Enantioselective access to chiral aliphatic amines and alcohols via Ni-catalyzed hydroalkylations

Shan Wang¹, Jian-Xin Zhang¹, Tian-Yi Zhang¹, Huan Meng¹, Bi-Hong Chen¹ & Wei Shu¹

Chiral aliphatic amine and alcohol derivatives 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 hydroalkylation of acyl enamines and enol esters with alkyl halides to afford enantioenriched α-branched aliphatic acyl amines and esters in good yields with excellent levels of enantioselectivity. The operationally simple protocol provides a straightforward access to chiral secondary alkyl-substituted amine and secondary alkyl-substituted 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 molecule 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 (Fig. 1a)\(^4\). Thus, the enantioselective synthesis of pure chiral 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, and 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 (Fig. 1b)\(^14\)–24. To control the enantioselectivity of asymmetric reactions for regular secondary alkyl-substituted amines and alcohols still remains a formidable challenge. In 2020, Zhou group reported a breakthrough in Ir-substituted amines and alcohols still remains a formidable challenge. In 2020, Zhou group reported a breakthrough in Ir-catalyzed asymmetric hydrogenation of dialkyl ketones to afford enantioenriched secondary alkyl amines\(^26\)–27. In 2016, Fu group set out to identify the reaction parameters using acyl enamine as substrate in the presence of silane. (Table 1 and Tables S1–S13; for more details on the condition optimization, please see the Supplementary information). First, a wide range of chiral ligands were tested for this reaction using NiBr\(_2\)-glyme (10 mol%) as the nickel catalyst precursor, and the propensity of chain-walking\(^46\),\(^47\). Recently, our group developed the Ni–H-catalyzed hydroarylation of acrylates via anti-Markovnikov hydrometalation, giving the enantioenriched a-tertiary amides by forging a stereogenic center originating from acrylates\(^48\). In 2021, Hu group reported a hydroalkylation of vinyl boronates to give chiral secondary alkyl boronates enabled by the anchoring effect of boron\(^49\). These examples showcased the feasibility of building a stereogenic carbon center originating from alkyl halides, hydroalkylation\(^36\)–38 and hydroalkylation\(^48\)–51 of alkenes.

As part of our continuous interest in the enantioselective hydrofunctionalizations of alkenes, we envisioned the use of alkene adjacent to nitrogen or oxygen to undergo enantioselective hydroalkylation would furnish enantioenriched secondary aliphatic amine and alcohol derivatives (Fig. 1c). Here, we report the Ni–H-catalyzed regio- and enantioselective hydroalkylation of acyl enamines and enol esters with alkyl halides to forge a stereogenic carbon center next to nitrogen or oxygen originating from alkenes high enantioselectivity, providing a unified protocol for rapid access to chiral secondary alkyl-substituted amine and alcohol derivatives which are difficult to access otherwise\(^30\)–52.

**Results**

**Reaction optimization.** 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–S13; for more details on the condition optimization, please see the Supplementary information). 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 hydroalkylation product \(3a\) was obtained in 54% and 29% yields with low

---

**Fig. 1 Impetus for the development of the reaction.** a Representative molecules containing chiral secondary alkyl-substituted amines and alcohols. b Representative ways to access chiral secondary alkyl-substituted amines and alcohols. c Ni-catalyzed hydroalkylation of acyl enamines and enol esters (This work).
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 3–6). Increasing the steric hindrance at α-position to oxygen increased the enantioselectivity of 3a to 50% ee (Table 1, entries 5 and 6). Modifying the methyl group on L4 to bulkier groups significantly improved the enantioselectivity of 3a (Table 1, entries 7–9). The use of L9 delivered 3a in 20% yield with 90% ee. Using diethoxymethylsilane (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 N,N-dimethylacetamide (DMA) or N,N-dimethylformamide (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%), dimethoxymethylsilane (DMMS) (3 equiv.) in Et_2O and DMF (3:1) gave 3a in 93% yield with 92% ee (Table 1, entry 19).

Substrate scope of dialkyl amides. 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. 2). Then, 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. Heterocyclic compounds, such as carbazoles, indoles, and thiophenes, worked well in the reaction, furnishing the regio- and

Table 1 Condition evaluation of the reaction.

| 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 | TMS  | Et_2O   | 14% (94%)   |
| 11    | NiBr_2.glyme | L9 | TMS  | Et_2O   | 24% (94%)   |
| 12    | NiBr_2.glyme | L9 | TMS  | DMF     | 99% (73%)   |
| 13    | NiBr_2.glyme | L9 | TMS  | DMF     | 56% (58%)   |
| 14    | NiBr_2.glyme | L9 | TMS  | Et_2O   | 98% (77%)   |
| 15    | NiBr_2.glyme | L9 | TMS  | Et_2O   | 99% (84%)   |
| 16    | Ni(COD)_2   | L9 | TMS  | Et_2O   | 99% (88%)   |
| 17    | Ni(COD)_2   | L9 | TMS  | Et_2O   | 94% (92%)   |
| 18    | Ni(COD)_2   | L9 | TMS  | Et_2O   | 99% (92%)   |
| 19    | Ni(COD)_2   | L9 | TMS  | Et_2O   | 93% (92%)   |

*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. L* = chiral ligand. TMS = trimethoxysilane. TES = triethoxysilane. DEMS = diethoxymethylsilane. DMMS = dimethoxymethylsilane. Et_2O/DMA = 3:1. DMA = N,N-dimethylacetamide. Et_2O/DMF = 3:1. Et_2O = diethyl ether. DMF = N,N-dimethylformamide. The reaction was run at 0 °C. The reaction was run for 24 h. Isolated yield after flash chromatography.
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, silyl ethers 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. Benzyl bromide was successfully converted to corresponding amide 3n in 88% yield with moderate enanitomereric excess. Second, internal acyl enamines were examined. Internal acyl enamines with diverse substituents could be converted to corresponding hydroalkylated products in good yields with excellent enantioselectivity. Acyl (E)-1-propaneamine reacted to give corresponding dialkyl amide 3o in 74% yield with 90% ee. Alternatively, acyl (Z)-1-propaneamine gave 3o in 80% yield with 81% ee under the same conditions. Longer alkyl chain- and benzyl-substituted internal acyl enamines were all good substrates for this reaction, affording corresponding amine derivatives (3p–3r) in 68–78% yields with 88–89% ee. Bromoindole containing alkyl iodide could be coupled with internal acyl enamine to deliver 3s in 63% yield with 92% ee.

Next, the scope of secondary acyl enamines was tested (Fig. 3). 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 hydroalkylation reaction, affording corresponding chiral amides (4p–4t) in

Fig. 2 Scope for alkyl iodides of tertiary acyl enamines and internal acyl enamines. For reaction conditions, see Table 1, entry 19 unless otherwise stated. 

aBenzyl bromide was used. bThe reaction was conducted using 1 (0.2 mmol), 2 (0.6 mmol) at 45 °C for 16 h.

ARTICLE NATURE COMMUNICATIONS | https://doi.org/10.1038/s41467-021-22983-7 | www.nature.com/naturecommunications
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. 4). Secondary acyl enamines gave better enantioselectivity using the analogue ligand L41. Then, 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 secondary alkyl-substituted amine derivative 5b was obtained by this protocol in 65% yield with 94% ee. Other 1-idoalkanes were also successfully converted to corresponding amine derivatives (5c–5e) in 63–80% yields with 93–98% ee. Chiral aminoaacohol 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, cholesteryl, 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.

### Substrate scope of dialkyl esters.

Next, enol esters were tested under the reaction conditions. To our delight, various enol esters could be tolerated and a wide range of chiral aliphatic alcohol derivatives were obtained in high enantioselectivity, which are difficult to access otherwise (Fig. 5). 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 iodide was tolerated in the reaction, furnishing the desired product (6j) in synthetic useful yields with 97% ee. Moreover, internal enol esters were well-tolerated in the reaction. Long-chain alkyl-substituted internal enol esters were successfully converted to corresponding chiral esters (6k–6m) in 58–70% yields with 91–94% ee. Chloro-containing alkyl-substituted internal enol ester underwent the desired hydroalkylation reaction to give 6n in 68% yield with 94% ee. The absolute configuration of the chiral ester was confirmed to be R by comparison to literature. Furthermore, literature procedures proved unprotected chiral aliphatic amines and

---

**Fig. 3 Scope for secondary acyl enamines.** The reaction was run on 0.2 mmol of acyl enamine and 0.4 mmol of alkyl iodide using DEMS (0.6 mmol) under indicated conditions unless otherwise stated. αDMMS was used instead of DEMS. βL41 was used as the ligand.
alcohols could be obtained via hydrolysis without erosion of enantioselectivities33,54, which further enhanced the synthetic utility of this method.

Mechanistic consideration. Then, we carried out the reaction using deuterated silane (Ph2SiD2)32 under otherwise identical to standard conditions (Fig. 6). The reaction of terminal acyl enamine with 3-phenyl-1-iodopropane in the presence of Ph2SiD2 afforded deuterated hydroalkylation product 7 in 61% yield with 93% ee (Fig. 6a). Only one deuterium incorporation (>95% D) was exclusively delivered to β-position to nitrogen of amide 7. No deuterium incorporation was found at α-position to nitrogen of 7. Next, the reactions of internal acyl enamine of both configurations were tested (Fig. 6b). The reaction of (E)-acyl enamine was slightly slower and delivered a lower yield and higher enantioselectivity of 9 in comparison to the generation of 8 from (Z)-acyl enamine50,51. These results indicated that Ni–H insertion onto acyl enamines to form alkyl-Ni species might be irreversible and enantio-determining.

Based on the mechanistic results and literature precedence28,34,42-45,48,49, two tentative mechanistic pathways are proposed and depicted in Fig. 7. In one possibility (Fig. 7a), nickel hydride species could be generated from ligated Ni(I) precursor in the presence of a silane and a 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. This M2 could oxidize an alkyl iodide (2) to form Ni(III) intermediate M3, which could undergo reductive elimination to give the final product 3 and regenerate Ni(I) catalyst. In the other possibility (Fig. 7b), ligated Ni(I) precursor undergoes single electron transfer with an alkyl iodide (2) to give an alkyl radical and Ni(II) intermediate. The latter could generate Ni(II)-H in the presence of a silane and a base, which could coordinate with 1 with the assistance of carbonyl group to form M1’. With regio- and enantioselective hydrometalation, M1’ generates alkyl nickel intermediate M2’, which could rebound with the alkyl radical to form Ni(III) intermediate M3’. M3’ undergoes reductive elimination to deliver the final product 3 and regenerate Ni(I) species.

Discussion
In summary, a unified protocol for Ni-catalyzed hydroalkylation of acyl enamines and enol esters with alkyl iodides under mild conditions was developed. The use of chiral BOX-based ligand enables the direct access of chiral secondary alkyl-substituted 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.

Methods
General procedure for hydroalkylation of tertiary acyl enamines. In a nitrogen-filled glovebox, Ni(COD)2 (5.5 mg, 0.02 mmol, 10 mol%) and L9 (21.8 mg, 0.024 mmol, 12 mol%) were dissolved in solvent (2 mL, Et2O: DMF = 3:1) in a Schlenk tube with screw-cap equipped with a magnetic stirrer. The mixture was stirred at room temperature for 10 min, then alkyl halide (0.4 mmol), tertiary acyl enamine (0.2 mmol), and K3PO4·H2O (0.6 mmol) were added sequentially. The mixture was cooled to 0 °C before DMMS (74 μL, 0.6 mmol, 3 equiv.) was added dropwise. The resulting mixture was stirred at 0 °C for 12–24 h (for 3o–s, stirred at 45 °C). After completion of the reaction, the mixture was filtered through a pad of silica gel and washed with ethyl acetate (3 × 15 mL). The filtrate was washed with water (15 mL). The organic phase was dried over Na2SO4, filtered, concentrated under reduced pressure, purified by flash chromatography with silica gel to give the pure product.
Fig. 5 Scope for the hydroalkylation of enol esters. The reaction was conducted on 0.2 mmol of enol ester (1.0 equiv.) and alkyl iodide (2.0 equiv.) using potassium phosphate monohydrate (3.0 equiv.) as base in Et₂O/DMF = 3:1 (0.1 M) at room temperature for 12 h unless otherwise stated. *5.0 equiv. of RI was used. b3.0 equiv. of RI was used. cThe reaction was conducted using alkyl iodide (3.0 equiv.) and potassium carbonate (3.0 equiv.) as base in Et₂O (3:1) in a Schlenk tube with screw-cap equipped with a magnetic stirrer. The mixture was stirred at room temperature for 10 min, then alkyl halide (0.4 mmol), acyl enamine (0.2 mmol), and K₃PO₄·H₂O (0.6 mmol) were added sequentially. The mixture was stirred at room temperature for another 5 min before DEMS (98 µL, 0.6 mmol, 3 equiv.) was added dropwise. The resulting mixture was stirred at room temperature for 12–24 h. After completion of the reaction, the mixture was filtered through a pad of silica gel and washed with ethyl acetate (3 × 15 mL). The filtrate was washed with water (15 mL). The organic phase was dried over Na₂SO₄, filtered, concentrated under reduced pressure, purified by flash chromatography with silica gel to give the pure product.

General procedure for hydroalkylation of secondary acyl enamines. In a nitrogen-filled glovebox, Ni(COD)₂ (5.5 mg, 0.02 mmol, 10 mol%) and L₄₁ (8.4 mg, 0.024 mmol, 12 mol%) were dissolved in solvent (2 mL, Et₂O: DMF = 3:1) in a Schlenk tube with screw-cap equipped with a magnetic stirrer. The mixture was stirred at room temperature for 10 min, then alkyl halide (0.4 mmol), acyl enamine (0.2 mmol), and K₃PO₄·H₂O (0.6 mmol) were added sequentially. The mixture was stirred at room temperature for another 5 min before DEMS (98 µL, 0.6 mmol, 3 equiv.) was added dropwise. The resulting mixture was stirred at room temperature for 12–20 h. After completion of the reaction, the mixture was filtered through a pad of silica gel and washed with ethyl acetate (3 × 15 mL). The filtrate was washed with water (15 mL). The organic phase was dried over Na₂SO₄, filtered, concentrated under reduced pressure, and purified by flash chromatography with silica gel to give the pure product.

Data availability
The authors declare that all other data supporting the findings of this study are available within the article and Supplementary information files, and also are available from the...
corresponding author upon reasonable request. The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers of CCDC 2042842 and CCDC 2042844. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: 15 December 2020; Accepted: 9 April 2021; Published online: 13 May 2021

References
1. Nugent, T. C. & El-Shazly, M. Chiral amine synthesis – recent developments and trends for enamide reduction, reductive amination, and imine reduction. Adv. Synth. Catal. 352, 753–819 (2010).
2. Kittakoop, P., Mahidol, C. & Ruchirawat, S. Alkaloids as important scaffolds for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers of CCDC 2042842 and CCDC 2042844. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Fig. 7 Proposed mechanism for the reaction. Ligand is omitted for clarity. a Ni(I)-H pathway. b Ni(II)-H pathway.

8. Nakafuku, K. M. et al. Enantioselective radical C–H amination for the synthesis of β-amino alcohols. Nat. Chem. 12, 697–704 (2020).
9. Liu, G. C., Cogan, D. A. & Ellman, J. A. Catalytic asymmetric synthesis of tert-butanesulfanilamide. Application to the asymmetric synthesis of amines. J. Am. Chem. Soc. 119, 9913–9914 (1997).
10. Fujihara, H., Nagai, K. & Tomioka, K. Copper-amidophosphine catalyst in asymmetric addition of organozinc to imines. J. Am. Chem. Soc. 122, 12055–12056 (2020).
11. Boezio, A. A. & Charette, A. B. Catalytic enantioselective addition of dialkylzinc to N-diphenylphosphinoylimines. A practical synthesis of a-chiral amines. J. Am. Chem. Soc. 125, 1692–1693 (2003).
12. Véguiès, M., Solá, R., Shaw, L. & Macià, B. Catalytic asymmetric addition of organolithium reagents to aldehydes. Eur. J. Org. Chem. 2016, 1788–1794 (2016).
13. Fernández-Mateos, E., Macià, R. & Yus, M. Catalytic enantioselective addition of allyl grignard reagents to aliphatic aldehydes. Adv. Synth. Catal. 355, 1249–1254 (2013).
14. Friedfeld, M. R., Zhong, H., Ruck, R. T., Shevlin, M. & Chirik, P. J. Cobalt-catalyzed asymmetric hydrogenation of enamides enabled by single-electron reduction. Science 360, 888–893 (2018).
15. Massaro, L., Zheng, I., Margarita, C. & Andersson, P. G. Enantioconvergent and enantiodivergent catalytic hydrogenation of isomeric olefins. Chem. Soc. Rev. 49, 2504–2522 (2020).
16. Jiang, Q., Jiang, Y., Xiao, D., Cao, P. & Zhang, X. Highly enantioselective hydrogenation of simple ketones catalyzed by a Rh-PennPhos complex. Angew. Chem. Int. Ed. 37, 1101–1103 (1998).
17. Ohkuma, T. et al. Asymmetric hydrogenation of tert-alkyl ketones. J. Am. Chem. Soc. 127, 8288–8289 (2005).
18. Yamamura, T., Nakatsuka, H., Tanaka, S. & Kitamura, M. Asymmetric hydrogenation of tert-alkyl ketones: DMSO effect in unification of stereoisomeric ruthenium complexes. Angew. Chem. Int. Ed. 52, 9313–9315 (2013).
19. Garbe, M. et al. Manganese(I)-catalyzed enantioselective hydrogenation of ketones using a defined chiral PNP pincer ligand. *Angew. Chem. Int. Ed.* 56, 11227–11241 (2017).

20. Štefánek, B. & Požgan, F. Advances in catalyst systems for the asymmetric hydrogenation and transfer hydrogenation of ketones. *Catal. Rev.* 56, 82–174 (2014).

21. Kobayashi, S., Mori, Y., Fossey, J. S. & Salter, M. M. Catalytic enantioselective formation of C−C bonds by addition to imines and hyrazones: a ten-year update. *Chem. Rev.* 111, 2626–2704 (2011).

22. Miyabe, H., Ushiro, C., Ueda, M., Yamakawa, K. & Naito, T. Asymmetric synthesis of α-amino acids based on carbon radical addition to glyoxylic oxime ether. *J. Org. Chem.* 65, 176–185 (2000).

23. Friestad, G. K., Shen, Y. & Ruggles, E. L. Enantioselective radical addition to N-acyl hydrazones mediated by chiral Lewis acids. *Angew. Chem. Int. Ed.* 42, 5061–5063 (2003).

24. Cho, D. H. & Jang, D. O. Enantioselective radical addition reactions to the C–N bond utilizing chiral quaternary ammonium salts of hypophosphorous acid in aqueous media. *Chem. Commun.* 2006, 5045–5047 (2006).

25. Zhang, F.-H., Zhang, F.-J., Li, M.-L., Xie, J.-H. & Zhou, Q.-L. Enantioselective hydrogenation of diacyl ketones. *Nat. Catal.* 3, 621–627 (2020).

26. Pirnot, M. T., Wang, Y.-M. & Buchwald, S. L. Copper hydride catalyzed hydroamination of alkenes and alkynes. *Angew. Chem. Int. Ed.* 55, 48–57 (2016).

27. Liu, R. Y. & Buchwald, S. L. CuI-catalyzed olefin functionalization: from hydrogenation to alkynylation. *Acc. Chem. Res.* 53, 1229–1243 (2020).

28. Lu, X. et al. Practical carbon–carbon bond formation from olefins through nickel-catalyzed reductive olefin hydrocarbonation. *Nat. Chem.* 7, 11129 (2016).

29. Lu, X., Xiao, B., Liu, L. & Fu, Y. Formation of C(sp)2–C(sp)3 bonds through nickel-catalyzed carboxylative deoxyhydrogenation reactions. *Chem. Eur. J.* 22, 11161–11164 (2016).

30. Zhou, F., Zhu, J., Zhang, Y. & Zhu, S. NiH-catalyzed reductive relay hydroalkylation: a strategy for the remote C(sp)3–H alkylation of alkenes. *Angew. Chem. Int. Ed.* 57, 4058–4062 (2018).

31. Sun, S.-Z., Börjesson, M., Martin-Montero, R. & Martin, R. Site-selective Ni-catalyzed reductive coupling of α-haloboranes with unactivated olefins. *J. Am. Chem. Soc.* 140, 12765–12769 (2018).

32. Bera, S. & Hu, X. Nickel-catalyzed regioselective hydroalkylation and hydroarylation of alkenyl boronic esters. *Angew. Chem. Int. Ed.* 58, 13854–13859 (2019).

33. Sun, S.-Z., Romano, C. & Martin, R. Site-selective catalytic deaminative alkylation of unactivated olefins. *J. Am. Chem. Soc.* 141, 16197–16201 (2019).

34. Qian, D. & Hu, X. Ligand-controlled regiodivergent hydroalkylation of pyrrolines. *Angew. Chem. Int. Ed.* 58, 18519–18523 (2019).

35. Wang, C., Xi, Y., Huang, W., Qu, J. & Chen, Y. Nickel-catalyzed regioselective hydroarylation of internal enamines. *Org. Lett.* 22, 9319–9324 (2020).

36. Fu, G. C. Transition-metal catalysis of nucleophilic substitution reactions: a rapid alternative to Sn1 and Sn2 processes. *ACS Cent. Sci.* 3, 692–700 (2017).

37. Cherney, A. H., Kadunce, N. T. & Reisman, S. E. Enantioselective and enantiospecific transition-metal-catalyzed cross-coupling reactions of organometallic reagents to construct C–C bonds. *Chem. Rev.* 115, 9587–9652 (2015).

38. Cuesta-Galisteo, S., Schörgenhuber, J., Wei, X., Merino, E. & Nevado, C. Nickel-catalyzed asymmetric synthesis of α-arylenamidines. *Angew. Chem. Int. Ed.* 60, 1605–1609 (2021).

39. He, Y., Liu, C., Yu, L. & Zhu, S. Enantio- and regioselective NiH-catalyzed reductive hydroarylation of vinylarenes with aryl iodides. *Angew. Chem. Int. Ed.* 59, 21530–21534 (2020).

40. He, Y., Song, H. & Zhu, S. NiH-catalyzed asymmetric hydroarylation of N-acetyl enamines: practical access to chiral benzylamines. *Nat. Commun.* 12, 638 (2021).

41. Liu, J., Gong, H. & Zhu, S. Nickel-catalyzed, regio- and enantioselective benzyl alkylation of olefins with alkylm bromide. *Angew. Chem. Int. Ed.* 50, 4060–4064 (2011).

42. Wang, Z., Yin, H. & Fu, G. C. Catalytic enantioconvergent coupling of secondary and tertiary electronophiles with olefins. *Nature* 563, 379–383 (2018).

43. Zhou, F., Zhang, Y., Xu, X. & Zhu, S. NiH-catalyzed remote asymmetric hydroalkylation of alkenes with racemic α-bromo amides. *Angew. Chem. Int. Ed.* 58, 1754–1758 (2019).

44. He, S.-J. et al. Nickel-catalyzed enantioconvergent reductive hydroalkylation of olefins with α-heteronatom phosphorus or sulfur alkyl electrophiles. *J. Am. Chem. Soc.* 142, 214–221 (2020).

45. Yang, Z.-P. & Fu, G. C. Convergent catalytic asymmetric synthesis of esters of chiral dialkyl carbamions. *J. Am. Chem. Soc.* 142, 5870–5875 (2020).

46. Sommer, H., Juhil-Hernández, F., Martin, R. & Marek, I. Walking metals for remote functionalization. *ACS Cent. Sci.* 4, 153–165 (2018).

47. Vasseur, A., Bruffaerts, J. & Marek, I. Remote functionalization through alkene isomerization. *Nat. Chem.* 8, 209–219 (2016).

48. Shi, L., Xing, L.-L., Hu, W.-B. & Shu, W. Regio- and enantioselective Ni-catalyzed formal hydroalkylation, hydroborylation, and hydropropargylation of acrylamides to α-tertiary amides. *Angew. Chem. Int. Ed.* 60, 1599–1604 (2021).

49. Bera, S., Mao, R. & Hu, X. Enantioselective C(sp)2-C(sp)3 cross-coupling of non-activated alkyl electrophiles via nickel hydride catalysis. *Nat. Chem.* 13, 270–277 (2021).

50. Wang, J.-W. et al. Catalytic asymmetric reductive hydroalkylation of enamides and enecarbamates to chiral aliphatic amines. *Nat. Commun.* 12, 3133 (2021).

51. Qian, D., Bera, S. & Hu, X. Chiral alky amine synthesis via catalytic enantioselective hydroalkylation of enecarbamates. *J. Am. Chem. Soc.* 143, 1959–1967 (2021).

52. Wang, S. et al. Enantioselective access to dialkyl amines and alcohols via Ni-catalyzed reductive hydroalkylations. Preprint at https://doi.org/10.26434/chemrxiv.13284416.v1 (2020).

53. Matteson, D. S., Ray, R., Rocks, R. R. & Tsai, D. J. S. Directed chiral synthesis by way of α-chloro boronic esters. *Organometallics* 2, 1536–1543 (1983).

54. Wei, X., Shu, W., García-Dominguez, A., Merino, E. & Nevado, C. Asymmetric Ni-catalyzed radical relayed reductive coupling. *J. Am. Chem. Soc.* 142, 13515–13522 (2020).

55. Klemán, P., González-Liste, P. J., García-Garrido, S. E., Ciudadro, V. & Pizzano, A. Highly enantioselective hydrogenation of 1-allylvinyl benzoates: a simple, nonenzymatic access to chiral 2-alkanols. *Chem. Eur. J.* 19, 16209–16212 (2013).