Enantioselective Access to Dialkyl Amines and Alcohols via Ni-Catalyzed Reductive Hydroalkylations

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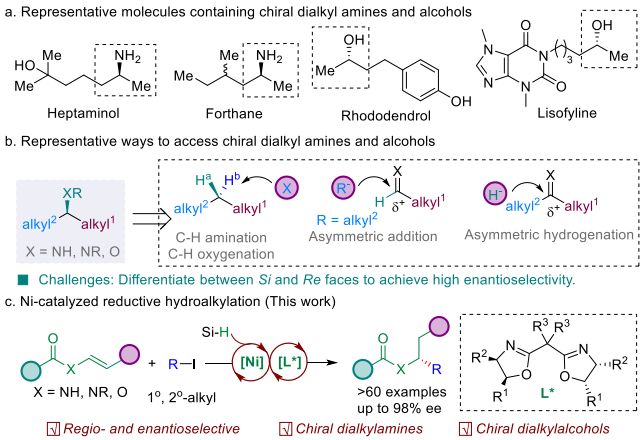
ABSTRACT: Chiral dialkyl amines and alcohols are ubiquitous in pharmaceuticals, pesticides, natural products and fine chemicals, yet difficult to access due to the challenge to differentiate between the spatially and electronically similar alkyl groups. Herein, we report a nickel-catalyzed enantioselective reductive hydroalkylation of enamides and enolates with alkyl halides to afford enantioenriched *α*-branched aliphatic amines and alcohols in good yields with excellent levels of enantioselectivity. The operationally simple protocol provides a straightforward access to chiral dialkyl amine and alcohol derivatives from simple starting materials with great functional group tolerance.

Chiral aliphatic amines and alcohols are widespread substructures in pharmaceutical molecules, natural products and organic materials, and serve as common chiral building blocks for other functional groups and value-added molecules synthesis.[1,2] Additionally, over half of small molecule drugs are the derivatives of chiral aliphatic amines and alcohols among the top 200 best-selling drugs (Scheme 1a).[3] Thus, the enantioselective synthesis of pure aliphatic amines and alcohols has been recognized as a long-term interest in chemistry community. Over the past decades, significant progress has been made in this field enabled by enantioselective C-H amination/oxygenation,[4,5] addition of alkyl organometallic reagents to imines or aldehydes,[6] hydrogenation of imines, enamines, ketones, or enolates.[7,8] However, chiral catalysts have difficulty in identifying different faces of prochiral centers bearing two alkyl groups with similar steric and electronic properties.[9] Thus, these methods are typically applied to build chiral aliphatic amines and alcohols with the stereogenic center adjacent to aryl or carbonyl groups (Scheme 1b).[7a,10] To control the stereoselectivity of asymmetric reactions for regular dialkyl amines or alcohols still remains challenging. In 2020, Zhou group reported a breakthrough in Ir-catalyzed asymmetric hydrogenation of dialkyl ketones to afford chiral aliphatic alcohols with good enantioselectivity enabled by a rationally designed bulky phosphine ligand.[11] Buchwald developed a seminal work on Cu-H catalyzed hydroamination of internal alkenes with to achieve chiral dialkyl amines.[12] Recently, Ni-H catalyzed reductive hydrofunctionalizations of alkenes with aryl or alkyl halides have become a promising alternative for traditional asymmetric C-C cross-coupling reaction to construct saturated stereogenic carbon centers.[13] The use of readily available and bench-stable alkenes as a masked nucleophile in the presence of silane circumvents the use of stoichiometric and often sensitive organometallic reagents, which usually require time-consuming preformation.[14] The abundance of alkene as well as the mild conditions significantly enhanced the scope and functional group tolerance of this reductive cross-coupling strategy. Fu group reported the seminal work on the reductive anti-Markovnikov hydroalkylation of alkenes with activated secondary alkyl halides to build a stereogenic center original from alkyl halides.[15] The use of unactivated alkyl halides to build stereogenic center original from alkenes remains elusive due to the reversible Ni-H insertion onto alkenes and the propensity of chain-walking.[16] Recently, our group developed the Ni-H catalyzed reductive hydroalkylation of acrylates via anti-Markovnikov hydrometalation, giving the enantioenriched tertiary amides by forging a stereogenic center original from acrylates.[17] In 2020, Hu group reported a reductive hydroalkylation of vinyl boronates to give chiral secondary alkyl boronates enabled by the anchoring effect of boron.[18] As part of our continuous interest in the enantioselective reductive hydrofunctionalizations of alkenes, we envisioned the use of alkene adjacent to nitrogen or oxygen to undergo enantioselective reductive hydroalkylation would furnish enantioenriched secondary aliphatic amine and alcohol derivatives (Scheme 1c). Herein, we reported the Ni-H catalyzed regio- and enantioselective reductive hydroalkylation of enamides and enolates with

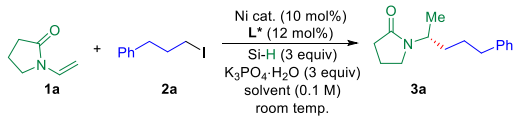
Scheme 1. Impetus for the Development of the Reaction.



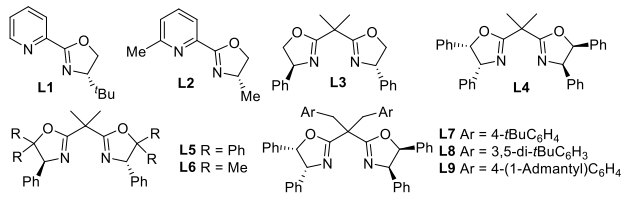
alkyl iodides to forge a stereogenic carbon center next to nitrogen or oxygen original from alkenes in high enantioselectivity, providing a unified protocol for rapid access to chiral dialkyl amine and alcohol derivatives which are difficult to access otherwise.[19]

To test the feasibility of the reaction, we set out to identify the reaction parameters using enamide **1a** with 1-iodo-3-phenylpropane **2a** as substrate in the presence of silane. (Table 1 and Tables S1-13).[20] First, a wide range of chiral ligands were tested for this reaction using $NiBr_2$·glyme (10 mol%) as the nickel catalyst precursor, trimethoxysilane (TMS) as hydride source, and potassium phosphate monohydrate as base in diethyl ether at room temperature (Table 1, entries 1-9 and Table S1). When Pyridine-oxazolidine ligand (**L1** or **L2**) was used, the desired reductive hydroalkylation product **3a** was obtained in 54% and 29% yields with low enantiomeric excesses (2% and 15%), respectively (Table 1, entries 1 and 2). Ph-Box ligands (**L3**-**L6**) could catalyze the reaction, giving **3a** in low yields with low enantioselectivities (Table 1, entries 3-5). Increasing the steric hindrance at α-position to oxygen increased the enantioselectivity of **3a** to 50% ee (Table 1, entries 6 and 7). Modifying the methyl group on **L4** to bulkier groups significantly improved the enantioselectivity of **3a** (Table 1, entries 8-10). The use of **L9** delivered **3a** in 20% yield with 90% ee. Using DEMS as hydride source slightly increased the enantioselectivity of **3a** to 94% (Table 1, entry 11). Next, the solvent for the reaction was evaluated. The use of DMA or DMF dramatically increased the efficiency of the reaction, delivering **3a** in up to 99% yield with diminished enantiomeric excess (Table 1, entries 12 and 13). The mixing of ether with DMA or DMF could increase the enantioselectivity of **3a** without erasing the efficiency of the reaction (Table 1, entries 14 and 15). Further optimization of the nickel precursor and reaction temperature improved the yield and enantioselectivity of **3a** (Table 1, entries 16-18). The use of $Ni(COD)_2$ (10 mol%), **L9** (12 mol%), DMMS (3 equiv) in Et_2O and DMF (3:1) gave **3a** in 93% yield with 92% ee (Table 1, entry 19).

Table 1. Condition Evaluation of the Reaction[a]



entry	Ni cat.	L*	Si-H	solvent	yield (ee)
1	$NiBr_2$·glyme	**L1**	TMS	Et_2O	54% (2%)
2	$NiBr_2$·glyme	**L2**	TMS	Et_2O	29% (15%)
3	$NiBr_2$·glyme	**L3**	TMS	Et_2O	32% (19%)
4	$NiBr_2$·glyme	**L4**	TMS	Et_2O	56% (13%)
5	$NiBr_2$·glyme	**L5**	TMS	Et_2O	29% (50%)
6	$NiBr_2$·glyme	**L6**	TMS	Et_2O	24% (16%)
7	$NiBr_2$·glyme	**L7**	TMS	Et_2O	62% (82%)
8	$NiBr_2$·glyme	**L8**	TMS	Et_2O	51% (85%)
9	$NiBr_2$·glyme	**L9**	TMS	Et_2O	20% (90%)
10	$NiBr_2$·glyme	**L9**	DEMS	Et_2O	14% (94%)
11	$NiBr_2$·glyme	**L9**	DEMS	Et_2O	24% (94%)
12	$NiBr_2$·glyme	**L9**	DEMS	DMA	99% (73%)
13	$NiBr_2$·glyme	**L9**	DEMS	DMF	56% (58%)
14	$NiBr_2$·glyme	**L9**	DEMS	Et_2O[b]	98% (77%)
15	$Ni(COD)_2$	**L9**	DEMS	Et_2O[c]	99% (84%)
16	$Ni(COD)_2$	**L9**	DEMS	Et_2O[c]	99% (88%)
17[d]	$Ni(COD)_2$	**L9**	DEMS	Et_2O[c]	94% (92%)
18[d,e]	$Ni(COD)_2$	**L9**	DEMS	Et_2O[c]	99% (92%)
19[d,e]	$Ni(COD)_2$	**L9**	DMMS	Et_2O[c]	93%[f] (92%)



[a] The reaction was conducted using **1a** (0.1 mmol) and **2a** (0.2 mmol) in 1 mL of solvent under indicated conditions for 12 h unless otherwise stated. Yield was determined by GC using *n*-dodecane as internal standard. The enantiomeric excess was determined by HPLC using a chiral stationary phase. TMS = trimethoxysilane. DEMS = diethoxymethylsilane. DMMS = diethoxymethylsilane. [b] Et_2O/DMA = 3:1. [c] Et_2O/DMF = 3:1. [d] The reaction was run at 0 °C. [e] The reaction was run for 24 h. [f] Isolated yield after flash chromatography.

With the optimized conditions in hand, we turned to evaluate the scope of this reaction. First, we tested different alkyl iodides with tertiary enamide **1a** (Fig. 1). 4-Phenylbutyliodide was converted to chiral amide **3b** in 93% yield with 92% ee. 2-Phenyl-1-iodoethane and α-branched alkyl iodides could be transformed into corresponding amine derivatives (**3c** and **3d**) in 87% and 58% yields with 89% ee. Heterocycles, such as carbazoles, indoles, and thiaphenes, worked well in the reaction, furnishing the regio- and enantioselective hydroalkylation products (**3e**-**3g**) in 64-94% yields with 91% ee. Other functional groups, such as amides, esters, ethers were also compatible under the reaction conditions, delivering the desired chiral amine derivatives (**3h**-**3k**) in 56-83% yields with 89%-92% ee. Moreover, silylethers and arylchlorides were tolerated in the reaction, giving the desired products (**3l** and **3m**) in 85% and 95% yields with 74% and 88% ee, leaving chemical handles for further elaboration. Internal enamide reacted to give corresponding dialkyl amide **3n** in moderate yield with 93% ee.

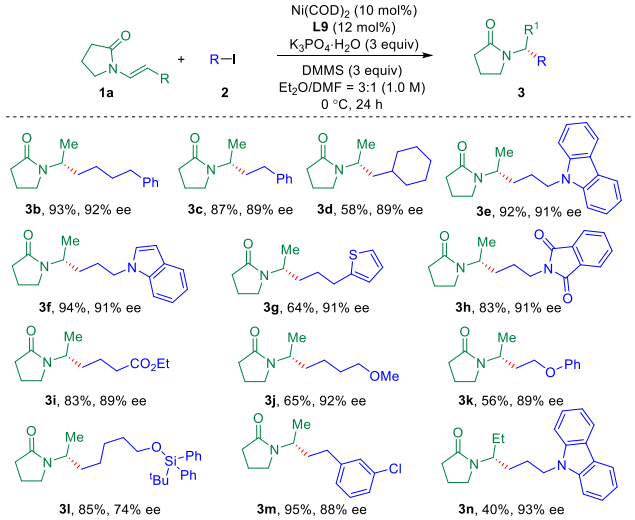


Figure 1. Scope of the alkyl iodides for tertiary enamides.

Next, the scope of enamides was tested (Fig. 2). A wide range of secondary enamides were well tolerated in this reaction, forming a myriad of enantioenriched amides in good efficiency with excellent levels of enantioselectivity in the presence of **L41**. Various aromatic amides were good substrates for this reaction (**4a**-**4o**). Electron-donating substituted aromatic enamides could be converted to corresponding hydroalkylated products (**4a**-**4f**) in 68%-90% yields with 90%-95% ee. Electron-withdrawing substituents, such as trifluoromethyl, cyano, ester, fluoride, were well-tolerated under the reaction conditions, giving the desired products (**4g**-**4j**) in 74%-89% yields with 93%-96% ee. Fused aromatic and heteroaromatic enamides, including naphthalene, furan, thiophene, and pyridine, were transformed into corresponding chiral amides (**4k**-**4o**) in 49-88% yields with 89%-95% ee. The structure and absolute configuration of the product was determined by the X-ray diffraction analysis of **4l**. Aliphatic enamides were also tested (**4p**-**4v**). Linear and α-branched aliphatic enamides with acidic α-proton, such as methyl, *n*-propyl, isopropyl, cyclopropyl, cyclohexyl, were all good substrates for this reductive hydroalkylation reaction, affording corresponding chiral amides (**4p**-**4t**) in 51-88% yields with 90%-96% ee. α-Tertiary alkyl enamides reacted to give **4u** in 84% yield with 92% ee. N-methyl aliphatic enamide was converted to **4v** in 79% yield with 80% ee.

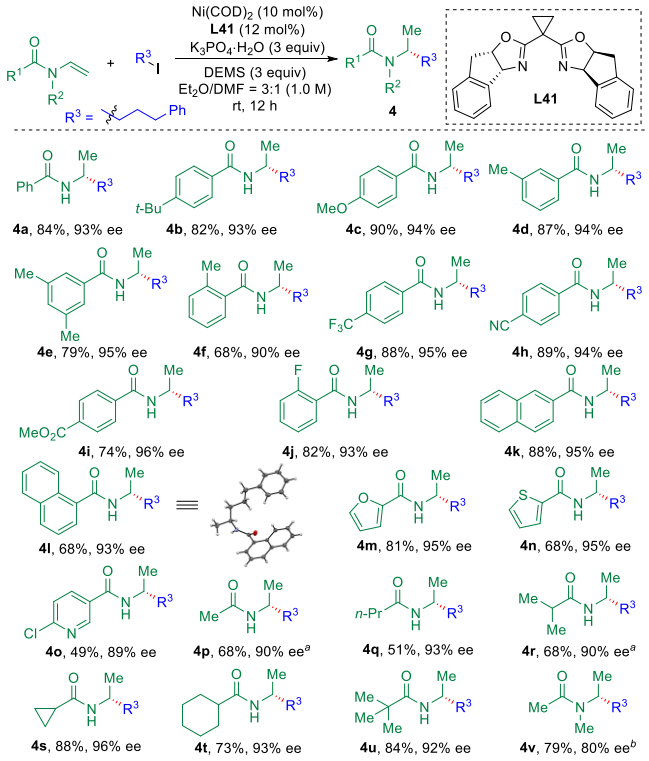


Figure 2. Scope for the enamides. [a] DMMS was used instead of DEMS. [b] **L4** was used as the ligand.

Then the scope for alkyl iodide for secondary enamides was examined (Fig. 3). 5-(2-Iodoethyl)-2,3-dihydrobenzofuran was successfully hydroalkylated to give **5a** in 84% yield with 96% ee. The structure and absolute configuration of **5a** was further determined by the X-ray diffraction analysis. It is noteworthy that the minimal structurally different dialkyl amine derivative **5b** was obtained by this protocol in 65% yield with 94% ee. Other 1-iodoalkanes were also successfully converted to corresponding amine derivatives (**5c**-**5e**) in 63-80% yields with 93%-98% ee. Chiral aminoalcohol and aminoester derivatives (**5f**-**5h**) were obtained in 62-72% yields with 92%-94% ee. Cyclic secondary alkyl iodides were also reactive under the reaction conditions to furnish the desired products **5i** and **5j** in 66% and 61% yields with 98% and 92% ee. To demonstrate the robustness and usefulness of this protocol, we applied this reaction to late-stage functionalization of natural product derivatives. (+)-Borneol, L-menthol, cholesterol, and vitamin E derived enamides could be transformed to give corresponding chiral amides (**5k**-**5n**) in 45%-87% yields with 97:3 to 98:2 dr.

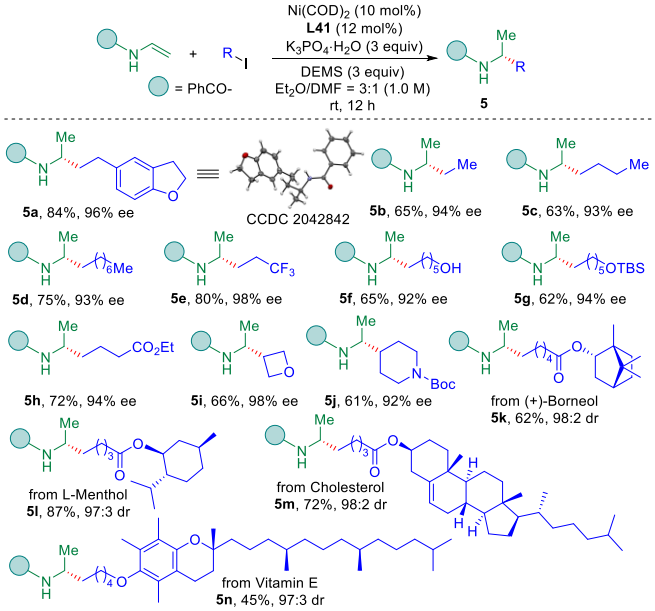


Figure 3. Scope for the alkyl iodides for secondary enamides.

Next, enolates were tested under the reaction conditions. To our delight, various enolates could be tolerated and a wide range of dialkyl alcohol derivatives were obtained in high enantioselectivity, which are difficult to access otherwise (Fig. 4). Aromatic or aliphatic acid derived enolates were all good substrates for this reaction, furnishing corresponding chiral esters (**6a**-**6c**)

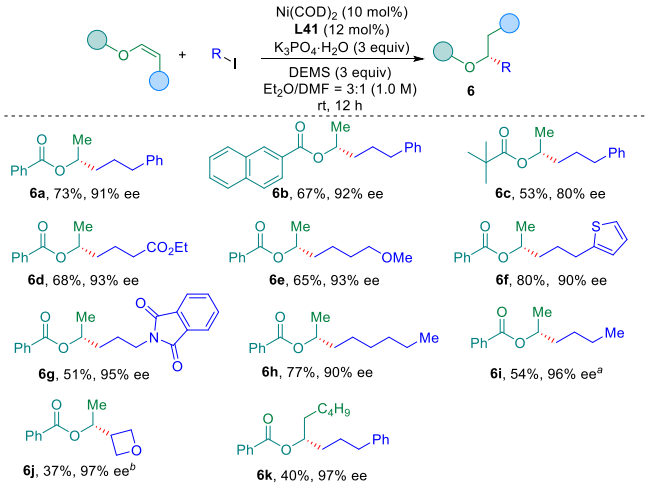
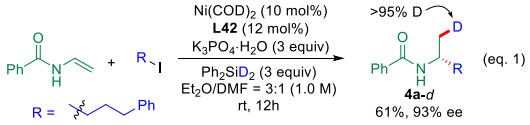


Figure 4. Scope for the reductive hydroalkylation of enolates. [a] 5 equiv of RI was used. [b] 3 equiv of RI was used.

in 53%-73% yields with 80-92% ee. Alkyl iodides containing ester, ether, thiophene, amide could be transformed to corresponding chiral alcohol derivatives (**6d**-**6g**) in 51%-80% yields with 90%-95% ee. Notably, 1-iodohexane and 1-iodobutane were successfully involved in the reaction to give octan-2-ol (**6h**) and hexan-2-ol (**6i**) derivatives in 77% and 54% yields with 90% and 96% ee, respectively. Secondary alkyl halides and internal enolates were both compatible in the reaction, furnishing the desired products (**6j** and **6k**) in synthetic useful yields with 97% ee.

Next, we carried out the reaction using deuterated silane ($PhSiD_2$)[13e] under otherwise identical to standard conditions (eq. 1). Deuterated hydroalkylation product **4a**-*d* was formed in 61% yield with 93% ee. Deuterium incorporation (>95% D) was exclusively delivered to *β*-position to nitrogen of amide **4a**-*d*. No deuterium incorporation was found at α-position to nitrogen of **4a**-*d*. The result indicated that Ni-H insertion onto enamides to form alkyl-Ni species might be irreversible and enantio-determining.



Based on the mechanistic results and literature,[13,15,17,18] a tentative mechanism is proposed and depicted in Fig. 5. Nickel hydride species could be generated from ligated Ni(I) precursor in the presence of silane and base. Ni-H would coordinate with enamides or enolates (**1**) to give **M1**, which could undergo regio- and enantioselective hydrometalation to generate alkyl nickel intermediate **M2**. **M2** could oxidize alkyl halides (**2**) to form Ni(III) intermediate **M3**, which could undergo reductive elimination to give final amine or alcohol derivatives **3** and regenerate Ni(I) catalyst.

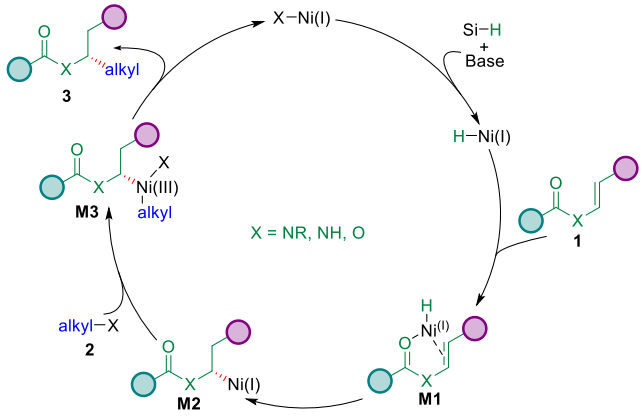


Figure 5. Proposed mechanism for the reaction. Ligand is omitted for clarity.

In summary, a unified protocol for Ni-catalyzed reductive hydroalkylation of enamides and enolates with alkyl iodides under mild conditions was developed for the first time. The use of chiral BOX-based ligand enables the direct access of chiral dialkyl amine and alcohol derivatives in good yields with excellent levels of enantioselectivity, providing a straightforward alternative to pure aliphatic amine and alcohol derivatives which are traditionally challenging to access.

ASSOCIATED CONTENT

General procedures for the synthesis of chiral amines and alcohols, conditions optimization, characterization of new compounds, copies of NMR spectra, and X-ray data of **4l** (CCDC 2042844) and **5a** (CCDC 2042842) (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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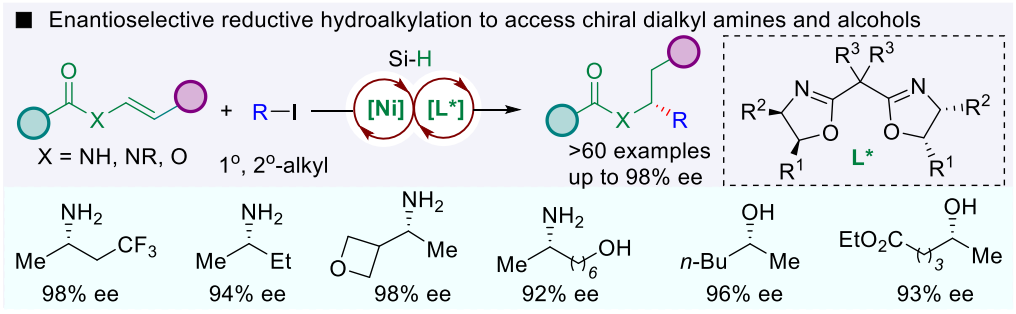
19. During the review of this manuscript, two preprints on the asymmetric reductive hydroalkylation of enamides: (a) Wang, J.-W.; Li, Y.; Nie, W.; Chang, Z.; Yu, Z.-A.; Zhao, Y.-F.; Lu, X.; Fu, Y. Catalytic Asymmetric Reductive Alkylation of Enamines to Chiral Aliphatic Amines. *ChemRxiv* doi.org/10.26434/chemrxiv.13102307.v1. (b) Qian, D.; Bera, S.; Hu, X. Chiral Alkyl Amine Synthesis via Catalytic Enantioselective Hydroalkylation of Enamides. *ChemRxiv* doi.org/10.26434/chemrxiv.13096121.v1.

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


■ Enantioselective reductive hydroalkylation to access chiral dialkyl amines and alcohols
Si-H
[Ni]
[L*]
X = NH, NR, O
1°, 2°-alkyl
>60 examples
up to 98% ee
L*
98% ee
94% ee
98% ee
92% ee
96% ee
93% ee