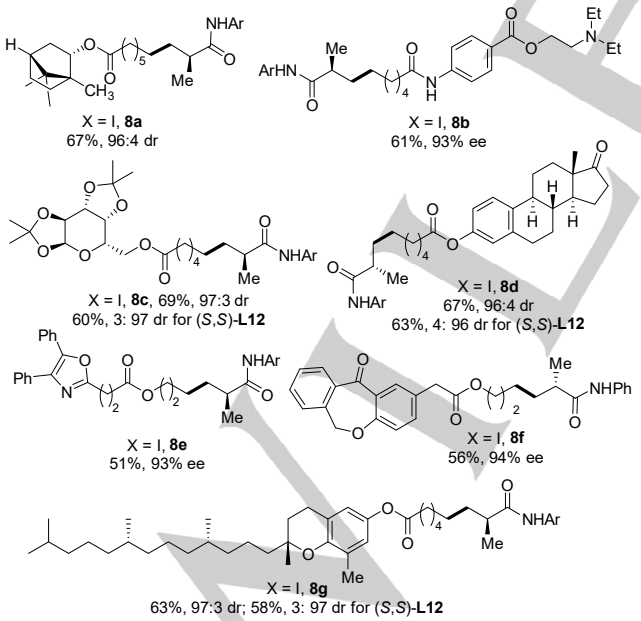
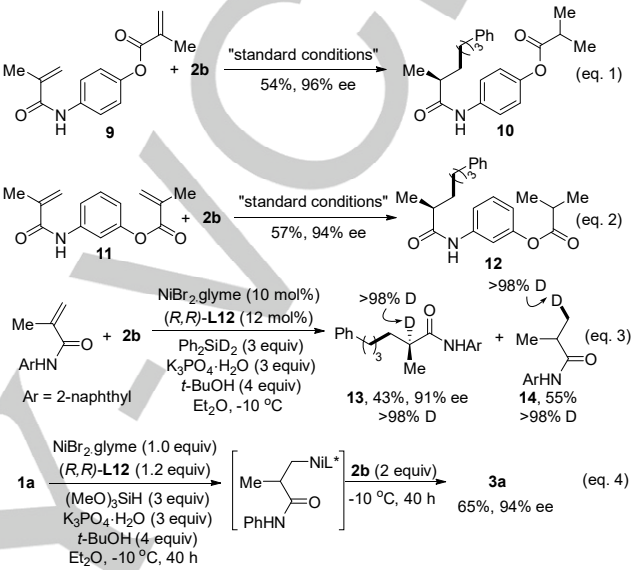
and **5i**) in 66% and 67% yields with 94% ee. Other functional groups, such as esters, nitriles, amides were also compatible under the reaction conditions, delivering the desired hydroalkylation amides (**5j**-**5n**) in 65-74% yields with 89-95% ee. The absolute configuration of the product was confirmed to be *S* by X-ray diffraction analysis of **5l**. Heterocycles, such as indoles, thiazoles, and carbazoles worked well in the reaction, furnishing the regio- and enantioselective hydroalkylation products (**5o**-**5q**) in 53-74% yields with 89-94% ee. Phenylalanine derived alkyl iodide was employed in the reaction to provide desired product **5r** in 79% yield with 97:3 dr. 1,1,1-Trifluoro-3-iodopropane was suitable with the reaction and formed desired enantioselective cross-coupling product **5s** in 78% yield with 94% ee. *α*-Bromoester and *α*-bromonitrile were also compatible in this reaction, generating the corresponding chiral amides (**5t** and **5u**) in 55% and 63% yields with 89% and 90% ee. Cyclic and symmetrical secondary alkyl halides were also reactive under the reaction conditions to furnish the desired products **5v** and **5w** in 53% and 68% yields with 99% and 94% ee. Isopropyliodide gave the desired product **5x** in poor yield and enantioselectivity. Next, propargyl bromides were tested. Propargyl halides are challenging since the alkynyl moiety is reactive towards nickel hydride. To our delight, propargyl bromides with alkyl, aryl, and silyl substituents were all suitable substrates for the reaction that underwent enantioselective hydropropargylation to exclusively furnish the C_{sp3}-C_{sp3} cross-coupling products (**6a**-**6c**) in good yields (65%-87%) with excellent enantioselectivities (91-95% ee). To the best of our knowledge, this is the first example of enantioselective hydropropargylation of alkenes.[13] Furthermore, various benzyl bromides could be subjected into the reaction to deliver enantioselective hydrobenzylation of acrylamide products (**7a**-**7e**) in 84-97% yields with 88-93% ee, representing the first intermolecular enantioselective hydrobenzylation of alkenes.[12]

Table 4. Late-stage functionalization of complex molecules[a]



[a] Standard conditions, see Table 2 for detail. Ar = 2-naphthyl.

To demonstrate the robustness and usefulness of this protocol, we applied this condition to late-stage functionalization of complex molecules, including natural products and drug molecules (Table 4). (+)-Borneol derivative could be tolerated to give corresponding chiral amide **8a** in 67% yield with 96:4 dr. Procaine derived alkyl iodides was converted to corresponding chiral amide **8b** in 61% yield with 93% ee. Diacetone-*D*-galactose was also compatible under the reaction conditions, provided galactose containing chiral amide **8c** in 69% yield with 97:3 dr. Estrone could be incorporated in the reaction to deliver **8d** in 67% yield with 96:4 dr. Drug molecules oxaprozin and isoxepac were transformed into corresponding chiral amide **8e** and **8f** in 51% and 56% yields with 93% and 94% ee. Vitamin E is also compatible with the reaction and formed the desired chiral amide **8g** in 63% yield with 97:3 dr. Moreover, the other diastereomers of **8c**, **8d,** and **8g** could be obtained in 60%, 63% and 58% yields, with 3:97, 4:96 and 3:97 drs when (*S*,*S*)-**L12** was used.



To shed light on the mechanism of this reaction, we set up a series of reactions to probe the reaction process. First, acrylamide and acrylate containing substrates **9** and **11** were subjected to standard conditions. It is interesting that **10** and **12** were obtained in 54% and 57% yields with 96% and 94% ee, respectively (eqs. 1 and 2). Enantioselective hydroalkylation occurred at acrylamide moiety efficiently, while 2-methylacrylate moiety was reduced to isobutyrate without further C_{sp3}-C_{sp3} bond-forming process. This outcome suggests the Ni-catalyzed C_{sp3}-C_{sp3} cross-coupling step is facilitated by the assistance of amide group. Next, we carried out the reaction using deuterated silane ($PhSiD_2$)[7e] under otherwise identical to standard conditions (eq. 3). Intriguingly, deuterated hydroalkylation product **13** was formed in 43% yield with 91% ee. Deuterium incorporation (>98% D) was exclusively delivered to α-position of amide **13**. No deuterium incorporation was found on methyl group of **13**. Reduction product **14** was obtained in 55% yield. Single deuterium (>98% D) was detected on one methyl. No deuterium was found on the other methyl group or α-position of amide **14**. These results indicate that Ni-H insertion step into alkene to form alkyl-Ni species is irreversible and enantio-determining. Moreover, a stepwise Ni-mediated reaction of **1a** with silane was conducted, followed by addition of **2b**, the desired product **3a** was obtained in 65% yield with 94% ee (eq. 4), indicating the hydrometalation intermediate of acrylate **1a** could lead to the cross-coupling product.

Based on the mechanistic results and relevant literature reports,[9,11] a plausible mechanism is depicted in Scheme 2. First, nickel (I) reduced from Ni (II) precursor[9,10,15] undergoes transmetalation with silane with assistance of base to generate nickel (I) hydride intermediate **A**. According to the results from equation 3, irreversible enantioselective hydrometalation of

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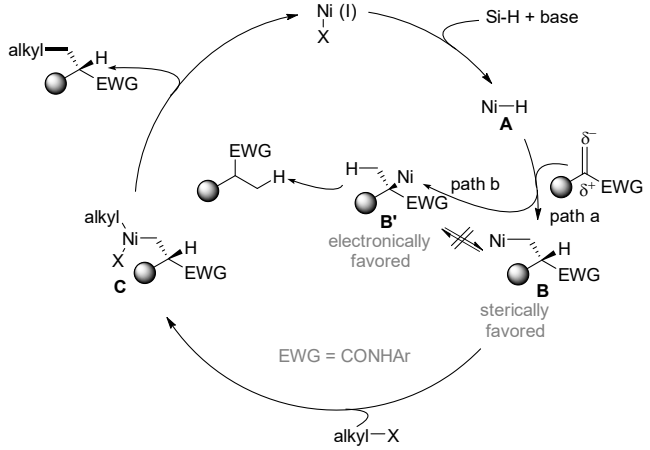
acrylamides to give alkyl nickel intermediates **B** (via path a) or **B'** (via path b). Intermediate **B'** could give formal hydrogenation byproduct via further protonation or β-hydride elimination/reductive elimination process. Intermediate **B** then undergoes an amide directed oxidative addition with alkyl halides to give Ni(III) intermediate **C**, which rapidly undergoes reductive elimination to forge the C_{sp3}-C_{sp3} bond of the final product and regenerate Ni (I) species.



Scheme 2. Proposed mechanism for the reaction.

In summary, a unified protocol for the Ni-catalyzed enantioselective intermolecular diverse formal hydrofunctionalizations of alkenes has been described for the first time. The use of a new developed BOX ligand enables the electronically-reversed enantioselective hydrometallation of acrylamides followed by a C_{sp3}-C_{sp3} bond-forming process to construct a α-stereogenic center to newly-formed C-C bond in good yields with excellent enantioselectivities, representing the first example of catalytic asymmetric formal hydroalkylation, hydrobenzylation, and hydropropargylation of alkenes. This method provides a general and practical access to enantioenriched amides containing an *α*-tertiary stereogenic carbon center facile to racemize. The mild conditions allow for the synthesis of a wide range of *α*-branched chiral amides with broad functional group tolerance.

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Keywords: hydroalkylation • hydropropargylation • hydrobenzylation • enantioselective • alkyl-alkyl cross-coupling

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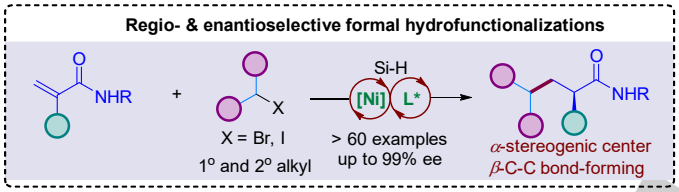

Alkyl-alkyl bond-forming with coinstantaneous formation of a stereogenic center is attractive yet challenging. Herein, we report the intermolecular, regio- and enantioselective formal hydrofunctionalizations of alkenes to forge a stereogenic center α-position to the newly formed alkyl-alkyl bond for the first time, providing a facile access to a wide range of *α*-branched chiral amides with broad functional group tolerance.