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 acyl enamines and enol esters 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.

Full Text

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.¹⁻³ 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).⁴ 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,⁵⁻⁸ addition of alkyl organometallic reagents to imines or aldehydes,⁹⁻¹³ hydrogenation of imines, enamines, ketones, or enol esters.¹⁴⁻¹⁹ However, chiral catalysts have difficulty in identifying different faces of prochiral centers bearing two alkyl groups with similar steric and electronic properties.²⁰ 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).^{14,21-24} 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.²⁵ Buchwald developed a seminal work on Cu-H catalyzed hydroamination of internal alkenes to achieve chiral dialkyl amines.^{26,27} In 2016, Fu group reported a pioneer work on Ni-H catalyzed racemic reductive hydrofunctionalizations of alkenes with aryl or alkyl halides,²⁸ which have become a promising alternative for traditional asymmetric C-C cross-coupling reaction to construct saturated stereogenic carbon centers.²⁸⁻³⁸ 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.^{39,40} 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.⁴¹⁻⁴⁴ 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.^{45,46} 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.⁴⁷ In 2020, Hu group reported a reductive hydroalkylation of vinyl boronates to give chiral secondary alkyl boronates enabled by the anchoring effect of boron.⁴⁸ 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 acyl enamines and enol esters with 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.⁴⁹⁻⁵¹

To test the feasibility of the reaction, we set out to identify the reaction parameters using acyl enamine **1a** with 1-iodo-3-phenylpropane **2a** as substrate in the presence of silane. (Table 1 and Tables S1-13).⁵² First, a wide range of chiral ligands were tested for this reaction using NiBr₂·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 Et₂O and DMF (3:1) gave **3a** in 93% yield with 92% ee (Table 1, entry 19).

With the optimized conditions in hand, we turned to evaluate the scope of this reaction. First, we tested different alkyl iodides with tertiary acyl enamine **1a** (Fig. 1). 4-Phenylbutyl iodide 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 thiophenes, 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 acyl enamine reacted to give corresponding dialkyl amide **3n** in moderate yield with 93% ee.

Next, the scope of acyl enamines was tested (Fig. 2). A wide range of secondary acyl enamines 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 acyl enamines 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 acyl enamines, 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 acyl enamines were also tested (**4p-4v**). Linear and α -branched aliphatic acyl enamines 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 acyl enamines reacted to give **4u** in 84% yield with 92% ee. N-methyl aliphatic acyl enamine was converted to **4v** in 79% yield with 80% ee.

Then the scope for alkyl iodide for secondary acyl enamines was examined (Fig. 3). Secondary acyl enamines gave better enantioselectivity using the analogue ligand **L41**. 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 acyl enamines could be transformed to give corresponding chiral amides (**5k-5n**) in 45%-87% yields with 97:3 to 98:2 dr.

Next, enol esters were tested under the reaction conditions. To our delight, various enol esters 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 enol esters were all good substrates for this reaction, furnishing corresponding chiral esters (**6a-6c**) 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 enol esters were both compatible in the reaction, furnishing the desired products (**6j** and **6k**) in synthetic useful yields with 97% ee. The absolute configuration of the chiral ester was confirmed to be *R* by comparison to literature.⁵³ Furthermore, literature procedures proved dialkyl free amines and alcohols could be obtained via hydrolysis without erosion of enantioselectivities,^{54,55} which further enhanced the synthetic utility of this method.

Then, we carried out the reaction using deuterated silane (PhSiD₂)³² under otherwise identical to standard conditions (eq. 1). Deuterated hydroalkylation product **4a-d** was formed in 61% yield with 93% ee. Only one 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 acyl enamines to form alkyl-Ni species might be irreversible.

Based on the mechanistic results and literature,^{28-34,41-44,47,48} 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 acyl enamines or enol esters (**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.

In summary, a unified protocol for Ni-catalyzed reductive hydroalkylation of acyl enamines and enol esters 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.

Declarations

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Supplementary Information

Table 1, Equation 1, and Scheme 1 are available in the Supplementary Files

Figures

Figure 1

Scope of the alkyl iodides for tertiary acyl enamines.

Figure 2

Scope for the acyl enamines. a DMMS was used instead of DEMS. b L4 was used as the ligand.

Figure 3

Scope for the alkyl iodides for secondary acyl enamines.

Figure 4

Scope for the reductive hydroalkylation of enol esters. a 5 equiv of RI was used. b 3 equiv of RI was used.

Figure 5

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

Supplementary Files

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