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Chiral Alkyl Amine Synthesis via Catalytic Enantioselective Hydroalkylation of Enecarbamates

Deyun Qian, Srikrishna Bera, and Xile Hu*

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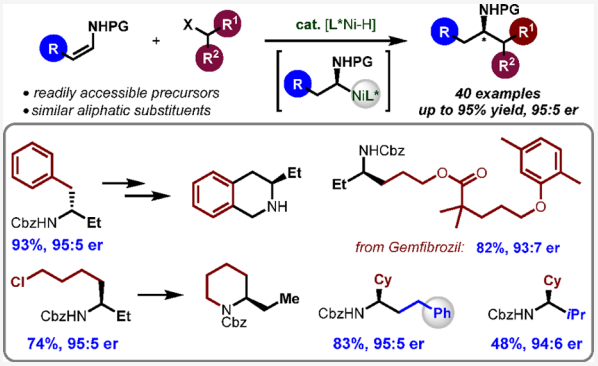
ABSTRACT: Chiral alkyl amines are omnipresent as bioactive molecules and synthetic intermediates. The catalytic and enantioselective synthesis of alkyl amines from readily accessible precursors is challenging. Here we develop a nickel-catalyzed hydroalkylation method to assemble a wide range of chiral alkyl amines from enecarbamates (*N*-Cbz-protected enamines) and alkyl halides with high regio- and enantioselectivity. The method works for both nonactivated and activated alkyl halides and is able to produce enantiomerically enriched amines with two minimally differentiated α-alkyl substituents. The mild conditions lead to high functional group tolerance, which is demonstrated in the postproduct functionalization of many natural products and drug molecules, as well as the synthesis of chiral building blocks and key intermediates to bioactive compounds.



1. INTRODUCTION

Enantiomerically pure amines are frequently encountered in natural products, pharmaceuticals, and agrochemicals (Figure 1A).[1] They are also important building blocks and chiral auxiliaries in asymmetric synthesis. General, catalytic, and enantioselective assembly of chiral amines, especially those with two minimally differentiated aliphatic substituents, represents a synthetic challenge.[1c] Although chiral amines can be prepared by the hydrogenation of imines, enamines, and their derivatives using precious-metal catalysts (Figure 1B), the catalysts are costly and the substrates typically have an α-aryl or α-carboxyl substituent.[2] Likewise, enantioselective addition of an alkyl organometallic reagent[1b,3] or an alkyl radical[1b,4] to imine derivatives is mostly applicable to the synthesis of chiral amines with one α-aryl or α-carboxyl group, in addition to requiring either highly activated substrates or high catalyst loadings (Figure 1C,D). Recent breakthroughs in CuH-catalyzed asymmetric hydroamination of internal alkenes provide a new approach to chiral amine synthesis (Figure 1E).[5] Nevertheless, trisubstituted, tetrasubstituted, and cis-disubstituted alkenes and alkenes bearing electron-donating substituents are still difficult substrates, limiting the types of chiral amines that can be prepared from this approach.[5a,6]

Ni-catalyzed hydroalkylation of alkenes[7] has emerged as an attractive alternative to traditional alkyl−alkyl cross-coupling.[8] By using stable and abundant alkenes as pro-nucleophiles instead of reactive organometallic reagents, hydroalkylation offers substantial advantages in practicality, scope, and functional group compatibility over conventional cross-coupling. Several elegant examples of asymmetric hydroalkylation to create a new stereocenter at the carbon originating from activated alkyl electrophiles have been reported.[9] However, enantioselective hydroalkylation to introduce a new stereocenter at the carbon originating from the alkenes is challenging due to the tendency of Ni−H to mediate chain walking of an internal alkene to form a terminal, nonchiral Ni−alkyl species.[10] By installing an α-directing group such as boryl and aryl, our group[11] and the Zhu group[12] were recently able to develop Ni-catalyzed enantioselective hydroalkylation and hydroarylation for the synthesis of chiral alkyl boronates and 1,1-diarylalkanes, respectively. The electron-withdrawing α-directing groups are essential in stabilizing the branched alkyl−Ni intermediates against chain walking. In this context, we envisioned enantioselective hydroalkylation of enamine derivatives for the synthesis of chiral amines (Figure 1F). If successful, this approach would be general and efficient in introducing a diverse set of alkyl groups at the α-position of chiral amines, a task difficult to achieve using existing methods. Moreover, because enamines can be easily prepared from readily available alkyl aldehydes or other precursors,[13] the approach will have a wide scope or be more practical than hydrogenation of imines, which requires less accessible dialkyl ketones as reagents. However, an *N*-based α-substituent as in enamine derivatives is typically considered an electron-

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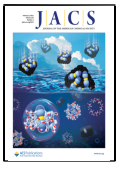

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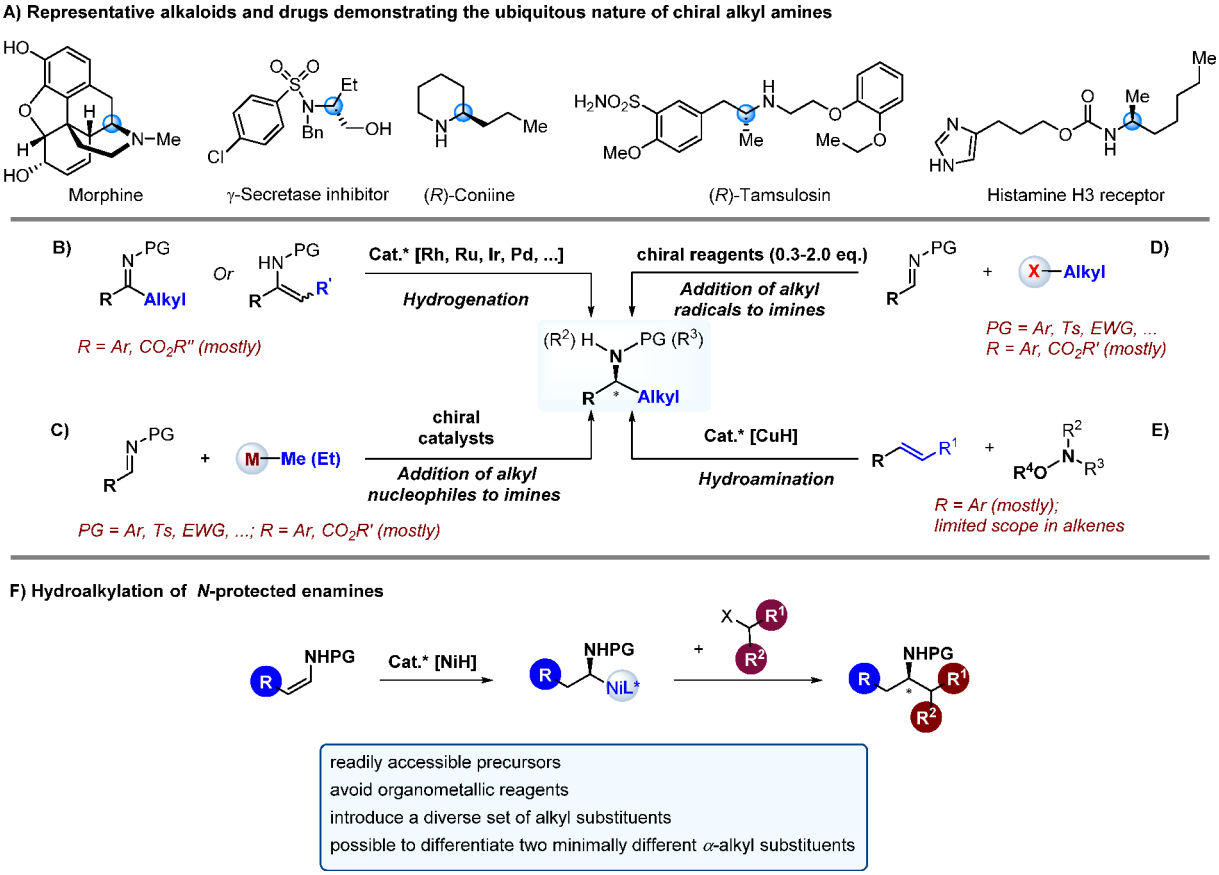


Figure 1. Significance of chiral α-alkyl amines and representative methods of their synthesis.

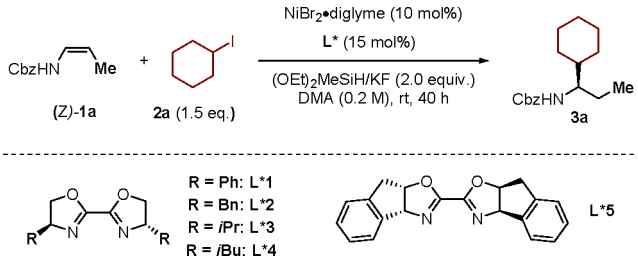
donating group.[2b] When we started, there was no prior report that such a group would stabilize a branched alkyl−Ni intermediate to direct enantioselective hydroalkylation, although a report of Ni-catalyzed enantioselective hydroarylation of *N*-vinyl amides appeared while we were writing this manuscript.[14]

Here we describe the development of a modular method based on this approach. The method allows the enantioselective coupling of a wide range of *N*-Cbz-protected enamines (Cbz = benzyloxycarbonyl) with both activated and non-activated alkyl halides to give enantiomerically enriched α-alkyl chiral amines. The method has high group tolerance and can be used for the functionalization of many natural products and bioactive compounds, as well as the synthesis of valuable chiral intermediates.

2. RESULTS AND DISCUSSION

2.1. Reaction Development of Enantioselective Hydroalkylation. We started the development by optimizing the hydroalkylation of benzyl (*Z*)-*N*-(prop-1-en-1-yl)-carbamate (**1a**, 1.0 equiv) using iodocyclohexane (**2a**, 1.5 equiv) as the alkylating agent, a silane or hydroborane (2.0 equiv) as the hydride source, and a nickel salt (10 mol %) in combination with a chiral nitrogen-based ligand (15 mol %) as the catalyst (Table 1). We chose Cbz as the *N*-protecting group because this carbamate group could be easily removed, unlike other acyl groups used in related studies.[14] An initial screening suggested room temperature and 40 h as appropriate conditions. The influence of ligands, Ni salts, hydride sources, bases, and solvents and the outcome of control experiments are described in Tables S1−S6 in the Supporting Information. A key summary is shown in Table 1. With diethoxymethylsilane

Table 1. Summary of the Effects of Key Reaction Parameters[a]



entry	variant	yield (%)	er[b]
1	**L*** = **L*1**	91	90:10
2	**L*** = **L*2**	83	65:35
3	**L*** = **L*3**	41	55:45
4	**L*** = **L*4**	97	70:30
5	**L*** = **L*5**	84	82:18
6	HBpin instead of DEMS	85	92:8
7	HBcat instead of DEMS	27	89:11
8	DMPU instead of DMA	92 (87)[c]	94:6

[a]See section 2 in the the Supporting Information for experimental details. All reactions were carried out in a 0.1 mmol scale with respect to **1a**, Corrected GC yields using *n*-dodecane as an internal standard were reported. Definitions: DMA, dimethylacetamide; DEMS, diethoxymethylsilane; DMPU, *N*,*N*′-dimethylpropyleneurea; Cbz, benzyloxycarbonyl; rt, room temperature. [b]The er values were determined by HPLC analysis. [c]Isolated yield.

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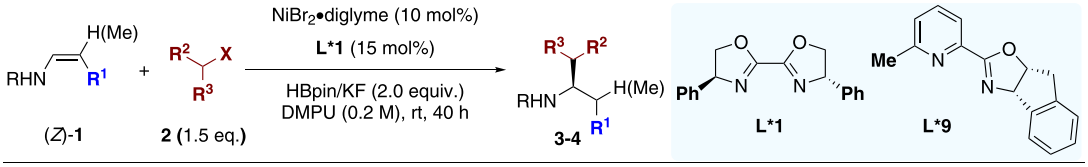
Table 2. Scope of Ni-Catalyzed Enantioselective Hydroalkylation of Enecarbamates[a]



Secondary alkyl iodides

(+)-3a
87%, 94:6 er
with *ent*-L*1:
(–)-3a
85%, 6:94 er

3b
86%, 91:9 er

3c
71%, 93:7 er

3d[b]
61%, 94:6 er

3e
65%, 95:5 er

3f
67%, 93:7 er

3g[b]
45%, 86:14 er

3h
91%, 93.5:6.5 er

2i
70:30
cis/trans

3i, 75:25 dr[c]
70%, 94:6 er

Primary alkyl iodides

3j
71%, 92:8 er

3k
81%, 94.5:5.5 er

3l
74%, 95:5 er

3m
65%, 93:7 er

3n[b]
60%, 94:6 er

3o[d]
52%, 92:8 er

3p[d]
63%, 92:8 er

3q[d]
64%, 90:10 er

3r
57%, 88:12 er

Benzylic bromides

3s
92%, 95:5 er

3t
82%, 95:5 er

3u
74%, 94.5:5.5 er

3v
51%, 95:5 er

3w
95%, 94:6 er

Enecarbamates

4a
63%, 94:6 er

4b, R = Cbz: 83%, 95:5 er
4c, R = Boc: 82%, 86:14 er

4d, X = CH_2: 65%, 95:5 er
4e, X = NBoc: 72%, 93:7 er

4f
54%, 94.5:5.5 er

4g
72%, 94:6 er

4h
72%, 93:7 er

4i
48%, 94:6 er

4j, 22%, 95:5 er[e]
85%, 93:7 er[f]

[a]Conditions unless noted otherwise: all reactions were carried out with $NiBr_2$·diglyme (15 mol %), ligand **L*1** (15 mol %), **1** (0.20 mmol), **2** (0.30 mmol), HBpin (0.40 mmol), KF (0.40 mmol), and DMPU (1.0 mL) at room temperature for 40 h. [b]$(OEt)_2MeSiH$ instead of HBpin. [c]The dr value was determined by ^1H NMR and HPLC analysis. [d]DMA instead of DMPU. [e]NiI_2·xH_2O, **L*9**, and DMA instead of the corresponding standard parameters. [f]**1i**:**2a** = 1.5:1; NiI_2·xH_2O, **L*9**, $(OEt)_3SiH$, and DMA instead of the corresponding standard parameters.

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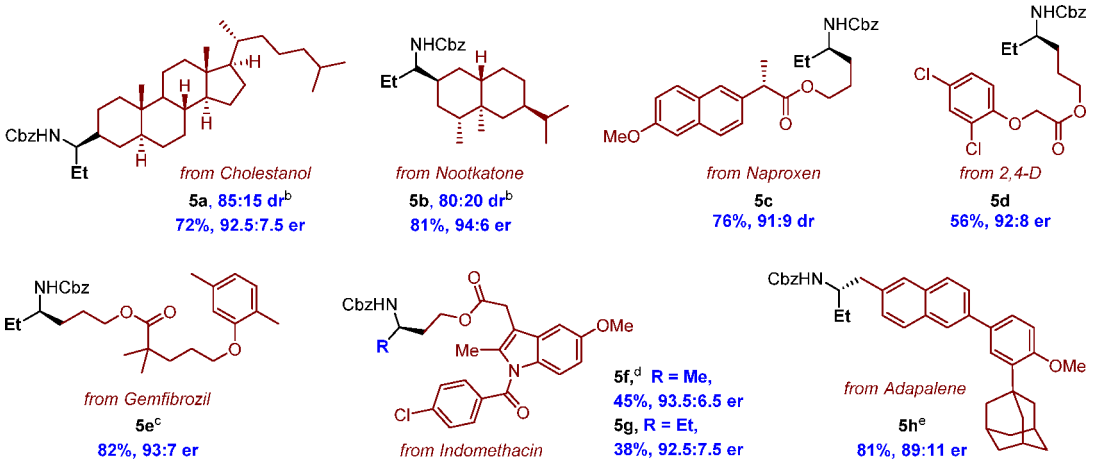
Table 3. Reactions of Substrates Derived from Natural Products and Drugs[a]



[a]Conditions unless specified otherwise: all reactions were carried out with $NiBr_2$·diglyme (15 mol %), ligand **L*1** (15 mol %), **1** (0.20 mmol), **2** (0.30 mmol), HBpin (0.40 mmol), KF (0.40 mmol), and DMPU (1.0 mL) at room temperature for 40 h. [b]The dr value was determined by ^{1}H NMR and HPLC analysis. [c]DMA instead of DMPU. [d]NiI_2·xH_2O, **L*9**, $(OEt)_3SiH$, and DMA instead of the corresponding standard parameters. [e]*ent*-**L*1** instead of **L*1**.

(DEMS) as the hydride source, 2,2-bis(2-oxazoline) (Bi-Ox) and pyridine-oxazoline (Py-Ox) ligands were effective, giving the desired product **3a** in various yields and enantiomeric ratios (ers), whereas bis-oxazoline (Box), pyridine bis-oxazoline (Pybox), and phosphinooxazoline (Phox) ligands gave no product (Table S1 in the Supporting Information). A large number of Bi-Ox ligands were screened, revealing the sensitivity of the reaction outcome on the substituents of the ligands. Aryl substituents typically gave higher ers than alkyl substituents (entries 1−5, Table 1), and the best result was obtained with the phenyl-substituted Bi-Ox ligand **L*1**, which gave a yield of 91% and an er of 90:10 (entry 1, Table 1). $NiBr_2$·diglyme was the best Ni source among various Ni(II) salts (Table S2 in the Supporting Information). Several hydrosiloxanes could be used as the hydride source with similar efficiency, but less electrophilic hydrosilanes such as Et_3SiH and Ph_2MeSiH were inefficient (Table S3 in the Supporting Information). The enantiomeric ratio was increased to 92:8 using pinacolborane (HBpin) as the hydride source (entry 6, Table 1), while the yield remained as high as 85%. A slightly lower er but much lower yield was obtained using catecholborane (HBcat) (entry 7, Table 1). Different bases gave similar enantioselectivities but very different yields, and KF was the best base (Table S4 in the Supporting Information). The yields and, to a lesser degree, the ers were sensitive to the solvents (Table S5 in the Supporting Information). A meticulous screening revealed *N,N′*-dimethylpropyleneurea (DMPU) to be the best solvent (entry 8, Table 1). Thus, the final optimized conditions were identified as $NiBr_2$·diglyme (10 mol %) plus Bi-Ox **L*1** (15 mol %) as the catalyst, HBpin (2.0 equiv) as the hydride source, KF (2.0 equiv) as the base, and DMPU as the solvent. Under these conditions, **3a** was obtained as a single regioisomer in 92% GC (87% isolated) yield with an er of 94:6 (entry 8, Table 1). In comparison to the Ni-catalyzed hydroalkylation of alkenyl boronates,[11] the best chiral ligand is the same while the optimized Ni salt, hydride source, and solvent are all different, indicating a strong influence of the directing group in the reactivity. Two recent reports describe Ni-catalyzed enantioselective hydroarylation of alkenes where the best ligands were based on bisimidazolines,[14a,c] a different class of ligands in comparison to the Bi-Ox used here. This difference suggests a mechanistic divergence in these related reactions.

2.2. Scope of Enantioselective Hydroalkylation. We then explored the scope of this enantioselective hydroalkylation method (Table 2). The method worked well for the coupling of various secondary alkyl iodides, including both acyclic and cyclic substrates, to give the corresponding chiral dialkyl amines with good yields and high enantioselectivity (**3a−i**). These products would be difficult to access via enantioselective cross-coupling,[8b,c] which is difficult for the coupling of two secondary alkyl fragments.[15] Cyclic groups relevant to medicinal chemistry such as 2*H*-pyran, piperidine, and oxetane were well tolerated (**3e−g**). Hydroalkylation with **2i** had a good yield and er but moderate diastereoselectivity (**3i**).

The hydroalkylation method worked for primary alkyl iodides as well. Functional groups such as chloride (**3l**), ether (**3m**), acetal (**3n**), ketone (**3o**), ester (**3p**), furan (**3p**), phthalimide (**3q**), indole (**3r**), and amine (**3r**) were all compatible. In addition to nonactivated alkyl halides, activated halides such as benzylic bromides were also suitable substrates for the hydroalkylation, yielding the corresponding chiral amines in good yields and high enantioselectivity (**3s−w**). The absolute configuration of **3s** was determined as *R* by comparing its optical rotation value to a reported compound (section 9 in the Supporting Information). We assigned the same absolute configuration to all analogous products. The reactions were insensitive to the electronic properties of the substituents of the benzylic bromides. An aryl bromide group was tolerated in the reaction (**3u**), reserving a reaction site for further downstream cross-coupling. The coupling of unactivated tertiary alkyl iodides such as *tert*-butyl iodide was unsuccessful.

An array of enecarbamates could be used as the pronucleophiles for the enantioselective hydroalkylation (**4a−j**). Not only CbzNH but also BocNH (**4c**, Boc = *tert*-butoxycarbonyl) was a viable directing group. The C−C bond formation was regioselective at the carbon α to the RNH group, even in the presence of an aryl group (**4b,c**). Functional groups such as alkyl chlorides (**4d,e**) and esters (**4f,g**) on

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enecarbamates were tolerated. Coupling of a sterically demanding β,β'-disubstituted enecarbamate had a modest yield (48%) but a high er (94:6) (**4i**). Vinylamine, a synthetically useful substrate that poses a challenge in regioselectivity,[16] was coupled to give a single regioisomer (**4j**) with a high yield and high enantioselectivity with modified reaction conditions. The reaction with a trisubstituted enecarbamate was unsuccessful, however (end of section 6 in the Supporting Information), probably due to steric hindrance that blocked Ni−H insertion.

2.3. Functionalization of Natural Products and Drugs. The enantioselective hydroalkylation method worked for alkyl halide substrates derived from natural products and drugs, generating chiral alkyl amines bearing the corresponding complex or bioactive alkyl fragments (Table 3).[17] Alkyl iodides derived from cholestanol, a biomarker (**5a**),[17a] nootkatone, a sesquiterpenoid (**5b**),[17b] and naproxen, a nonsteroidal anti-inflammatory drug (**5c**),[17c] which contained one or more stereocenters, reacted to give the corresponding chiral alkyl amines in good yields, high enantioselectivity, and modest to good diastereoselectivity. Alkyl iodides derived from drugs such as gemfibrozil (**5e**), indomethacin (**5f,g**), and adapalene (**5h**) as well as from the herbicide 2,4-D (**5d**) were viable reaction partners. These results underscore the high group tolerance of the hydroalkylation method and its potential application in the synthesis of bioactive chiral amines.

2.4. Synthetic Applications. The chiral alkyl amines produced from the above hydroalkylation method proved to be useful synthetic intermediates.[18] For example, simple silyl ether deprotection of **3m** afforded the amino alcohol **6** in high yield (Figure 2). Compound **6** is a common synthon in asymmetric organic synthesis because its OH moiety can be easily converted to other functional groups without erosion in enantiomeric excess: for instance, in the synthesis of a chiral piperidine (**7a**)[18a] and a β-amino acid (**7b**).[18b] In another example, a Finkelstein reaction of **3l** followed by base treatment provided a (*R*)-coniine analogue (**8**) in 53% yield and 94:6 er. The chiral amine (−)-**3s** was a reported intermediate to (*R*)-1,2,3,4-tetrahydroisoquinoline (**11**), an inhibitor of phenylethanolamine *N*-methyltransferase. Previously (−)-**3s** was prepared in three steps from **10**, which was in turn prepared by organocatalytic conjugate addition of a nitroalkane to vinylsulfone.[18c] With the current method, (−)-**3s** was prepared in one step from enecarbamate **1a** and benzyl bromide. Deprotection of the Cbz moiety in (−)-**3s** by Pd/C-catalyzed hydrogenation gave the primary amine, which was converted without isolation into intermediate **9** with perfect stereocontrol.

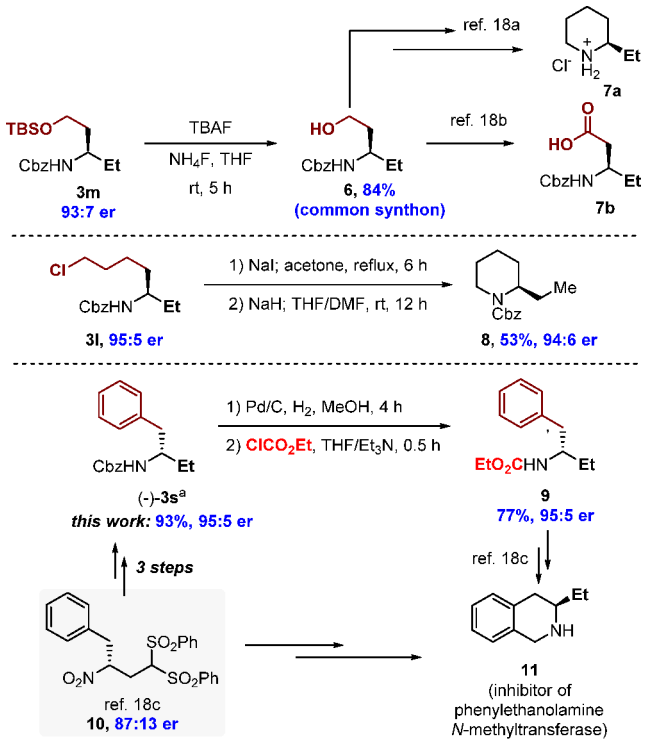

Figure 2. Synthetic applications. See section 7 in the Supporting Information for full details. TBAF = tetrabutylammonium fluoride. Legend: (a) with *ent*-**L*1**.

2.5. Mechanistic Investigation. Several experiments were conducted to probe the origin of the enantioselectivity in the present hydroalkylation reactions. When the *E* isomer of **1a** was subjected to the standard conditions (entry 8, Table 1), **3a** was produced just using (*Z*)-**1a**. The reaction of (*E*)-**1a** was slightly slower and had a lower yield and enantioselectivity in comparison to the reaction of (*Z*)-**1a** (Figure 3a). This result is consistent with Ni−H insertion into the alkene as the enantiodetermining step. If reductive elimination were the enantiodetermining step, a similar er would be expected for reactions using either (*Z*)-**1a** or (*E*)-**1a**.[12,14,19] The reactions of (*Z*)-**1a** and (*E*)-**1a** with DBpin gave diastereomerically pure **D-3h** and **D-3h′** (Figure 3b,c). Likewise, reactions of (*Z*)-**1c** and its deuterated analogue, enecarbamate **D**-(*Z*)-**1c**, gave diastereomerically pure **D-4k** and **D-4k′**, respectively (Figure 3d,e). These results again suggest that *syn*-hydrometalation of NiH or NiD to *N*-Cbz enamine is the enantiodetermining step. Otherwise, a diastereomeric mixture of deuterated products would be formed. In the reactions involving deuterated substrates, the enantioselectivity was not influenced by the deuteration. The ^{1}H NMR spectrum of **D-4k′** indicated that no H/D exchange occurred at the N α-position, suggesting that the hydride insertion step was irreversible. Overall, the above results indicate that a reaction pathway involving reversible Ni−alkyl homolysis followed by stereoselective reductive elimination[12,14,19] can be excluded for the current system.

When the allylic amine derivative **1a′** was used as the pronucleophile, **3a** was also produced, albeit in a lower yield and er, together with other regioisomers (Figure 3f). This result indicates chain walking of the distal alkenyl group mediated by Ni−H to form an α-CbzHN-stabilized Ni−alkyl species.[10] When the *N*-methyl enecarbamate (*Z*)-**1a′′** was used as the substrate, less than 5% hydroalkylation occurred (Figure 3g). The low activity toward this tertiary carbamate might be due to the conformational rigidity of a tertiary carbamate, which precluded the Cbz group to act as a directing group for Ni−H insertion (see below). To probe the possibility of Ni-catalyzed hydroboration of enecarbamate followed by alkyl−alkyl Suzuki cross-coupling, we treated the hydroboration product relevant to the hydroalkylation reaction. However, no cross-coupling occurred, ruling out the Suzuki coupling pathway (Figure 3h). When 1.0 equiv of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), a radical scavenger, was added to the reaction mixture, the conversion decreased to 54% and the yield decreased to 12% while the er remained the same (Figure 3i). This result is consistent with the intermediate of an alkyl

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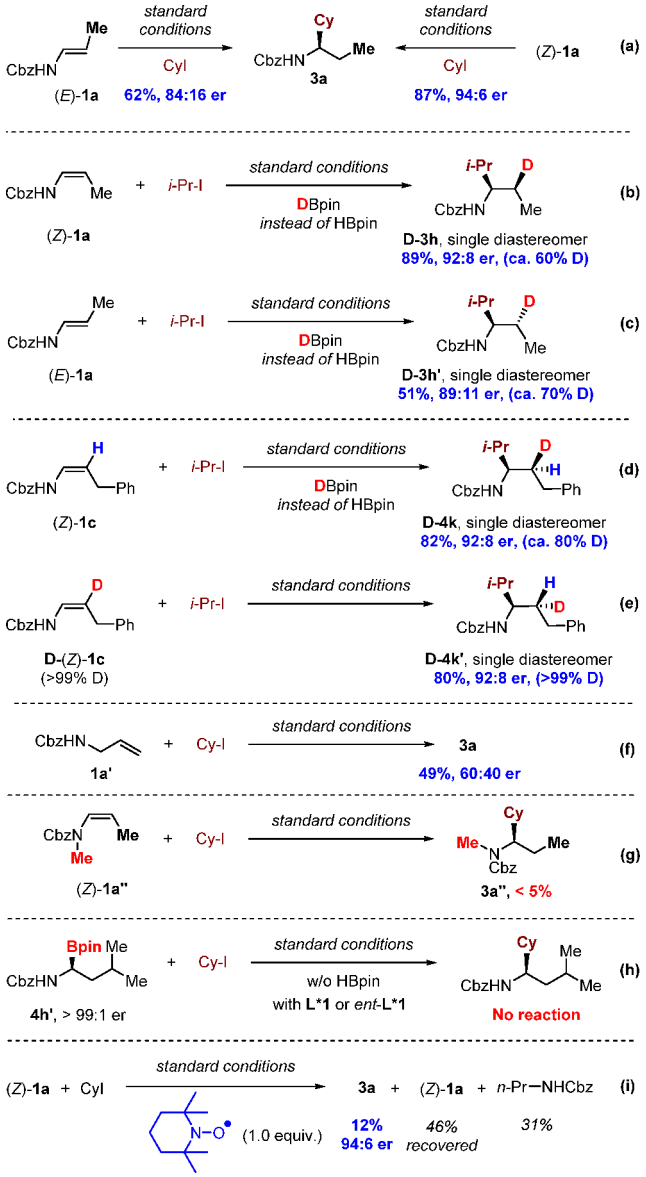

Figure 3. Results of mechanistic experiments.

radical in the hydroalkylation reaction, which was inhibited by TEMPO.[9a] Meanwhile, the hydrogenation product was obtained in 31% yield, revealing that the Ni–alkyl species formed upon Ni–H insertion underwent mostly C–H reductive elimination instead of alkyl–alkyl coupling in the presence of TEMPO. We cannot rule out the possibility that TEMPO inhibited the reaction by abstracting an H atom from a Ni–H species. Thus, we conducted additional reactions using radical clock substrates. The reactions of 5-iodopent-1-ene and an alkyl iodide containing a cyclopropyl ring gave ring-closed and ring-opened products, respectively, albeit in low yields (<10%) probably due to side reactions (see section 8.2 in the Supporting Information). This result supports the intermediacy of alkyl radicals.[21] However, direct addition of alkyl radicals to alkenes is not a viable pathway, as indicated by the regioselectivity of α-alkylation.

The reaction progress of (*Z*)-**1a** with **2a** was monitored over time (Figure 4a). While the yield increased gradually over the course of the reaction, the er remained at about 94:6. This result ruled out a kinetic resolution mechanism. Moreover, the

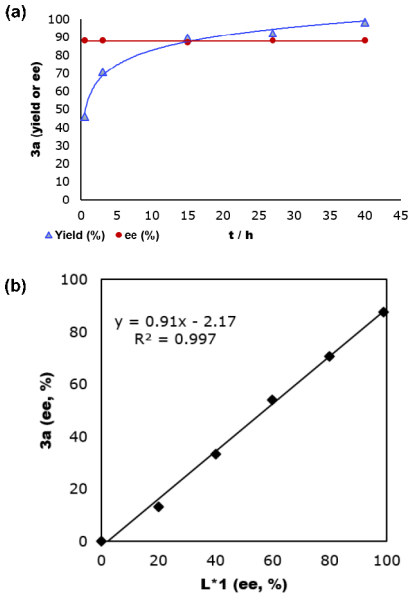

Figure 4. (a) Monitoring of the reaction progress of (*Z*)-**1a** with **2a** over time. (b) Nonlinear effect study.

enantiomeric excess of the product and catalyst followed a linear relationship, indicating a monomeric nature of the active catalyst (Figure 4b).

Following previous proposals on Ni-catalyzed hydroalkylation[9,11] and considering the results above, we propose two limiting catalytic cycles for the present enantioselective hydroalkylation of *N*-protected enamines (Figure 5). In one possibility (Figure 5a), under the reaction conditions, a chiral **L***Ni^{I}–X species (**A**) is formed as the actual catalyst, which reacts with a hydride source and base (e.g, HBpin + KF) to generate the Ni–H species **L***Ni^{I}–H (**C**). The hydride species inserts into the alkene moiety of the enamine.[20] The resulting Ni^{I}–alkyl species (**D**) reacts with an alkyl halide via a halogen atom abstraction followed by alkyl radical trapping to give a Ni^{III}–bis(alkyl) intermediate (**D** to **E** to **F**).[21] The last species undergoes reductive elimination to give the coupling product and regenerate the Ni^{I}–X catalyst (**A**). In another possibility (Figure 5b), species **A** first abstracts a halogen atom from an alkyl iodide to generate an alkyl radical and X**L***Ni^{II}–I (**B′**). The latter reacts with a hydride source (e.g, HBpin + KF) to generate the Ni–H species X**L***Ni^{II}–H (**C′**) that inserts into the enamine. The resulting Ni–alkyl intermediate (**D′**) then recombines with the alkyl radical to give a formal Ni(III) complex (**E′**), which undergoes reductive elimination to give the product and regenerate the Ni(I) catalyst. The key difference between the two catalytic cycles is the Ni species that activates the alkyl halide. In the first catalytic cycle, it is a Ni^{I}–alkyl species; in the second catalytic cycle, it is a Ni^{I}–X species. Both possibilities were proposed in the literature.[7,9,14,21]

We expect that the coordination of the Cbz group of the enecarbamate substrate to the Ni center facilitates regio- and enantioselective Ni–H insertion into the alkene moiety.[20] A cis conformation of the carbamate is necessary for the Cbz group to act as a directing group. The low activity toward a tertiary carbamate substrate (Figure 3g) is likely due to a dominant trans conformation of the substrate, which has a high rotational barrier as well. The addition of hydride into the carbon β to the NHCbz group is favored over the insertion into the α-

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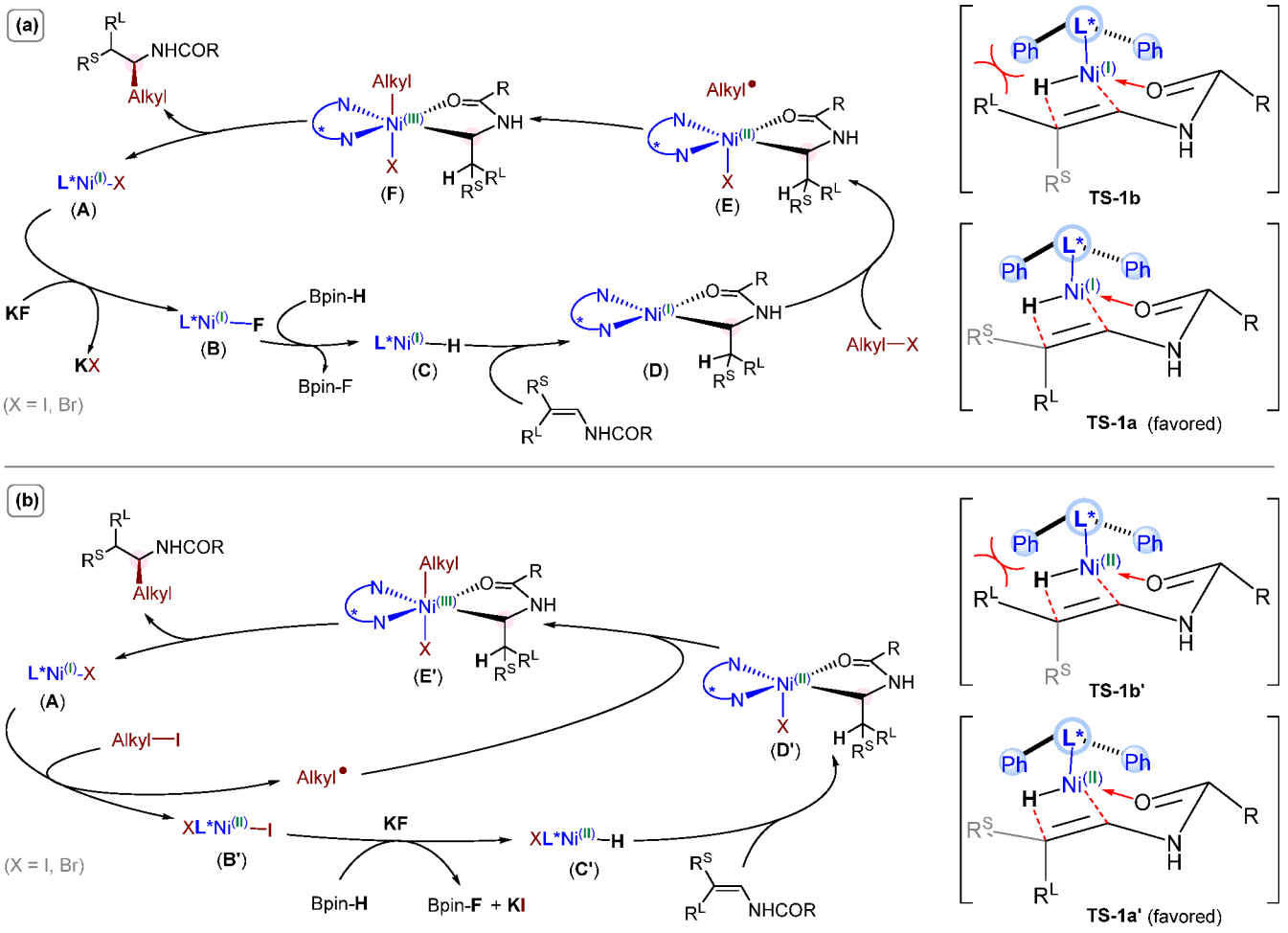

Figure 5. Proposed catalytic cycle: X = I, Br; R^L = large group; R^S = small group.

carbon due to the formation of a more stable five-membered nickelacycle in comparison to a six-membered nickelacycle in the latter case. The enantioselectivity of insertion is dictated by the steric interaction of the phenyl substituent with the alkene substituents (R^L and R^S). In the favored transition state, the phenyl group is far from the R^L group (**TS-1a** or **TS-1a′**). In the opposite configuration, the phenyl group would experience steric repulsion from the R^L group (**TS-1b** or **TS-1b′**). A lower enantioselectivity was observed for a Boc-protected enamine in comparison to its Cbz-protected analogue (**4b** vs **4c**). This difference indicates an influence of the protecting group in the stereoselectivity of the reaction, possibly due to steric effects (Boc is bulkier than Cbz and might hinder metal coordination) or a $\pi-\pi$ stacking interaction (Cbz has a Ph group). The details of the catalytic cycle will be subjected to a dedicated study.

3. CONCLUSIONS

In summary, we have developed a method for the Ni-catalyzed enantioselective hydroalkylation of enecarbamates. This method allows the synthesis of a wide range of enantiomerically enriched chiral alkyl amines from readily available and stable alkenes while avoiding sensitive organometallic reagents. The method operates under mild conditions and has high functional group tolerance. It has been applied for the postfunctionalization of many natural products and drug molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c11630.

Experimental procedures, mechanistic investigation, characterization data, and ^{1}H NMR, ^{13}C NMR, and HPLC spectra for new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Xile Hu − *Laboratory of Inorganic Synthesis and Catalysis, Institute of Chemical Sciences and Engineering, École Polytechnique Fédérale de Lausanne (EPFL), ISIC-LSCI, BCH 3305, Lausanne 1015, Switzerland;* orcid.org/0000-0001-8335-1196; Email: xile.hu@epfl.ch

Authors

Deyun Qian − *Key Laboratory of Medicinal Chemistry for Natural Resource, Ministry of Education and Yunnan Province, Yunnan University, Kunming 650091, People's Republic of China; Laboratory of Inorganic Synthesis and Catalysis, Institute of Chemical Sciences and Engineering, École Polytechnique Fédérale de Lausanne (EPFL), Lausanne 1015, Switzerland*

Srikrishna Bera − *Laboratory of Inorganic Synthesis and Catalysis, Institute of Chemical Sciences and Engineering,*

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École Polytechnique Fédérale de Lausanne (EPFL), Lausanne 1015, Switzerland

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.0c11630

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Nugent, T. C. *Chiral amine synthesis: methods, developments and applications*; Wiley: 2010. (b) Li, W.; Zhang, X. *Stereoselective formation of amines*; Springer: 2014. (c) Trowbridge, A.; Walton, S. M.; Gaunt, M. J. New Strategies for the Transition-Metal Catalyzed Synthesis of Aliphatic Amines. *Chem. Rev.* **2020**, *120*, 2613−2692.

(2) (a) Nugent, T. C.; El-Shazly, M. Chiral Amine Synthesis - Recent Developments and Trends for Enamide Reduction, Reductive Amination, and Imine Reduction. *Adv. Synth. Catal.* **2010**, *352*, 753−819. (b) Xie, J.-H.; Zhu, S.-F.; Zhou, Q.-L. Transition Metal-Catalyzed Enantioselective Hydrogenation of Enamines and Imines. *Chem. Rev.* **2011**, *111*, 1713−1760. (c) Seo, C. S. G.; Morris, R. H. Catalytic Homogeneous Asymmetric Hydrogenation: Successes and Opportunities. *Organometallics* **2019**, *38*, 47−65.

(3) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. Catalytic Enantioselective Formation of C-C Bonds by Addition to Imines and Hydrazones: A Ten-Year Update. *Chem. Rev.* **2011**, *111*, 2626−2704.

(4) (a) 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.* **2000**, *65*, 176−185. (b) Friestad, G. K.; Shen, Y.; Ruggles, E. L. Enantioselective Radical Addition to N-Acyl Hydrazones Mediated by Chiral Lewis Acids. *Angew. Chem., Int. Ed.* **2003**, *42*, 5061−5063. (c) 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. (d) Lee, S.; Kim, S. Enantioselective radical addition reactions to imines using binaphthol-derived chiral N-triflyl phosphoramides. *Tetrahedron Lett.* **2009**, *50*, 3345−3348.

(5) (a) Liu, R. Y.; Buchwald, S. L. CuH-Catalyzed Olefin Functionalization: From Hydroamination to Carbonyl Addition. *Acc. Chem. Res.* **2020**, *53*, 1229−1243. (b) Yang, Y.; Shi, S.-L.; Niu, D.; Liu, P.; Buchwald, S. L. Catalytic asymmetric hydroamination of unactivated internal olefins to aliphatic amines. *Science* **2015**, *349*, 62−66. (c) Niu, D.; Buchwald, S. L. Design of Modified Amine Transfer Reagents Allows the Synthesis of α-Chiral Secondary Amines via CuH-Catalyzed Hydroamination. *J. Am. Chem. Soc.* **2015**, *137*, 9716−9721.

(6) (a) Zhu, S.; Niljianskul, N.; Buchwald, S. L. Enantio- and Regioselective CuH-Catalyzed Hydroamination of Alkenes. *J. Am. Chem. Soc.* **2013**, *135*, 15746−15749. (b) Zhu, S.; Buchwald, S. L. Enantioselective CuH-Catalyzed Anti-Markovnikov Hydroamination of 1,1-Disubstituted Alkenes. *J. Am. Chem. Soc.* **2014**, *136*, 15913−15916. (c) Shi, S.-L.; Buchwald, S. L. Copper-catalysed selective hydroamination reactions of alkynes. *Nat. Chem.* **2015**, *7*, 38−44. (d) Yu, L.; Somfai, P. Regio- and Enantioselective Formal Hydroamination of Enamines for the Synthesis of 1,2-Diamines. *Angew. Chem., Int. Ed.* **2019**, *58*, 8551−8555.

(7) (a) Lu, X.; Xiao, B.; Zhang, Z.; Gong, T.; Su, W.; Yi, J.; Fu, Y.; Liu, L. Practical carbon-carbon bond formation from olefins through nickel-catalyzed reductive olefin hydrocarbonation. *Nat. Commun.* **2016**, *7*, 11129. (b) Lu, X.; Xiao, B.; Liu, L.; Fu, Y. Formation of $C(sp^3)$-$C(sp^3)$ Bonds through Nickel-Catalyzed Decarboxylative Olefin Hydroalkylation Reactions. *Chem. - Eur. J.* **2016**, *22*, 11161−11164. (c) 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.* **2018**, *140*, 12765−12769. (d) 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.* **2018**, *57*, 4058−4062. (e) Bera, S.; Hu, X. Nickel-Catalyzed Regioselective Hydroalkylation and Hydroarylation of Alkenyl Boronic Esters. *Angew. Chem., Int. Ed.* **2019**, *58*, 13854−13859. (f) Qian, D.; Hu, X. Ligand-Controlled Regiodivergent Hydroalkylation of Pyrrolines. *Angew. Chem., Int. Ed.* **2019**, *58*, 18519−18523. (g) Sun, S.-Z.; Romano, C.; Martin, R. Site-Selective Catalytic Deaminative Alkylation of Unactivated Olefins. *J. Am. Chem. Soc.* **2019**, *141*, 16197−16201. (h) Wang, C.; Xi, Y.; Huang, W.; Qu, J.; Chen, Y. Nickel-Catalyzed Regioselective Hydroarylation of Internal Enamides. *Org. Lett.* **2020**, *22*, 9319−9324.

(8) (a) Hu, X. Nickel-catalyzed cross coupling of non-activated alkyl halides: a mechanistic perspective. *Chem. Sci.* **2011**, *2*, 1867−1886. (b) Choi, J.; Fu, G. C. Transition metal-catalyzed alkyl-alkyl bond formation: another dimension in cross-coupling chemistry. *Science* **2017**, *356*, eaaf7230. (c) Fu, G. C. Transition-Metal Catalysis of Nucleophilic Substitution Reactions: A Radical Alternative to SN1 and SN2 Processes. *ACS Cent. Sci.* **2017**, *3*, 692−700.

(9) (a) Wang, Z.; Yin, H.; Fu, G. C. Catalytic enantioconvergent coupling of secondary and tertiary electrophiles with olefins. *Nature* **2018**, *563*, 379−383. (b) Zhou, F.; Zhang, Y.; Xu, X.; Zhu, S. NiH-Catalyzed Remote Asymmetric Hydroalkylation of Alkenes with Racemic α-Bromo Amides. *Angew. Chem., Int. Ed.* **2019**, *58*, 1754−1758. (c) He, S.-J.; Wang, J.-W.; Li, Y.; Xu, Z.-Y.; Wang, X.-X.; Lu, X.; Fu, Y. Nickel-Catalyzed Enantioconvergent Reductive Hydroalkylation of Olefins with α-Heteroatom Phosphorus or Sulfur Alkyl Electrophiles. *J. Am. Chem. Soc.* **2020**, *142*, 214−221. (d) Yang, Z.-P.; Fu, G. C. Convergent Catalytic Asymmetric Synthesis of Esters of Chiral Dialkyl Carbinols. *J. Am. Chem. Soc.* **2020**, *142*, 5870−5875. (e) Shi, L.; Xing, L.-L.; Hu, W.-B.; Shu, W. Regio- and Enantioselective Ni-Catalyzed Formal Hydroalkylation, Hydrobenzylation, and Hydropropargylation of Acrylamides to α-Tertiary Amides. *Angew. Chem., Int. Ed.* **2021**, *60*, 1599.

(10) (a) Vasseur, A.; Bruffaerts, J.; Marek, I. Remote functionalization through alkene isomerization. *Nat. Chem.* **2016**, *8*, 209−219. (b) Sommer, H.; Juliá-Hernández, F.; Martin, R.; Marek, I. Walking Metals for Remote Functionalization. *ACS Cent. Sci.* **2018**, *4*, 153−165.

(11) Bera, S.; Mao, R.; Hu, X. Enantioselective $C(sp^3)$-$C(sp^3)$ cross-coupling of non-activated alkyl electrophiles via nickel hydride catalysis. *Nat. Chem.* **2020**.

(12) He, Y.; Liu, C.; Yu, L.; Zhu, S. Enantio- and Regioselective NiH-Catalyzed Reductive Hydroarylation of Vinylarenes with Aryl Iodides. *Angew. Chem., Int. Ed.* **2020**, *59*, 21530−21534.

(13) (a) Mecozzi, T.; Petrini, M. A Stereoselective Synthesis of Primary (Z)-Enecarbamates from α-Amidoalkylphenyl Sulfones. *Synlett* **2000**, *2000*, 73−74. (b) Gooßen, L. J.; Salih, K. S. M.; Blanchot, M. Synthesis of Secondary Enamides by Ruthenium-Catalyzed Selective Addition of Amides to Terminal Alkynes. *Angew. Chem., Int. Ed.* **2008**, *47*, 8492−8495. (c) Trost, B. M.; Cregg, J. J.; Quach, N. Isomerization of N-Allyl Amides To Form Geometrically Defined Di-, Tri-, and Tetrasubstituted Enamides. *J. Am. Chem. Soc.* **2017**, *139*, 5133−5139.

(14) (a) Cuesta-Galisteo, S.; Schörgenhumer, J.; Wei, X.; Merino, E.; Nevado, C. Nickel-Catalyzed Asymmetric Synthesis of α-Arylbenzamides. *Angew. Chem., Int. Ed.* **2021**, *60*, 1605−1609. (b) During the review of this manuscript, there were several preprints on the asymmetric reductive hydroarylation and hydroalkylation of enamides: Jia-Wang, W.; Yan, L.; Wan, N.; Zhe, C.; Zi-An, Y.; Yi-Fan, Z.; Xi, L.; Yao, F. Catalytic Asymmetric Reductive Alkylation of Enamines to Chiral Aliphatic Amines. *ChemRxiv*, DOI: 10.26434/chemrxiv.13102307.v1. (c) Yuli, H.; Huayue, S.; Shaolin, Z. NiH-Catalyzed Asymmetric Hydroarylation of N-Acyl Enamines: Practical Access to Chiral Benzylamines. *ChemRxiv*, DOI: 10.26434/chemrxiv.13084946.v1. (d) Shan, W.; Tian-Yi, Z.; Jian-Xin, Z.; Huan, M.; Bi-Hong, C.; Shu, W. Enantioselective Access to Dialkyl

Amines and Alcohols via Ni-Catalyzed Reductive Hydroalkylations. *ChemRxiv*, DOI: 10.26434/chemrxiv.13284416.v1.

(15) (a) Cordier, C. J.; Lundgren, R. J.; Fu, G. C. Enantioconvergent Cross-Couplings of Racemic Alkylmetal Reagents with Unactivated Secondary Alkyl Electrophiles: Catalytic Asymmetric Negishi α-Alkylations of N-Boc-pyrrolidine. *J. Am. Chem. Soc.* **2013**, *135*, 10946−10949. (b) Mu, X.; Shibata, Y.; Makida, Y.; Fu, G. C. Control of Vicinal Stereocenters through Nickel-Catalyzed Alkyl-Alkyl Cross-Coupling. *Angew. Chem., Int. Ed.* **2017**, *56*, 5821−5824. (c) Huo, H.; Gorsline, B. J.; Fu, G. C. Catalyst-controlled doubly enantioconvergent coupling of racemic alkyl nucleophiles and electrophiles. *Science* **2020**, *367*, 559−564.

(16) (a) Boyington, A. J.; Seath, C. P.; Zearfoss, A. M.; Xu, Z.; Jui, N. T. Catalytic Strategy for Regioselective Arylethylamine Synthesis. *J. Am. Chem. Soc.* **2019**, *141*, 4147−4153. (b) Wei, X.; Shu, W.; García-Domínguez, A.; Merino, E.; Nevado, C. Asymmetric Ni-Catalyzed Radical Relayed Reductive Coupling. *J. Am. Chem. Soc.* **2020**, *142*, 13515−13522.

(17) (a) Bethell, P. H.; Goad, L. J.; Evershed, R. P.; Ottaway, J. The Study of Molecular Markers of Human Activity: The Use of Coprostanol in the Soil as an Indicator of Human Faecal Material. *J. Archaeol. Sci.* **1994**, *21*, 619−632. (b) Mander, L. Overview and Introduction. *Comprehensive natural products II* **2010**, 1−3. (c) Mitchell, J. A.; Akarasereenont, P.; Thiemermann, C.; Flower, R. J.; Vane, J. R. Selectivity of nonsteroidal antiinflammatory drugs as inhibitors of constitutive and inducible cyclooxygenase. *Proc. Natl. Acad. Sci. U. S. A.* **1993**, *90*, 11693−11697.

(18) (a) Etxebarria, J.; Vicario, J. L.; Badía, D.; Carrillo, L. A general and enantiodivergent method for the asymmetric synthesis of piperidine alkaloids: concise synthesis of (R)-pipecoline, (S)-coniine and other 2-alkylpiperidines. *Tetrahedron* **2007**, *63*, 11421−11428. (b) Bahamonde, A.; Al Rifaie, B.; Martín-Heras, V.; Allen, J. R.; Sigman, M. S. Enantioselective Markovnikov Addition of Carbamates to Allylic Alcohols for the Construction of α-Secondary and α-Tertiary Amines. *J. Am. Chem. Soc.* **2019**, *141*, 8708−8711. (c) Zhu, Q.; Lu, Y. Enantioselective Conjugate Addition of Nitroalkanes to Vinyl Sulfone: An Organocatalytic Access to Chiral Amines. *Org. Lett.* **2009**, *11*, 1721−1724.

(19) Gutierrez, O.; Tellis, J. C.; Primer, D. N.; Molander, G. A.; Kozlowski, M. C. Nickel-Catalyzed Cross-Coupling of Photoredox-Generated Radicals: Uncovering a General Manifold for Stereoconvergence in Nickel-Catalyzed Cross-Couplings. *J. Am. Chem. Soc.* **2015**, *137*, 4896−4899.

(20) For the promotion of NiH insertion into olefins via coordination of the directing group, see: Jeon, J.; Lee, C.; Seo, H.; Hong, S. NiH-Catalyzed Proximal-Selective Hydroamination of Unactivated Alkenes. *J. Am. Chem. Soc.* **2020**, *142*, 20470−20480.

(21) (a) Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. Ligand Redox Effects in the Synthesis, Electronic Structure, and Reactivity of an Alkyl-Alkyl Cross-Coupling Catalyst. *J. Am. Chem. Soc.* **2006**, *128*, 13175−13183. (b) Breitenfeld, J.; Ruiz, J.; Wodrich, M. D.; Hu, X. Bimetallic Oxidative Addition Involving Radical Intermediates in Nickel-Catalyzed Alkyl-Alkyl Kumada Coupling Reactions. *J. Am. Chem. Soc.* **2013**, *135*, 12004−12012. (c) Yin, H.; Fu, G. C. Mechanistic Investigation of Enantioconvergent Kumada Reactions of Racemic α-Bromoketones Catalyzed by a Nickel/Bis(oxazoline) Complex. *J. Am. Chem. Soc.* **2019**, *141*, 15433−15440. (d) Richmond, E.; Moran, J. Recent Advances in Nickel Catalysis Enabled by Stoichiometric Metallic Reducing Agents. *Synthesis* **2018**, *50*, 499−513.

https://dx.doi.org/10.1021/jacs.0c11630
J. Am. Chem. Soc. 2021, 143, 1959−1967