Enantioselective Hydroalkylation of α,β-Unsaturated Amides through Reversed *syn*-Hydrometallation of NiH

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Supporting Information Placeholder

ABSTRACT: Enantioselective synthesis of a wide range of structurally diverse β-chiral amides has been achieved through nickel-catalyzed regio-reversed hydroalkylation of α,β-unsaturated amides with alkyl iodides in the presence of a hydrosilane. Different from the classical homolysis/enantioconvergent recombination process of Ni(III) intermediates as the enantio-determining step, chiral induction in this reductive hydroalkylation was achieved through an enantiodifferentiating regio-reversed *syn*-hydrometallation process of α,β-unsaturated amides.

A method to improve the clinical activity of a compound, is to increase the stereocenters in drug candidates.[1] Construction of sp^3-hybridized carbon with stereochemical control has long been a goal in organic synthesis, and significantly involves transition metal catalysis.[2] As a catalyst, nickel has many advantages such as its easy access to diverse oxidation states and its ability to allow facile oxidative addition. Over the past two decades, it has emerged as a powerful catalyst in enantioselective C(sp^3) cross-coupling reactions.[3]

Generation of organometallic reagents *in situ* by catalytic hydrometallation of alkenes with metal hydrides is a strategy which avoids the special preparation of organometallic reagents.[4] This attractive method could also circumvent another issue encountered in conventional cross-coupling, that the basic and nucleophilic nature of pregenerated organometallic reagents can often lead to limited functional-group compatibility rendering it unable to handle sensitive functionality. With alkenes as potential organometallic replacements, metal-hydride catalyzed asymmetric hydrofunctionalization can substantially streamline synthetic efforts and has led to the discovery of a variety of valuable transformations proceeding under mild reaction conditions.

Recently, nickel hydride[5-11] has proved to be an efficient catalyst for enantioselective reductive hydrofunctionalization[8,10] (Figure 1a). In this process, chiral induction could occur in one of two possible steps: (i) enantioconvergent conversion of Ni(III) intermediates through fast homolysis and enantioconvergent recombination to form enantioenriched Ni(III) intermediates before reductive elimination - an example is hydroarylation[10e,10h,10i]; or (ii) enantioselective *syn*-hydrometallation of NiH with an alkene to form enantioenriched alkylnickel species. Hydroalkylation[10d,10g,10j-l] is an example of the latter process. Previously, when electron-deficient alkenes such as β-alkyl-α,β-unsaturated carbonyl compounds were used in hydrocupration reactions, an α-copper intermediate was produced in a manner consistent with the electronic requirements which limit the subsequent functionalization to the α-position[12] (Figure 1b, left). We questioned if the classical regioselectivity of hydrometallation could be reversed[13] by nickel hydride and whether the stereoselectivity could be simultaneously controlled. In such a case, a wide range of structurally diverse, enantiopure β-functionalized carbonyl compounds could be obtained (Figure 1b, right). As shown in Figure 1c, we speculated that the amide group could serve as a good directing group for an appropriately ligated NiH species to undergo a regio-reversed *syn*-hydrometallation. In terms of enantiomeric control, such a hydrometallation step with an appropriate chiral ligand could be enantioselective producing enantioenriched β-nickel(I) intermediates which could undergo subsequent stereospecific cross-coupling with alkyl iodides to produce the enantioenriched β-alkylation product. Successful implementation of this transformation will also require that the obtained oxidative addition Ni(III) intermediates obtained in this way will not undergo homolysis and recombination before reductive elimination to form the final product. This is essential as otherwise, loss of enantiomeric purity would result. In this communication, we report a mild and robust protocol for such a strategy and demonstrate that by using a chiral PyrOx-nickel complex as the sole catalyst, a highly enantioselective hydroalkylation of α,β-unsaturated amides can be realized through such an enantioselective regio-reversed hydrometallation step (Figure 1c).

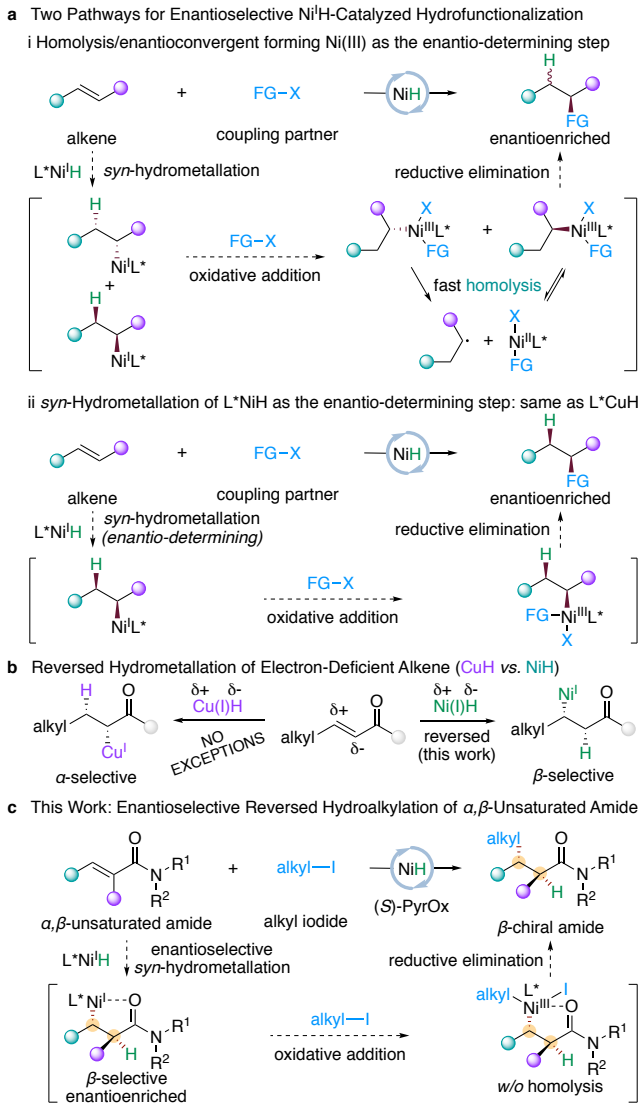
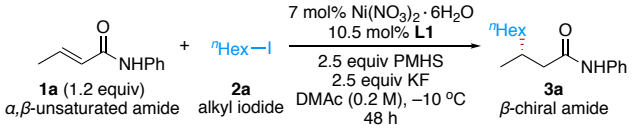


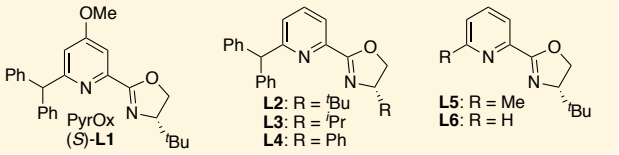
Figure 1. Enantioselective regio-reversed hydroalkylation of α,β-unsaturated amides.

This catalytic regio-reversed hydroalkylation was first evaluated by using α,β-unsaturated amide (**1a**) and 1-iodohexane (**2a**) as model substrates (Table 1). After examination of the reaction parameters and evaluation of different ligands, it was determined that $Ni(NO_3)_2{\cdot}6H_2O$ and the C6-substituted PyrOx ligand (**L1**) could generate the desired β-selective hydroalkylation product as a single regioisomer [rr (β-product : all other isomers) > 99:1] in 90% isolated yield with excellent enantioselectivity (entry 1). Other nickel sources such as $NiI_2{\cdot}xH_2O$ led to significantly lower yields and a moderate rr (entry 2). Screening of ligands revealed that ligands lacking the C4-methoxy substituent gave similar results (entry 3) while a ligand with a *tert*-butyl group on its oxazoline ring shown the highest ee (entry 3 vs. entries 4, 5). Ligands with different C6-substituents on the pyridyl ring were screened and a ligand with sterically bulkier C6-substituent gave the best ee and yield (entry 3 vs. entries 6, 7). Evaluation of other hydride sources showed that diethoxy(methyl)silane (DEMS) and pinacolborane (HBpin) were equally effective (entries 8, 9). Polymethylhydrosiloxane (PMHS), an inexpensive, environmentally friendly and common silicone industry byproduct was used in subsequent investigations. NaF was shown to be an unsuitable base (entry 10) and DME was shown to be an unsuitable solvent (entry 11). Similar results were obtained when the reaction was conducted at 0 °C (entry 12). A slightly diminished yield was obtained when the catalyst loading was reduced to 5 mol% (entry 13) and the reaction was found to be insensitive to moisture and air (entries 14, 15).

Table 1. Variation of Reaction Parameters



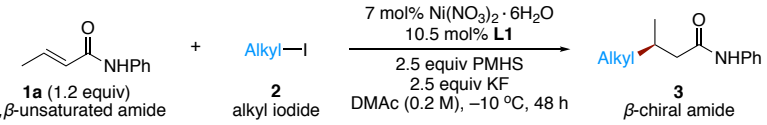
entry	variations from above conditions	yield **3a** (%)[a]	rr[b]	ee (%)[c]
1	None	99 (90)	>99:1	98
2	$NiI_2{\cdot}xH_2O$ instead of $Ni(NO_3)_2{\cdot}6H_2O$	20	90:10	87
3	**L2** instead of **L1**	92	>99:1	98
4	**L3** instead of **L1**	80	>99:1	31
5	**L4** instead of **L1**	77	>99:1	54
6	**L5** instead of **L1**	51	>99:1	79
7	**L6** instead of **L1**	39	>99:1	70
8	$(EtO)_2MeSiH$ instead of PMHS	95	>99:1	97
9	HBpin instead of PMHS	95	>99:1	96
10	NaF instead of KF	3	>99:1	ND
11	DME instead of DMAc	5	>99:1	93
12	0 °C instead of –10 °C	95	>99:1	98
13	5 mol% catalyst	93	>99:1	96
14	1.0 equiv H_2O added	93	>99:1	97
15	under air in a closed vial	80	>99:1	98



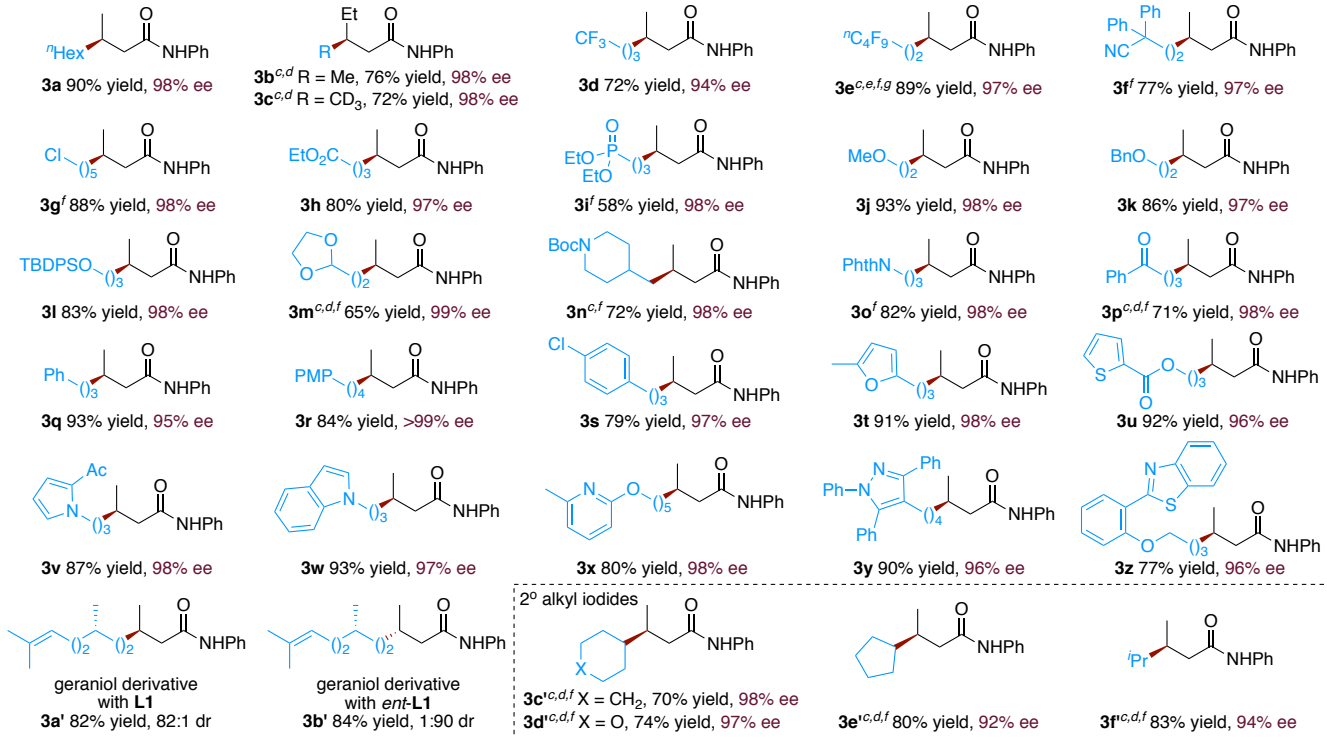
[a]Yields were determined by GC using *n*-tetradecane as the internal standard, the yield in parentheses is the isolated yield and is an average of two runs (0.20 mmol scale). [b]rr refers to regioisomeric ratio, representing the ratio of the major product to the sum of all other isomers as determined by GC analysis. [c]Enantiomeric excess (ee) was determined by chiral-stationary-phase HPLC analysis. PMHS, polymethylhydrosiloxane; DMAc, *N*,*N*-dimethylacetamide; DME, dimethoxyethane.

With these optimal conditions in hand, we examined the scope of the alkyl iodide reaction partner. As shown in Table 2, both primary (**2a**–**2a'**) and secondary (**2c'**–**2f'**) alkyl iodides reacted. Methyl-d_3 iodide (**2c**) was also compatible, providing the β-methyl-d_3 substituted amide smoothly. Under these mild conditions, not only were a nitrile (**2f**), esters (**2h**, **2u**), a phosphonate (**2i**), ethers (**2j**–**2l**, **2x**, **2z**, **2d'**), an acetal (**2m**), a *N*-Boc carbamate (**2n**), and a phthaloyl amide (**2o**) tolerated, but a trisubstituted alkene (**2a'**) and easily reduced ketones (**2p**, **2v**) remained intact. Notably, the reaction is orthogonal to alkyl chlorides (**2g**) and aryl chlorides (**2s**), providing coupling handles that can be used for further derivatization. Various medicinally relevant heterocycles including furan (**2t**), thiophene (**2u**), pyrrole (**2v**), indole (**2w**), pyridine (**2x**), pyrazole (**2y**), and benzothiazole (**2z**) were also found to be compatible.

Table 2. Scope of Alkyl Iodides[a,b]



1a (1.2 equiv) *α,β*-unsaturated amide + **2** alkyl iodide → **3** *β*-chiral amide



3a 90% yield, 98% ee

3b[c,d] R = Me, 76% yield, 98% ee
3c[c,d] R = CD_3, 72% yield, 98% ee

3d 72% yield, 94% ee

3e[c,e,f,g] 89% yield, 97% ee

3f[f] 77% yield, 97% ee

3g[f] 88% yield, 98% ee

3h 80% yield, 97% ee

3i[f] 58% yield, 98% ee

3j 93% yield, 98% ee

3k 86% yield, 97% ee

3l 83% yield, 98% ee

3m[c,d,f] 65% yield, 99% ee

3n[c,f] 72% yield, 98% ee

3o[f] 82% yield, 98% ee

3p[c,d,f] 71% yield, 98% ee

3q 93% yield, 95% ee

3r 84% yield, >99% ee

3s 79% yield, 97% ee

3t 91% yield, 98% ee

3u 92% yield, 96% ee

3v 87% yield, 98% ee

3w 93% yield, 97% ee

3x 80% yield, 98% ee

3y 90% yield, 96% ee

3z 77% yield, 96% ee

geranyl derivative with **L1**
3a' 82% yield, 82:1 dr

geranyl derivative with *ent*-**L1**
3b' 84% yield, 1:90 dr

2° alkyl iodides

3c'[c,d,f] X = CH_2, 70% yield, 98% ee
3d'[c,d,f] X = O, 74% yield, 97% ee

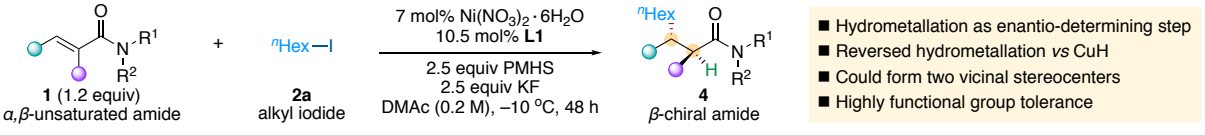
3e'[c,d,f] 80% yield, 92% ee

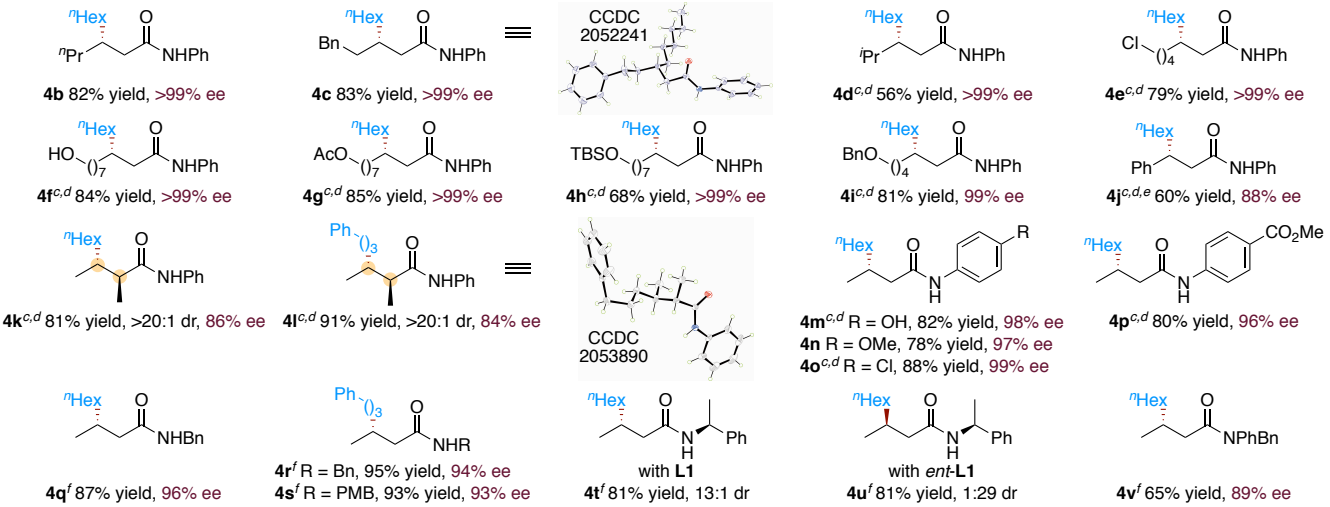
3f'[c,d,f] 83% yield, 94% ee

[a]Isolated yields on 0.20 mmol scale (average of two runs). [b]Enantiomeric excess (ee) was determined by chiral-stationary-phase HPLC analysis. [c]DMAc (0.25 M) was used. [d]1.5 equivalent alkyl iodide (**2**) was used. [e]1.5 equivalent (**1a**) was used. [f]10 mol% catalyst was used. [g]Reaction was performed at rt.

The optimized conditions also proved efficient for the various α,β-unsaturated amide components (Table 3). Both β-alkyl (**1b**–**1i**) and β-aryl (**1j**) substituted acrylamides were readily accommodated but in case of the β-aryl acrylamide (**1j**), a slightly decreased enantioselectivity was observed. Under these exceptionally mild reaction conditions, a variety of functional groups were readily accommodated, including an alkyl chloride (**1e**), esters (**1g**, **1p**), ethers (**1h**, **1i**, **1n**), an aryl chloride (**1o**), a free alcohol (**1f**), and an unprotected phenol (**1m**). Notably, α,β-disubstituted acrylamides (**1k**, **1l**) could also undergo reversed hydroalkylation to afford the enantioenriched amides as a single diastereoisomer with two stereocenters, although a marginal erosion in the ee was observed. The absolute configuration of **4l** was unambiguously determined by X-ray diffraction analysis, and supports our hypothesis that *syn*-hydrometallation is the enantio-determining step. Moreover, α,β-unsaturated amides with aryl (**1m**–**1p**, **1v**) or alkyl (**1q**, **1t**) substituents on the nitrogen atom all were found to be compatible. α,β-Unsaturated amide bearing electron-donating (**1m**, **1n**) or electron-withdrawing (**1o**, **1p**) substituents on the *N*-aryl ring were well-tolerated. Finally, α,β-unsaturated amide with a stereocenter adjacent to the nitrogen atom proceeded with excellent catalyst control (**1t**).

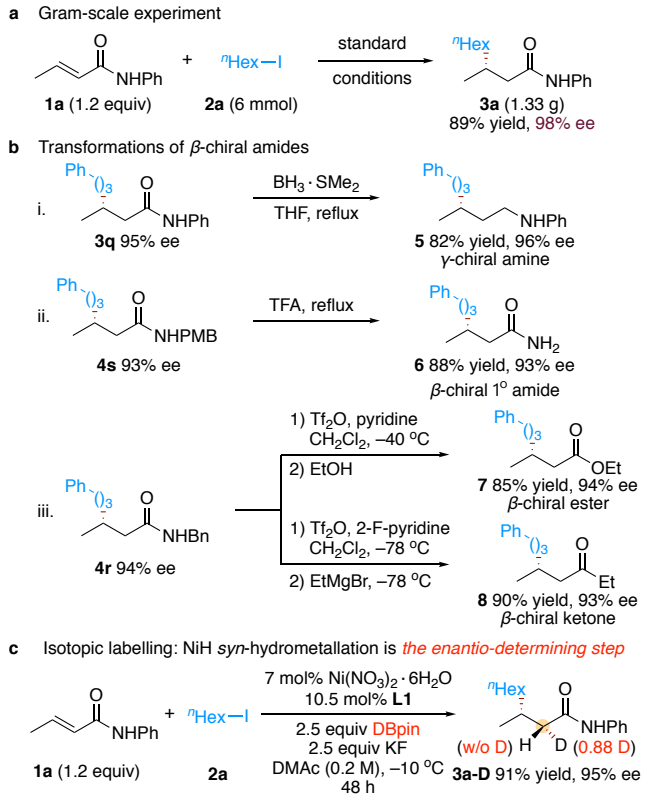
Table 3. Scope of the α,β-Unsaturated Amide[a,b]





[a]Isolated yields on 0.20 mmol scale (average of two runs). [b]Enantiomeric excess (ee) was determined by chiral-stationary-phase HPLC analysis. [c]10 mol% catalyst. [d]DMAc (0.25 M) was used. [e]2.0 equivalent alkyl iodide (**2a**) was used. [f]Reaction was performed with 11 mol% $Ni(NO_3)_2{\cdot}6H_2O$, 17 mol% **L1**, 1.5 equivalent **1**, 1.0 equivalent **2**, 0.40 equivalent NaI, DMAc/THF (0.20 M, 4:1).

The model reaction proceeded smoothly on a 6 mmol scale without any decrease of yield or enantioselectivity demonstrating the scalability of this process (Scheme 1a). The synthetic utility of the method was shown by subsequent syntheses. As illustrated in Scheme 1b, the obtained enantiopure β-substituted amides could be transformed into versatile enantioenriched motifs including an amine (**5**), primary amide (**6**), ester (**7**), or ketone (**8**). Finally, an isotope labelling experiment was conducted (Scheme 1c) in an effort to understand the hydrometallation process. With deuteropinacolborane as hydride source, the desired deuteroalkylation product (**3a-D**) was obtained as only one diastereoisomer together with the partial hydroalkylation product (**3a**), indicating the *syn*-hydroalkylation is the enantio-determining step. This conclusion was further supported by the observation of diastereoisomerically pure products in case of **4k** or **4l** (see Table 3).



Scheme 1. Gram-scale Experiment, Versatile Transformations, and Isotopic Labelling Experiment

In conclusion, we have developed a NiH-catalyzed strategy for enantioselective regio-reversed hydroalkylation of α,β-unsaturated amides to form enantiopure β-functionalized carbonyl compounds. This reversed hydrometallation of nickel hydride with α,β-unsaturated amides differs from the regioselectivity of hydrocupration of β-alkyl-α,β-unsaturated carbonyls, and allows access to β-selective hydroalkylation products. A preliminary isotope labeling experiment indicated that the

syn-hydrometallation of NiH is the enantio-determining step. With an olefin as a nucleophile, broad substrate scope, and mild conditions of this protocol have been demonstrated. Studies directed toward the development of a migratory enantioselective version of this transformation are currently in progress.

ASSOCIATED CONTENT

Experimental procedures, characterization data for all compounds, and crystallographic data of **4c** and **4l** (CIF).

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

Support was provided by NSFC (21822105, 21772087), NSF of Jiangsu Province (BK20201245), and programs for high-level entrepreneurial and innovative talents introduction of Jiangsu Province (group program). We thank Dr. Yuanzheng Cheng, Jingjie Yang, and Yuhang Xue for providing some substrates. We gratefully acknowledge Dr. Penglong Wang (Professor Congqing Zhu group) for acquiring X-ray crystal structure.

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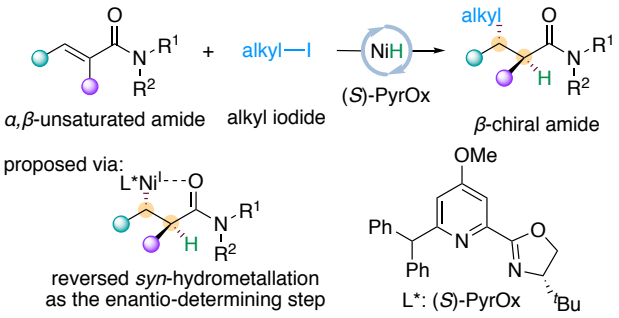
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L*: (S)-PyrOx
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